World Cancer Research Fund International Systematic Literature Review

The Associations between Food, Nutrition and Physical Activity and the Risk of Breast Cancer

Imperial College London

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List of Abbreviations used in the CUP Report

AHEI	Alternate Healthy Eating Index
aMDS	Alternate Mediterranean Diet Score
BC	Breast cancer
BRCA	Breast cancer susceptibility protein
CFA	Confirmation factor analysis
CI	Confidence interval
CUP	Continuous Update Project
DASH	Dietary Approaches to Stop Hypertension
DFE	Dietary folate equivalent
DQI-R	Diet Quality Index-Revised
ER	Estrogen receptor
HEI	Healthy Eating Index
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HT/HRT	Hormone therapy/hormone replacement therapy
LCI	Lower limit confidence interval
MDS	Mediterranean Diet Score
MET-hour	Metabolic Equivalent of Task-hour
MHT/PHT	Menopausal hormone therapy/postmenopausal hormone therapy
OC/OCP	Oral contraceptive/oral contraceptive pill
PCA	Principal components factor analysis
PR	Progesterone receptor
RFS	Recommended Food Score
RR	Relative risk
SIR	Standardised incidence ratio
SLR	Systematic literature review
UCI	Upper limit confidence interval
WCRF/AICR	World Cancer Research Fund/American Institute for Cancer Research

List of Abbreviations of cohort study names used in the CUP report

40-y	Age 40-programme
ACLS	Aerobic Center Longitudinal Study
AICHI	Three-Prefecture Cohort Study in Aichi
AHS	Agricultural Health Study
AHS, 1974	Adventist Health Study
AMBER Consortium	African American Breast Cancer Epidemiology and Risk Consortium
ANZDCC	Australian and New Zealand Diabetes and Cancer Collaboration
APCSC	Asia-Pacific Cohort Studies Collaboration
ARIC	Atherosclerosis Risk in Communities Study
BBD cohort-CLUE II	Benign Breast Disease-Campaign Against Cancer and Heart Disease
BCAC	Breast Cancer Association Consortium Studies
BCDDP	Breast Cancer Detection Demonstration Project Follow-up Study
BCSC	Breast Cancer Surveillance Consortium
BOCS	Boyd Orr Cohort
BRHS	British Regional Heart Study
BSE	Breast Self-Exam
BWHS	Black Women's Health Study
CAHS	College Alumni Health Study
CARE	Women's CARE Study
CBET Manila	Clinical Breast Exam Trial, Manila
CCHS	Copenhagen City Heart Study
CCPPS	Copenhagen Center for Prospective Population Studies
CDBCPT	Canadian Diet and Breast Cancer Prevention Study
CECS	Chinese Elderly Cohort Study
CGHFBC	Collaborative Group on Hormonal Factors in Breast Cancer
CHDS	Children Health and Development Study
CLUE I/II	Campaign Against Cancer and Heart Disease I/II
CNBSS	Canadian National Breast Screening Study
CNRPCS	China Nationally Representative Prospective Cohort Study
Columbia, MO cohort	Columbia Missouri Breast Cancer Serum Bank
CONOR	The Cohort of Norway
CPRD	Clinical Practice Research Datalink
CPS I/II	American Cancer Society - Cancer Prevention Study I/II
CPS II-Nutrition Cohort	Cancer Prevention Study II- Nutrition Cohort
CSDLH	Canadian Study of Diet, Lifestyle and Health
CSECK	Cancer Screening Examination Cohort, Korea
CSHRR	Copenhagen School Health Records Register
CTS	California Teachers Study
DCH	Danish Diet Cancer and Health Study
DOM-project Utrecht	DOM project for the early detection of breast cancer
DOS	Danish Obesity Study

DSDA	Danish Seventh-Day Adventists
E3N EPIC-France	E3N-EPIC
EPIC	European Prospective Investigation into Cancer and Nutrition
ERFC	Emerging Risk Factors Collaboration
FAHBS	Finnish adult health behaviour survey
FFTC	Finnish Female Teachers Cohort
FHS	Framingham Study
FHS-Offspring Cohort	Framingham Heart Study - Offspring Cohort
GPRDC	General Practitioners Research Database Cohort
HAHS	Harvard Alumni Cohort
HBCCS	Hereditary Breast Cancer Clinical Study
HEBON	Hereditary Breast and Ovarian Cancer Study (HBOCS)
HEC2000	Health Examinee Cohort in 2000
HHP	Honolulu Heart Program
HUNT	HUNT (North-Trøndelag Health Study), Norway
IBCCS	The International BRCA1/2 Carrier Cohort Study
Iowa 65 and RHS	Iowa 65+ Rural Health Study
IWHS	Iowa Women's Health Study
JACC	Japan Collaborative Cohort study
JAMS	Japanese Alcoholic Men Study
JPC	Japanese Physicians Cohort
JPHC	Japan Public Health Center-based Prospective Study
KCPS	Korean Cancer Prevention Study
KCS	Kangwha Cohort Study
KNHIC	Korean National Health Insurance Corporation Study
KPMCP	Kaiser Permanent Medical Care Program
KWC	Korean Women's Cohort
MCCS	The Melbourne Collaborative Cohort Study
MCS	Miyagi Cohort Study
MDCS	Malmö Diet and Cancer Study
MEC	Hawaii-Los Angeles Multiethnic Cohort Study
Me-Can	The Metabolic Syndrome and Cancer Project
MPCDRF	Monitoring Project on Cardiovascular Disease Risk Factors (Netherlands)
MPP	Malmö Preventive Project
MRC-NSHD	Medical Research Council National Survey of Health and Development
MWS	Million Women Study
NCI-DES	National Cancer Institute Combined Diethylstilbestrol Cohorts
NCS	Norwegian Counties Study
NCVSC	Norwegian Cardiovascular Screening Cohort
NHANES I	National Health and Nutrition Examination Survey I
NHEFS	National Health and Nutrition Examination Survey I Epidemiologic

	Follow-up Study
NHIS	National Health Interview Survey
NHS	Nurses' Health Study
NIH-AARP	National Institute of Health (NIH)-AARP (formerly the American Association for Retired Persons) Diet and Health Study
NLCS	The Netherlands Cohort Study
NOWAC	Norwegian Women and Cancer Study
NSABP – P1	National Surgical Adjuvant Breast and Bowel Project - Breast Cancer Prevention Trial
NSHD	(MRC) National Survey of Health and Development
NSHDC	Northern Sweden Health and Disease Cohort
NSPT	Norwegian Screening Programme for Tuberculosis
NYS	New York State Cohort
NYUWHS	New York Women's Health Study
NSMSC	Northern Sweden Mammary Screening Study
OHSAKI	Ohsaki National Health Insurance Cohort Study (OCS)
OMCC	Osaka Medical Center for Cancer and Cardiovascular Diseases Study
ORDET	Hormones and Diet in the Etiology of Breast Cancer Study
P-1 and STAR	Breast Cancer Prevention Trial (P-1) and Study of Tamoxifen and Raloxifene (STAR)
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
Pooling Project	The Pooling Project of Diet and Cancer of Prospective Studies of Diet and Cancer
PSC	Prospective Studies Consortium
SCCS	Southern Community Cohort Study
SCHS	Singapore Chinese Health Study
SDA	Seventh-day Adventists Cohort
SIMS	Swedish Intergenerational Mortality Study
SMC	Sweden Mammography Screening Cohort
SOF	Study of Osteoporotic Fractures,
SPVLBW	Upsala birth cohort
SPCJ	Six Prefecture Cohort, Japan
SU.VI.MAX	The Supplémentation en Vitamines et Minéraux Antioxydants Study
SWHS	Shanghai Women's Health Study
TAKAYAMA	Takayama Study
TCCJ	Takayama City Cohort, Japan
TNCS	Third National Cancer Survey
UKCTOCS	UK Collaborative Trial of Ovarian Cancer Screening
UKDCC	UK Dietary Cohort Consortium
UKGPR	UK General Practice Research
UKWCS	UK Women's Cohort Study
VCS	Vlaardingen cohort study
VHM-PP	The Vorarlverg Health Monitoring and Prevention Programme

VIP	Vasterbotten Intervention Project
VITAL	Vitamins And Lifestyle Study
VMC	Vermont Mammography Cohort
WACS	Women's Antioxidant Cardiovascular Study
WEB	WEB Study
WHI	Women's Health Initiative
WHI-CT and OS	Women's Health Initiative Clinical Trials and Observational Study
WHI-DM	Women's Health Initiative Dietary Modification Trial
WHO	WHO Neoplasia 12-centres
WHS	Women's Health Study
WLHS	Swedish Women Lifestyle Health Cohort Study
WLHS, Sweden and Norway	Women Lifestyle Health Cohort Study, Sweden and Norway
WLS	Wisconsin Longitudinal Study
WMCS	Wisconsin Marshfield Clinic Study
WRC, New York	Women at Risk Cohort, New York

Background

The objective of the present systematic literature review is to update the evidence from prospective studies and randomised controlled trials on the association between foods, nutrients, physical activity, body adiposity and the risk of breast cancer in women. The conclusions remained unchanged in the 2010 CUP Report.

This SLR does not present conclusions or judgements on the strength of the evidence. The CUP Panel will discuss and judge the evidence presented in this review.

The methods of the SLR are described in details in the protocol for the CUP review on breast cancer (see Appendix 1). Figure 1 Summary of judgements of the WCRF-AICR Second Expert Report, 2007

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE BREAST (PREMENOPAUSE)

In the judgement of the Panel, the factors listed below modify the risk of cancer of the breast (premenopause). Judgements are graded according to the strength of the evidence.

	DECREASES RISK	INCREASES RISK
Convincing	**Lactation**	**Alcoholic drinks**
Probable	**Body fatness**	**Adult attained height[1]** **Greater birth weight**
Limited — suggestive	Physical activity[2]	
Limited — no conclusion	Cereals (grains) and their products; dietary fibre; potatoes; vegetables; fruits; pulses (legumes); soya and soya products; meat; poultry; fish; eggs; milk and dairy products; fats and oils; total fat; vegetable fat; fatty acid composition, *trans*-fatty acids; cholesterol; sugar (sucrose); other sugars; sugary foods and drinks; coffee; tea; carbohydrate; starch; glycaemic index; protein; vitamin A; riboflavin; vitamin B6; folate; vitamin B12; vitamin C; vitamin D; vitamin E; calcium; iron; selenium; carotenoids; isoflavones; dichlorodiphenyldichloroethylene; dichlorodiphenyltrichloroethane; dieldrin; hexachlorobenzene; hexachlorocyclohexane; *trans*-nonachlor; polychlorinated biphenyls; dietary patterns; culturally defined diets; adult weight gain; energy intake; being breastfed	
Substantial effect on risk unlikely	None identified	

1 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.1.3).
2 Physical activity of all types: occupational, household, transport, and recreational.

For an explanation of all the terms used in the matrix, please see chapter 3.5.1, the text of this section, and the glossary.

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE BREAST (POSTMENOPAUSE)

In the judgement of the Panel, the factors listed below modify the risk of cancer of the breast (postmenopause). Judgements are graded according to the strength of the evidence.

	DECREASES RISK	INCREASES RISK
Convincing	**Lactation**	**Alcoholic drinks** **Body fatness** **Adult attained height[1]**
Probable	**Physical activity[2]**	**Abdominal fatness** **Adult weight gain**
Limited — suggestive		Total fat
Limited — no conclusion	Cereals (grains) and their products; dietary fibre; potatoes; vegetables and fruits; pulses (legumes); soya and soya products; meat; poultry; fish; eggs; milk and dairy products; fats and oils; vegetable fat; fatty acid composition; cholesterol; sugar (sucrose); sugary foods and drinks; coffee; tea; carbohydrate; starch; glycaemic index; protein; vitamin A; riboflavin; vitamin B6; folate; vitamin B12; vitamin C; vitamin D; vitamin E; calcium; iron; selenium; carotenoids; isoflavones; dichlorodiphenyldichloroethylene; dichlorodiphenyltrichloroethane; dieldrin; hexachlorobenzene; hexachlorocyclohexane; *trans*-nonachlor; polychlorinated biphenyls; dietary patterns; culturally defined diets; birth weight; birth length; energy intake; being breastfed	
Substantial effect on risk unlikely	None identified	

1 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.1.3).
2 Physical activity of all types: occupational, household, transport, and recreational.

For an explanation of all the terms used in the matrix, please see chapter 3.5.1, the text of this section, and the glossary.

Modifications to the existing protocol

The protocol on breast cancer was prepared in 2007 (see Appendix 1). The following modifications had been introduced:

Review team: Snieguole Vingeliene, Dagfinn Aune, Elli Polemiti, Ana Rita Vieira, Leila Abar joined the team as research assistants. Christophe Stevens joined the team as database manager.

Timeline: The current review includes publications included in Medline up to April 30th 2015.

Methods:

Meta-analysis was performed when the number of studies amount to five or more – a criterion for updating the dose-response meta-analysis in the protocol (see Appendix 1).

Pooled analysis was included with other individual studies in the meta-analysis when possible.

Non-linear dose response curves were plotted using restricted cubic splines for each study, with knots fixed at percentiles 10%, 50%, and 90% through the distribution. These were combined using multivariate meta-analysis. When the number of studies with three or more categories of exposure – a requirement of the method- was low or there was no suggestion of non-linear dose response association from the studies, non-linear meta-analysis was not conducted. The analyses were performed in Stata 12.0.

Notes on methods

The search and WCRF database update for the 2008 CUP report ended in May 31st 2008. The CUP team at ICL updated the search from June 1st 2008 up to April 30th 2015 (see Flowchart).

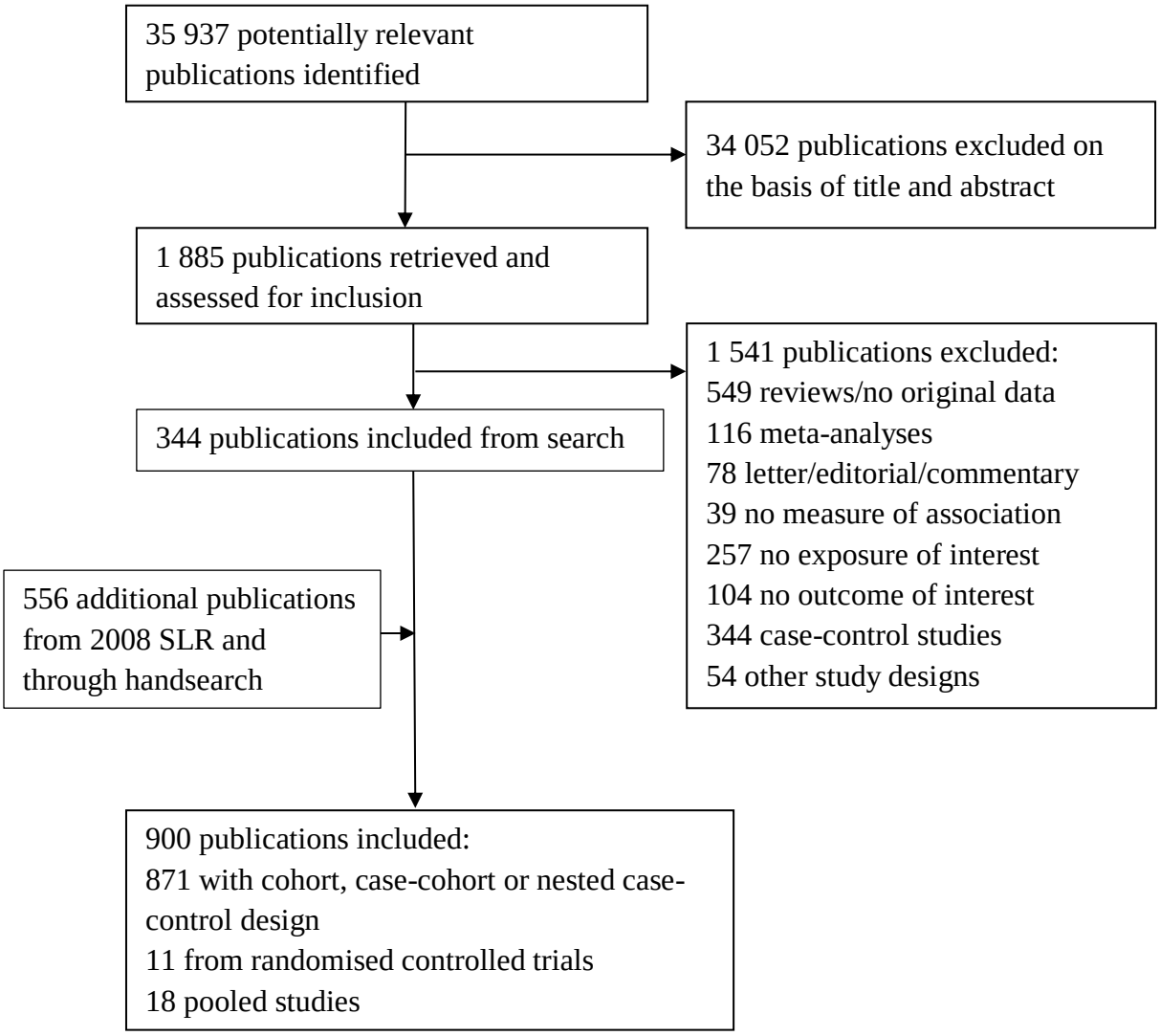
Breast cancer in women of unspecified menopausal age (any breast cancer), premenopausal women (premenopausal breast cancer), and postmenopausal women (postmenopausal breast cancer) were reviewed separately.
Linear dose-response meta-analysis were updated when at least three new publications with enough data for dose-response meta-analysis were identified during the CUP and if there were in total five cohort studies or five randomised controlled trials. The meta-analyses include studies identified during the 2005 SLR and studies identified during the CUP SLR.
The increment units used in the linear dose-response analyses were chosen to be consistent with other CUP SLRs, which may not be comparable with those used in the meta-analyses in the previous SLR. However, if most of the identified studies reported servings, times, these were used as increment unit, as indicated in the Protocol.
The statistical methods to derive missing data are described in the protocol.

The total number of cases included in a meta-analysis was the summation of the numbers of cases provided by the studies. Occasionally, a study may not report such number; in which case, a > sign is used.
The method of Hamling (Hamling, 2008) was used to recalculate relative risks (RRs) and confidence intervals (CIs) for a categorical comparison alternative to that reported by the study.
The interpretation of heterogeneity tests should be cautious when the number of studies is low. Visual inspection of the forest plots and funnel plots is recommended.
The I^2 statistic describes the proportion of total variation in study estimates that is due to heterogeneity (Higgins, 2002). Low heterogeneity might account for less than 30 per cent of the variability in point estimates, and high heterogeneity for substantially more than 50 per cent. These values are tentative, because the practical impact of heterogeneity in a meta-analysis also depends on the size and direction of effects.
Only the summary relative risks estimated using random effect models are shown.
Highest vs lowest forest plots show the relative risk estimates for the highest vs the reference category in each study. The overall summary estimate was only calculated when linear dose-response meta-analysis was not possible, e.g. physical activity.
The dose-response forest plots show the relative risk per unit of increase for each study (most often derived by the CUP review team from categorical data). The relative risk is denoted by a box (larger boxes indicate that the study has higher precision, and greater weight). Horizontal lines denote 95% confidence intervals (CIs). Arrowheads indicate truncations. The diamond at the bottom shows the summary relative risk estimate and corresponding 95% CI. The unit of increase is indicated in each figure and in the summary table for each exposure.
When the 95% CI of a RR spanned 1.00, the association was considered as statistically not significant. When the upper or lower CI was 1.00, the association was considered of borderline significance.
Dose-response plots showing the RR estimates for each exposure level in the studies are also presented for each exposure in the review. The relative risks estimates were plotted in the mid-point of each category level (x-axis) and connected through lines.
Exploratory non-linear dose-response meta-analyses were conducted only when there were five or more studies with three or more categories of exposure – a requirement of the restricted cubic splines method. Non-linear meta-analyses are not included in the sections for the other exposures when there were not enough studies with the required data. One exception was for processed meat intake where data reported by the studies were not sufficient to use in the restricted cubic spline analysis. A second family fractional polynomial regression model was used.
The non-linear dose-response curve and the bubble graph were presented when a significant non-linear association was observed. The interpretation of the non-linear dose-response analyses should be based on the shape of the curve and not only on the p-value because the number of observations tended to be low. Bubble graphs are also presented to support the interpretation.
Loss to follow up was defined as low when <10% was reported by the study.

Continuous Update Project: Results of the search

Figure 2 Flow chart of the search for breast cancer – Continuous update project

Search period June 1st 2008-April 30th 2015



Results by exposure

Table 1 Number of relevant publications identified during the 2008 SLR and the CUP and total number of publications by exposure.

The exposure code is the exposure identification in the database. Only exposures identified during the CUP are shown.

Exposure Code	Exposure Name	Number of publications (RCT/cohorts)		Total number of publications
		2008 CUP	CUP	
1.	**Patterns of diet**			
1.1.1	Mediterranean diet	1	7	8
1.4	Low fat diet	3	4	7
1.4	Dietary guideline index score	3	13	16
1.4	A *posteriori* derived dietary patterns	2	7	9
1.6.1	Breastfeeding - mother	13	9	22
2.	**Foods**			
2.2	Fruit and (non-starchy) vegetables	6	8	14
2.2.1	Total vegetables	10	12	22
2.2.2	Fruits	12	10	22
2.2.2.1	Citrus fruits	2	4	6
2.3	Pulses (legumes)	4	6	10
2.3.1	Soy products	1	5	6
2.3.1.1	Miso soup	1	3	4
2.3.2.2	Tofu	4	1	5
2.5.1	Meat	8	5	13
2.5.1.1	Unprocessed red meat	6	6	12
2.5.1.2	Processed meat	11	8	19
2.5.1.3	Red and processed meat	6	5	11
2.5.1.4	Poultry	9	2	11
2.5.2	Fish	16	8	24
2.5.2.5	Oily fish	2	2	4
2.5.4	Eggs	9	4	13
2.7	Milk and dairy products	10	5	15
2.7.1	Milk	12	4	16
2.7.1	Whole milk, full-fat milks	5	3	8
2.7.2	Cheese	10	3	13

Exposure Code	Exposure Name	Number of publications (RCT/cohorts)		Total number of publications
		2008 CUP	CUP	
2.7.3	Yoghurt	5	3	8
3.	**Beverages**			
3.5	Fruit juices	3	3	6
3.6.1	Coffee	13	10	23
3.6.2	Tea	5	8	14
4.	**Food production, preservation processing and preparation**			
4.4.2.7	Acrylamide	3	5	8
5.	**Dietary constituents**			
5.1	Carbohydrates	13	8	21
5.1.2	Dietary fibre	24	7	31
5.1.2.1	Cereal fibre	7	3	10
5.1.2.2	Vegetable fibre	7	3	10
5.1.2.3	Fruit fibre	6	3	9
5.1.2.3	Legume fibre	5	3	8
5.1.2.3	Soluble fibre	3	3	6
5.1.2.3	Insoluble fibre	4	3	7
5.1.5	Glycemic index	9	9	18
5.1.5	Glycemic load	9	9	18
5.2	Total fat	33	6	39
5.2.2	Saturated fat	27	6	33
5.2.3	Monounsaturated fat	21	6	27
5.2.4	Polyunsaturated fat	18	5	23
5.2.4.1	Alpha-linolenic	4	4	8
5.2.4.1	DHA (docosahexaenoic adic)	2	2	4
5.2.4.1	EPA (eicosapentaenoic acid)	2	2	4
5.2.4.1	N-3 fatty acids	4	3	7
5.2.4.1	Arachidonic fatty acid	4	4	8
5.2.4.2	Linoleic fatty acid	11	4	15
5.2.4.2	N-6 fatty acids	3	3	6
5.2.4.2	Trans fatty acids	1	4	5
5.4.1	Alcohol (as ethanol)	61	59	120
5.4.1.1	Alcohol (as ethanol) from beer	16	8	24
5.4.1.2	Alcohol (as ethanol) from wine	16	10	26
5.4.1.3	Alcohol (as ethanol) from liquor	16	8	24
5.5.1.1	Retinol, blood	9	5	14

Exposure Code	Exposure Name	Number of publications (RCT/cohorts)		Total number of publications
		2008 CUP	CUP	
5.5.1.2.1	Alpha-carotene, blood	8	9	17
5.5.1.2.2	Dietary beta-carotene	10	6	16
5.5.1.2.2	Beta-carotene, blood	10	9	19
5.5.1.2.3	Beta-cryptoxanthin, blood	7	7	14
5.5.2	Carotenoids, blood	4	7	11
5.5.2.1	Lutein, blood	3	2	5
5.5.2.2	Lutein and zeaxanthin, blood	3	5	8
5.5.2.3	Lycopene, blood	7	9	16
5.5.3.1	Total folate	13	5	18
5.5.3.2	Dietary folate	15	7	22
5.5.3.3	Folate from supplements	2	4	6
5.5.4	Total riboflavin (vitamin B2)	1	1	2
5.5.4	Dietary riboflavin (vitamin B2)	2	4	6
5.5.4	Riboflavin from supplements	0	1	1
5.5.6	Niacin (vitamin B3)	2	1	3
5.5.7	Total pyridoxine (vitamin B6)	3	2	5
5.5.7	Dietary pyridoxine (vitamin B6)	3	4	7
5.5.7	Pyridoxine from supplements	0	1	1
5.5.8	Total cobalamin (vitamin B12)	2	2	4
5.5.8	Dietary cobalamin (vitamin B12)	2	4	6
5.5.9	Vitamin C, diet and supplement	19	4	23
5.5.9	Vitamin C, supplement	9	4	13
5.5.10	Dietary vitamin D	6	4	10
5.5.10	Vitamin D, supplement	3	2	5
5.5.10	25-hydroxyvitamin D, blood	4	14	18
5.5.11	Vitamin E, diet and supplement	18	3	21
5.5.11	Tocopherol, blood	2	4	6
5.5.11	Alpha-tocopherol, blood	5	2	7
5.5.13	Multivitamin supplement	9	6	15
5.6.2	Iron	1	5	6
5.6.3	Calcium, diet and supplement	2	2	4
5.6.3	Dietary calcium	7	6	13
5.6.3	Calcium, supplement	2	4	6
5.6.3	Calcium, blood	1	3	4
5.6.6	Cadmium	0	6	6

Exposure Code	Exposure Name	Number of publications (RCT/cohorts)		Total number of publications
		2008 CUP	CUP	
5.7.6	Caffeine	3	4	7
5.7.5	Isoflavones	7	5	12
5.8	Flavonoids	0	5	5
6.	**Physical activity**			
6.1	Total physical activity	9	14	23
6.1.1.1	Occupational physical activity	17	5	22
6.1.1.2	Recreational physical activity	29	18	49
6.1.1.2	Recreational physical activity, at different age	5	6	11
6.1.1.2	Walking	7	8	15
6.1.1.3	Household activity	4	4	8
6.1.3	Vigorous physical activity	14	11	25
6.2	Sitting	2	6	8
7.	**Energy balance**			
7.1	Energy intake	28	10	38
7.1.1	Energy from fat	16	5	21
7.1.0.1	Energy from saturated fat	11	4	15
7.1.0.1	Energy from monounsaturated fat	9	4	13
7.1.0.1	Energy from polyunsaturated fat	9	4	13
7.1.0.2	Energy from protein	3	2	5
7.1.0.3	Energy from carbohydrates	5	3	8
8.	**Anthropometry**			
8.1.1	BMI	97	86	183
8.1.1	BMI at young adulthood	21	15	36
8.1.6	Weight gain	23	15	38
8.1.6	Weight loss	10	12	22
8.1.6	BMI change	6	4	10
8.2.1	Waist circumference	21	22	43
8.2.3	Waist to hip ratio	25	14	39
8.3.1	Height (and proxy measures)	63	25	88
8.4.1	Birthweight	22	7	29

Note: Linear dose-response meta-analysis were updated when at least three new publications **with enough data for dose-response meta-analysis** were identified during the CUP and if there were in total five cohort studies or five randomised controlled trials with enough data for dose-response meta-analysis

1 Patterns of diet

1.1.1 Mediterranean diet

Cohort studies

Overall summary

Eight publications from 10 studies on Mediterranean diet score (MDS) or modified/alternative Mediterranean diet score were identified. This included one pooled study (Pot, 2014, UKDCC, four cohorts).

The Mediterranean diet score based on Trichopoulou *et al.* included alcohol consumption (Trichopoulou, 2010). As alcohol consumption is an established risk factor for breast cancer, some studies excluded the alcohol component from the score, or examined both scores (see study characteristics table below).

Dose-response meta-analysis was not conducted as the number of studies was low. Results for the highest compared with the lowest Mediterranean diet score were presented in a forest plot.

Breast cancer (any)

Seven publications from nine studies were identified. The highest versus the lowest forest plot of eight studies shows inconsistent and non-significant associations with Mediterranean diet score, with or without alcohol. The RR estimates ranged from 0.84 (95% CI=0.59-1.20) in EPIC-Greece (Trichopoulou, 2010) to 1.42 (95% CI=0.99-2.05) in WLHS, Sweden (Couto, 2013).

One study (Tognon, 2012, VIP) excluded from plot was on breast cancer mortality, which observed a non-significant positive association (RR per one score= 1.12, 95% CI=0.97-1.28).

Two studies reported results by breast cancer hormone receptor status and observed inconsistent and non-significant associations. Buckland, 2013 observed inverse associations with adapted relative Mediterranean diet score that excluded alcohol for ER-PR- and ER+PR+ breast cancers (RRs for the highest vs the lowest score=0.84, 95% CI=0.69-1.02; 0.92, 95 % CI=0.85-1.00, respectively). Couto, 2013 reported positive associations with full Mediterranean diet score (RRs per 2-point=1.14, 95% CI=0.97-1.34 for ER-negative breast cancer; 1.01, 95% CI=0.93-1.10 for ER-positive breast cancer).

Premenopausal breast cancer

Four studies (four publications) were identified and all were shown in the highest versus the lowest forest plot. The associations with Mediterranean diet score, with or without alcohol were inconsistent. The RR estimates ranged from 0.65 (95% CI=0.42-1.02) in Cade, 2011 (UKWCS) to 2.17 (95% CI= 1.42-3.30) in WLHS (Couto, 2013). The Swedish WLH cohort study (736 breast cancer cases in premenopausal women) reported a statistically significant

positive association for each two-point increase of full Mediterranean diet score (RR=1.10, 95% CI=1.01-1.21); and without the alcohol component, a positive association (RR=1.07, 95% CI=0.98-1.18) (Couto, 2013).

The two studies that reported results by breast cancer hormone receptor status observed non-significant associations, positive for ER-PR- breast cancer (RR for the highest vs the lowest score=1.09, 95% CI=0.65-1.82) (Buckland, 2013) and ER-negative breast cancer (RR per 2-point=1.19, 95% CI=0.96-1.47), as well as ER-positive breast cancer (RR per 2-point=1.02, 95% CI= 0.91-1.14) (Couto, 2013); and inverse for ER+PR+ breast cancer (RR for the highest vs the lowest score=0.86, 95 % CI=0.66-1.13 (Buckland, 2013).

Postmenopausal breast cancer

Six publications from eight studies were identified. All studies were shown in the highest versus the lowest forest plot. Studies observed an inverse association with Mediterranean diet score, with or without alcohol (RR estimates ranged from 0.59 to 0.98), of which the EPIC study, with 9 009 postmenopausal breast cancer cases from 23 European study centres, reported a significant association (RR=0.93, 95% CI=0.87-0.99; P trend=0.037 with the adapted relative Mediterranean diet score that excluded alcohol) (Buckland, 2013).

The exception is the pooled study (Pot, 2014, UKDCC) that reported a non-significant positive association with Mediterranean diet score (RR=1.10, 95% CI=0.80-1.51, P trend=0.46) (RR =1.14, 95% CI=0.76-1.71, P trend=0.57 for Mediterranean diet score with no alcohol). Four UK cohorts with dietary information from the food diaries were pooled in this study with 409 postmenopausal breast cancer cases (Pot, 2014).

Three studies reported results by breast cancer hormone receptor status and most associations were non-significant. For the highest compared with the lowest score, Buckland, 2013 reported RR estimates of 0.80 (95% CI=0.65-0.99) for ER-PR- breast cancer and 0.92 (95% CI=0.85-1.01) for ER+PR+ breast cancer. Fung, 2006 observed an inverse association for ER-negative breast cancer (RR=0.79, 95 % CI=0.60-1.03) and a positive association for ER-positive breast cancer (RR=1.05, 95 % CI=0.91-1.18). Couto, 2013 reported per 2-point increase, a positive association for ER-negative breast cancer (RR=1.17, 95% CI=0.87-1.59) and an inverse association for ER-positive breast cancer (RR=0.98, 95% CI=0.86-1.11).

Table 2 Mediterranean diet score and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified[1]	10 (8 publications)
Studies included in forest plot of highest compared with lowest exposure	8[2] (5 publications) breast cancer risk 4 (4 publications) premenopausal breast cancer risk 8[2] (5 publications) postmenopausal breast cancer risk

Studies included in linear dose-response meta-analysis	Insufficient data
Studies included in non-linear dose-response meta-analysis	Insufficient data

[1]Numbers of studies and publications identified overall.
[2]Included one pooled study of four cohorts (Pot, 2014).

Table 3 Mediterranean diet score and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Meta-analyses							
Schwingshackl, 2014	10 studies (5 cohorts, 5 case-controls)	15 912	Canada, Europe, USA	Incidence and mortality	Highest vs lowest Overall Cohort studies Case-control studies	0.95 (0.84-1.06) (0.88-1.16) 0.82 (0.69-0.97)	52%, 0.03 63%, 0.03 0%, 0.53

*All cohort studies identified were included in the present review.

Table 4 Mediterranean diet score and breast cancer risk. Main characteristics of studies identified.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Pot, 2014 UK	UKDCC, Pooled study of four cohorts* Mean age cases 56.6 years controls 57.2 years, W (*EPIC-Norfolk, EPIC-Oxford, UKWCS, Whitehall-II)	610 cases/ 1 891 controls	Record linkage with National Statistics and cancer registries	Food diaries, Mediterranean diet score (MDS) (alcohol, vegetables, legumes, fruits and nuts, cereals, fish and seafood, dairy, meat and meat products, monounsaturated fatty	Incidence, breast cancer	T3 vs T1	1.20 (0.92-1.56)	Age, parity, HRT use, weight, height, physical activity, menopausal status	Included in the highest vs the lowest forest plot
		409/ 1 360 controls			Incidence, postmenopausal breast cancer	T3 vs T1	1.10 (0.80-1.51)		Included in the highest vs the lowest forest plot

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
				acid/saturated fatty acid ratio)					
		610 cases/ 1 891 controls		Mediterranean diet score (MDS), excluding alcohol	Incidence, breast cancer	T3 vs T1	1.15 (0.83-1.60)	As above, and alcohol consumption	Superseded by Buckland, 2013
		409/ 1 360 controls			Incidence, postmenopausal breast cancer	T3 vs T1	1.14 (0.76-1.71)		Superseded by Buckland, 2013
Buckland, 2013 BRE80433 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	10 225/ 335 062 11 years	Cancer registries, health Insurance records, pathology records & active follow up	Semi-quantitative FFQ, diet history questionnaires, or semi-quantitative FFQ combined with a food record, adapted relative Mediterranean diet (arMED), excluding alcohol (fruits, nuts and seeds, vegetables (excluding potatoes), legumes, fish (excluding fish products and preserved fish), olive oil,	Incidence, breast cancer	10-16 vs 0-5 score	0.94 (0.88-1.00) Ptrend:0.048	Age, age at first child birth, age at menarche, alcohol, BMI, breastfeeding, centre location, educational level, energy, height, HRT use, menopausal status, oral contraceptive history, physical activity, saturated fat, smoking	Included in the highest vs the lowest forest plot
		5 862/			Incidence, breast cancer ER+/PR+	10-16 vs 0-5 score	0.92 (0.85-1.00) Ptrend:0.051		
		1 018/			Incidence, breast cancer ER-/PR-	10-16 vs 0-5 score	0.84 (0.69-1.02) Ptrend:0.076		
		1 216/			Incidence, breast cancer, premenopausal	10-16 vs 0-5 score	0.97 (0.81-1.15) Ptrend:0.839	As above, without menopausal status and HRT use	Included in the highest vs the lowest forest plot
		549/			Incidence, breast cancer ER+/PR+, premenopausal	10-16 vs 0-5 score	0.86 (0.66-1.13) Ptrend:0.299		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
		146/		cereals, meat, and dairy products)	Incidence, breast cancer ER-/PR-, premenopausal	10-16 vs 0-5 score	1.09 (0.65-1.82) Ptrend:0.730		
		9 009/			Incidence, breast cancer, postmenopausal	10-16 vs 0-5 score	0.93 (0.87-0.99) Ptrend:0.037	As above and age at menopause and without menopausal status	Included in the highest vs the lowest forest plot
		5 313/			Incidence, breast cancer ER+/PR+, postmenopausal	10-16 vs 0-5 score	0.92 (0.85-1.01) Ptrend:0.071		
		872/			Incidence, breast cancer ER-/PR-, postmenopausal	10-16 vs 0-5 score	0.80 (0.65-0.99) Ptrend:0.043		
Couto, 2013 BRE80454 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	1 278/ 49 258 16 years	Cancer registry	FFQ, Mediterranean diet score (alcohol, vegetables, fruits, legumes, cereals, fish, unsaturated to saturated fat ratio, dairy and meat products)	Incidence, breast cancer	8-9 vs 0-2 score	1.42 (0.99-2.05) Ptrend:0.05	Age at first child birth, age at menarche, benign breast disease, beverage Intake, educational level, egg, energy Intake, height, history of breast cancer, number of childbirths, potatoes, smoking, sweet products	Included in the highest vs the lowest forest plot
						per 2 point	1.08 (1.00-1.15)		
		736/ 40 031			Incidence, breast cancer, premenopausal	8-9 vs 0-2 score	2.12 (1.39-3.24) Ptrend:0.08		Included in the highest vs the lowest forest plot
						per 2 point	1.10 (1.01-1.21)		
		448/ 27 509			Incidence, breast cancer, postmenopausal	8-9 vs 0-2 score	0.63 (0.29-1.37) Ptrend:0.55		Included in the highest vs the lowest forest plot

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
						per 2 point	1.02 (0.91-1.15)		
		1 278/ 49 258 16 years		Mediterranean diet score, excluding alcohol	Incidence, breast cancer	8 vs 0-2 score	1.42 (0.99-2.03) Ptrend:0.12	As above, and alcohol consumption	Included in the highest vs the lowest forest plot
						per 2 point	1.06 (0.98-1.13)		
		736/ 40 031			Incidence, breast cancer, premenopausal	8 vs 0-2 score	2.17 (1.42-3.30) Ptrend:0.05		Included in the highest vs the lowest forest plot
						per 2 point	1.07 (0.98-1.18)		
		448/ 27 509			Incidence, breast cancer, postmenopausal	8 vs 0-2 score	0.59 (0.27-1.28) Ptrend:0.89		Included in the highest vs the lowest forest plot
						per 2 point	1.02 (0.90-1.15)		
		874/		Mediterranean diet score (alcohol, vegetables, fruits, legumes, cereals, fish, unsaturated to saturated fat ratio, dairy and meat products)	Incidence, breast cancer ER+	per 2 point	1.01 (0.93-1.10)	Age at first child birth, age at menarche, benign breast disease, beverage Intake, educational level, egg, energy Intake, height, history of breast cancer, number of	
		227/			Incidence, breast cancer ER-	per 2 point	1.14 (0.97-1.34)		
		722/			Incidence, breast cancer PR+	per 2 point	1.01 (0.92-1.11)		
		368/			Incidence, breast cancer PR-	per 2 point	1.09 (0.96-1.24)		
		680/			Incidence, breast cancer ER+/PR+	per 2 point	1.03 (0.93-1.13)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
		185/			Incidence, breast cancer ER-/PR-	per 2 point	1.23 (1.03-1.47)	childbirths, potatoes, smoking, sweet products	
		183/			Incidence, breast cancer ER+/PR-	per 2 point	0.98 (0.81-1.17)		
		42/			Incidence, breast cancer ER-/PR+	per 2 point	0.82 (0.56-1.20)		
		478/		Mediterranean diet score (alcohol, vegetables, fruits, legumes, cereals, fish, unsaturated to saturated fat ratio, dairy and meat products)	Incidence, breast cancer ER+, premenopausal	per 2 point	1.02 (0.91-1.14)	Age at first child birth, age at menarche, benign breast disease, beverage Intake, educational level, egg, energy Intake, height, history of breast cancer, number of childbirths, potatoes, smoking, sweet products	
		131/			Incidence, breast cancer ER-, premenopausal	per 2 point	1.19 (0.96-1.47)		
		425/			Incidence, breast cancer PR+, premenopausal	per 2 point	1.02 (0.91-1.15)		
		177/			Incidence, breast cancer PR-, premenopausal	per 2 point	1.15 (0.95-1.38)		
		395/			Incidence, breast cancer ER+/PR+, premenopausal	per 2 point	1.05 (0.93-1.18)		
		102/			Incidence, breast cancer ER-/PR-, premenopausal	per 2 point	1.34 (1.05-1.71)		
		75/			Incidence, breast cancer ER+/PR-, premenopausal	per 2 point	0.93 (0.70-1.23)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
		30/			Incidence, breast cancer ER-/PR+, premenopausal	per 2 point	0.77 (0.49-1.20)		
		347/		Mediterranean diet score (alcohol, vegetables, fruits, legumes, cereals, fish, unsaturated to saturated fat ratio, dairy and meat products)	Incidence, breast cancer ER+, postmenopausal	per 2 point	0.98 (0.86-1.11)	Age at first child birth, age at menarche, benign breast disease, beverage Intake, educational level, egg, energy Intake, height, history of breast cancer, number of childbirths, potatoes, smoking, sweet products	
		64/			Incidence, breast cancer ER-, postmenopausal	per 2 point	1.17 (0.87-1.59)		
		250/			Incidence, breast cancer PR+, postmenopausal	per 2 point	0.98 (0.84-1.15)		
		158/			Incidence, breast cancer PR-, postmenopausal	per 2 point	1.05 (0.87-1.28)		
		246/			Incidence, breast cancer ER+/PR+, postmenopausal	per 2 point	0.97 (0.83-1.14)		
		59/			Incidence, breast cancer ER-/PR-, postmenopausal	per 2 point	1.18 (0.86-1.62)		
		99/			Incidence, breast cancer ER+/PR-, postmenopausal	per 2 point	0.98 (0.77-1.25)		
		4/			Incidence, breast cancer ER-/PR+, postmenopausal	per 2 point	3.07 (0.60-15.75)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Tognon, 2012 BRE80513 Sweden	VIP, Prospective Cohort, Age: 30-60 years, W	80/ 77 151 9 years	VIP database with the Swedish national cause-of-death registry	Validated FFQ, Modified Mediterranean diet score (alcohol, vegetables and potatoes, fruit and juices, whole grain cereals, fish and fish products, ratio of monounsaturated fatty acids and polyunsaturated fatty acids to saturated fatty acids, meat and meat products, dairy products)	Mortality, breast cancer	per 1 score	1.12 (0.97-1.28)	Age, educational level, obesity, physical activity, smoking status	Excluded, outcome was breast cancer mortality
Cade, 2011 BRE80379 UK	UKWCS, Prospective Cohort, Age: 35-69 years, W, Premenopausal+ postmenopausal	718/ 33 731 9 years	Population registers	FFQ, Mediterranean diet score (alcohol, vegetables, fruits, legumes, cereals, fish, polyunsaturated: saturated fatty acid ratio, meat, poultry, dairy)	Incidence, breast cancer	7-10 vs 0-2 score	0.96 (0.70-1.32) Ptrend:0.4	Age, age at menarche, BMI, breastfeeding, contraception, educational level, energy Intake, energy-adjusted Intake of fat, ethanol, HRT use, menopausal status (combined	Superseded by Pot, 2014
		350/			Incidence, premenopausal breast cancer	7-10 vs 0-2 score	0.65 (0.42-1.02) Ptrend:0.09		Included in the highest vs the lowest forest plot
		478/			Incidence, postmenopausal breast cancer	7-10 vs 0-2 score	1.30 (0.83-2.05) Ptrend:0.9		Superseded by Pot, 2014

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								analysis), parity, physical activity, SES, smoking	
Butler, 2010 BRE80295 Singapore	SCHS, Prospective Cohort, Age: 45-74 years, W	629/ 34 028 10.7 years	Cancer registry	FFQ Mediterranean diet score (alcohol, vegetables, fruit/nuts, legumes, cereals, fish and seafood, monounsaturated: saturated fat ratio, meat, dairy products, carbohydrates)	Incidence, breast cancer	≥7 score vs 0-4 score	0.96 (0.76-1.21)	Age, BMI, dialect group, educational level, energy Intake, family history of cancer, parity, year of Interview	Included in the highest vs the lowest forest plot
Trichopoulou, 2010 BRE80320 Greece	EPIC-Greece, Prospective Cohort, Age: 20-68 years	240/ 14 807 9.8 years	Medical records and pathology reports	FFQ, Mediterranean diet score (alcohol, vegetables, fruit and nuts, legumes, cereals, fish and seafood, monounsaturated to saturated fat ratio, dairy,	Incidence, breast cancer	6-9 vs 0-3	0.84 (0.59-1.20)	Age, educational level, smoking status, BMI, height, MET-hour, energy intake, age of menarche, parity, age at first delivery, menopausal status, age at menopause, HRT use,	Included in the highest vs the lowest forest plot
						per 2 point	0.88 (0.75-1.03)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
				meat and meat products)				interaction term for BMI and menopausal status	
		113/ 6 534			Incidence, breast cancer, premenopausal	6-9 vs 0-3	1.13 (0.69-1.85)	As above, without menopausal status, age at menopause, interaction term for BMI and menopausal status	Included in the highest vs the lowest forest plot
						per 2 point	1.01 (0.80-1.28)		
		127/ 8 273			Incidence, breast cancer, postmenopausal	6-9 vs 0-3	0.59 (0.34-1.03)	As above, without menopausal status, interaction term for BMI and menopausal status	Included in the highest vs the lowest forest plot
						per 2 point	0.78 (0.62-0.98)		
Fung, 2006 BRE80107 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Postmenopausal	3 580/ 121 700 18 years	Medical records	FFQ, Alternate Mediterranean Diet Index (aMed) (alcohol, vegetables (excluding potato products), fruits, nuts, legumes, cereals	Incidence, postmenopausal breast cancer	Q5 vs Q1	0.98 (0.88-1.10) Ptrend:0.69	Age , age at menopause, benign breast disease, BMI, weight at 18 years, weight change since age 18 years, energy Intake , family history, HRT use, physical	Included in the highest vs the lowest forest plot
		2 367/			Incidence, postmenopausal breast cancer ER+	Q5 vs Q1	1.05 (0.91-1.18) Ptrend:0.23		
		575/			Incidence, postmenopausal	Q5 vs Q1	0.79 (0.60-1.03) Ptrend:0.03		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
				(whole-grain products only), fish, monounsaturated to saturated fat ratio, red and processed meats)	breast cancer ER-			activity , smoking habits, supplements	

Figure 3RR (95% CI) of breast cancer for the highest compared with the lowest level of Mediterranean diet score

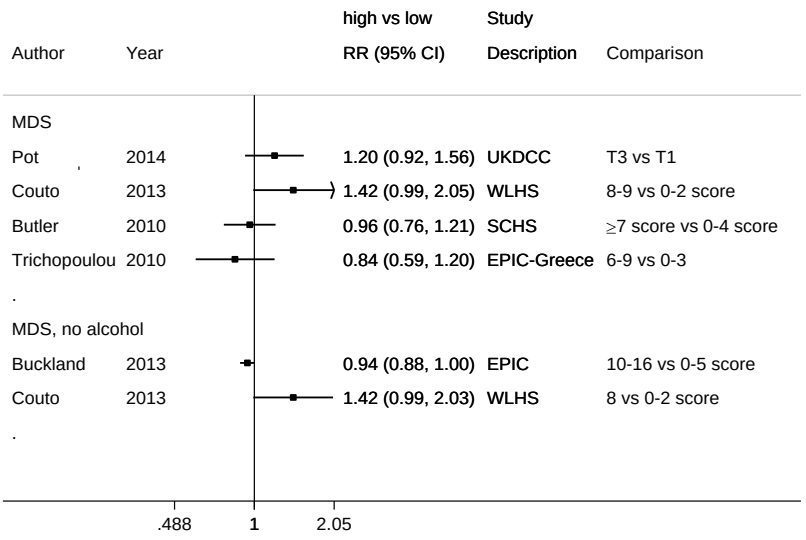


Figure 4 RR (95% CI) of premenopausal breast cancer for the highest compared with the lowest level of Mediterranean diet score

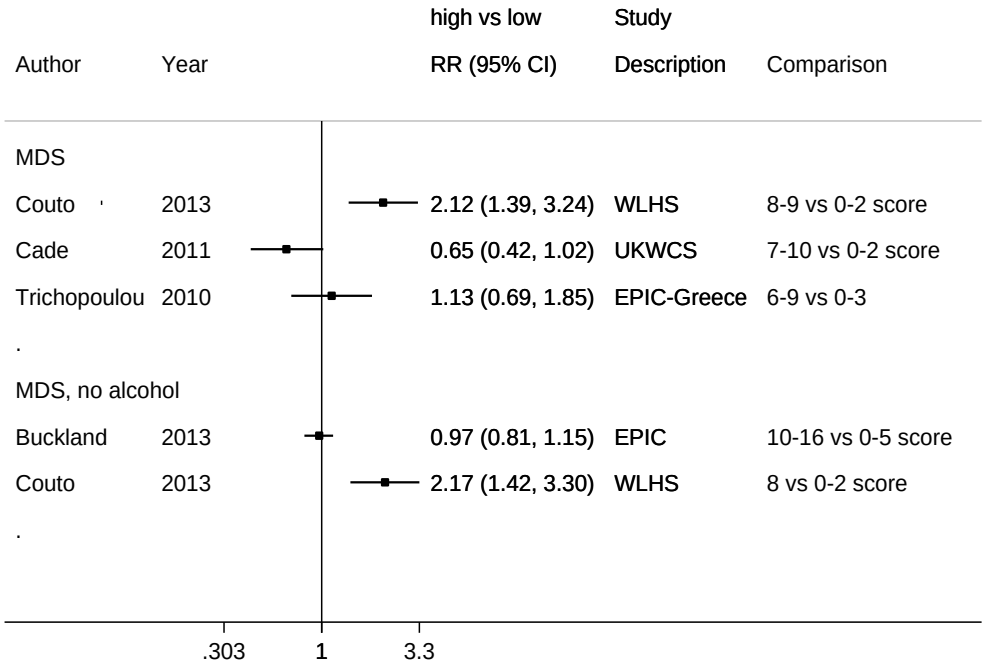
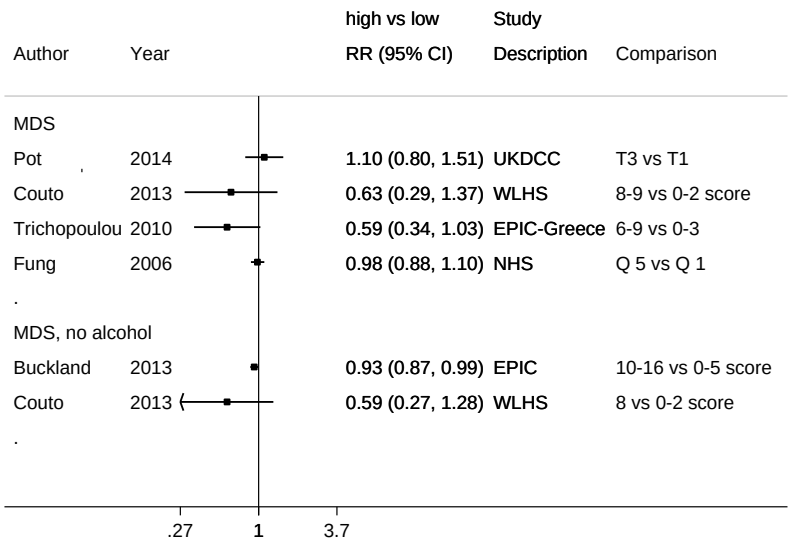


Figure 5 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest level of Mediterranean diet score



Note: UKDCC (Pot, 2014) included the component studies – EPIC-Norfolk and EPIC-Oxford of the EPIC study (Buckland, 2013)

1.4 Individual level dietary patterns

1.4 Low fat diet

Randomised controlled trials

Two dietary interventional trials (five publications) – Women's Health Initiative-Dietary Modification Trial (WHI DM trial) (Thomson, 2014a; Caan, 2009; Prentice, 2007; Prentice, 2006) and Canadian Diet and Breast Cancer Prevention Trial (CDBCP trial) (Martin, 2011), that comprised a low-fat diet were identified.

Findings from both the WHI DM trial (Prentice, 2007, Prentice, 2006) and the CDBCP trial (Martin, 2011) did not support a significant effect of low-fat dietary intervention on breast cancer prevention. Postintervention follow-up of the WHI DM trial showed that dietary fat intake increased in the intervention group and there was no long-term reduction in breast cancer risk (Thomson, 2014a) (see details below and in study characteristics table).

Women's Health Initiative-Dietary Modification Trial (WHI DM trial)

WHI-DM trial (recruitment 1993-1998, end of intervention 2005, postintervention follow-up until 2010) was designed to promote dietary change with the goals of reducing intake of total fat to 20% of energy and increasing consumption of vegetables and fruit to at least 5 servings daily and grains to at least 6 servings daily. Comparison group participants were not asked to make dietary changes.

Postmenopausal women (age 50-79 years) with ≥33% of total energy from fat were randomly assigned to the intervention group (40%, n=19 541) or the comparison group (60%, n=29 294). 83% of the women (n=37 858) agreed to be follow-up postintervention.

Results for an average 8.1 years of follow-up showed a non-significant reduction in invasive breast cancer risk with the low-fat dietary intervention (HR for intervention vs comparison=0.91, 95% CI=0.83-1.01) (655 breast cancer cases in the intervention group and 1 072 in the comparison group) (Prentice, 2006; Prentice, 2007). On average, the target of reducing intake of dietary fat to 20% of energy was not achieved.

Further analyses by study periods which extended to an average of 12.3 years of follow-up also showed no significant intervention effect (HR=0.92, 95% CI=0.84-1.01 during intervention; HR=1.08, 95% CI=0.94-1.24 during the postintervention period; HR=0.97, 95% CI=0.89-1.05 during cumulative follow-up) (overall 998 breast cancer cases in the intervention group and 1 565 in the comparison group) (Thomson, 2014a). Dietary fat intake remained lower in the intervention group but appeared to increase with time.

Women with higher percent energy from fat at baseline had a larger reduction in risk during the intervention compared with women with lower percent energy from fat (HR=0.78, 95% CI=0.64-0.95 for women >36.8% energy; HR=0.97, 95% CI=0.79-1.20 for women <27.9% energy) (P for interaction=0.04) (Prentice, 2006). The same was not observed postintervention (HR=1.11, 95% CI=0.84-1.46; 0.98, 95% CI=0.72-1.33, respectively) (Thomson, 2014a).

The dietary effect may vary by hormone receptor characteristics of the tumour, Prentice, 2006 reported a significant reduction of ER+PR- breast cancer risk (HR=0.64, 95% CI=0.49-0.84), which was also observed postintervention, though not significant (HR=0.76, 95% CI=0.48-1.20) (HR=0.70, 95% CI=0.56-0.88 during cumulative follow-up) (Thomson, 2014a). HRs were 1.02 (95% CI =0.92-1.13) for ER+PR+ breast cancer, 1.11 (95% CI= 0.58-2.12) for ER-PR+ breast cancer, and 0.98 (0.79-1.22) for ER-PR- breast cancer during cumulative follow-up (Thomson, 2014a).

The presence of vasomotor symptoms may modify the effect of the low-fat dietary intervention. HRs for intervention vs comparison were 0.65 (95% CI=0.42-1.01) in women with hot flashes and 0.93 (95% CI=0.84-1.03) in women without hot flashes at baseline (P for interaction=0.12) (Caan, 2009).

Canadian Diet and Breast Cancer Prevention Trial (CDBCP trial)

Dietary intervention carried out by the CDBCP trial (recruitment 1988-1998, end of intervention 2005) involved the reduction of fat intake to 15% of energy and the increase of carbohydrate intake to 65% of energy. The comparison group was given printed dietary guideline materials and was not counseled to change their intake of fat.

Women (age 30-65 years) with extensive mammographic density were recruited and randomly assigned to the intervention group (n=2 341) or the comparison group (n=2 349).

A non-significant increase in invasive breast cancer risk with the low-fat dietary intervention (HR for intervention vs comparison=1.19, 95% CI=0.91-1.55) was observed (118 breast cancer cases in the intervention group and 102 in the comparison group after an average of 10 years) (Martin, 2011). Percent of energy from fat decreased from 30% at baseline to 20% after randomisation in the intervention group (although not reaching the 15% target) and remained lower than the comparison group throughout the trial. Findings suggested that a

sustained reduction in dietary fat intake did not reduce breast cancer risk in women with extensive mammographic density.

Cohort studies

Two cohort studies on low fat habit/pattern were identified.

Byrne, 1996 (NHANES) reported an increased risk of breast cancer (RR=3.5, 95% CI=1.7-7.4) for having none versus two or more low-fat habits (salad dressing, skin on poultry, or leanness of meat). There were only 52 cases from 6 156 women after 4 years of follow-up.

Park, 2009a (NIH-AARP) observed an increased risk of postmenopausal breast cancer (RR=1.10, 95% CI=0.97-1.24) when comparing the low-fat-low-fibre group to the high-fat-low-fibre group.

Table 5Low fat diet and breast cancer risk. Main characteristics of studies identified.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Thomson, 2014a BRE80527 USA	Follow-up of the WHI-DM trial, Age: 50-79 years, W, Postmenopausal	998/ 14 716 intervention group 1 565/ 22 994 comparison group 12.3 years	Through annual clinic visits during the trial and self-report in semi-annual mailed questionnaires, verified by medical records	Validated FFQ	Incidence, Invasive breast cancer During intervention	Intervention vs comparison	0.92 (0.84-1.01)	Age, disease at baseline, randomisation
		796/			During postintervention	Intervention vs comparison	1.08 (0.94-1.24)	
		2 563/			During cumulative follow-up	Intervention vs comparison	0.97 (0.89-1.05)	
		371/			During intervention: <27.9 % energy from fat	Intervention vs comparison	0.97 (0.79-1.20)	
		459/			27.9-<32.3 % energy from fat	Intervention vs comparison	1.08 (0.90-1.30)	
		451/			32.3-<36.8 % energy from fat	Intervention vs comparison	0.87 (0.72-1.06)	
		456/			>=36.8 % energy from fat	Intervention vs comparison	0.76 (0.62-0.92)	
		169/			During postintervention: <27.9 % energy from fat	Intervention vs comparison	0.98 (0.72-1.33)	
		198/			27.9-<32.3 % energy from fat	Intervention vs	1.06 (0.80-1.41)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
						comparison		
		209/			32.3-<36.8 % energy from fat	Intervention vs comparison	1.14 (0.86-1.50)	
		207/			>=36.8 % energy from fat	Intervention vs comparison	1.11 (0.84-1.46)	
		1 080/			Incidence, ER+/PR+ breast cancer, During intervention	Intervention vs comparison	0.99 (0.87-1.12)	
		574/			During postintervention	Intervention vs comparison	1.08 (0.92-1.28)	
		1 654/			During cumulative follow-up	Intervention vs comparison	1.02 (0.92-1.13)	
		270/			Incidence, ER+/PR- breast cancer, During intervention	Intervention vs comparison	0.69 (0.53-0.89)	
		86/			During postintervention	Intervention vs comparison	0.76 (0.48-1.20)	
		356/			During cumulative follow-up	Intervention vs comparison	0.70 (0.56-0.88)	
		28/			Incidence, ER-/PR+ breast cancer, During intervention	Intervention vs comparison	0.84 (0.39-1.82)	
		10/			During postintervention	Intervention vs comparison	2.36 (0.67-8.38)	
		38/			During cumulative follow-up	Intervention vs comparison	1.11 (0.58-2.12)	
		229/			Incidence, ER-/PR- breast	Intervention vs	0.92 (0.70-1.20)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					cancer, During intervention	comparison		
		100/			During postintervention	Intervention vs comparison	1.14 (0.76-1.69)	
		329/			During cumulative follow-up	Intervention vs comparison	0.98 (0.79-1.22)	
		50/			Incidence, HER-2 + breast cancer, During intervention	Intervention vs comparison	0.92 (0.52-1.62)	
		27/			During postintervention	Intervention vs comparison	1.70 (0.80-3.61)	
		77/			During cumulative follow-up	Intervention vs comparison	1.14 (0.73-1.79)	
		110/			Incidence, triple negative breast cancer, During intervention	Intervention vs comparison	0.82 (0.55-1.21)	
		60/			During postintervention	Intervention vs comparison	1.05 (0.63-1.76)	
		170/			During cumulative follow-up	Intervention vs comparison	0.90 (0.66-1.23)	
					Incidence, breast cancer PR- During cumulative follow-up	Intervention vs comparison	0.83 (0.71-0.97)	
Martin, 2011 BRE80319 Canada	CDBCP, Randomised Control Trial, Age: 47 years, W, with	118/ 2 341 intervention group 102/ 2 349	Self-reported during active follow-up, confirmed by pathology reports	Food records Intervention – group sessions that advised on decrease fat	Incidence, Invasive breast cancer	Intervention vs comparison	1.19 (0.91-1.55)	Age, age at first child birth, age at menarche, family history of breast cancer, HRT use, menopausal status,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	mammographic density in ≥50% of the breast determined through mammography screening	comparison group 10 years		intake to 15% of energy and increase carbohydrate to 65% of energy; total energy intake was maintained as before intervention Comparison – received general advice based on Canada's Food Guide				number of childbirths, parity, site, smoking, weight
Caan, 2009 BRE80363 USA	WHI-DM trial Randomised Control Trial, Age: 50-79 years, W, Postmenopausal, ≥33% energy from fat at baseline, Mammography screening at baseline and per 2 years	1 727/ 48 835 8.1 years	Self-report, medical record and pathology report reviewed by centrally trained physician	4-day food record & FFQ,	Incidence, breast cancer	Intervention vs comparison	0.91 (0.83-1.01) Ptrend:0.07	Age, age at first child birth, alcohol, BMI, calcium Intake, duration of HRT use, family history of breast cancer, Gail model risk, HRT use, mammography, menopausal age, parity, physical activity, race, smoking, treatment allocation, vitamin D Intake
					No hot flashes	Intervention vs comparison	0.93 (0.84-1.03)	
					Hot flashes	Intervention vs comparison	0.65 (0.42-1.01)	
					ER+PR+ breast cancer No hot flashes	Intervention vs comparison	1.01 (0.88-1.15)	
					ER+PR+ breast cancer Hot flashes	Intervention vs comparison	0.56 (0.30-1.03)	
					Other breast cancers No hot flashes	Intervention vs comparison	0.75 (0.62-0.90)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					Other breast cancers Hot flashes	Intervention vs comparison	0.76 (0.34-0.70)	
Park, 2009a BRE80264 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W, Postmenopausal	5 461/ 185 598 7 years	Cancer registry	FFQ	Incidence, breast cancer, postmenopausal	low fat low fibre vs high fat low fibre	1.10 (0.97-1.24)	Age, age at first child birth, age at menopause, alcohol Intake, BMI, breast biopsies, educational attainment, energy Intake, family history of cancer, fat Intake, fruits and vegetables Intake, menopausal hormone use, oophorectomy/hysterectomy, parity, physical activity, race, smoking status
Prentice, 2006 BRE80155 USA (same results in Prentice, 2007)	WHI-DM trial Randomised Control Trial, Age: 50-79 years, W, Postmenopausal, ≥33% energy from fat at baseline, Mammography screening at	655/ 19 541 intervention group 1 072/ 29 294 comparison group 8.1 years	Through annual clinic visits during the trial and self-report in semi-annual mailed questionnaires, verified by medical records	4-day food record & FFQ, Intervention – group sessions that advised on decrease fat intake to 20% of total energy, increase fruit and vegetables	Incidence, Invasive breast cancer	Intervention vs comparison	0.91 (0.83-1.01)	Age, randomised treatment assignment
		366/			<27.9 % energy from fat	Intervention vs comparison	0.97 (0.79-1.200	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	baseline and per 2 years	445/		intake to ≥5 servings/day, increase grains intake to ≥6 servings/day; total energy was not restricted and weight loss was not advocated Comparison – received a printed copy of *Nutrition and Your Health: Dietary Guidelines for Americans*	27.9-<32.3 % energy from fat	Intervention vs comparison	1.08 (0.89-1.30)	
		443/			32.3-<36.8 % energy from fat	Intervention vs comparison	0.85 (0.70-1.03)	
		442/			≥36.8 % energy from fat	Intervention vs comparison	0.78 (0.64-0.95)	
		1 303/			Incidence, breast cancer ER+	Intervention vs comparison	0.89 (0.80-1.00)	
		253/			Incidence, breast cancer ER-	Intervention vs comparison	0.89 (0.69-1.14)	
		1 041/			Incidence, breast cancer PR+	Intervention vs comparison	0.96 (0.85-1.09)	
		481/			Incidence, breast cancer PR-	Intervention vs comparison	0.76 (0.63-0.92)	
		1 015/			Incidence, breast cancer ER+/PR+	Intervention vs comparison	0.97 (0.86-1.10)	
		256/			Incidence, breast cancer ER+/PR-	Intervention vs comparison	0.64 (0.49-0.84)	
		26/			Incidence, breast cancer ER-/PR+	Intervention vs comparison	0.67 (0.29-1.54)	
		220/			Incidence, breast cancer ER-/PR-	Intervention vs comparison	0.89 (0.68-1.17)	
		441/			Incidence, In situ breast cancer	Intervention vs comparison	1.01 (0.83-1.22)	
		80/			Mortality, Invasive breast cancer	Intervention vs comparison	0.77 (0.48-1.22)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Byrne, 1996 BRE05719 USA	NHEFS, Prospective Cohort, Age: 25-74 years, W	52/ 6 156 3.9 years	Medical records + death certificate	FFQ	Incidence, breast cancer	None vs 2 or more low-fat diet habits	3.50 (1.70-7.40)	Age

1.4 Dietary guideline index score

Cohort studies

Overall summary

Sixteen publications from fourteen studies on dietary guideline index score were identified.

Various guidelines or indexes were examined, including ACS and WCRF guidelines for cancer prevention, Healthy Eating Index (HEI), Diet Quality Index-Revised (DQI-R), Recommended Food Score (RFS), Dietary Approaches to Stop Hypertension score (DASH), Healthy Nordic Food Index (HNFI), WHO Healthy Diet Index (HDI), and other health index scores (see study characteristics table below).

Dose-response meta-analysis was not conducted as the number of studies on any one score is low. Results for the highest compared with the lowest dietary guideline index score were presented in a forest plot.

Breast cancer (any)

Eight studies (eight publications) were identified. All studies were shown in the highest versus the lowest forest plot, apart from Makarem, 2015 (FHS-Offspring Cohort) which only reported a dose-response result. A non-significant inverse association for breast cancer risk was reported for each point adherence to the WCRF guidelines (RR=0.87, 95% CI=0.74-1.03) (Makarem, 2015).

Five out of seven studies reported an inverse association. The RR estimates ranged from 0.49 (95% CI=0.05-5.07) in a Korean cohort of cancer screening (Wie, 2014) to 0.94 (95% CI=0.67-1.32) in UKWCS (Cade, 2011). Two studies (Kabat, 2015a, NIH-AARP; Catsburg, 2014a, CNBSS) on ACS guidelines and one study (Romaguera, 2012, EPIC) on WCRF guidelines observed significant results.

No association was observed for adherence to the low carbohydrate and high protein diet (RR=1.00, 95% CI=0.79-1.27) (Nilsson, 2013, VIP). A non-significant positive association with the Healthy Nordic Food Index were reported (RR for the highest vs the lowest score=1.08, 95% CI=0.92-1.27) (Li, 2015, WLHS).

Only one study reported results by breast cancer hormone receptor status, which observed non-significant associations (Li, 2015).

Premenopausal breast cancer

All four studies (four publications) identified were shown in the highest versus the lowest forest plot. Non-significant inverse associations with different indexes were reported in three studies (Li, 2015; Dartois, 2014; Cade, 2011) (RR estimates ranged from 0.80 to 0.92). The other study (Nilsson, 2013) observed a non-significant positive association with adherence to the low carbohydrate and high protein diet (RR=1.04, 95% C=0.57-1.89).

Non-significant associations were observed in the only study reported results by breast cancer hormone receptor status (Li, 2015).

Postmenopausal breast cancer

All 10 studies (11 publications) identified on 16 different guidelines and indexes were shown in the highest versus the lowest forest plot. The associations were inconsistent, although the inverse association was more evident in several studies. RR estimates ranged from 0.40 (95% CI=0.25-0.65) in VITAL on WCRF guidelines (Hastert, 2013) to 1.21 (95% CI=0.98-1.49) in WLHS on the Healthy Nordic Food Index (Li, 2015).

Significant inverse associations were reported by four studies. One was the VITAL study (Hastert, 2013) as mentioned; the others were IWHS on dietary guidelines for Americans (Harnack, 2002) (RR for the highest vs the lowest score=0.76, 95% CI= 0.65-0.89), WHI-OS on ACS guidelines (Thomson, 2014b) (RR=0.78, 95% CI=0.67-0.92), and EPIC on a health index that combined dietary, physical activity, smoking, alcohol consumption, and anthropometry components (RR=0.74, 95% CI=0.66-0.83) (McKenzie, 2015).

Four studies reported results by breast cancer hormone receptor status, of which two studies (McKenzie, 2015, EPIC; Fung, 2011, NHS) reported for the highest versus the lowest score comparison and were presented in a forest plot. Two studies (Hastert, 2013, VITAL; Li, 2005, WLHS) reported only dose-response results. Inverse associations, significant in some, appeared more evident with ER-negative breast cancer compared with ER-positive breast cancer. For each one-point adherence to the WCRF guideline, RRs were 0.84 (95% CI=0.72-0.99) for ER-negative breast cancer and 0.90 (95% CI=0.85-0.96) for ER-positive breast cancer (Hastert, 2013). For the highest versus the lowest score, RRs were 0.60 (95% CI=0.40-0.90) and 0.81 (95% CI=0.67-0.98) for ER-PR- and ER+PR+ breast cancers, respectively for healthy lifestyle index (McKenzie, 2015), and 0.69 (95% CI=0.51-0.94) and 1.06 (95% CI=0.92-1.23) for ER-negative and ER-positive breast cancers, respectively for Recommended Food Score (Fung, 2006). WLHS (Li, 2005) on Nordic Food Index observed non-significant results.

Table 6 Dietary guideline index score and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified[1]	14 (16 publications)
Studies included in forest plot of highest compared with lowest exposure	7 (7 publications) breast cancer risk 4 (4 publications) premenopausal breast cancer risk 10 (11 publications) postmenopausal breast cancer risk
Studies included in linear dose-response meta-analysis	Insufficient data
Studies included in non-linear dose-response meta-analysis	Insufficient data

[1]Numbers of studies and publications identified overall.

Table 7 Dietary guideline index score and breast cancer risk. Main characteristics of studies identified.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Kabat, 2015a BRE80605 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W	9 072/ 189 575 10.5 years	Cancer registry	Semi-quantitative FFQ, ACS guidelines	Incidence, breast cancer	8-11 vs 0-3 scores	0.81 (0.76-0.87) Ptrend:<0.0001	Age, age at first child birth, age at menarche, educational level, energy Intake, ethnicity, HRT use, marital status, menopausal status, parity, smoking status	Included in the highest vs the lowest forest plot
Li, 2015 BRE80550 Sweden	WLHS, Prospective Cohort, Age: 29-49 years, W	1 464/ 44 296 20 years	Cancer registry and death registry	FFQ, Healthy Nordic food index (HNFI) (Whole grain bread, oatmeal, apples and pears, cabbages, root vegetables, fish and shellfish)	Incidence, breast cancer	4-6 vs 0-1 points	1.08 (0.92-1.27)	Age, age at first child birth, age at menarche, alcohol, benign breast disease, BMI, breastfeeding, cigarettes per day, educational level, energy Intake, family history of breast cancer, height, number of children, oral contraceptive use, saturated fat Intake, smoking	Included in the highest vs the lowest forest plot
		549/			Incidence, breast cancer, premenopausal	4-6 vs 0-1 points	0.92 (0.71-1.19)		Included in the highest vs the lowest forest plot
		915/			Incidence, breast cancer, postmenopausal	4-6 vs 0-1 points	1.21 (0.98-1.49)		Included in the highest vs the lowest forest plot
		1 098/			Incidence, breast cancer ER+	per 1 points	1.00 (0.96-1.05)		
		251/			Incidence, breast cancer ER-	per 1 points	1.03 (0.94-1.14)		
		913/			Incidence, breast	per 1 points	0.98 (0.93-1.03)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					cancer PR+				
		421/			Incidence, breast cancer PR-	per 1 points	1.08 (1.00-1.16)		
		122/			Incidence, breast cancer HER-2 +	per 1 points	1.00 (0.88-1.15)		
		676/			Incidence, breast cancer HER-2 -	per 1 points	0.97 (0.92-1.03)		
		886/			Incidence, breast cancer ER+ & PR+	per 1 points	0.98 (0.93-1.03)		
		186/			Incidence, breast cancer ER- & PR-	per 1 points	1.02 (0.91-1.14)		
		57/			Incidence, breast cancer ER+ & PR+ & HER-2+	per 1 points	1.01 (0.83-1.23)		
		61/			Incidence, breast cancer ER- & PR- & HER-2-	per 1 points	1.00 (0.83-1.21)		
		387/			Incidence, breast cancer ER+, premenopausal	per 1 points	0.99 (0.92-1.07)		
		105/			Incidence, breast cancer ER-, premenopausal	per 1 points	1.10 (0.95-1.28)		
		354/			Incidence, breast cancer PR+,	per 1 points	0.98 (0.91-1.06)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					premenopausal				
		135/			Incidence, breast cancer PR-, premenopausal	per 1 points	1.09 (0.96-1.24)		
		30/			Incidence, breast cancer HER-2 +, premenopausal	per 1 points	0.95 (0.73-1.25)		
		176/			Incidence, breast cancer HER-2 -, premenopausal	per 1 points	0.93 (0.83-1.04)		
		337/			Incidence, breast cancer ER+ & PR+, premenopausal	per 1 points	0.98 (0.90-1.06)		
		71/			Incidence, breast cancer ER- & PR-, premenopausal	per 1 points	1.04 (0.87-1.24)		
		17/			Incidence, breast cancer ER+ & PR+ & HER-2+, premenopausal	per 1 points	1.04 (0.73-1.49)		
		12/			Incidence, breast cancer ER- & PR- & HER-2-, premenopausal	per 1 points	0.72 (0.46-1.14)		
		711/			Incidence, breast cancer ER+, postmenopausal	per 1 points	1.01 (0.96-1.07)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		146/			Incidence, breast cancer ER-, postmenopausal	per 1 points	0.99 (0.87-1.12)		
		559/			Incidence, breast cancer PR+, postmenopausal	per 1 points	0.99 (0.93-1.05)		
		286/			Incidence, breast cancer PR-, postmenopausal	per 1 points	1.07 (0.98-1.17)		
		92/			Incidence, breast cancer HER-2 +, postmenopausal	per 1 points	1.02 (0.88-1.20)		
		500/			Incidence, breast cancer HER-2 -, postmenopausal	per 1 points	0.99 (0.93-1.06)		
		549/			Incidence, breast cancer ER+ & PR+, postmenopausal	per 1 points	0.99 (0.92-1.05)		
		115/			Incidence, breast cancer ER- & PR-, postmenopausal	per 1 points	1.01 (0.88-1.16)		
		40/			Incidence, breast cancer ER+ & PR+ & HER-2+, postmenopausal	per 1 points	1.00 (0.79-1.27)		
		49/			Incidence, breast cancer ER- &	per 1 points	1.08 (0.87-1.35)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					PR- & HER-2-, postmenopausal				
Makarem, 2015 BRE80589 USA	FHS-Offspring Cohort, Prospective Cohort, W	124/ 1 602 11.5 years	Death certificate and medical records	Semi-quantitative FFQ, WCRF guidelines	Incidence, breast cancer	per 1 points	0.87 (0.74-1.03)	Age, smoking status	Excluded, dose-response result only
McKenzie, 2015 BRE80534 Europe	EPIC, Prospective Cohort, Age: 25-70 years, W, Postmenopausal	7 756/ 242 918 10.9 years	Record linkage with population-based In 6 countries, Insurance, cancer records & self-report verified by medical records In the rest	FFQ, Healthy lifestyle index (Diet (cereal fibre, folate, polyunsaturated: saturated fat ratio, fatty fish, margarine, glycemic load and fruits and vegetables), physical activity, smoking, alcohol consumption and anthropometry)	Incidence, Invasive breast cancer, postmenopausal	≥16 vs 6-10 points	0.74 (0.66-0.83)	Age, age at first child, age at menarche, breastfeeding, centre location, educational level, height, HRT use, non-alcohol energy, OC use	Included in the highest vs the lowest forest plot
		2 586/			Incidence, breast cancer ER+ & PR+, postmenopausal	≥16 vs 6-10 points	0.81 (0.67-0.98) Ptrend:0.002		Included in the highest vs the lowest forest plot
						per 1 score	0.96 (0.95-0.98)		
		703/			Incidence, breast cancer ER- & PR-, postmenopausal	≥16 vs 6-10 points	0.60 (0.40-0.90) Ptrend:0.009		Included in the highest vs the lowest forest plot
						per 1 score	0.96 (0.94-0.99)		
Catsburg, 2014a BRE80536 Canada	CNBSS, Prospective Cohort,	1 938/ 48 840 16.6 years	Cancer registry	FFQ, ACS guidelines	Incidence, Invasive breast cancer	6 vs 0-1 scores	0.69 (0.49-0.97) Ptrend:0.003	Age, age at first child birth, age at menarche,	Included in the highest vs the lowest forest

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Age: 40-59 years, W							family history of breast cancer, history of breast disease, HRT use, menopausal status, OC use, parity, study center	plot
		1 970/		WCRF guidelines	Incidence, Invasive breast cancer	6-7 vs 0-1 scores	0.79 (0.57-1.10) Ptrend:0.004		Included in the highest vs the lowest forest plot
Dartois, 2014 BRE80514 France	E3N EPIC-France, Prospective Cohort, Age: 43-68 years, W	609/ 64 732 8 years	Self report verified by reviewing medical and pathological records by physicians	Self-administered questionnaire, Health index (Tobacco smoking, BMI, alcohol consumption, fruit and vegetable consumption, and recreational physical activity)	Incidence, premenopausal breast cancer	4.5-5 vs 0-2 scores	0.80 (0.58-1.12) Ptrend:0.288	Age at first child birth, age at menarche, educational level, family history of cancer In first degree relatives, number of children, professional activity, residence, use of oral contraception	Included in the highest vs the lowest forest plot
Thomson, 2014b BRE80508 USA	WHI-OS, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	3 549/ 65 838 12.6 years	Mailed annual questionnaire, cancer registries, national death Index and medical records	FFQ, ACS guidelines	Incidence, breast cancer, postmenopausal	7-8 vs 0-2 score	0.78 (0.67-0.92) Ptrend:0.001	Age, aspirin use, educational level, family history of cancer, having a healthcare provider, mammography,	Included in the highest vs the lowest forest plot
		192/			Mortality, breast cancer, postmenopausal	6-8 vs 0-3 score	0.67 (0.43-1.03) Ptrend:0.049		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								multivitamin supplement Intake, NSAID use, parous/nulliparous, race, smoking, pack-years, total energy Intake, unopposed estrogen use	
Wie, 2014 BRE80609 Korea	Cancer Screening Examination Cohort, Korea (CSECK), Prospective Cohort, W	29/ 3 486 7 years	Cancer registry and medical records	3-day food record, Dietary risk factors score (Red meat, vegetables and fruits, sodium, and obesity)	Incidence, breast cancer	≥3 vs ≤2 scores	0.49 (0.05-5.07)	Age, alcohol Intake, BMI, educational level, energy, Income, marital status, physical activity, smoking	Included in the highest vs the lowest forest plot
Hastert, 2013 BRE80481 USA	VITAL, Prospective Cohort, Age: 50-76 years, W, Postmenopausal	899/ 30 797 6.7 years	SEER registry	FFQ, WCRF Guidelines	Incidence, breast cancer, postmenopausal	5-6 vs ≤0 score	0.40 (0.25-0.65) Ptrend:<0.001	Age, age at first child birth, age at menarche, age at menopause, educational level, energy Intake, family history of breast cancer, mammography, race, years of	Included in the highest vs the lowest forest plot
					Incidence, breast cancer ER+, postmenopausal	per 1 score	0.90 (0.85-0.96)		
					Incidence, breast cancer ER-, postmenopausal	per 1 score	0.84 (0.72-0.99)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								HRT use	
Nilsson, 2013 BRE80471 Sweden	VIP, Prospective Cohort, Age: 30- years, W	581/ 31 185 9.7 years	Cancer registry	FFQ & 24-hr dietary recall, Low carbohydrate and high protein diet score	Incidence, breast cancer	14-20 vs 2-8 points	1.00 (0.79-1.27) Ptrend:0.924	Age, alcohol, educational level, energy Intake, obesity, saturated fat, sedentary behaviour, smoking	Included in the highest vs the lowest forest plot
		104/			Incidence, breast cancer, age at diagnosis <49 years	14-20 vs 2-8 points	1.04 (0.57-1.89) Ptrend:0.343		
		184/			Incidence, breast cancer, age at diagnosis >55 years	14-20 vs 2-8 points	1.02 (0.67-1.55) Ptrend:0.707		
Romaguera, 2012 BRE80567 France, Italy, Spain, UK, Netherlands, Greece, Germany, Sweden, Denmark, Norway	EPIC, Prospective Cohort, Age: 25-70 years, W	9 358/ 260 098 11 years	Cancer registries, health Insurance records, pathology rec & active follow up	FFQ and 24 hour recall, WCRF Guidelines	Incidence, breast cancer	5-7 vs 0-3	0.84 (0.78-0.90) Ptrend:<0.0001	Age, age at first child, age at menarche, disease at baseline, educational level, energy Intake, HRT use, menopause status, OC use, smoking Intensity, smoking status, study centre	Included in the highest vs the lowest forest plot
Cade, 2011 BRE80379 UK	UKWCS, Prospective Cohort, Age: 35-69	828/ 33 731 9 years	Population registers	FFQ, WHO HDI	Incidence, breast cancer	7-10 vs 0-2 score	0.94 (0.67-1.32) Ptrend:0.8	Age, age at menarche, BMI, breastfeeding, contraception,	Included in the highest vs the lowest forest plot
		350/			Incidence,	7-10 vs 0-2	0.83 (0.50-1.39)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	years, W				premenopausal breast cancer	score	Ptrend:0.6	educational level, energy Intake, energy-adjusted Intake of fat, ethanol, HRT use, menopausal status, parity, physical activity, SES, smoking	
		478/			Incidence, postmenopausal breast cancer	7-10 vs 0-2 score	0.99 (0.63-1.55) Ptrend:0.9		
Fung, 2011 BRE80385 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Postmenopausal	5 522/ 866 621 26 years	Self reported/death certificate/pathology reports	FFQ, DASH (Fruits, vegetables, nuts and legumes, low-fat dairy products, and whole grains and sodium, sweetened beverages, and red and processed meats)	Incidence, Invasive breast cancer, postmenopausal	Q5 vs Q1	0.97 (0.89-1.06) Ptrend:0.98	Age, alcohol, benign breast disease, BMI, energy, family history of breast cancer, height, HRT use, multivitamin Intake, physical activity, smoking, weight at 18 yrs	Included in the highest vs the lowest forest plot
		3 318/			ER+ breast cancer, postmenopausal	Q5 vs Q1	0.96 (0.85-1.08) Ptrend:0.89		
		827/			ER- breast cancer, postmenopausal	Q5 vs Q1	0.80 (0.64-1.01) Ptrend:0.02		
		5 522/		Low-carbohydrate-diet score (For fat and	Incidence, Invasive breast cancer, postmenopausal	Q5 vs Q1	1.02 (0.93-1.11) Ptrend:0.92		
		3 318/			ER+ breast	Q5 vs Q1	1.01 (0.90-1.13)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
				protein, 10 points for the highest category, for carbohydrates, 10 points for the lowest category)	cancer, postmenopausal		Ptrend:0.61		
		827/			ER- breast cancer, postmenopausal	Q5 vs Q1	1.06 (0.85-1.33) Ptrend:0.73		
		5 522/		Animal low-carbohydrate-diet score (Based on the percent of energy from carbohydrates, animal protein, and animal fat)	Incidence, Invasive breast cancer, postmenopausal	Q5 vs Q1	1.02 (0.94-1.11) Ptrend:0.91		
		3 307/			ER+ breast cancer, postmenopausal	Q5 vs Q1	1.05 (0.93-1.17) Ptrend:0.78		
		827/			ER- breast cancer, postmenopausal	Q5 vs Q1	1.13 (0.91-1.41) Ptrend:0.75		
		5 522/		Vegetable low-carbohydrate-diet score (Based on the percent of energy from carbohydrates, vegetable protein, and vegetable fat)	Incidence, Invasive breast cancer, postmenopausal	Q5 vs Q1	0.95 (0.87-1.03) Ptrend:0.16		
		3 321/			ER+ breast cancer, postmenopausal	Q5 vs Q1	0.99 (0.89-1.10) Ptrend:0.47		
		827/			ER- breast cancer, postmenopausal	Q5 vs Q1	0.81 (0.65-1.01) Ptrend:0.03		
Fung, 2006 BRE80107	NHS, Prospective	3 580/ 121 700	Medical records	FFQ,	Incidence, breast cancer,	Q5 vs Q1	1.04 (0.92-1.18) Ptrend:0.68	Age , age at menopause,	Included in the highest vs the

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
USA	Cohort, Age: 30-55 years, W, Postmenopausal	18 years		HEI (Grains, vegetables, fruits, milk, meat, total fat (% energy), saturated fat (% energy), cholesterol, sodium, diet variety)	postmenopausal			benign breast disease, BMI, weight at 18 years weight change since 18 years, energy Intake , family history, HRT use, physical activity , smoking habits, multivitamin use (except for AHEI), alcohol (except for AHEI, DQI-R)	lowest forest plot
		2 367/			ER+ breast cancer, postmenopausal	Q5 vs Q1	1.10 (0.95-1.28) Ptrend:0.69		
		575/			ER- breast cancer, postmenopausal	Q5 vs Q1	0.92 (0.68-1.24) Ptrend:0.47		
		3 580/		AHEI (Vegetables, fruits, nuts and soy, cereal fibre, ratio of white to red meat, trans fat (% energy), polyunsaturated: saturated fat ratio, alcohol, duration of vitamin use)	Incidence, breast cancer, postmenopausal	Q5 vs Q1	0.99 (0.88-1.11) Ptrend:0.84		
		2 367/			ER+ breast cancer, postmenopausal	Q5 vs Q1	1.05 (0.91-1.21) Ptrend:0.19		
		575/			ER- breast cancer, postmenopausal	Q5 vs Q1	0.78 (0.59-1.04) Ptrend:0.01		
		3 580/		DQIR (Grains, vegetables, fruits, total fat	Incidence, breast cancer, postmenopausal	Q5 vs Q1	1.03 (0.91-1.16) Ptrend:0.83		
		2 367/			ER+ breast cancer, postmenopausal	Q5 vs Q1	1.09 (0.94-1.27) Ptrend:0.55		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		575/		(% energy), saturated fat (% energy), cholesterol, iron, calcium, diet diversity, diet moderation)	ER- breast cancer, postmenopausal	Q5 vs Q1	0.97 (0.72-1.31) Ptrend:0.35		
		3 580/		RFS (Specific items of fruits, vegetables, whole grains, low saturated fat proteins, low fat dairy products)	Incidence, breast cancer, postmenopausal	Q5 vs Q1	0.98 (0.87-1.11) Ptrend:0.56		
		2 367/			ER+ breast cancer, postmenopausal	Q5 vs Q1	1.06 (0.92-1.23) Ptrend:0.44		
		575/			ER- breast cancer, postmenopausal	Q5 vs Q1	0.69 (0.51-0.94) Ptrend:0.003		
Mai, 2005 BRE23275 USA	BCDDP Prospective Cohort, Age: 61 years, W	1 472/ 37 135 9.5 years	Medical records + self-reported	FFQ, RFS	Incidence, breast cancer, postmenopausal	Q4 vs Q1	1.05 (0.90-1.23) Ptrend:0.81	Age at menarche, age at menopause, alcohol, BMI, energy Intake , mammography screening, NSAID use, parity/pregnancies, smoking habits	Included in the highest vs the lowest forest plot
		100/			Mortality, breast cancer, postmenopausal	Q4 vs Q1	1.43 (0.81-2.53) Ptrend:0.17		
Harnack, 2002 BRE19762 USA	IWHS, Prospective Cohort, Age: 55-69	34 708 13 years	Partially histological - over 80%	FFQ-semi-quantitative, Dietary	Incidence, breast cancer, postmenopausal	12.2-17.6 vs 2.1-8.3	0.76 (0.65-0.89)	Age , benign breast disease, educational level, energy	Included in the highest vs the lowest forest plot

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	years, W, Postmenopausal			Guidelines for Americans				Intake , family history, height, HRT use, other specified factor, other specified factor, parity/pregnancies, smoking habits	

Figure 6 RR (95% CI) of breast cancer for the highest compared with the lowest level of dietary guideline index score

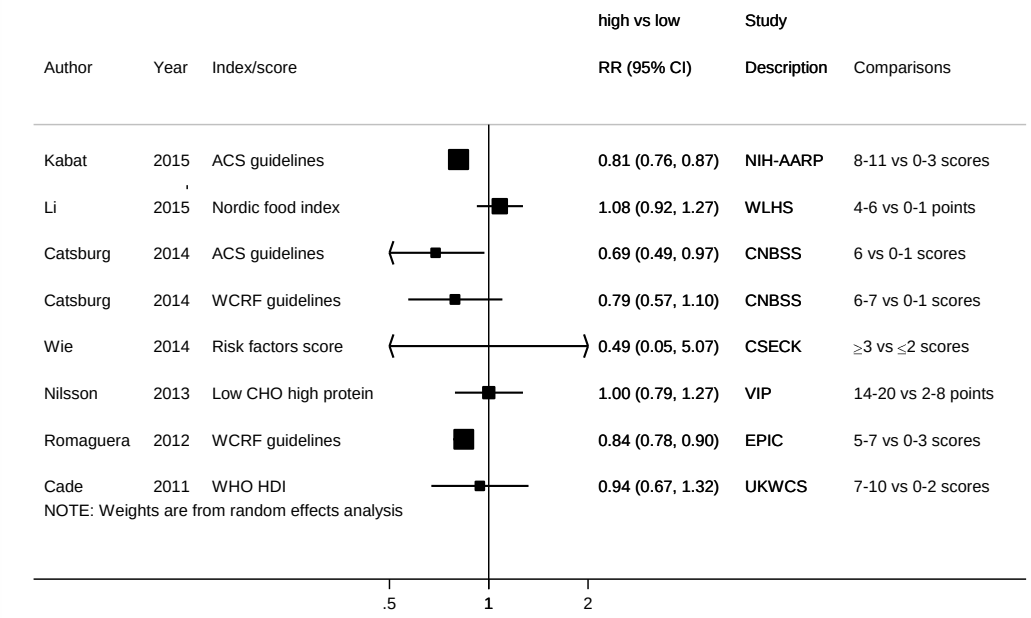


Figure 7 RR (95% CI) of premenopausal breast cancer for the highest compared with the lowest level of dietary guideline index score

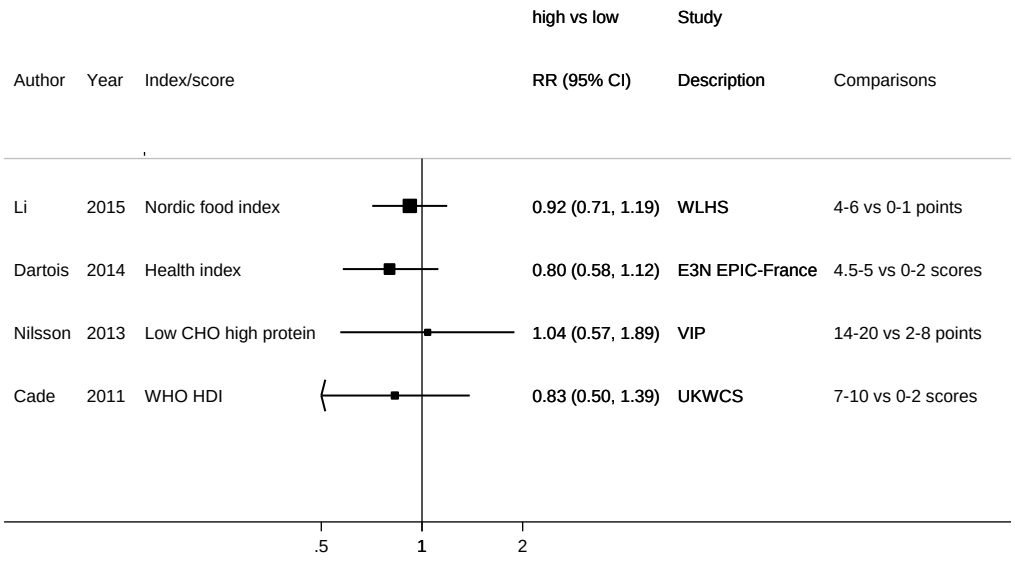
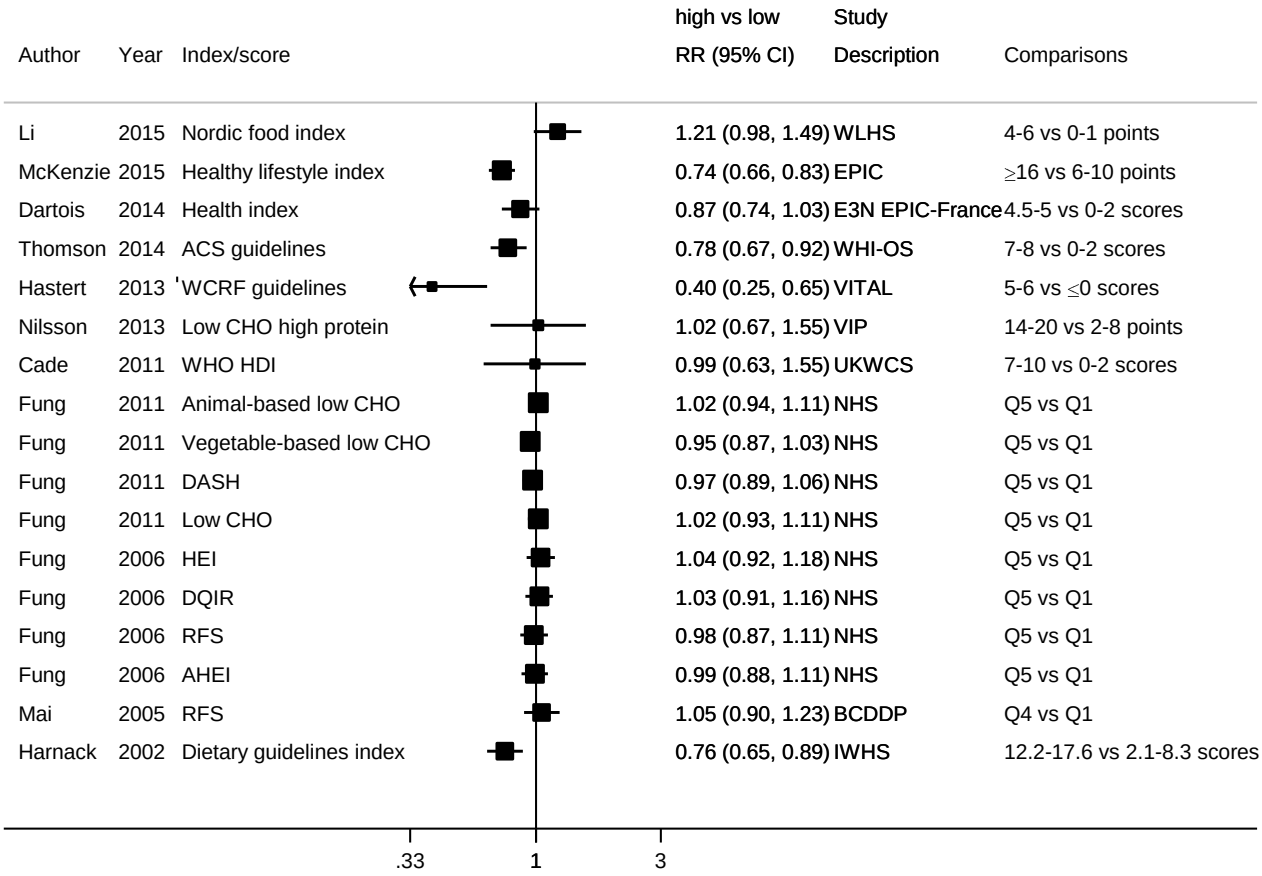
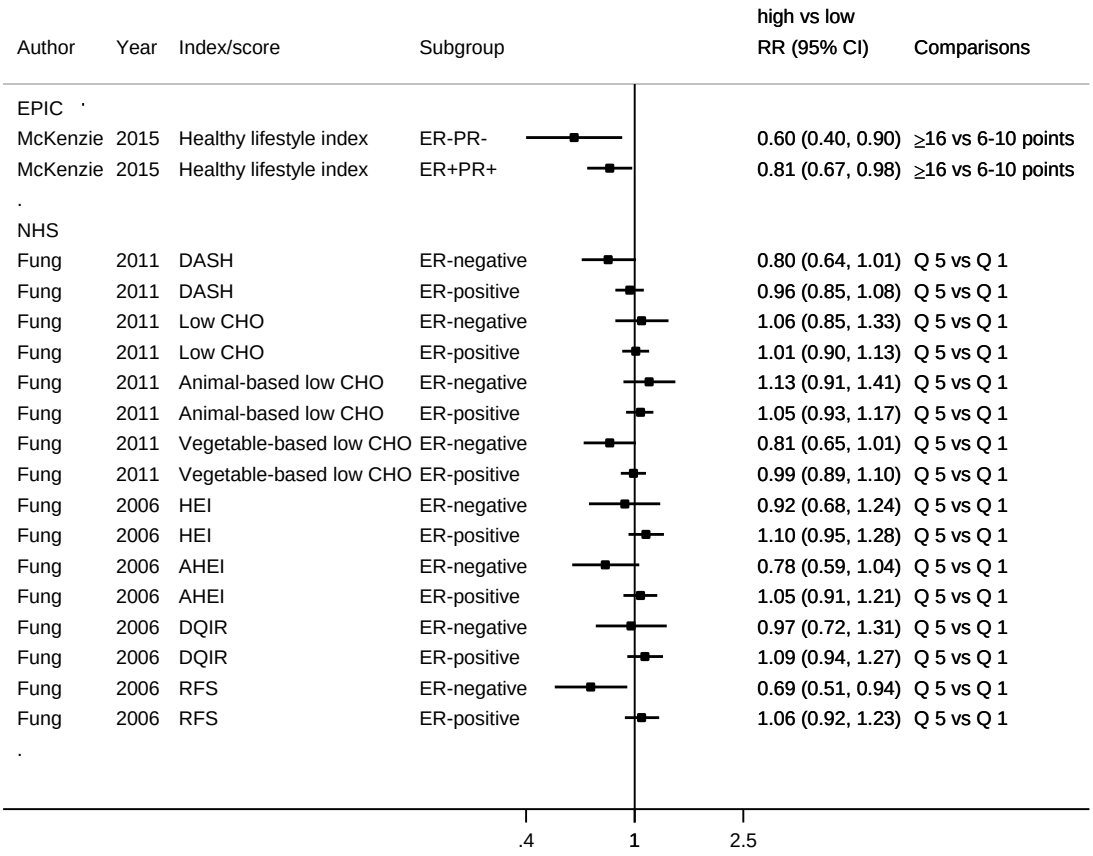


Figure 8 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest level of dietary guideline index score



Note: E3N, EPIC-France (Dartois, 2014) was a component study of EPIC (McKenzie, 2015). The index scores were different between the two studies. Dartois, 2014 included tobacco smoking, BMI, alcohol consumption, fruit and vegetable consumption, and recreational physical activity and McKenzie, 2015 included diet (cereal fibre, folate, polyunsaturated: saturated fat ratio, fatty fish, margarine, glycemic load and fruits and vegetables), physical activity, smoking, alcohol consumption and anthropometry.

Figure 9 RR (95% CI) of hormone receptor-defined postmenopausal breast cancer for the highest compared with the lowest level of dietary guideline index score



1.4 *A posteriori* derived dietary patterns

Cohort studies

Overall summary

Seventeen publications from 19 studies on *a posteriori* derived dietary patterns were identified. This included two pooled studies (Pot, 2014, UKDCC, four cohorts; Mannisto, 2005, three cohorts).

Dietary patterns were derived through factor or principal components analysis or reduced rank regression method, basing on the dietary information in the cohorts and thus differ between the studies (see study characteristics table below). Generally, there were prudent or healthy patterns, fruits and vegetables-related patterns, Western pattern, meat-related patterns, high fat pattern, alcohol pattern, ethnic pattern, and other mixed patterns.

Dose-response meta-analysis was not conducted because of the variability of the dietary patterns. Results for the highest compared with the lowest dietary pattern were presented in a forest plot.

Breast cancer (any)

Overall 12 publications from 15 studies were identified. All studies were shown in the highest versus the lowest forest plot. One publication reported results by HER-2 status only (Sant, 2007).

The associations between prudent, healthy, or fruits and vegetables-related patterns and breast cancer risk were inconsistent (RR estimates ranged from 0.73 to 1.12), although inverse associations appeared more evident. Nine out of 14 studies reported results observed an inverse association for the highest compared with the lowest pattern, of which the Canadian Study of Diet Lifestyle and Health (CSDLH) on healthy pattern (Catsburg, 2015) and the California Teachers Study on plant-based pattern (Link, 2013) reported significant results (RR=0.73, 95% CI= 0.58-0.91; RR=0.85, 95% CI=0.76-0.95, respectively). Five studies, four from the UK Dietary Cohort Consortium (UKDCC) (Pot, 2014) that pooled data in the UK and EPIC-Norway (Engeset, 2009), reported a non-significant positive association with high fibre pattern and healthy pattern, respectively (RR=1.08, 95% CI= 0.84-1.38; RR=1.12, 95% CI=0.85-1.47, respectively).

Western, fat, or meat-related patterns appeared to associate positively with breast cancer risk, although inverse associations were also reported (RR estimates ranged from 0.69 to 2.34). Seven out of 10 studies reported results found a positive association, with high fat pattern reported in EPIC-Potsdam (Schulz, 2008) being significant (RR=2.34, 95% CI=1.45-3.79). Meat and dim sum pattern in the Singapore Chinese Health Study (Butler, 2010, SCHS), and pork, processed meat and potatoes pattern in the Swedish Mammography Cohort (SMC) and the Netherland Cohort Study (NLCS) (Mannisto, 2005) were inversely associated with breast cancer risk (RR=0.84, 95% CI=0.65-1.10; RR=0.92, 95% CI=0.78-1.09; RR=0.69, 95% CI=0.52-0.92, respectively).

Positive associations (two significant (Link, 2013; Terry, 2011); one borderline significant (Pot, 2014, four studies); one non-significant (Engeset, 2009)) were reported in the seven studies on alcohol-related patterns (RR estimates ranged from 1.01 to 1.27).

Other patterns including ethnic, high protein or carbohydrate, fish, bread, canteen, and other mixed patterns were non-significantly associated with breast cancer risk (RR estimates ranged from 0.91 to 1.25).

Four studies reported results by subtypes of breast cancer and were shown in the highest versus the lowest forest plots. Inverse associations, significant in some, appeared more evident with ER-negative breast cancer compared with ER-positive breast cancer. For the highest versus the lowest pattern, RRs were 0.55 (95% CI=0.32-0.93) and 0.92 (95% CI=0.69-1.22) for ER-negative and ER-positive breast cancers, respectively for fruit and salad pattern (Baglietto, 2011), and 0.66 (95% CI=0.48-0.91) and 1.03 (95% CI=0.74-1.41) for ER-PR- and ER+PR- breast cancers, respectively for plant-based pattern (Link, 2013). BWHS (Agurs-Collins, 2009) on prudent pattern observed a significant inverse association with ER-negative breast cancer (RR=0.52, 0.28-0.94) and no association with ER-positive breast cancer (results not shown in publication).

Western pattern associated positively with ER-positive breast cancer (RR=1.21, 95% CI= 0.88-1.66) and inversely with ER-negative breast cancer (RR=0.86, 95% CI=0.50-1.47) (Baglietto, 2011). The same for alcohol patterns (RR=1.10, 95% CI= 0.80-1.50; RR=0.85 95% CI=0.63 1.14, respectively) (Link, 2013).

Premenopausal breast cancer

All seven publications from eight studies identified were shown in the highest versus the lowest forest plot.

The associations between various dietary patterns and breast cancer risk in premenopausal women were inconsistent (RR estimates ranged from 0.66 to 1.23 for prudent/healthy patterns; 0.79 to 1.50 for Western/meat patterns; 0.86 and 1.12 for alcohol pattern; 0.90 to 1.58 for other patterns). Most studies reported non-significant results. Only one study, the Black Women Health Study (BWHS) (Agurs-Collins, 2009), reported a significant inverse association with prudent pattern (RR=0.70, 95% CI=0.52-0.96).

Postmenopausal breast cancer

All 11 publications from 14 studies identified shown in the highest versus the lowest forest plot.

Results on prudent, healthy, or fruits and vegetables-related patterns and postmenopausal breast cancer risk were inconsistent; with half of the studies observed an inverse association and another half observed a positive association for the highest compared with the lowest pattern (RR estimates ranged from 0.70 to 1.29). Only two studies, the study of Singaporean Chinese women on vegetable, fruit, and soy pattern (Butler, 2010) and the E3N study on healthy/Mediterranean pattern (Cottet, 2009) reported significant inverse associations (RR=0.70, 95% CI=0.51-0.95; RR=0.85, 95% CI=0.75-0.95, respectively).

Associations with Western, or meat-related patterns were also unclear. There were five positive associations and four inverse associations, all being non-significant (RR estimates ranged from 0.85 to 1.49).

Positive associations were evident in the seven studies reported results on alcohol related-patterns (three significant (Pot, 2014, four studies; Cottet, 2009; Terry, 2001); one non-significant (Engeset, 2009)).

Other patterns including ethnic, oestrogen level-correlated foods, fish, bread, and other mixed patterns were non-significantly associated with postmenopausal breast cancer risk (RR estimates ranged from 0.89 to 1.51).

Four studies (five publications) reported results by subtypes of postmenopausal breast cancer. Results were shown in the highest versus the lowest forest plots and study characteristics table. Prudent pattern was negatively associated with ER-negative and positively associated with ER-positive postmenopausal breast cancers (RR=0.62, 95% CI= 0.45-0.88; RR=1.10, 95% CI=0.93-.1.31, respectively) (Fung, 2005). Healthy/Mediterranean pattern was negatively associated with all breast cancer subtypes (ER-PR-, ER+PR+, ER+PR-) other than ER-PR+ breast cancer (Cottet, 2009). Associations with alcohol or Western patterns were not

significant, apart from the positive association with ER+PR+ breast cancer (RR=1.33, 95% CI=1.07-1.65) (Cottet, 2009).

Table 8 A posteriori derived dietary patterns and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified[1]	19 (17 publications)
Studies included in forest plot of highest compared with lowest exposure	15 (11 publications) breast cancer risk 8 (7 publications) premenopausal breast cancer risk 14 (11 publications) postmenopausal breast cancer risk
Studies included in linear dose-response meta-analysis	Insufficient data
Studies included in non-linear dose-response meta-analysis	Insufficient data

[1]Numbers of studies and publications identified overall. Included two pooled studies (Pot, 2014, UKDCC, four cohorts; Mannisto, 2005, three cohorts).

Table 9 A posteriori derived dietary patterns and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI) P trend	Heterogeneity (I^2, p value)
Meta-analyses							
Brennan, 2010	18 (10 cohorts, 8 case-control studies)	23 107	China, Canada, France, Italy, Japan, Sweden, the Netherlands, US, Uruguay	Incidence, breast cancer (any)	Highest vs lowest Western/unhealthy pattern Overall Cohort studies Case-control studies Prudent/healthy pattern Overall Cohort studies Case-control studies Drink pattern Overall	 1.09 (0.98-.122) 0.99 (0.90-1.08) 1.31 (1.04-1.63) 0.89 (0.82-0.99) 0.93 (0.88-0.98) 0.84 (0.67-1.04) 1.21 (1.04-1.41)	 68%, <0.001 35%, 0.13 63%, <0.001 71%, <0.001 0%, 0.51 85%, <0.001 (15%, 0.32)

*All cohort studies identified were included in the present review.

Table 10 A posteriori derived dietary patterns and breast cancer risk. Main characteristics of studies identified.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Catsburg, 2015 BRE80593 Canada (one	CNBSS, Prospective Cohort, Age: 40-59 years,	3 659/ 89 835 23 years	Cancer registry and death registry	86-item semi-quantitative FFQ, Healthy pattern	Incidence, Invasive breast cancer	Q5 vs Q1	0.84 (0.65-1.10) trend:0.199	Age, BMI, energy Intake, family history, physical activity, each	Included in the highest vs the lowest forest plot
		1 795/			Incidence, Invasive breast	Q5 vs Q1	0.90 (0.61-1.32) Ptrend:0.863		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
publication, two studies – CNBSS, CSDLH)	W			(CFA – Broccoli, cauliflower, green beans/snap beans, tomatoes, carrots, squash, zucchini, eggplant, lettuce, Brussels sprouts, onions, sweet potatoes, beets, bean or lentils, other vegetables)	cancer, Premenopausal			dietary pattern	
		1 864/			Incidence, Invasive breast cancer, Postmenopausal	Q5 vs Q1	0.82 (0.56-1.18) Ptrend:0.150		
		3 659/		Ethnic pattern (CFA – Spinach/green leafy vegetables, noncreamed soups, rice, oil in cooked vegetables, fish, egg, liver)	Incidence, Invasive breast cancer	Q5 vs Q1	1.20 (0.83-1.74) Ptrend:0.294		
		1 795/			Incidence, Invasive breast cancer, Premenopausal	Q5 vs Q1	0.90 (0.53-1.52) Ptrend:0.566		
		1 864/			Incidence, Invasive breast cancer, Postmenopausal	Q5 vs Q1	1.51 (0.90-2.53) Ptrend:0.067		
		3 659/		Meat and potatoes pattern (CFA – pork chop, roast beef, steak, pork roast, baked ham, potatoes, bacon)	Incidence, Invasive breast cancer	Q5 vs Q1	1.06 (0.86-1.31) Ptrend:0.552		
		1 795/			Incidence, Invasive breast cancer, Premenopausal	Q5 vs Q1	0.83 (0.61-1.12) Ptrend:0.172		
		1 864/			Incidence, Invasive breast	Q5 vs Q1	1.31 (0.98-1.76) Ptrend:0.043		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					cancer, Postmenopausal				
Catsburg, 2015 BRE80592 Canada (one publication, two studies – CNBSS, CSDLH)	CSDLH, Case Cohort, Age: 49-72 years, W	1 496/ 4 417 13 years	Cancer registry and death registry	86-item semi-quantitative FFQ, Healthy pattern (PCA factor loadings >0.3 – Broccoli, cauliflower, green beans/snap beans, tomatoes, carrots, squash, zucchini, eggplant, green pepper, lettuce, asparagus, Brussels sprouts, onions, sweet potatoes, beets, cucumber, bean or lentils, other vegetables)	Incidence, Invasive breast cancer	Q5 vs Q1	0.73 (0.58-0.91) Ptrend:0.001	BMI, energy Intake, family history, physical activity, each dietary pattern	Included in the highest vs the lowest forest plot
		591/			Incidence, Invasive breast cancer, Premenopausal	Q5 vs Q1	1.01 (0.75-1.37) Ptrend:0.725		
		625/			Incidence, Invasive breast cancer, Postmenopausal	Q5 vs Q1	0.84 (0.52-1.36) Ptrend:0.248		
		1 496/		Ethnic pattern (PCA factor loadings >0.3 – Spinach/green leafy vegetables, noncreamed soups, rice, oil in cooked vegetables, fish, egg, liver, tofu/tempeh, salted dried meat)	Incidence, Invasive breast cancer	Q5 vs Q1	1.18 (0.96-1.46) Ptrend:0.073		
		591/			Incidence, Invasive breast cancer, Premenopausal	Q5 vs Q1	1.16 (0.86-1.55) Ptrend:0.181		
		625/			Incidence, Invasive breast cancer, Postmenopausal	Q5 vs Q1	1.02 (0.75-1.39) Ptrend:0.752		
		1 496/		Meat and potatoes	Incidence,	Q5 vs Q1	1.13 (0.92-1.39)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
				pattern (PCA factor loadings >0.3 – pork chop, roast beef, steak, pork roast, baked ham, gravy, potatoes, bacon, meat stew)	Invasive breast cancer		Ptrend:0.275		
		591/			Incidence, Invasive breast cancer, Premenopausal	Q5 vs Q1	0.99 (0.73-1.34) Ptrend:0.240		
		625/			Incidence, Invasive breast cancer, Postmenopausal	Q5 vs Q1	1.26 (0.92-1.73) Ptrend:0.043		
Pot, 2014 UK	UKDCC, Pooled study of four cohorts* Mean age cases 56.6 years controls 57.2 years, W (*EPIC-Norfolk, EPIC-Oxford, UKWCS, Whitehall-II)	610 cases/ 1 891 controls	Record linkage with National Statistics and cancer registries	Food diaries, (PCA factor loadings >0.25 – cheese, crisps and savoury snacks, fresh fruit, legumes, low fat milk, nuts and seeds, other fruit, rice/pasta/other grains, sauces, vegetable mixed dishes, potatoes, poultry, red meat, water)	Incidence, breast cancer	T3 vs T1	1.18 (0.91-1.53) Ptrend: 0.19	Age, parity, HRT use, weight, height, physical activity, menopausal status	Included in the highest vs the lowest forest plot
		409 cases/ 1 360 controls			Incidence, postmenopausal breast cancer	T3 vs T1	1.27 (0.93-1.73) Ptrend: 0.13		
		610 cases/ 1 891 controls		RRR – High alcohol pattern	Incidence, breast cancer	T3 vs T1	1.27 (1.00-1.62) Ptrend:0.04		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		409 cases/ 1 360 controls		(Scores >0.2 – Total wines, spirits, and beers and ciders)	Incidence, postmenopausal breast cancer	T3 vs T1	1.46 (1.08-1.98) Ptrend:0.01		
		610 cases/ 1 891 controls		RRR – High fibre pattern (Scores >0.2 – Fresh fruit, vegetables raw and boiled, high fibre bread, high fibre breakfast cereals, legumes, yoghurts)	Incidence, breast cancer	T3 vs T1	1.08 (0.84-1.38) Ptrend:0.55		
		409 cases/ 1 360 controls			Incidence, postmenopausal breast cancer	T3 vs T1	1.23 (0.91-1.66) Ptrend:0.18		
Link, 2013 BRE80489 USA	CTS, Prospective Cohort, Age: 50 years, W	4 140/ 91 779 14.1 years	Cancer registry	103-item FFQ Plant-based pattern (PCA factor loadings ≥0.35 – peaches, apricots (fresh and dry), strawberries, other berries, carrots, mixed vegetables with carrots, apples, apple sauce, other fruit, oranges, broccoli, bananas, watermelon, cantaloupe, other vegetables, string beans, green beans, peas, cauliflower, Brussels sprouts)	Incidence, Invasive breast cancer	Q5 vs Q1	0.85 (0.76-0.95) Ptrend:0.003	Age, age at menarche, BMI, dietary preference, energy Intake, family history of breast cancer, height, history of benign breast disease, HRT use, menopausal status, parity and age at first birth, physical activity, race/ethnicity, socio-economic status	Included in the highest vs the lowest forest plot
		2 422/			ER+PR+ breast	Q5 vs Q1	0.91 (0.78-1.05)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					cancer		Ptrend:0.19		
		509/			ER+PR- breast cancer	Q5 vs Q1	1.03 (0.74-1.41) Ptrend:0.94		
		514/			ER-PR- breast cancer	Q5 vs Q1	0.66 (0.48-0.91) Ptrend:0.03		
		4 140/		High-protein, high-fat pattern (PCA factor loadings ≥0.35 – Butter, margarine, or fat added to vegetables, beef roasts, steaks, sandwiches, sausage, bacon, pork, hamburgers, cheeseburgers, fried chicken, beef stew or pot pie with vegetables, eggs, fried potatoes, butter on bread or rolls, salad dressing or mayonnaise)	Incidence, Invasive breast cancer	Q5 vs Q1	1.00 (0.88-1.14) Ptrend:0.60		Included in the highest vs the lowest forest plot
		2 422/			ER+PR+ breast cancer	Q5 vs Q1	1.02 (0.86-1.21) Ptrend:0.52		
		509/			ER+PR- breast cancer	Q5 vs Q1	0.90 (0.62-1.31) Ptrend:0.70		
		514/			ER-PR- breast cancer	Q5 vs Q1	1.02 (0.70-1.47) Ptrend:0.64		
		4 140/		High-carbohydrate pattern (PCA factor loadings ≥0.35 – Fried potatoes, burritos or tacos with	Incidence, Invasive breast cancer	Q5 vs Q1	0.91 (0.79-1.05) Ptrend:0.11		Included in the highest vs the lowest forest plot
		2 422/			ER+PR+ breast cancer	Q5 vs Q1	0.91 (0.76-1.10) Ptrend:0.26		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		509/		meat or beans, pizza, salsa, ketchup, taco sauce, tortillas, spaghetti, lasagne, other pasta with tomato sauce, bagels, English muffins, hamburger buns)	ER+PR- breast cancer	Q5 vs Q1	0.69 (0.45-1.06) Ptrend:0.05		
		514/			ER-PR- breast cancer	Q5 vs Q1	0.99 (0.66-1.48) Ptrend:0.88		
		4 140/		Ethnic pattern (PCA factor loadings ≥0.35 – Lentil, pea, and bean soups, bean, tofu, bean curd, vegetable soups, rice, meat substitutes made from soy, mustard turnip greens, collards, sweet potatoes, yams)	Incidence, Invasive breast cancer	Q5 vs Q1	0.94 (0.85-1.05) Ptrend:0.24		Included in the highest vs the lowest forest plot
		2 422/			ER+PR+ breast cancer	Q5 vs Q1	0.89 (0.78-1.02) Ptrend:0.07		
		509/			ER+PR- breast cancer	Q5 vs Q1	1.03 (0.76-1.40) Ptrend:0.45		
		514/			ER-PR- breast cancer	Q5 vs Q1	1.06 (0.79-1.42) Ptrend:0.89		
		4 140/		Salad and wine pattern (PCA factor loadings ≥0.35 – Green salad, fish, wine, champagne, salad dressing or mayonnaise (low-fat), coffee, tea, tomatoes, tomato juice)	Incidence, Invasive breast cancer	Q5 vs Q1	1.12 (1.01-1.25) Ptrend:0.01		Included in the highest vs the lowest forest plot
		2 422/			ER+PR+ breast cancer	Q5 vs Q1	1.29 (1.12-1.49) Ptrend:<0.001		
		509/			ER+PR- breast cancer	Q5 vs Q1	1.10 (0.80-1.50) Ptrend:0.22		
		514/			ER-PR- breast cancer	Q5 vs Q1	0.85 (0.63-1.14) Ptrend:0.41		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Fung, 2012 BRE80403 USA	NHS, Prospective Cohort, Age: 30-55 years, W, nurses	4 596/ 67 802 22 years	Self report verified by medical record	FFQ, Estrogen food pattern RRR – food groups correlated with estradiol and estrone sulphate levels in participants (red meat, coffee, legumes, whole grains, pizza)	Incidence, postmenopausal breast cancer	Q5 vs Q1	0.95 (0.86-1.05) Ptrend:0.47	Age, alcohol, benign breast disease, BMI at age 18 years, energy, HRT use, multivitamin supplement Intake, physical activity, weight change	Included in the highest vs the lowest forest plot
		2 938/			Incidence, postmenopausal ER+ breast cancer	Q5 vs Q1	0.94 (0.83-1.07) Ptrend:0.36		
		689/			Incidence, postmenopausal ER- breast cancer	Q5 vs Q1	1.03 (0.79-1.34) Ptrend:0.73		
Baglietto, 2011 BRE80328 Australia	MCCS, Prospective Cohort, Age: 31-76 years, W	815/ 20 967 14 years	Record linkages with the cancer registry/death and population registry	121-item FFQ, plus olive and vegetable oil, alcohol from wine Vegetables pattern (PCA factor loadings >0.2 – Boiled rice, white bread, wholemeal bread, yoghurt, boiled chicken, chicken dish, fish, tomato, capsicum, salad	Incidence, breast cancer	Q5 vs Q1	0.98 (0.76-1.28) Ptrend:0.97	Age at menarche, alcohol Intake, BMI, country of birth, duration of lactation, educational level, HRT use, menopausal status, oral contraceptive history, parity, physical	Included in the highest vs the lowest forest plot

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
				greens, cucumber, celery/fennel, beetroot, coleslaw, potato cooked without fat, carrot, cabbage/brussels sprouts, cauliflower, broccoli, leafy greens, green beans/peas, cooked dried legumes, pumpkin, onion/leek, mushroom, sweet corn, zucchini/squash/eggplant , vegetable dish, fruit salad, banana)				activity, smoking, total energy Intake	
		575/			ER+ breast cancer	Q5 vs Q1	1.04 (0.75-1.43) Ptrend:0.6		
		202/			ER- breast cancer	Q5 vs Q1	0.92 (0.55-1.55) Ptrend:0.53		
		426/			PR+ breast cancer	Q5 vs Q1	1.06 (0.74-1.53) Ptrend:0.47		
		349/			PR- breast cancer	Q5 vs Q1	0.98 (0.64-1.48) Ptrend:0.61		
					Breast cancer, Attained age ≤55 year during follow-up	Q5 vs Q1	1.23 (0.74-2.05) Ptrend:0.72		
					Breast cancer, Attained age >55 year during follow-up	Q5 vs Q1	0.93 (0.69-1.24) Ptrend:0.84		
				Fruit and salad pattern (PCA factor loadings >0.2 – Salad greens, cucumber, fruit salad, orange/mandarin, apple, banana, peach/nectarine, pear)	Incidence, breast cancer	Q5 vs Q1	0.81 (0.63-1.03) Ptrend:0.03		Included in the highest vs the lowest forest plot
		575/			ER+ breast cancer	Q5 vs Q1	0.92 (0.69-1.22) Ptrend:047		
		202/			ER- breast cancer	Q5 vs Q1	0.55 (0.32-0.93) Ptrend:0.004		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		426/			PR+ breast cancer	Q5 vs Q1	0.92 (0.66-1.28) Ptrend:0.58		
		349/			PR- breast cancer	Q5 vs Q1	0.67 (0.46-0.98) Ptrend:0.01		
					Breast cancer, Attained age ≤55 year during follow-up	Q5 vs Q1	0.66 (0.40-1.07) Ptrend:0.10		
					Breast cancer, Attained age >55 year during follow-up	Q5 vs Q1	0.86 (0.65-1.13) Ptrend:0.11		
				Traditional Australian pattern (PCA factor loadings >0.2 – Olive oil, sweet biscuits, cakes/sweet pastries, puddings, pasta/noodle dish, cheese, ice cream, custard, cream/sour cream, margarine, beef/veal schnitzel, lamb roast/chops, sausage/frankfurter, bacon, steamed fish, legume soup, tomato, capsicum, salad greens, cucumber, celery/fennel, potato cooked without	Incidence, breast cancer	Q5 vs Q1	1.25 (0.90-1.74) Ptrend:0.24		Included in the highest vs the lowest forest plot
		575/			ER+ breast cancer	Q5 vs Q1	1.19 (0.81-1.74) Ptrend:0.39		
		202/			ER- breast cancer	Q5 vs Q1	1.51 (0.69-3.33) Ptrend:0.34		
		426/			PR+ breast cancer	Q5 vs Q1	1.40 (0.89-2.19) Ptrend:0.11		
		349/			PR- breast cancer	Q5 vs Q1	1.25 (0.71-2.21) Ptrend:0.73		
					Breast cancer, Attained age ≤55 year during follow-up	Q5 vs Q1	1.58 (0.87-2.85) Ptrend:0.04		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
				fat, green beans/pea, cooked dried legumes, pumpkin)	Breast cancer, Attained age >55 year during follow-up	Q5 vs Q1	1.17 (0.82-1.66) Ptrend:0.64		
				Meat pattern (PCA factor loadings >0.2 – fried rice, white bread, pizza, savoury pastries, feta cheese, fried egg, egg dish, beef and beef dish, roast/fried chicken, lamb and lamb dish, pork roast/chops, salami, bacon, fried fish, pickled vegetables, potato cooked in fat)	Incidence, breast cancer	Q5 vs Q1	1.12 (0.85-1.46) Ptrend:0.45		Included in the highest vs the lowest forest plot
		575/			ER+ breast cancer	Q5 vs Q1	1.21 (0.88-1.66) Ptrend:0.66		
		202/			ER- breast cancer	Q5 vs Q1	0.86 (0.50-1.47) Ptrend:0.48		
		426/			PR+ breast cancer	Q5 vs Q1	1.13 (0.78-1.64) Ptrend:0.60		
		349/			PR- breast cancer	Q5 vs Q1	1.04 (0.69-1.55) Ptrend:0.69		
					Breast cancer, Attained age ≤55 year during follow-up	Q5 vs Q1	1.50 (0.88-2.55) Ptrend:0.11		
					Breast cancer, Attained age >55 year during follow-up	Q5 vs Q1	1.03 (0.77-1.38) Ptrend:0.93		
Butler, 2010 BRE80295 Singapore	SCHS, Prospective Cohort, Age: 45-74 years,	629/ 34 028 10.7 years	Cancer registry	165-item FFQ, Vegetable-fruit-soy pattern	Incidence, breast cancer	Q4 vs Q1	0.82 (0.63-1.05) Ptrend:0.03	Age, BMI, dialect group, educational level, energy Intake, family	Included in the highest vs the lowest forest plot

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	W			(PCA factor loadings ≥0.3 – 23 vegetables, 5 soy foods, and 5 fruits)				history of cancer, parity, year of Interview	
		190/			Premenopausal breast cancer	Q4 vs Q1	1.09 (0.68-1.73) Ptrend:0.91		
		439/			Postmenopausal breast cancer	Q4 vs Q1	0.70 (0.51-0.95) Ptrend:0.01		
		184/			Postmenopausal ER+ breast cancer	Q4 vs Q1	0.69 (0.43-1.10) Ptrend:0.06		
		143/			Postmenopausal PR- breast cancer	Q4 vs Q1	0.71 (0.42-1.19) Ptrend:0.12		
		57/			Postmenopausal ER+/PR- breast cancer	Q4 vs Q1	0.50 (0.22-1.13) Ptrend:0.08		
		629/		Meat-dim sum (PCA – factors loadings ≥0.3 – 7 meat items, 12 dim sum items, 4 starch items, 3 combined meat-starch items, 1 egg item)	Incidence, breast cancer	Q4 vs Q1	0.84 (0.65-1.10) Ptrend:0.35		Included in the highest vs the lowest forest plot
		190/			Premenopausal breast cancer	Q4 vs Q1	0.79 (0.50-1.26) Ptrend:0.28		
		439/			Postmenopausal breast cancer	Q4 vs Q1	0.85 (0.62-1.17) Ptrend:0.73		
Agurs-Collins, 2009 BRE80239 USA	BWHS, Prospective Cohort, Age: 21-69	1 094/ 50 778 443 742 person-	Self report verified by medical record	69-item FFQ, Western pattern	Incidence, breast cancer	Q5 vs Q1	1.06 (0.81-1.37) Ptrend:0.86	Age, age at first child, age at menarche, alcohol	Included in the highest vs the lowest forest plot

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	years, W	years		(PCA factor loadings ≥0.4 – Refined grains, high-fat dairy products, total meat, processed meat, eggs, margarine, butter, and mayonnaise, potato, French fries, sweets, soda, snacks)				consumption, BMI, educational level, energy Intake, family history of cancer, HRT use, menopausal status, physical activity, smoking status	
		509/			Incidence, breast cancer, premenopausal	Q5 vs Q1	1.14 (0.80-1.61) Ptrend:0.70		
		442/			Incidence, breast cancer, postmenopausal	Q5 vs Q1	0.95 (0.60-1.49) Ptrend:0.62		
		1094/		Prudent pattern (PCA factor loadings ≥0.4 – Cruciferous vegetables, other vegetables, tomatoes, fruit, whole grains, fish, soup, beans)	Incidence, breast cancer	Q5 vs Q1	0.86 (0.68-1.08) Ptrend:0.06		Included in the highest vs the lowest forest plot
		509/			Incidence, breast cancer, premenopausal	Q5 vs Q1	0.70 (0.52-0.96) Ptrend:0.01		
		442/			Incidence, breast cancer, postmenopausal	Q5 vs Q1	1.19 (0.76-1.84) Ptrend:0.66		
		229/			Incidence, ER- breast cancer	Q5 vs Q1	0.52 (0.28-0.94) Ptrend<0.01		
		304/			Incidence, PR- breast cancer	Q5 vs Q1	0.66 (0.39-1.09) Ptrend:0.03		
					Incidence, ER- PR- breast cancer	Q5 vs Q1	0.66 (0.34-1.26) Ptrend:0.04		
Cottet, 2009 BRE80233 France	E3N EPIC-France, Prospective Cohort,	2 381/ 65 374 9.7 years	Self report verified by medical record	Diet history questionnaire Alcohol/Western pattern	Incidence, breast cancer, postmenopausal	4 vs 1 score	0.85 (0.75-0.95) Ptrend:0.003	Age, age at first child birth, age at menarche, area, benign	Included in the highest vs the lowest forest plot

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	W, Postmenopausal			(PCA factor loadings >0.25 – Potatoes, pulses, rice, pasta, semolina, French fries, appetizers, pizza, pies, sandwiches, cakes, processed meat, ham, offal, eggs, canned fish, crustanceans, mayonnaise, butter, cream, high-alcohol beverages, wine)				breast disease, BMI, breastfeeding, educational level, energy Intake, family history of cancer, height, HRT use, lobular carcinoma In situ, ocp use, pap smears, physical activity, smoking habits, supplement Intake, supplement use	
		1 084/			Incidence, postmenopausal breast cancer ER+/PR+	4 vs 1 score	1.33 (1.07-1.65) Ptrend:0.005		
		299/			Incidence, postmenopausal breast cancer ER-/PR-	4 vs 1 score	0.84 (0.56-1.27) Ptrend:0.56		
		60/			Incidence, postmenopausal breast cancer ER-/PR+	4 vs 1 score	0.75 (0.32-1.79) Ptrend:0.42		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		404/			Incidence, postmenopausal breast cancer ER+/PR-	4 vs 1 score	1.38 (0.97-1.97) Ptrend:0.09		
		2 381/		Healthy/Mediterranean pattern (PCA factor loadings >0.25 – Fruits, raw vegetables, cooked vegetables, crustaceans, fish, olive oil, sunflower oil)	Incidence, breast cancer, postmenopausal	4 vs 1 score	1.20 (1.03-1.38) Ptrend:0.007		Included in the highest vs the lowest forest plot
		1 084/			Incidence, postmenopausal breast cancer ER+/PR+	4 vs 1 score	0.88 (0.74-1.05) Ptrend:0.13		
		299/			Incidence, postmenopausal breast cancer ER-/PR-	4 vs 1 score	0.78 (0.56-1.10) Ptrend:0.17		
		62/			Incidence, postmenopausal breast cancer ER-/PR+	4 vs 1 score	1.18 (0.58-2.42) Ptrend:0.71		
		404/			Incidence, postmenopausal breast cancer ER+/PR-	4 vs 1 score	0.65 (0.49-0.87) Ptrend:0.001		
Engeset, 2009 BRE80213 Norway	EPIC-Norway, Prospective Cohort, Age: 48 years, W	546/ 34 471 7 years	Cancer registry	86-item semi-quantitative FFQ, 50-item used in analysis Traditional fish eaters	Incidence, breast cancer	fish pattern vs average	1.04 (0.66-1.62)	Age, alcohol, energy Intake, oral contraceptive use, smoking status	Included in the highest vs the lowest forest plot

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		284/		(PCA, factor loadings ≥0..3 – High in boiled coffee , potatoes , lean, white fish , fish products , carrots , fatty fish , fish on bread , sour cream, with fat on fish , sour cream, reduced fat on fish , sour cream, without fat on fish , melted fat on fish , fish roe , sour cream, full fat on fish , fish liver and low in pasta , rice , pizza with meat , chocolate , salty snack , white bread) Average, less fish, less healthy (PCA, factor loadings ≥0..3 – Low in course bread , vegetables, except carrots , juice , fish products , carrots , lean, white fish , cheese , fatty fish , egg , fat on bread , meat on bread , fish on bread , cod liver oil)	Incidence, breast cancer, premenopausal	fish pattern vs average	0.94 (0.45-1.95)		
		262/			Incidence, breast cancer, postmenopausal	fish pattern vs average	1.14 (0.64-2.00)		
		546/		Healthy	Incidence, breast	healthy pattern	1.12 (0.85-1.47)		Included in the

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					cancer	vs average			highest vs the lowest forest plot
		284/		(PCA, factor loadings ≥0..3 – High in fruit , vegetables, except carrots , juice , skimmed milk , instant coffee , yoghurt , rice , breakfast cereal , chicken , crisp bread , cod liver oil and low in filtered coffee , potatoes , semi-skimmed milk , meat products , boiled coffee , soft drink with sugar , red meat , whole milk , sauce with fat on fish , melted fat on fish , sour cream, full fat on fish)	Incidence, breast cancer, premenopausal	healthy pattern vs average	0.96 (0.65-1.44)		
		262/			Incidence, breast cancer, postmenopausal	healthy pattern vs average	1.29 (0.88-1.88)		
		546/		Western (PCA, factor loadings ≥0..3 – High in meat products , soft drink with sugar , bakery product , dessert , pizza with meat , chocolate , salty snack.)	Incidence, breast cancer	western pattern vs average	1.37 (0.99-1.89)		Included in the highest vs the lowest forest plot
		284/			Incidence, breast cancer, premenopausal	western pattern vs average	1.28 (0.84-1.96)		
		262/			Incidence, breast cancer, postmenopausal	western pattern vs average	1.49 (0.90-2.46)		
		546/		Traditional bread eaters (PCA, factor loadings ≥0..3 – High in course	Incidence, breast cancer	bread pattern vs average	1.13 (0.84-1.53)		Included in the highest vs the lowest forest plot
		284/			Incidence, breast cancer,	bread pattern vs average	1.13 (0.76-1.70)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
				bread , semi-skimmed milk , cheese , jam , whole milk and low in skimmed milk , instant coffee , soft drink without sugar , beer , chicken , wine , shellfish , liquor)	premenopausal				
		262/			Incidence, breast cancer, postmenopausal	bread pattern vs average	1.13 (0.72-1.77)		
		546/		Alcohol users (PCA, factor loadings ≥0..3 – High in filtered coffee , beer , soft drink without sugar , wine , red meat , egg , fat on bread , meat on bread , white bread , shellfish , liquor and low in fruit , bakery product , yoghurt , dessert , jam , crisp bread , rice porridge , breakfast cereal)	Incidence, breast cancer	alcohol pattern vs average	1.01 (0.71-1.45)		Included in the highest vs the lowest forest plot
		284/			Incidence, breast cancer, premenopausal	alcohol pattern vs average	0.86 (0.51-1.45)		
		262/			Incidence, breast cancer, postmenopausal	alcohol pattern vs average	1.19 (0.73-1.93)		
Schulz, 2008 BRE80160 Germany	EPIC, Prospective Cohort, Age: 35-65 years, W	137/ 15 351 6 years	Cancer registry and mortality registry	148-item FFQ-semi-quantitative High fat pattern (RRR - low consumption of bread, and fruit juices, and high consumption of processed meat, fish, butter and other animal	Incidence, breast cancer	≥0.7 vs ≤-0.85	2.34 (1.45-3.79) Ptrend:0.0004	Age, age at menarche, alcohol consumption, beta carotene, BMI, diet, educational level, energy Intake, fibre, HRT use,	Included in the highest vs the lowest forest plot

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
				fats, and margarine explaining .42% of total variation in fatty acid intake (SFA, MUFA, n-3 PUFA, n-6 PUFA)				menopausal status, parity, smoking status, vitamin c, vitamin e	
Sant, 2007 BRE80036 Italy	ORDET, Prospective Cohort, Age: 34-70 years, W	40/ 8 861 11.5 years	Cancer registry	107-item FFQ, Salad vegetables (Factor analysis - High in raw vegetables and olive oil)	Incidence, breast cancer HER-2 +	T3 vs T1	0.25 (0.10-0.64) Ptrend:0.001	Age , age at menarche, body weight, canteen diet, educational level, energy Intake , height, menopausal status, parity/pregnancies, salad vegetable diet, smoking habits, western diet	Excluded, results by HER2 status only
		198/			Incidence, breast cancer HER-2 -	T3 vs T1	0.71 (0.48-1.03) Ptrend:0.072		
		40/		Western pattern (Factor analysis - High in potatoes, ravioli, red and processed meat, eggs, butter, seed oil (as added fat) and cakes)	Incidence, breast cancer HER-2 +	T3 vs T1	0.75 (0.27-2.08) Ptrend:0.584		
		198/			Incidence, breast cancer HER-2 -	T3 vs T1	0.88 (0.55-1.40) Ptrend:0.651		
		40/		Canteen pattern (Factor analysis - High in pasta, tomato sauce, olive oil and wine)	Incidence, breast cancer HER-2 +	T3 vs T1	1.39 (0.50-3.84) Ptrend:0.530		
		198/			Incidence, breast cancer HER-2 -	T3 vs T1	1.14 (0.75-1.75) Ptrend:0.520		
		40/		Prudent pattern (Factor analysis - Cooked vegetables, rice, poultry, fish and low consumption of alcohol)	Incidence, breast cancer HER-2 +	T3 vs T1	0.72 (0.35-1.48) Ptrend:0.372		
		198/			Incidence, breast cancer HER-2 -	T3 vs T1	1.36 (0.93-1.98) Ptrend:0.126		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Adebamowo, 2005 BRE21538 USA	NHS II, Prospective Cohort, Age: 26-46 years, W, Registered nurses	710/ 90 638 9 years	Pathology report + self-reported	142-item FFQ-semi-quantitative, Prudent pattern (PCA factor loadings ≥0.15 – Dark yellow, cruciferous, or leafy vegetables, other vegetables, fruit, legumes, tomatoes, fish, poultry, onions, whole grains, salad dressing, fruit juice, low-fat dairy, garlic, refined grains, potatoes, snacks, nuts)	Incidence, Invasive breast cancer, premenopausal	Q5 vs Q1	0.90 (0.68-1.18) Ptrend:0.36	Age at first child, age at menarche, alcohol, benign breast disease, BMI, energy Intake , family history, height, OC use, parity/pregnancies, physical activity , smoking habits, supplements	Included in the highest vs the lowest forest plot
				Western pattern (PCA factor loadings ≥0.15 – Legumes, poultry, refined grains, desserts, red meat, processed meats, French fries, pizza, potatoes, snacks, eggs, high-sugar drinks, margarine, high-fat dairy products, mayonnaise, nuts, cream soup, condiments, butter)		Q5 vs Q1	0.97 (0.71-1.33) Ptrend:0.97		
Fung, 2005 BRE22370 USA	NHS, Prospective Cohort,	3 026/ 71 058 16 years	Medical records + self-reported	116-item FFQ, Prudent pattern	Incidence, breast cancer, postmenopausal	Q5 vs Q1	0.97 (0.86-1.11) Ptrend:0.43	Age , age at first child, age at menarche, age at	Included in the highest vs the lowest forest

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Age: 30-55 years, W, Registered nurses			(Factors loadings ≥0.15 – High intake of other vegetables, Leafy vegetables, Cruciferous vegetables, Fruit, Yellow vegetables, Legumes, Fish, Tomatoes, Poultry, Whole grain products, Low-fat dairy products, Salad dressings, Fruit juice, Organ meat, garlic)				menopause, alcohol, benign breast disease, BMI, energy Intake , family history, height, HRT use, menopausal status, other anthropometric Index, parity/pregnancies, physical activity , smoking habits, supplements	plot
		1 728/			Incidence, ER+ breast cancer, postmenopausal	Q5 vs Q1	1.10 (0.93-1.31) Ptrend:0.77		
		446/			Incidence, ER- breast cancer, postmenopausal	Q5 vs Q1	0.62 (0.45-0.88) Ptrend:0.006		
		3 026/		Western pattern (Factors loadings ≥0.15 – High intake Refined grains, Desserts and sweets, Processed meats, Red meats, French fries, Condiments, Potatoes, Pizza, Full-fat dairy products, Sweetened beverages, Mayonnaise, Margarine, Snacks, Eggs, Cream soup, butter, tea and French fries)	Incidence, breast cancer, postmenopausal	Q5 vs Q1	0.97 (0.83-1.14) Ptrend:0.88		
		1 728/			Incidence, ER+ breast cancer, postmenopausal	Q5 vs Q1	1.00 (0.81-1.24) Ptrend:0.83		
		446/			Incidence, ER- breast cancer, postmenopausal	Q5 vs Q1	1.18 (0.77-1.82) Ptrend:0.85		
Mannisto, 2005 The	DIETSCAN Pooled study,	1 127/ 1 598	National or local cancer	150-item semi-quantitative FFQs	Incidence, invasive breast	Q4 vs Q1	0.90 (0.67-1.20) Ptrend:0.31	Age, body mass index, height,	Included in the highest vs the

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Netherlands, Italy, Sweden	NLCS, Case Cohort, Age: 55-69 years W	7 years	registers	Vegetables pattern (PCA ≥0.35 factor loadings – Legumes, cabbages, leaf vegetables, allium, carrots, tomatoes, tomatoes, mushrooms, rice, pasta, oil)	cancer	Per 1 unit	0.93 (0.84-1.04)	education, smoking (current smoking status, number of cigarettes/day, years smoked), family history of breast cancer, age at menarche, age at menopause, age at first birth, ever use of oral contraceptive, ever use of hormone replacement therapy, alcohol intake and energy	lowest forest plot
				Pork, processed meat, potatoes pattern		Q4 vs Q1	0.69 (0.52-0.92) Ptrend:0.02		
				(PCA ≥0.35 factor loadings – Pork, processed meat, coffee, butter, low-fat margarine)		Per 1 unit	0.90 (0.81-0.99)		
	DIETSCAN Pooled study, ORDET Prospective Cohort, Age: 35-69 years W	212/ 10 788 9 years		107-item FFQ, Vegetables pattern (PCA ≥0.35 factor loadings – leaf vegetables (raw), carrots, tomatoes, oil, dressings)	Incidence, invasive breast cancer	Q4 vs Q1	0.79 (0.50-1.27) Ptrend:0.32	Age, body mass index, height, education, smoking (status), family history of breast cancer, ever use of oral contraceptive, ever use of hormone replacement	Included in the highest vs the lowest forest plot
						Per 1 unit	0.88 (0.72-1.07)		
				Pork, processed meat, potatoes pattern		Q4 vs Q1	1.07 (0.58-1.98) Ptrend:0.95		
						Per 1 unit	0.93 (0.70-1.22)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
				(PCA ≥0.35 factor loadings Processed meat, potatoes, beef and veal, butter)				therapy, alcohol intake and energy	
	DIETSCAN Pooled study, SMC Prospective Cohort, Age: 40-74 years W, Mammography screening study	1 932/ 61 463 13 years		67-item FFQ, Vegetables pattern (PCA ≥0.35 factor loadings leaf vegetables (raw), carrots, tomatoes, oil, dressings)	Incidence, invasive breast cancer	Q4 vs Q1	0.91 (0.79-1.05) Ptrend:0.19	Age, BMI, education, family history of breast cancer, age at first birth, parity, alcohol intake and energy	Included in the highest vs the lowest forest plot
						Per 1 unit	0.97 (0.91-1.03)		
				Pork, processed meat, potatoes pattern (PCA ≥0.35 factor loadings Pork, processed meat, beef and veal, pasta, rice, poultry, liver)		Q4 vs Q1	0.92 (0.78-1.09) Ptrend:0.47		
						Per 1 unit	1.02 (0.94-1.14)		
Velie, 2005 BRE24436 USA	BCDDP, Prospective Cohort, W, Postmenopausal	1 868/ 40 559 8 years	Partially histological - over 80%	61-item FFQ, Vegetable-fish/poultry-fruit pattern (PCA factor loadings ≥0.2 – Green salad, broccoli, fish, chicken, carrot and mixed vegetables, tomatoes and tomato juice, spinach, apple, applesauce, pears,	Incidence, breast cancer, postmenopausal	Q5 vs Q1	1.03 (0.88-1.20) Ptrend:0.95	Age , age at first child, age at menarche, alcohol, BMI, educational level, energy Intake , family history, height, HRT use, parity/pregnancies, physical activity , smoking habits	Included in the highest vs the lowest forest plot

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
				coleslaw, cabbage, sauerkraut, grapefruit, cantaloupe, oranges, doughnuts, cookies, and cakes, ice cream, pies, 2% fat milk, chocolate, white bread, cereal)					
		1 868/		Beef/pork-starch pattern (PCA factor loadings ≥0.2 – pork, beef, bacon, hamburger, French fries and fried potatoes, sausage, fried chicken, hot dogs, eggs, liver, ham and lunch meats, beef stew and pot pie, bran and granola cereal, skim milk, chicken, fish, dark bread, cooked cereal, apples)	Incidence, breast cancer, postmenopausal	Q5 vs Q1	1.03 (0.89-1.20) Ptrend:0.7		Included in the highest vs the lowest forest plot
		1 868/		Traditional southern pattern (PCA factor loadings ≥0.2 – Cooked greens, beans and legumes, sweet potatoes, corn bread, muffins, tortillas, coleslaw, cabbage, and	Incidence, breast cancer, postmenopausal	Q5 vs Q1	0.89 (0.76-1.05) Ptrend:0.21		Included in the highest vs the lowest forest plot
		850/			Incidence, breast cancer ER+, postmenopausal	Q5 vs Q1	0.75 (0.59-0.96) Ptrend:0.01		
		186/			Incidence, breast	Q5 vs Q1	0.78 (0.46-1.34)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
				sauerkraut, fried fish, cooked cereal, rice, fried chicken, beef stew and pot pie, fruit drinks, carrots and mixed vegetables, cheese and cheese spread, mayonnaise and salad dressing, wine, liquor, salty snacks)	cancer ER-, postmenopausal		Ptrend:0.41		
		715/			Incidence, breast cancer PR+, postmenopausal	Q5 vs Q1	0.69 (0.53-0.89) Ptrend:0.003		
		294/			Incidence, breast cancer PR-, postmenopausal	Q5 vs Q1	0.91 (0.60-1.36) Ptrend:0.36		
		679/			Incidence, breast cancer ER+PR+, postmenopausal	Q5 vs Q1	0.70 (0.53-0.91) Ptrend:0.01		
		146/			Incidence, breast cancer ER-PR-, postmenopausal	Q5 vs Q1	0.82 (0.45-1.49) Ptrend:0.53		
		35/			Incidence, breast cancer ER-PR+, postmenopausal	Q5 vs Q1	0.46 (0.11-1.86) Ptrend:0.33		
		146/			Incidence, breast cancer ER+PR-, postmenopausal	Q5 vs Q1	0.99 (0.56-1.73) Ptrend:0.55		
Sieri, 2004 BRE16671 Italy	ORDET, Prospective Cohort, Age: 34-70 years, W	207/ 8 984 9.5 years	Partially histological - over 80%	107- item FFQ- quantitative Salad vegetables pattern (Factor loadings >0.25 – mixed vegetables, raw and cooked leaf vegetables, raw	Incidence, Invasive breast cancer	T3 vs T1	0.66 (0.47-0.95) Ptrend:0.016	Age , age at menarche, educational level, energy Intake , height, menopausal status, parity/pregnancies, smoking	Superseded by Mannisto, 2005

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
				tomatoes, other fruiting vegetables, raw carrots, olive oil)				habits	
				Western pattern (Factor loadings >0.25 – Potatoes, other pasta, beef, veal, pork, processed meat, offal, eggs, seed oils, butter, cakes)		T3 vs T1	0.90 (0.58-1.41) Ptrend:0.705		Superseded by Mannisto, 2005
				Canteen pattern (Factor loadings >0.25 – Cooked tomatoes, other fruiting vegetables, pulses, pasta, bread, veal, olive oil, wine)		T3 vs T1	0.95 (0.63-1.45) Ptrend:0.935		Included in the highest vs the lowest forest plot
				Prudent pattern (Factor loadings >0.25 – Potatoes, cooked leaf vegetables, other fruiting vegetables, raw and cooked carrots, pulses, yoghurt, rice, poultry, fish, olive oil, wine, spirits)		T3 vs T1	1.28 (0.90-1.83) Ptrend:0.169		Superseded by Mannisto, 2005

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Terry, 2001 BRE12203 Sweden	SMC, Prospective Cohort, Age: 40-76 years, W, Screening Program	1 328/ 61 463 9.6 years	Partially histological - over 80%	67-item FFQ, Healthy pattern (Vegetables, fruit, fish, wholegrains, low-fat dairy, poultry, cereal, eggs, juice, margarine, tea, sweets, meat)	Incidence, breast cancer	Q5 vs Q1	0.92 (0.76-1.13) Ptrend:0.52	Age , age at first child, BMI, educational level, energy Intake , family history, parity/pregnancies	Superseded by Mannisto, 2005
		420/			Incidence, breast cancer Premenopausal	Q5 vs Q1	0.91 (0.63-1.31) Ptrend:0.68		Included in the highest vs the lowest forest plot
		908/			Incidence, breast cancer Postmenopausal	Q5 vs Q1	0.91 (0.72-1.16) Ptrend:0.52		Included in the highest vs the lowest forest plot
		1 328/		Western pattern (Whole grains, eggs, processed meat, sweets, refined grains, half-fat dairy, meat, soda, potato, pea soup, coffee, snacks)	Incidence, breast cancer	Q5 vs Q1	1.00 (0.79-1.26) Ptrend:0.92		Superseded by Mannisto, 2005
		420/			Incidence, breast cancer Premenopausal	Q5 vs Q1	1.08 (0.70-1.67) Ptrend:0.95		Included in the highest vs the lowest forest plot
		908/			Incidence, breast cancer Postmenopausal	Q5 vs Q1	0.98 (0.74-1.28) Ptrend:0.89		Included in the highest vs the lowest forest plot
		1 328/		Drinker pattern (Fish, whole grains, low-fat dairy, poultry, eggs,	Incidence, breast cancer	Q5 vs Q1	1.27 (1.06-1.52) Ptrend:0.002		Included in the highest vs the lowest forest plot

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment*	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		420/		margarine, tea, meat, potato, wine, liquor, beer snacks,)	Incidence, breast cancer Premenopausal	Q5 vs Q1	1.12 (0.79-1.58) Ptrend:0.35		Included in the highest vs the lowest forest plot
		908/			Incidence, breast cancer Postmenopausal	Q5 vs Q1	1.31 (1.05-1.63) Ptrend:0.002		Included in the highest vs the lowest forest plot

*CFA – confirmatory factor analysis; PCA – principal components factor analysis

Figure 10 RR (95% CI) of breast cancer for the highest compared with the lowest level of A posteriori derived dietary pattern

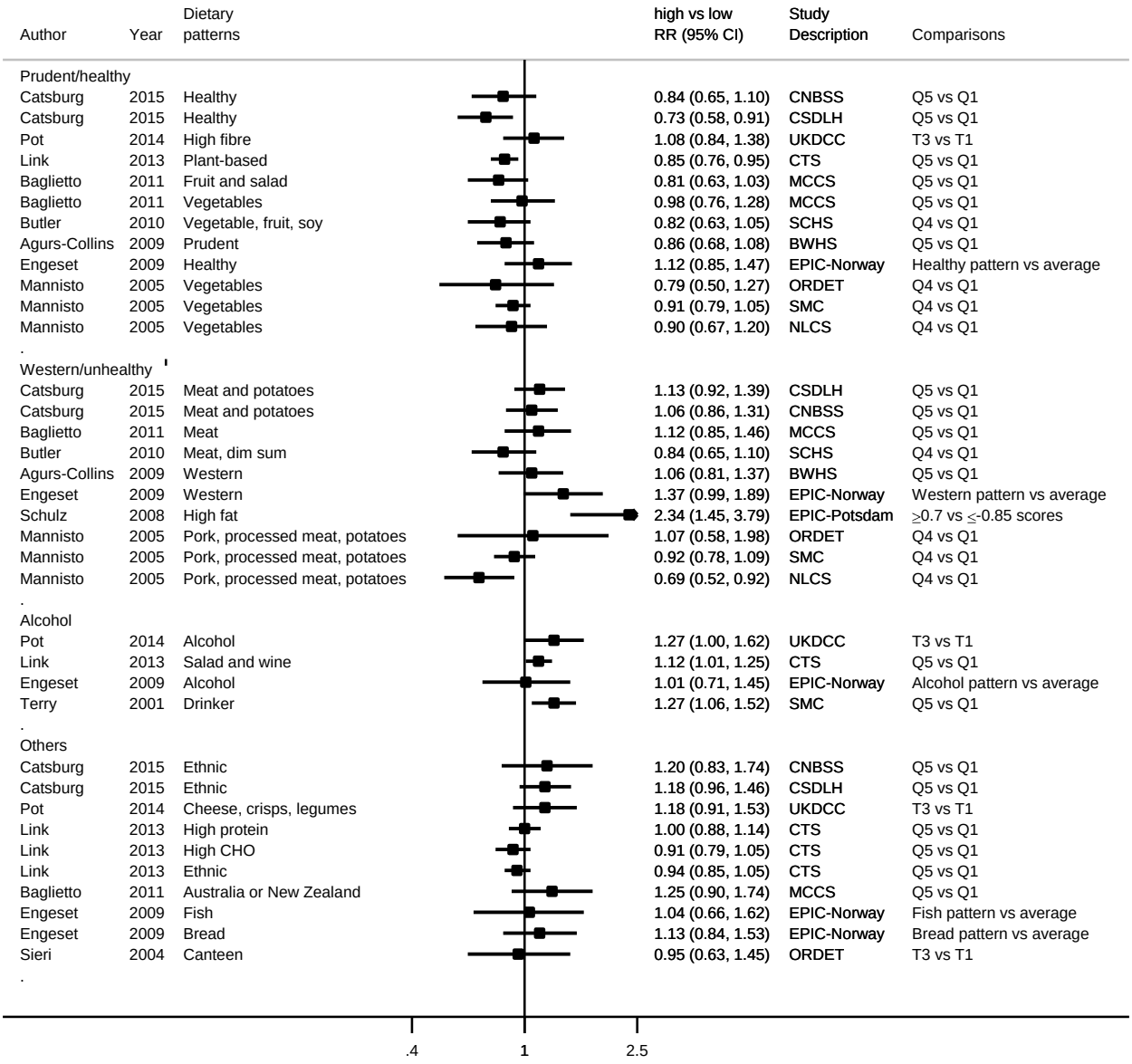


Figure 11 RR (95% CI) of premenopausal breast cancer for the highest compared with the lowest level of A posteriori derived dietary pattern

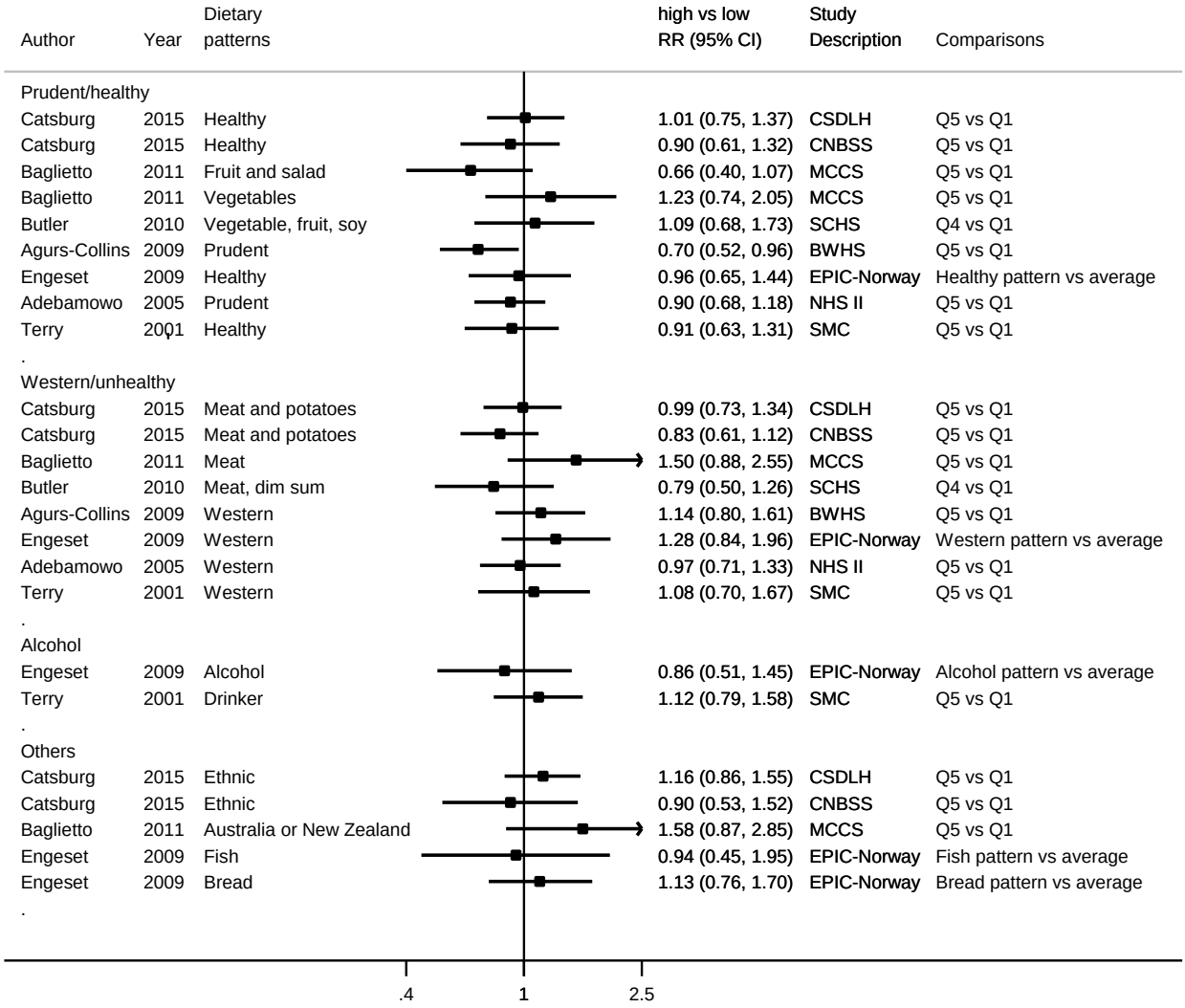
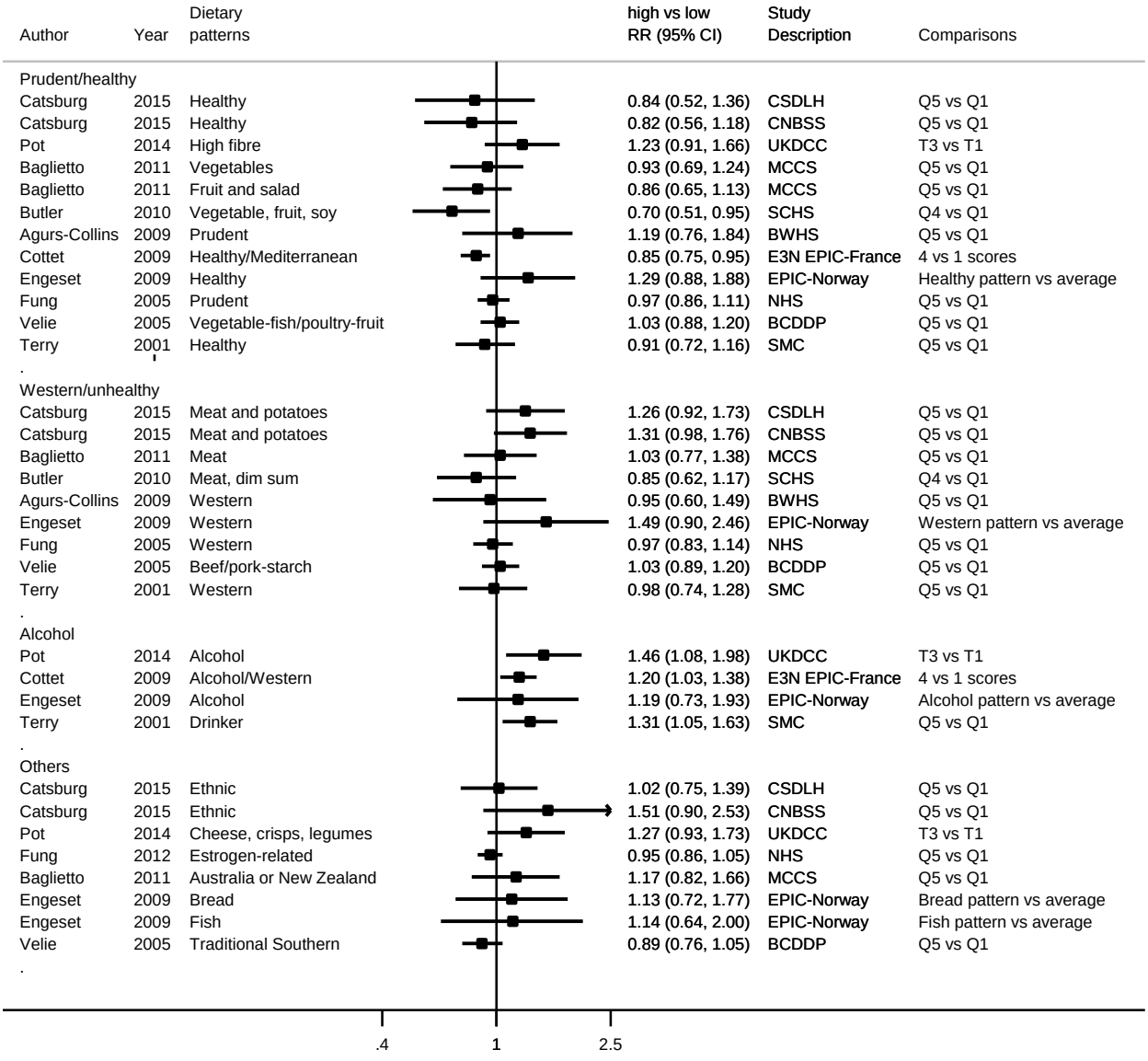


Figure 12 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest level of A posteriori derived dietary pattern



Note: Baglietto, 2011 had two fruits and vegetables-related pattern – fruit and salad and vegetables patterns.

Figure 13 RR (95% CI) of breast cancer subtypes for the highest compared with the lowest level of prudent pattern

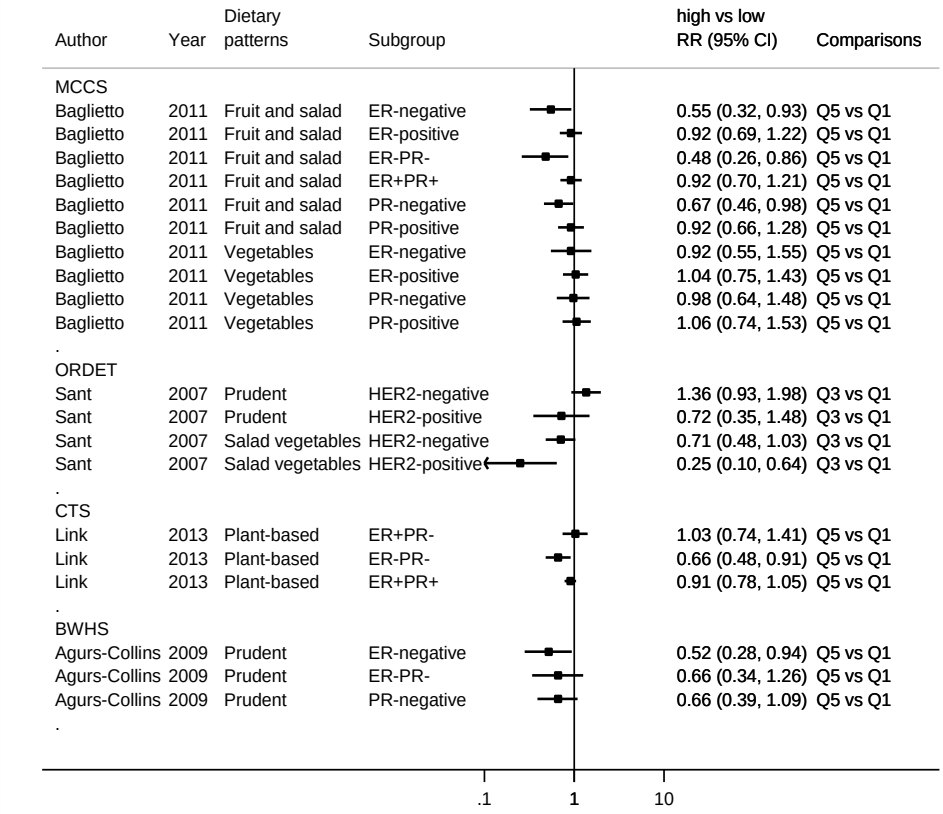


Figure 14 RR (95% CI) of breast cancer subtypes for the highest compared with the lowest level of Western pattern or alcohol pattern

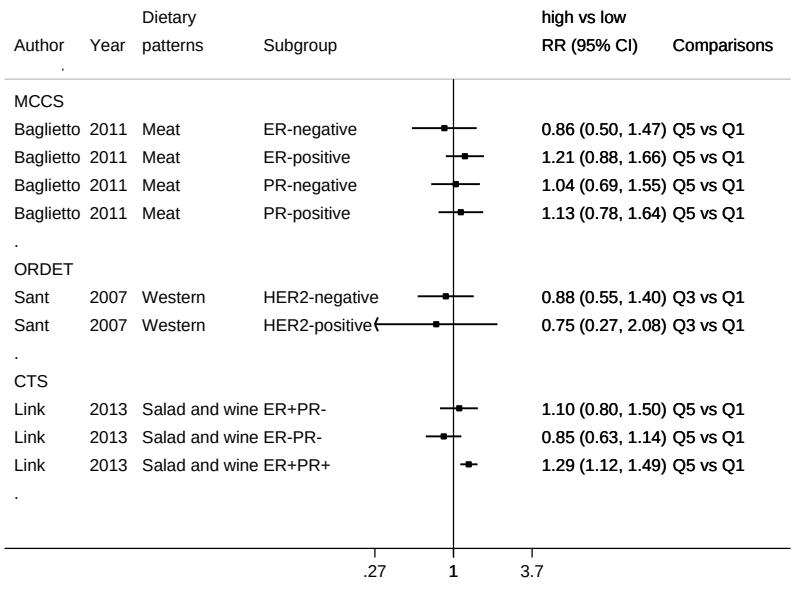


Figure 15 RR (95% CI) of postmenopausal breast cancer subtypes for the highest compared with the lowest level of prudent pattern

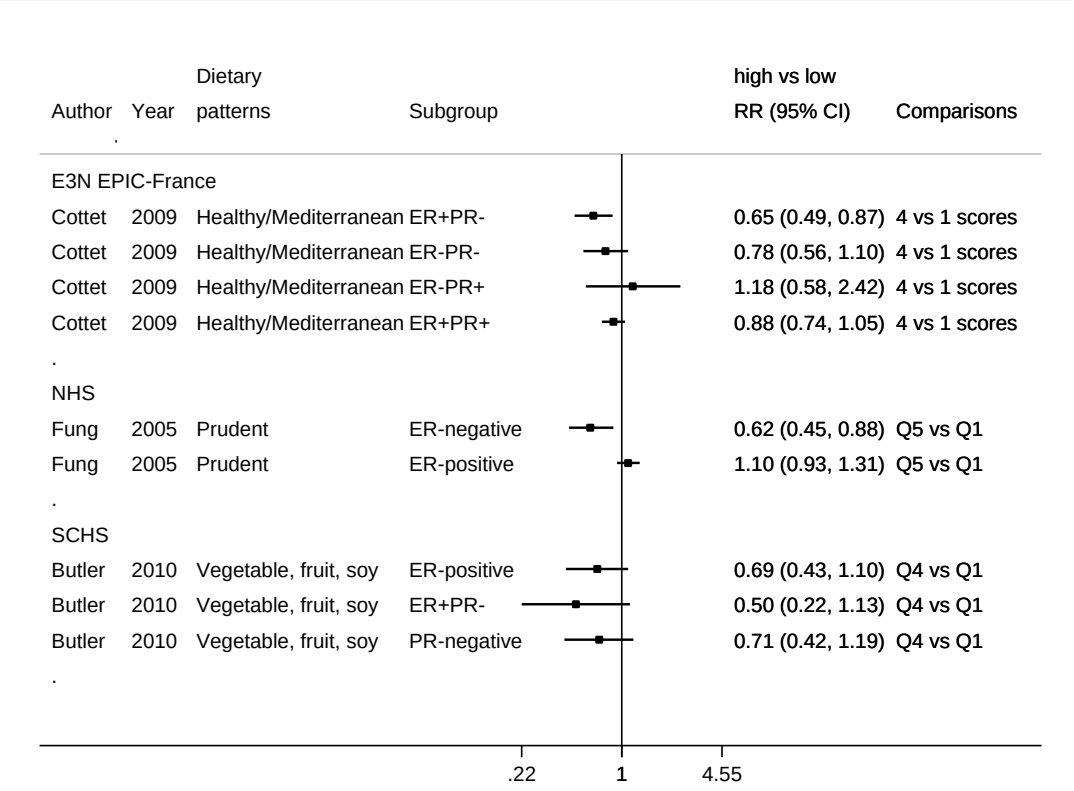
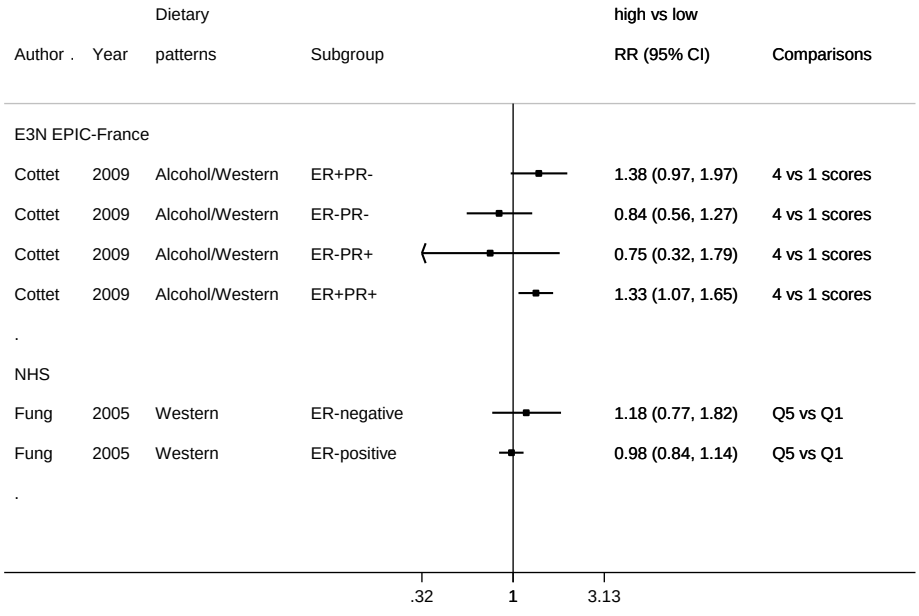


Figure 16 RR (95% CI) of postmenopausal breast cancer subtypes for the highest compared with the lowest level of Western pattern or alcohol pattern



1.6.1 Breastfeeding - mother

Cohort studies

Overall summary:

Eighteen cohort studies (17 publications) investigated breastfeeding and risk of breast cancer (pre-and postmenopausal), 7 cohort studies (9 publications) investigated premenopausal breast cancer and 6 cohort studies and a follow-up of a randomised controlled trial of low-fat diet intervention (9 publications) investigated postmenopausal breast cancer.

Dose-response meta-analyses on total duration of breastfeeding and risk of breast cancer were conducted. The study results for the highest compared to the lowest category of breast feeding used in the studies (duration, having breastfed or not) are shown in forest plots.

An inverse significant dose-response relationship was observed with total duration of breastfeeding in studies that include pre-and postmenopausal breast cancers. Inverse but not significant association was observed in the limited number of studies in premenopausal breast cancer and no association was observed for postmenopausal breast cancers.

Table 11 Summary of results of the dose-response meta-analysis of breastfeeding duration and breast cancer in the 2005 SLR and the CUP SLR

	2005 SLR	**CUP SLR**		
Breast cancer type	**Breast cancer (any)**	**Breast cancer (any)**	**Premenopausal breast cancer**	**Post-menopausal breast cancer**
Increment unit used	Per 5 months	Per 5 months	Per 5 months	Per 5 months
Studies (n)	4	13	4	5*
Cases	2 739	11 610	1321	7359
RR (95%CI)	0.98 (0.97-1.00)	0.98 (0.97-0.99)	0.95 (0.89-1.01)	1.00 (0.99-1.02)
Heterogeneity (I^2, p-value)	0% (0%-85.5%)[±]	0%, 0.51	63.4%, 0.04	4.6%, 0.4
P value Egger test	Not reported	0.90	0.25	0.63

*The results of the WHI randomised trial and observational study are shown in the figures by study arm

[±] Confidence interval of I^2

Breast cancer (any)

Main results:

Thirteen cohort studies (9 publications) on total duration of breastfeeding were included in the dose-response meta-analysis for any breast cancer.

Breastfeeding was significantly inversely associated with breast cancer risk (summary RR per increment of 5 months=0.98, 95% CI=0.97-0.99) (I^2=0%, P=0.51). There was no evidence of significant publication or small studies bias (P for Egger's test=0.90).

Three studies on duration of breastfeeding were excluded from the analysis because these studies investigated specific breast cancer types.

Sensitivity analyses:

In influence analysis, no study showed strong influence in the summary result. Specifically the inverse association remained significant after exclusion of the pooled analysis of five cohorts (CGHFBC, 2002) that had 53% weight in the analysis.

Non-linear dose-response meta-analysis was not conducted.

Study quality:

Total duration of breastfeeding was assessed through questionnaires at the time of cohort enrolment in all studies except one. In the nested case-control study in the BSE (Li, 2005), a randomised trial of breast self-examination of participants working in Shanghai Textile Industry Bureau, breastfeeding duration was assessed at the time of the biopsy for the cases, and at the time of selection for the study for controls. No significant association was observed in this study.

Case ascertainment was adequate in the studies. All studies except the CLUE II study adjusted for main risk factors. The publication of the American CLUE II (Visvanathan, 2007) was a small nested case-control study on genetic polymorphisms and alcohol intake; the odds ratios for lactation duration shown in a descriptive table of main potential confounders were not adjusted. Cases were matched to controls by race, freeze/thaw status, age (within 1 year), availability of FFQ, and menopausal status at baseline. This is the only study that did not adjust the analysis for parity. A non-significant inverse association was observed.

One study, the IBCCS, 1997 (Andrieu, 2006) was in BRCA 1/2 mutation carriers. Exclusion of the study did not influence the overall result of the meta-analysis.

Table 12 Breastfeeding and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	18
Studies included in forest plot of highest compared with lowest exposure	11
Studies included in linear dose-response meta-analysis	13
Studies included in non-linear dose-response meta-analysis	Not enough data

Table 13 Breastfeeding and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR	**CUP**
Increment unit used	**Per 5 months**	**Per 5 months**
Studies (n)	4	13
Cases	2 739	11 610
RR (95%CI)	0.98 (0.97-1.00)	0.98 (0.97-0.99)
Heterogeneity (I^2, p-value)	0%	0%, 0.51
P value Egger test	Not reported	0.90

Table 14 Breastfeeding and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Islami, 2015	7* cohort studies	>1777	USA,	Incidence, breast cancer, ER-PR-	Ever vs never	0.84 (0.72-0.97)	50%, 0.06
	3 cohort studies			Triple negative		0.73 (0.62-0.87)	0%, 0.43
	4 cohort studies			ER+PR+		1.00 (0.90-1.10)	54%, 0.09
	7 cohort studies			ER+ and/or PR+		0.97 (0.88-1.07)	78%, <0.001
Zhou, 2015	3 cohort studies, 23 case-control, one cross-sectional	13 907	Asia, Europe, Africa, Puerto Rico	Incidence, breast cancer	Highest vs lowest	0.51 (0.41-0.63)	88%, <0.001
	3* cohort studies	3 849	Europe			1.00 (0.91-1.08)	0%, 0.84
Pan, 2014	3 studies of BRCA1 or BRCA2 mutation carriers (1 case-control, 1 prospective cohort, 1 retrospective cohort)			Incidence, breast cancer	Ever vs never	0.88 (0.76-1.02)	0.11
					Longest duration vs never	0.74 (0.57-0.96)	0.13

*****All prospective cohorts were identified in the present review.

Table 15 Breastfeeding and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Butt, 2014 BRE80542 Sweden	MDCS, Prospective Cohort, W Nulliparous excluded from the analysis Parous women who never breastfed included in the analysis	400/ 14 092 10.2 years	Cancer and mortality registries	Questionnaire Total duration defined as mean breastfeeding time multiplied by parity (up to seven children)	Incidence, breast cancer	≥13 vs ≤3.9 months	1.10 (0.78-1.54) Ptrend:0.45	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, educational level, height, hormone replacement therapy, marital status, oophorectomy ever, oral contraceptive use, parity, smoking, socio-economic status	Person-years per category, mid-point of exposure categories
		292/			Incidence, breast cancer HER-2 -	≥13 vs ≤3.9 months	1.07 (0.72-1.59) Ptrend:0.44		Dose-response meta-analysis by cancer subtypes was not conducted
		40/			Incidence, breast cancer HER-2 +	≥13 vs ≤3.9 months	1.35 (0.46-3.97) Ptrend:0.59		
		286/			Incidence, ductal carcinomas	≥13 vs ≤3.9 months	1.20 (0.81-1.78) Ptrend:0.26		
		73/			Incidence, lobular carcinoma	≥13 vs ≤3.9 months	0.65 (0.29-1.45) Ptrend:0.44		
		27/			Incidence, tubular breast cancer	≥13 vs ≤3.9 months	1.56 (0.37-6.70) Ptrend:0.75		
Visvanathan, 2007 BRE80020 USA	CLUE II, Nested Case Control, Age: 57 years, W	67/ 68 controls		FFQ + questionnaire	Incidence, breast cancer	≥6.1 vs ≤0 months	0.79 (0.45-1.41)	Age, menopausal status, race	Mid-points of exposure categories
Andrieu, 2006 BRE80136 UK, France, Netherlands, Canada	IBCCS, 1997, Historical Cohort, Age: 18- years, W, BRCA1, BRCA2 carriers	647/ 1 601 0	Screening examinations	Questionnaire Breastfeeding duration was the sum of all breastfeeding periods	Incidence, breast cancer	≥24.1 vs ≤0 months	1.08 (0.62-1.89)	Birth cohort, county of residence, number of children, oophorectomy or hysterectomy	Mid-points of exposure categories
						ever vs never	1.04 (0.81-1.34)		
		582/			BRCA I	≥24.1 vs ≤0 months	1.01 (0.57-1.79)		
						ever vs never	1.07 (0.81-1.40)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		215/			BRCA II	ever vs never	0.79 (0.44-1.39)		
						≥24.1 vs ≤0 months	1.21 (0.32-4.54)		
Li, 2005 BRE23123 China	Shanghai BSE, Nested Case Control, W Analysis restricted to parous women	122/ 1025 controls	All histology	Questionnaire. Cases interviewed at the time of the biopsy. Controls interviewed after selection	Incidence, breast cancer	≥25 vs ≤0 months/life	1.10 (0.30-4.00) Ptrend:0.36	Age, year of interview, parity/pregnancies	Mid-points of exposure categories
The Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC), 2002	Nested case-control in 5 cohort studies: RERF (Japan), Guernsey (UK), (Tulinius) Iceland, Shanghai textile workers (China), MWS (UK)	4 185/26 762	Variable in each cohort	Questionnaires Total (lifetime) duration of breastfeeding was ascertained (not differentiation between only breastfeeding or also with supplement-ation)	Incidence, breast cancer	Per 12 months increment	4.6% (SE 1.8%) risk reduction	Age, ethnicity, education, mother or sister with breast cancer, age at menarche, menopausal status, height, weight, BMI, previous use of hormonal contraceptives, alcohol use, tobacco use	Standard error used to estimate CIs, RR rescaled for an increment of 5 months
Tryggvadottir, 2002 BRE12507 Iceland	Iceland, 1979, Nested Case Control, Age: 20-81 years, W	3 572 17 years	Population cancer registry	Questionnaire	Incidence, breast cancer	per 6 months/life	0.95 (0.91-0.99)	Age at first child, age at menarche, body weight, height, oral contraceptive use, parity/pregnancies, parous/nulliparous	RR rescaled for an increment of 5 months
Goodman, 1997 BRE03352 Japan	LSS, 1969, Prospective Cohort, W, Atomic bomb	56/ 22 200 8.31 years	Active follow-up matched with cancer registry and death certificate	Questionnaire	Incidence, breast cancer	≥24 vs <12 months/life	0.83 (0.42-1.64) Ptrend:0.74	Age , other age Indicator, other specified factor, parity/pregnancies, place of residence	Mid-points of exposure categories

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	survivors								
Michels, 1996a BRE17829 USA	NHS I, Prospective Cohort, W, Registered nurses	1 459/ 89 887 6 years	Active follow-up, with medical verification	Questionnaire Duration of breastfeeding for all births combined	Incidence, invasive breast cancer	Ever vs never	0.93 (0.83-1.03)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, family history, HRT use, nutrients, oral contraceptive use, parity/pregnancies, physical activity	
						≥24 vs ≤0 months/life	1.11 (0.90-1.38) Ptrend:.65		Mid-points of exposure categories
Kvåle, 1988 BRE17728 Norway	Norway, 1956, Prospective Cohort, Age: 27-69 years, W, Screening Program	1 102/ 48 607 20 years	Linkage to Cancer Registry of Norway	Questionnaire Total duration of breastfeeding Nulliparous excluded	Incidence, breast cancer	per 6 months/life	0.96 (0.93-0.99)	Age, place of residence and parity	RR rescaled for an increment of 5 months

Table 16 Breastfeeding and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Horn, 2014a BRE80583 Norway	Norwegian Nord-Trøndelag Health Study, Prospective Cohort, Age: 48 years, W	463/ 21 532 667 461 person-years	Cancer registry	Questionnaire	Incidence, luminal breast cancer	never vs ever	0.84 (0.56-1.27)	Age, age at first child birth, birth cohort, number of childbirths	Dose-response meta-analysis by cancer subtypes was not conducted
		438/				per 6 months	1.01 (0.94-1.08)		
						>24 vs 4-12 months	0.98 (0.70-1.39)		
		266/			Incidence, luminal A breast cancer	never vs ever months	0.80 (0.45-1.41)		
		253/				>24 vs 4-12 months	0.90 (0.58-1.41)		
						per 6 months	1.00 (0.91-1.10)		
		103/			Incidence, non-luminal breast cancer	never vs ever months	2.13 (1.11-4.07)		
		92/				≥25 vs 4-12 months	1.24 (0.63-2.46)		
						per 6 months	1.02 (0.88-1.18)		
		43/			Incidence, non-luminal, basal-like breast cancer	never vs ever months	1.06 (0.32-3.51)		
		40/				≥25 vs 4-12 months	1.43 (0.47-4.41)		
						per 6 months	1.09 (0.86-1.38)		
Ritte, 2013a BRE80486 Denmark,France, Germany,Greece, Italy,Netherlands,	EPIC, Prospective Cohort, Age: 51.1 years,	2 855/ 311 097 11.3 years	Multiple methods	Questionnaire	Incidence, breast cancer ER+/PR+	yes vs no	0.99 (0.89-1.09)	Age, alcohol, BMI, educational level, height, HRT use,	Dose-response meta-analysis by tumour receptor status was not conducted
		2 273/				≥18 vs 0.1-0.9 months	1.11 (0.92-1.33) Ptrend:0.90		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Norway,Spain,Sweden, UK	W	794/			Incidence, breast cancer ER-/PR-	yes vs no	0.98 (0.81-1.17)	menopausal status, physical activity, smoking status, study centre	
		635/				≥18 vs 0.1-0.9 months	1.07 (0.75-1.51) Ptrend:0.54		
Tamimi, 2012 USA	NHS I, Prospective Cohort, Age: 30-55 years, W, Registered nurses	1267/121 700	Self-report verified by medical records, death certificates	Questionnaire	Incidence, breast cancer luminal A	4+ months vs never	0.80 (0.70-1.00)	Age at menopause, family history of breast cancer, personal history of benign beast disease, BMI at age 18, weight change since age 18, age at menarche, parity or age at first birth, alcohol, menopausal status or PMH use, smoking	Superseded by Michels 1996
		321/			luminal B		0.80 (0.60-1.10)		
		113/			HER-2		0.90 (0.60-1.50)		
		226/			basal-like		0.60 (0.40-0.90)		
		95/			unclassified		0.60 (0.40-1.10)		
Palmer, 2011 USA	BWHS, Prospective Cohort, Age: 21-69, W	343/36 060	Medical records, cancer registry	Questionnaire	Incidence, breast cancer, ER+/PR+	≥6 months vs no	1.17 (0.87-1.57)	Age, time, geographic region, age at menarche, age at menopause, use of MHT, use of oral contraceptives, BMI, physical activity, alcohol intake, cigarette smoking, family history	Dose-response meta-analysis by tumour receptor status was not conducted
						yes vs no	1.13 (0.91-1.42)		
		102/			ER+/PR-	≥6 months vs no	1.18 (0.68-2.06)		
						yes vs no	1.25 (0.83-1.89)		
		257/			ER-/PR-	≥6 months vs no	0.79 (0.56-1.13)		
						yes vs no	0.78 (0.60-1.03)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								of breast cancer , number of births, age at first birth, years since last birth	
Kawai, 2010a BRE80627 Japan	MCS, Prospective Cohort, Age: 40-64 years, W	235/ 24 064 12.8 years	Medical records, cancer registry and death certificate	Questionnaire	Incidence, Invasive breast cancer, parous women	Yes vs no	1.00 (0.72-1.39)	Age, age at first child birth, age at menarche, alcohol drinking, BMI, educational level, family history of breast cancer, parity, smoking, walking	Only two levels of exposure
Iwasaki, 2007a BRE80169 Japan	JPHC, Prospective Cohort, Age: 40-69 years, W	373/ 555 370 10.2 years	Major local hospitals and population-based cancer registries	Questionnaire	Incidence, breast cancer	yes vs no	0.86 (0.65-1.15)	Age, age at last child birth, age at menarche, area, BMI, height, history of mastopathy, menopausal status, miso soup consumption, number of childbirths	Only two levels of exposure
Tryggvadottir, 2001 BRE12506 Iceland	Iceland, 1979, Nested Case Control, Age: 20-81 years, W,	973/ 9449 controls 16 years	Population cancer registry	Questionnaire	Incidence, invasive breast cancer	≥105 vs 0-4 week/life	0.48 (0.31-0.74)	Age at first child, age at menarche, body weight, height, oral contraceptive	Superseded by Tryggvadottir, 2002

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Screening Program							use, parity/pregnancies	
London, 1990 BRE15914 USA	NHS I, Prospective Cohort, Age: 30-55 years, W, Registered nurses	1 262/ 89 413 11 years	Medical record/ pathology report/self/ family report	Questionnaire	Incidence, breast cancer	≥24 vs ≤0 months/life	0.95 (0.73-1.23) Ptrend:0.20	Age , age at first child, age at menarche, benign breast disease, family history, menopausal status, oral contraceptive use, parity/ pregnancies	Superseded by Michels, 1996a

Figure 17 RR estimates of breast cancer by total duration of breastfeeding

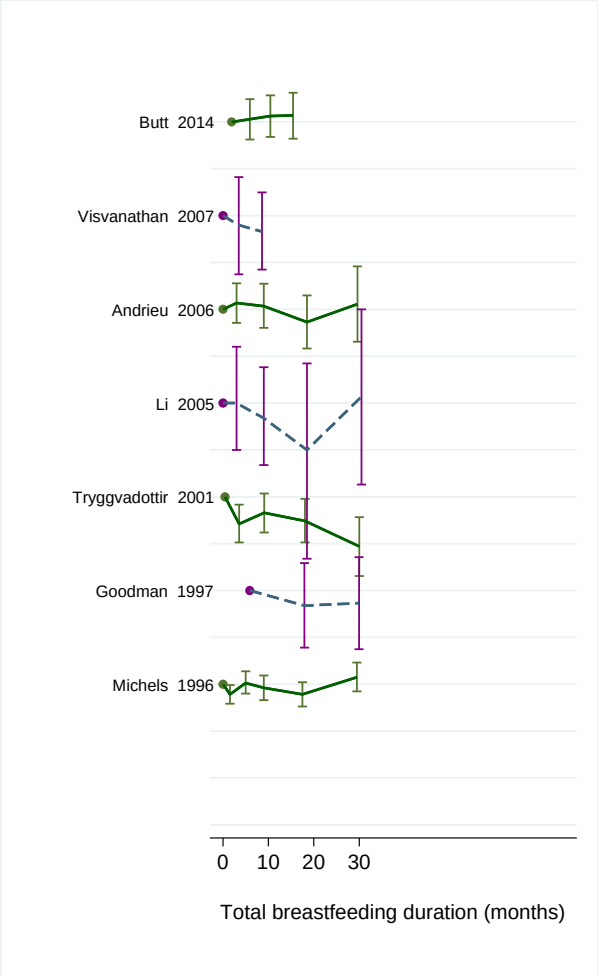
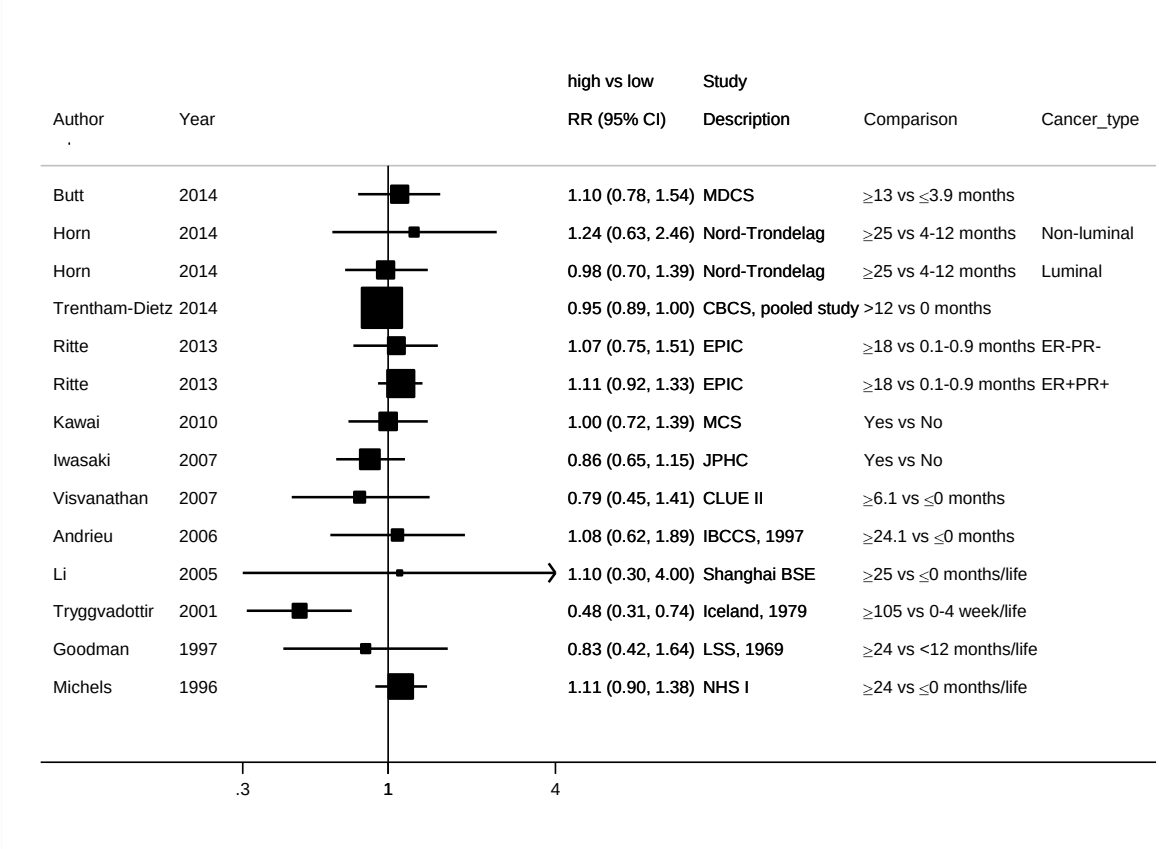


Figure 18 RR (95% CI) of breast cancer for the highest compared with the lowest category of breastfeeding



Note: Cancer type is indicated only when the RR (95% CI) is for a specific breast cancer type

Figure 19 Relative risk of breast cancer for 5 month increase in breastfeeding duration

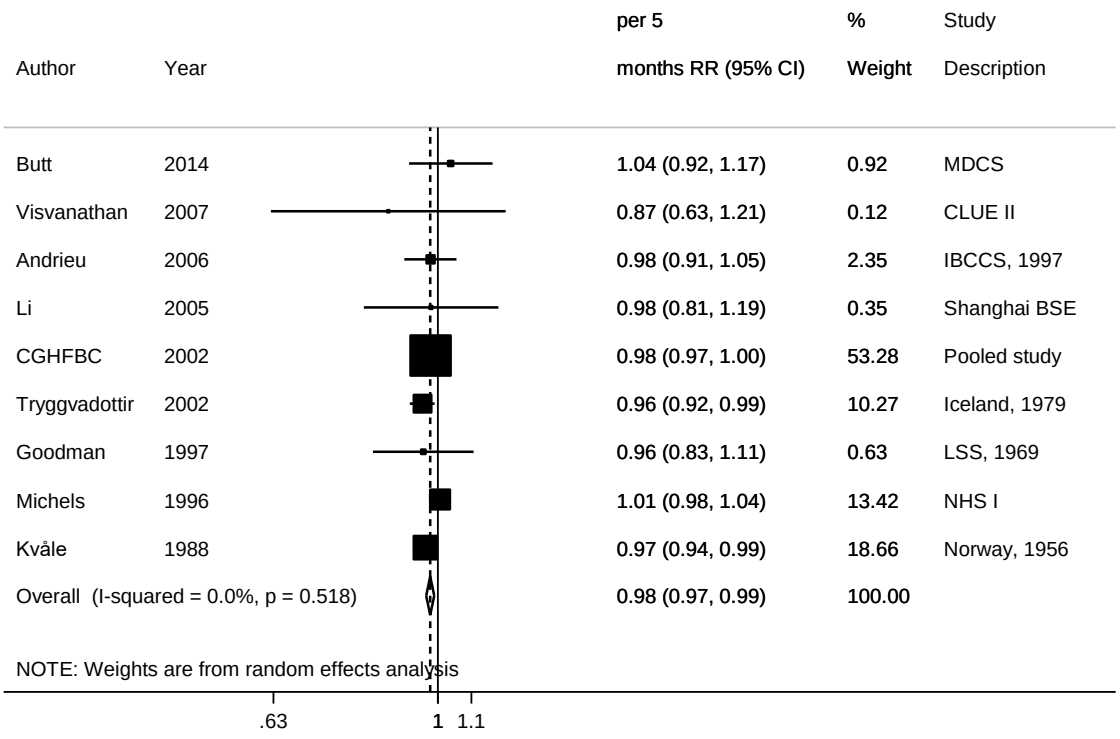
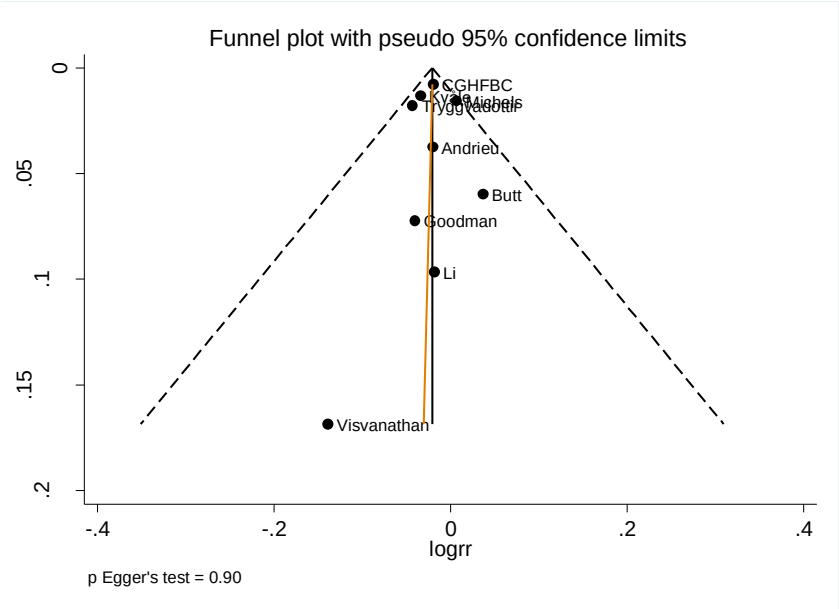


Figure 20 Funnel plot of studies included in the dose response meta-analysis of breastfeeding duration and breast cancer risk



Premenopausal breast cancer

Summary

Main results:

Eight cohort studies (9 publications) investigated breastfeeding and risk of premenopausal breast cancer.

Four studies were included in the dose-response meta-analysis. A non-significant inverse dose-response was observed. There was significant heterogeneity across study results. The smallest study (Tryggvadir, 2001) showed a stronger inverse association than the other studies.

Table 17 Breastfeeding and premenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR	**CUP**
Increment unit used	**Per 5 months**	**Per 5 months**
Studies (n)	2	4
Cases	616	1321
RR (95%CI)	0.96 (0.93-1.00)	0.95 (0.89-1.01)
Heterogeneity (I^2, p-value)	80%	63.4%, 0.04
P value Egger test	-	0.25

Study quality:

Total duration of breastfeeding was assessed through questionnaires at the time of cohort enrollment in all studies. Case ascertainment was adequate in the studies. All studies adjusted for main risk factors.

Table 18 Breastfeeding and premenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Stuebe, 2009 BRE80283 USA	NHS II, Prospective Cohort, Age: 25-42 years, W, Premenopausal	608/ 60 075 8 years	Self-report verified by medical record	Questionnaire Contributions from all pregnancies were summed to determine lifetime duration	Incidence, Invasive breast cancer	>36 months vs never	0.63 (0.40-0.99) Ptrend:0.95	Age, height, current BMI, BMI at age 18 years, history of benign breast disease, family history of breast cancer, year of first birth, birth weight of participant, age at menarche, parity and age at first birth, use of medications to suppress lactation, use of oral contraceptives, consumption of alcohol, physical activity	Mid-points of exposure categories
						ever vs never	0.75 (0.56-1.00)		
		497/			No family history of breast cancer	>36 months vs never	0.68 (0.41-1.12) Ptrend:0.73		
		111/			With family history of breast cancer		0.42 (0.16-1.09) Ptrend:0.16		
Lee, 2003 BRE17745 Korea	KWC, Prospective Cohort, Age: 20- years, W, Premenopausal	360/ 110 604 6 years	Medical records + death certificate	Questionnaire Duration of breastfeeding was from summation of lactation duration for each child per mother (up to 5 children)	Incidence, breast cancer, premenopausal	>24 months vs never	0.60 (0.30-1.00) Ptrend:0.001	Age, age at first child, age at menarche, BMI, oral contraceptive use, parity/ pregnancies, physical activity, smoking habits	Mid-points of exposure categories
Tryggvadottir,	Iceland, 1979,	97/	Population	Questionnaire	Incidence, breast	per 6	0.76 (0.59-0.99)	Age at first child,	Rescaled to

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
2002 BRE12507 Iceland	Nested Case Control, Age: 20-81 years, W	970 controls 17 years	cancer registry		cancer, premenopausal	months/life		age at menarche, body weight, height, oral contraceptive use, parity/ pregnancies, parous/nulliparous	5 month increment
Michels, 1996a BRE17829 USA	NHS I, Prospective Cohort, W, Registered nurses	256/ 89 887 6 years	Medical records + self-reported	Questionnaire	Incidence, Invasive breast cancer, premenopausal	≥24 vs ≤0 months/life	0.90 (0.53-1.54) Ptrend:0.98	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, family history, nutrients, oral contraceptive use, parity/ pregnancies, physical activity	Mid-points of exposure categories

Table 19 Breastfeeding and premenopausal breast cancer. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reason for exclusion
Warner, 2013 BRE80503 USA	NHS I and II, Prospective Cohort, W, Premenopausal	1 003/ 196 499 33 years	Self-report verified by medical record and pathology report	Questionnaire	Incidence, breast cancer, age at diagnosis >=40y	≥24 vs ≤0.9 months	0.81 (0.68-1.03) Ptrend:0.19	Age, age at first child birth, age at menarche, alcohol consumption, benign breast disease, BMI at age 18 years, family history of breast cancer, height, oral contraceptive use, weight change	Superseded by Stuebe, 2009 and Michels, 1996a
						ever vs never (<1 month)	0.85 (0.72-0.99)		
		183/			Age at diagnosis <40y	≥24 vs ≤0.9 months	0.68 (0.40-1.17) Ptrend:0.84		
						ever vs never (<1 month)	0.84 (0.57-1.22)		
		154/			ER-/PR-, age at diagnosis >=40y	ever vs never <1 month	0.72 (0.32-1.61)		
		45/			ER-/PR-, age at diagnosis <40y	ever vs never <1 month	0.79 (0.38-1.64)		
Kawai, 2010a BRE80627 Japan	MCS, Prospective Cohort, Age: 40-64 years, W	111/ 24 064 12.8 years	Medical records, cancer registry and death certificate	Questionnaire	Incidence, Invasive breast cancer, parous premenopausal women	Yes vs no	1.22 (0.78-1.91)	Age, age at first child birth, age at menarche, alcohol drinking, BMI, educational level, family history of breast cancer, parity, smoking, walking	Only two levels of exposure
Iwasaki, 2007a BRE80169 Japan	JPHC, Prospective Cohort, Age: 40-69 years, W	176/ 555 370 10.2 years	Major local hospitals and population-based cancer registries	Questionnaire	Incidence, breast cancer, premenopausal	yes vs no	0.80 (0.55-1.17)	Age, age at last child birth, age at menarche, area, BMI, height, history of mastopathy, menopausal status, miso soup consumption,	Only two levels of exposure

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reason for exclusion
								number of childbirths	
Tryggvadottir, 2001 BRE12506 Iceland	Iceland, 1979, Nested Case Control, Age: 20-81 years, W, Screening Program	84/ 2 870 16 years	Population cancer registry	Questionnaire	Incidence, Invasive breast cancer, premenopausal	per 6 months/life	0.77 (0.59-1.00)	Age at first child, age at menarche, body weight, height, oral contraceptive use, parity/ pregnancies	Superseded by Trygg-vadottir, 2002
London, 1990 BRE15914 USA	NHS I, Prospective Cohort, Age: 30-55 years, W, Registered nurses	624/ 89 413 11 years	Medical record/patholog y report/self-family report	Questionnaire	Incidence, breast cancer, premenopausal	≥24 vs ≤0 months/life	1.06 (0.75-1.50) Ptrend:0.59	Age , age at first child, age at menarche, benign breast disease, family history, oral contraceptive use, parity/pregnancie s	Superseded by Michels, 1996a

Figure 21 RR estimates of premenopausal breast cancer by total duration of breastfeeding

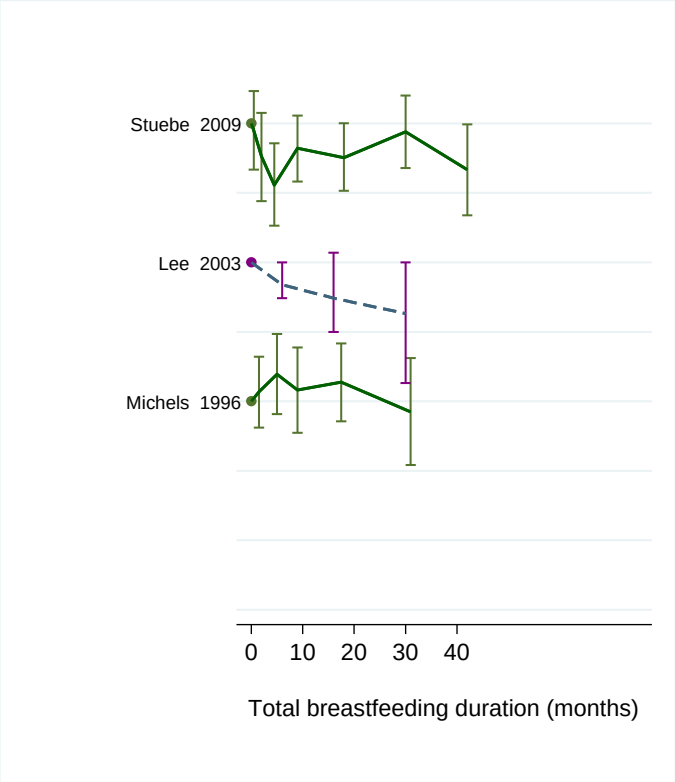


Figure 22 Relative risk of premenopausal breast cancer for 5 month increase in breastfeeding duration

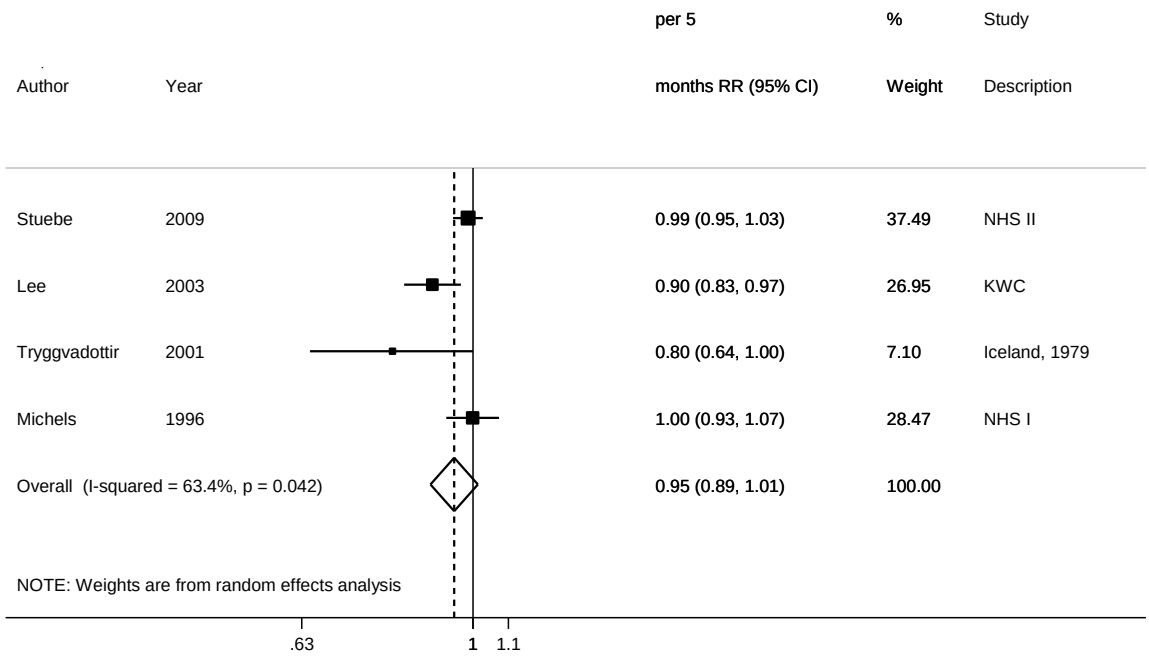


Figure 23 Funnel plot of studies included in the dose response meta-analysis of breastfeeding duration and premenopausal breast cancer risk

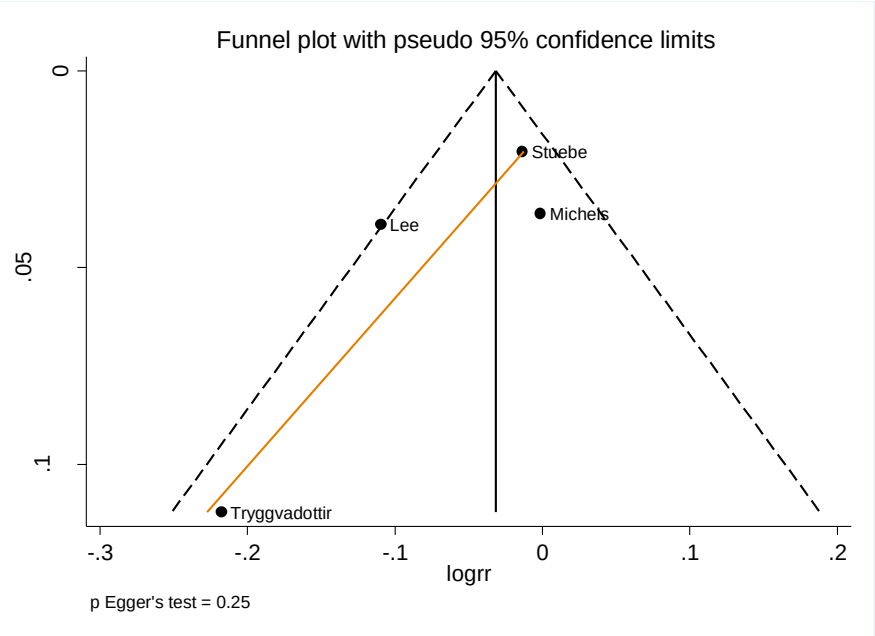
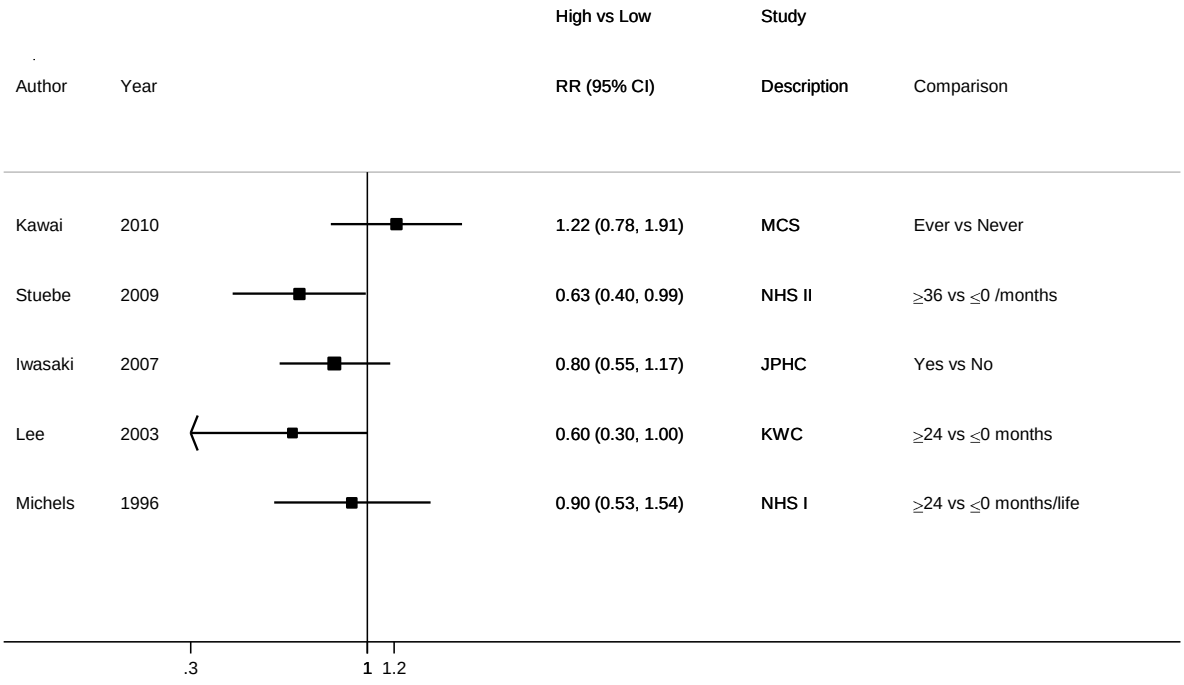


Figure 24 RR (95% CI) of premenopausal breast cancer for the highest compared with the lowest category of breastfeeding



Postmenopausal breast cancer

Main results:

Seven cohort studies (12 publications) on breastfeeding and postmenopausal breast cancer were identified.

Five studies were included in the dose-response meta-analysis. Duration of breastfeeding was not related to risk of postmenopausal breast cancer.

Study quality:

Total duration of breastfeeding was assessed through questionnaires at the time of cohort enrollment in all studies. Case ascertainment was adequate in the studies. All studies adjusted for main risk factors except the small nested case-control study in the Malmo and Diet cohort (Wirfalt, 2005) in which a no significant inverse association of postmenopausal breast cancer risk and breastfeeding duration was observed. The nested case-control study aimed to investigate fat from foods and breast cancer risk and the data on breastfeeding duration was shown in the description of the cohort.

Table 20 Breastfeeding and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Stendell-Hollis, 2013 BRE80555 USA	WHI-OS and hormone trial (post-hoc cohort analysis) 69,358 post-menopausal women aged 50-79 years, with at least 1 live birth and known duration of lactation	WHI-OS 45 263/ 638/ 7.9 years	Self-report verified by medical record	Questionnaire	Incidence, invasive breast cancer, no prior HRT	≥24 vs ≤0 months	1.22 (0.90-1.66)	Age, race/ethnicity, BMI, smoking, family history of breast cancer, number live births, age at first birth, years since menopause, duration of prior hormone therapy use, and participation in WHI extension study	Person-years by category. Mid-points of exposure categories
		311/			prior HRT	≥24 vs ≤0 months	1.05 (0.64-1.72)		
		324/			Conjugated equine estrogen (CEE)	≥24 vs ≤0 months	0.96 (0.55-1.68)		
		299/			Medroxyprogesterone acetate (MPA)	≥24 vs ≤0 months	1.32 (0.84-2.06)		
		WHI-Hormone 24095/ 143/			CEE arm	≥24 vs ≤0 months	0.64 (0.27-1.49)	Age, race/ethnicity, BMI, smoking, family history of breast cancer, age at first birth, age at menarche, participation in WHI extension, stratified by arm in dietary modification trial	
		111			CEE placebo	≥24 vs ≤0 months	0.71 (0.30-1.64)		
		271			CEE/MPA arm	≥24 vs ≤0 months	0.89 (0.54-1.45)		
		218			CEE/MPA placebo	≥24 vs ≤0 months	0.70 (0.40-1.24)		
Ma, 2010 BRE80331 USA	CTS, Prospective Cohort,	2 193/ 52 464 10.5 years	Cancer registry	Questionnaire	Incidence, invasive postmenopausal	≥24 vs never months	0.99 (0.84-1.18) Ptrend:0.56	Age, age at menarche, BMI, family history of breast cancer, HRT use,	Mid-points of exposure categories

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	W, Postmenopausal				breast cancer			race, number of full-term pregnancies, age at first full-term pregnancy	
		1 620/			ER+	≥24 vs never months	1.02 (0.83-1.25) Ptrend:0.52		
		264/			ER-	≥24 vs never months	1.00 (0.61-1.66) Ptrend:0.78		
		1 260/			ER+/PR+	≥24 vs never months	1.00 (0.80-1.27) Ptrend:0.54		
		248/			ER-/PR-	≥24 vs never months	1.06 (0.64-1.78) Ptrend:0.65		
Wirfält, 2005 BRE11111 Sweden	MDCS, Nested Case Control, Age: 50- years, Postmenopausal	237/ 673 controls	Cancer registry	Questionnaire	Incidence, breast cancer, postmenopausal	≥7 vs 0 months	0.72 (0.50-1.05)	Year of birth, year and month of visit to the study centre	Mid-points of exposure categories
Tryggvadottir, 2002 BRE12507 Iceland	Iceland, 1979, Nested Case Control, Age: 20-81 years, W	589/ 5299 controls 17 years	Population cancer registry	Questionnaire	Incidence, breast cancer, >55 years at diagnosis	per 6 months/life	0.96 (0.91-1.01)	Age at first child, age at menarche, body weight, height, oral contraceptive use, parity/pregnancies, parous/nulliparous	Rescaled to 5 months increment
Michels, 1996a BRE17829 USA	NHS I, Prospective Cohort, W, Registered nurses	1 189/ 89 887 6 years	Medical records + self-reported	Questionnaire	Incidence, invasive breast cancer, postmenopausal	≥24 vs ≤0 months/life	1.21 (0.96-1.54) Ptrend:0.49	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, family history, HRT use, nutrients, oral contraceptive use, parity/pregnancies, physical activity	Mid-points of exposure categories

Table 21 Breastfeeding and postmenopausal breast cancer. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Hartz, 2013 BRE80483 USA	WHI, Prospective Cohort, Age: 55-70 years, W, Postmenopausal	147 202 8 years	Self-reported/death certificate/ medical records	Questionnaire	Incidence, postmenopausal breast cancer	Yes vs no	0.90 (0.80-1.02)	Age, race, study	Only two levels of exposure
Phipps, 2011 USA	WHI, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	2 186/132 767	Self-report verified by medical record	Questionnaire	Incidence, postmenopausal ER+ breast cancer	>12 months vs never	0.98 (0.85-1.13)	Age, study arm, race, education level, family history of breast cancer, BMI, hormone therapy use, smoking history, history of mammog-raphy (at baseline), mammography during follow-up, age at menarche, age at menopause, nulliparity, oral contraceptive use	Superseded by Stendell-Hollis 2013
		176/130 666			Triple negative		0.81 (0.53-1.26)		
Kawai, 2010a BRE80627 Japan	MCS, Prospective Cohort, Age: 40-64 years, W	103/ 24 064 12.8 years	Medical records, cancer registry and death certificate	Questionnaire	Incidence, invasive breast cancer, parous and postmenopausal	Yes vs no	0.68 (0.40-1.15)	Age, age at first child birth, age at menarche, age at menopause, alcohol drinking, BMI, educational level, family history of breast cancer, parity, smoking, type of menopause, walking	Only two levels of exposure
Chlebowski, 2007 BRE80607	WHI, Prospective Cohort,	2 373/ 147 916 5 years	Self-reported validated by pathology	Questionnaire	Incidence, breast cancer ER+,	≥1.1 vs ≤0 years	1.03 (0.89-1.20)	Age at first child birth, age at menarche, age at menopause, age at	Superseded by Stendell-Hollis 2013

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
USA	Age: 50-79 years, W, Postmenopausal	453/	report		postmenopause ER-		1.05 (0.76-1.45)	screening, alcohol consumption, BMI, breast biopsies, estrogen use, ethnicity, family history of breast cancer, parity, physical activity, progestin + estrogen use, smoking	
Iwasaki, 2007a BRE80169 Japan	JPHC, Prospective Cohort, Age: 40-69 years, W	193/ 555 370 10.2 years		Questionnaire	Incidence, breast cancer, postmenopause	yes vs no	0.94 (0.60-1.47)	Age, age at last child birth, age at menarche, area, BMI, height, history of mastopathy, menopausal status, miso soup consumption, number of childbirths	Only two levels of exposure
Tryggvadottir, 2001 BRE12506 Iceland	Iceland, 1979, Nested Case Control, Age: 20-81 years, W, Screening Program	510/ 2 870 16 years	Population cancer registry	Questionnaire	Incidence, Invasive breast, >55 years at diagnosis	per 6 months	0.96 (0.91-1.01)	Age at first child, age at menarche, body weight, height, oral contraceptive use, parity/pregnancies	Superseded by Tryggvadottir, 2002
London, 1990 BRE15914 USA	NHS I, Prospective Cohort, Age: 30-55 years, W, Registered nurses	511/ 89 413 11 years	Medical record/ pathology report/self-family report	Questionnaire	Incidence, breast cancer, postmenopausal	≥24 vs ≤0 months/life	0.87 (0.55-1.39) Ptrend:0.55	Age , age at first child, age at menarche, benign breast disease, family history, oral contraceptive use, other menstrual characteristics, parity/pregnancies	Superseded by Michels, 1996a

Figure 25 Relative risk of postmenopausal breast cancer for 5 month increase in breastfeeding duration

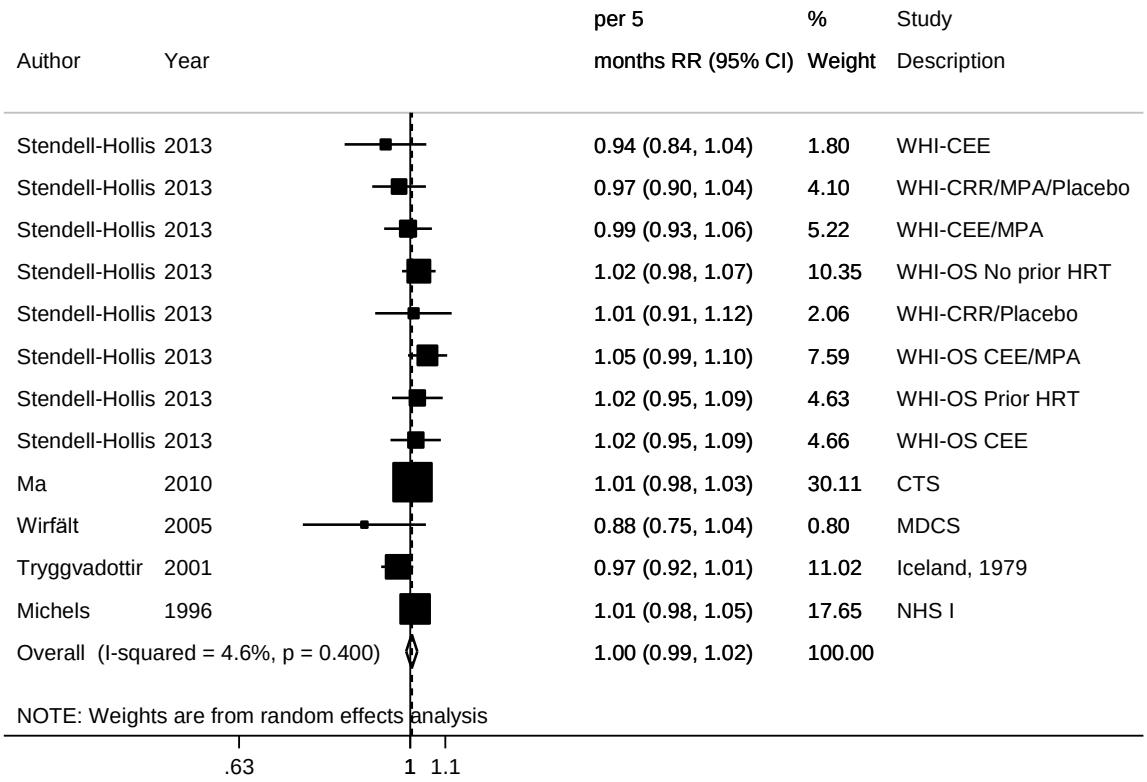


Figure 26 Funnel plot of studies included in the dose response meta-analysis of breastfeeding duration and postmenopausal breast cancer risk

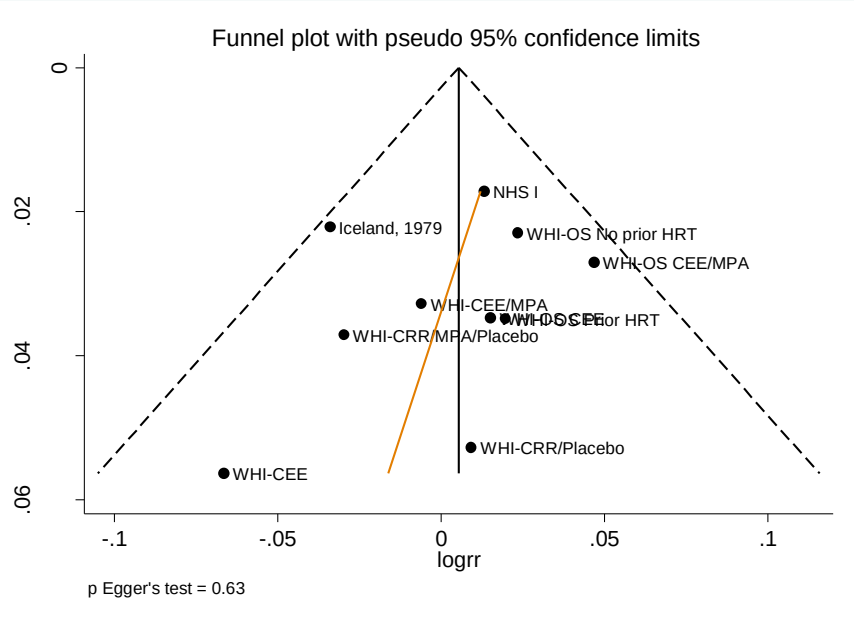
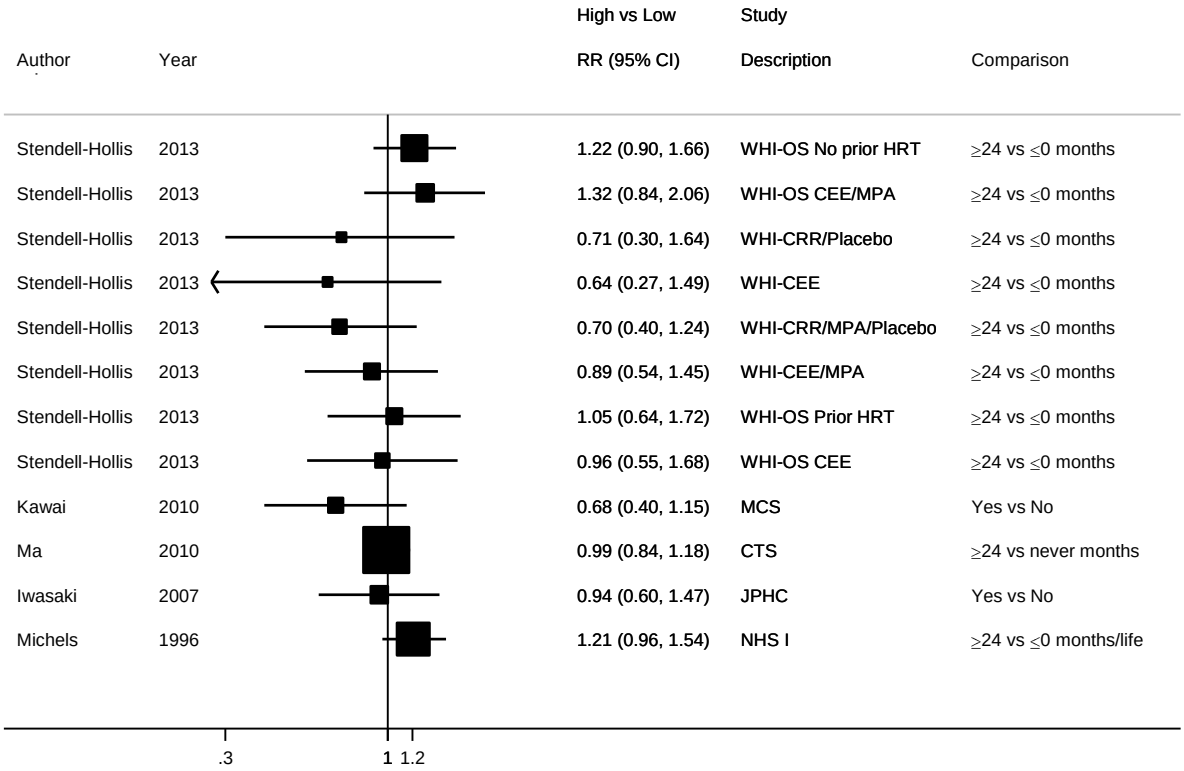


Figure 27 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest category of breastfeeding



Breastfeeding and breast cancer subtypes

Hormone receptor status

Five cohort studies examined breastfeeding and the risk of breast cancer by hormone receptor status. There was not adequate data to do dose-response meta-analysis. No consistent pattern of association emerged in the studies.

In the EPIC study breastfeeding (ever vs never) or duration of breastfeeding were not related to the risk of ER+PR+ (3 567 cases) or ER-PR- breast cancers (998 cases) (Ritte, 2013a).

In the NHSI and II, ever breastfeeding was inversely although not significantly related to ER+PR+ and ER-PR- breast cancers. The RR estimates were of similar magnitude in all subgroups (Warner, 2013).

In African American women, breastfeeding (ever vs never) or breastfeeding duration was not significantly related to risk of breast cancer by hormone receptor status subtypes. Compared to parous women who never breastfed, the RR estimates were above 1 for ER=PR= and ER+PR- tumors, and below 1 for ER-PR- (Palmer, 2011).

In the California Teachers Study (Ma, 2011) duration of breastfeeding was not related to risk of ER+, ER-, ER+PR+ or ER-PR- breast cancers. The RR were close to 1 for >24 months compared to never in all subgroups.

In the WHI (Phipps, 2011) breastfeeding was not related to the risk of ER+ or triple-negative breast cancer. In another publication of the same study (Chlebowski, 2007) duration of breastfeeding was not related to ER+ and ER- breast cancers.

2 Foods

2.2 Fruit and vegetables

Nine studies on fruit and vegetable intake and breast cancer risk were identified. Four studies investigated postmenopausal breast cancers, two were on premenopausal breast cancers, and five were on pre- and postmenopausal breast cancers combined. Study characteristics and results for all cancer types are shown in the Table.

Study quality:

Fruit and vegetable intake was estimated from food intake assessed by FFQ in all, but one study (Wie, 2014), which used a 3 day food record. One study used a combination of dietary assessment methods including FFQ, dietary records, and dietary interviews (Sonestedt, 2008a).

Loss to follow-up was low for the studies that reported such data, although some studies did not provide data.

Cancers were identified by record linkages to health registries, cancer registries, mortality registries, or death indexes.

All studies adjusted for at least age, and most of the studies adjusted for most of the established breast cancer risk factors, including: age, parity, age at menarche, age at menopause, physical activity, BMI, and alcohol consumption.

Breast cancer (any)

Nine studies (6825 cases) were included in the dose-response meta-analysis. The summary RR for a 200 g/d increase in fruit and vegetable intake was 0.97 (95% CI: 0.94-1.01) and there was low heterogeneity, I^2=21.8%, $p_{heterogeneity}$=0.25. There was some indication of small study bias or publication bias with Egger's test, p=0.10, but this appeared to be explained by one outlying study (Makarem et al, 2015), and when excluded, p=0.30. The summary RR ranged from 0.96 (95% CI: 0.93-0.99) when the Danish Diet, Cancer, and Health Study (Olsen, 2003) was excluded to 0.98 (95% CI: 0.94-1.02) when the Malmo Diet and Cancer Study (Sonestedt, 2008a) was excluded.

Nonlinear dose-response analysis

There was indication of a nonlinear association, $p_{nonlinearity}$=0.001, with reductions in risk observed up to an intake of 400 g/d, but no further reductions in risk were observed at higher intakes.

Premenopausal breast cancer

Two studies (899 cases) were included in the dose-response meta-analysis of fruit and vegetable intake and premenopausal breast cancer. The summary RR per 200 g/day increase in fruit and vegetable intake was 1.02 (95% CI: 0.78-1.34) and there was moderate heterogeneity, I^2=86.5%, $p_{heterogeneity}$=0.007.

Postmenopausal breast cancer

Four studies (2894 cases) were included in the dose-response meta-analysis of fruit and vegetable intake and postmenopausal breast cancer. The summary RR per 200 g/d increase in fruit and vegetable intake was 1.02 (95% CI: 0.98-1.06), with low heterogeneity, I^2=0%, $p_{heterogeneity}$=0.58.

Fruit and vegetable intake and breast cancer risk by hormone receptor status

Total fruit and vegetable consumption was non-statistically significantly associated with risk of ER− breast cancer (pooled multivariable RR comparing the highest vs lowest quintile = 1.00, 95% CI = 0.94-1.07), ER+ breast cancer (RR same comparison =0.90, 95% CI=0.81-1.01), PR- cancers (RR =0.97, 95% CI=0.87-1.09), and PR+ cancers (RR=0.99 95% CI= 0.92-1.07) in the Pooling project of cohort studies (Jun, 2013). However, the pooled multivariable relative risks for ER− breast cancer for a 300g/day increment (approximately three servings/day) in intake was 0.94 (95% CI = 0.91 to 0.98) (Pheterogeneity > 0.34). Total fruit and vegetables intake was non-statistically significantly inversely associated with risk of PR− breast cancer. No associations or non-statistically significant positive associations were observed for the risk of ER+ and PR+ breast cancer (data not shown in the publication). No significant associations were observed when breast cancers were classified simultaneously by ER and PR status, except for ER-PR+ tumours (pooled multivariable RR comparing the highest vs lowest quintile = 0.70, 95% CI = 0.51-0.96).

One additional study (Emaus, 2016, EPIC), identified after the search period, reported results by hormone receptor subtype. When included in a meta-analysis with two other studies with sufficient data (Suzuki, 2013; Boggs, 2010), statistically non-significant assocations were observed. The summary RRs for a 200 g/d increase in fruit and vegetable intake were 0.99 (95% CI=0.96-1.02) for ER+PR+ breast cancer, 1.03 (95% CI=0.88-1.22) for ER+PR- breast cancer, and 0.93 (95% CI=0.88-0.99) for ER-PR- breast cancer. There was evidence of high heterogeneity for ER+PR- (I^2=0%, $p_{heterogeneity}$=0.99; I^2=54.8%, $p_{heterogeneity}$=0.11; I^2=0%, $p_{heterogeneity}$=0.88, respectively).

The Nurses' Health Study (Fung, 2013) reported a non-significant inverse association with ER-negative breast cancer in postmenopausal women (RR for highest vs lowest intake=0.82, 95% CI=0.62-1.08).

Table 22 Fruit and vegetable intake and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	9
Studies included in forest plot of highest compared with lowest intake	Breast cancer: 8 Premenopausal: 2 Postmenopausal: 4

Studies included in linear dose-response meta-analysis	Breast cancer: 8 Premenopausal: 2 Postmenopausal: 4
Studies included in non-linear dose-response meta-analysis	Breast cancer: 6 Premenopausal: not enough studies Postmenopausal: not enough studies

Table 23 Fruit and vegetable intake and breast cancer risk. Summary of the linear dose-response meta-analysis in the CUP (no dose-response meta-analysis was conducted in the 2005 SLR)

	Breast cancers (any)	**Premenopausal**	**Postmenopausal**
Increment unit used	200 g/day		
Studies (n)	9	2	4
Cases (total number)	6825	899	2894
RR (95%CI)	0.97 (0.94-1.01)	1.02 (0.78-1.34)	1.02 (0.98-1.06)
Heterogeneity (I^2, p-	21.8%, p=0.25	86.5%, p=0.007	0%, p=0.58
P value Egger test	0.08	-	-

Stratified analyses

Geographic area	**Asia**	**Europe**	**North-America**
Studies (n)	2	3	4
RR (95%CI)	1.02 (0.94-1.10)	0.98 (0.88-1.10)	0.96 (0.91-1.01)
Heterogeneity (I^2, p- value)	0%, p=0.42	75.3%, p=0.04	6.6%, p=0.36

Table 24 Fruit and vegetable intake and hormone receptor-defined breast cancer risk. Summary of the linear dose-response meta-analysis in the CUP SLR

ER-status	**ER+PR+**	**ER+PR-**	**ER-PR-**
Increment unit used	200 g/day	200 g/day	200 g/day
Studies (n)	3	3	3
Cases	3950	1229	1346
RR (95%CI)	0.99 (0.96-1.02)	1.03 (0.88-1.22)	0.93 (0.88-0.99)
Heterogeneity (I^2, p-value)	0%, 0.99	55%, 0.11	0%, 0.88

Table 25 Fruits and vegetables and breast cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Pooled analyses								
Aune D, 2012	6	6273	North America, Denmark, Sweden	Incidence, all	Highest vs. lowest category	0.89 (0.80-0.99)	-	0%, p=0.67
					Per 200 g/d	0.96 (0.93-1.00)	-	2%, p=0.41
Jung S, 2013	20	34526	North America, Netherlands, Sweden, Italy, Australia, Japan	Incidence, all	Quintile 5 vs. 1, all	0.98 (0.93-1.02)	0.30	0.16
					Quintile 5 vs. 1, ER-	0.90 (0.81-1.01)	0.03	0.25
					Quintile 5 vs. 1, ER+	1.00 (0.94-1.07)	0.91	0.06
					Quintile 5 vs. 1, PR-	0.97 (0.87-1.09)	0.60	0.04
					Quintile 5 vs. 1, PR+	0.99 (0.92-1.07)	0.88	0.08
					Quintile 5 vs. 1, ER-/PR-	0.93 (0.80-1.08)	0.29	0.06
					Quintile 5 vs. 1, ER-/PR+	0.70 (0.51-0.96)	0.21	0.30
					Quintile 5 vs. 1, ER+/PR-	1.02 (0.90-1.14)	0.41	0.69
					Quintile 5 vs. 1, ER+/PR+	1.00 (0.93-1.08)	0.87	0.12

Table 26 List of studies included in the dose-response analysis of fruit and vegetable intake and breast cancer risk

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors
Makarem, 2015 BRE80589 USA	FHS-Offspring Cohort, Prospective Cohort, W	124/ 1 602 11.5 years	Death certificate and medical records	Semi-quantitative FFQ	Incidence, breast cancer	per 1 points	0.62 (0.37-1.04)	Age, smoking status
Catsburg, 2014a BRE80536 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	48 840 16.6 years	Cancer registry	FFQ	Incidence, Invasive breast cancer	adhered vs not adhered	0.96 (0.87-1.06)	Age, age at first child birth, age at menarche, alcohol, BMI, energy, family history of breast cancer, history of breast disease, HRT use, menopausal status, oc use, parity, physical activity, red and processed meat, sodium, study center, whole grains
					Incidence, Invasive breast cancer	adhered vs not adhered	0.92 (0.83-1.01)	
Wie, 2014 BRE80609 Korea	Cancer Screening Examination Cohort, Korea (CSECK), Prospective Cohort, W	29/ 3 486 7 years	Cancer registry and medical records	3-day food record	Incidence, breast cancer	per 100 g/day	0.90 (0.68-1.18)	Age, alcohol Intake, BMI, educational level, energy, Income, marital status, physical activity, smoking
					Incidence, breast cancer	≥600 vs <600 g/day	0.12 (0.01-1.14)	
Suzuki, 2013 BRE80491 Japan	JPHC, Prospective Cohort, W	452/ 47 289 10.2 years		FFQ	Incidence, breast cancer	per 100 g/day	1.01 (0.97-1.05)	Age, age at first child birth, age at menarche, alcohol, BMI, BMI at age 20 years, height, HRT use, Isoflavone, leisure time physical activity, menopausal status, parity, smoking status, study area, vitamin c supplement
					Incidence, breast cancer	764 vs 246 g/day	1.17 (0.89-1.54)	
					Incidence, breast cancer, postmenopausal	780 vs 255 g/day	1.14 (0.84-1.56)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors
					Incidence, breast cancer unknown ER/PR status	per 100 g/day	0.99 (0.94-1.05)	
					Incidence, breast cancer, premenopausal	703 vs 223 g/day	1.61 (0.90-2.85)	
					Incidence, breast cancer ER+/PR+	per 100 g/day	0.99 (0.91-1.07)	
					Incidence, breast cancer ER-/PR-	per 100 g/day	0.99 (0.89-1.10)	
					Incidence, breast cancer ER+/PR-	per 100 g/day	1.07 (0.97-1.19)	
Löf, 2011 BRE80364 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	1 067/ 44 838 14 years	Cancer registry	FFQ	Incidence, breast cancer	per 200 gday	0.94 (0.86-1.03)	Age, alcohol, BMI, educational level, energy Intake, smoking
Boggs, 2010a BRE80332 USA	BWHS, Prospective Cohort, Age: 21-69 years, W	1 268/ 51 928 554 528 person-years	Self-report verified by medical record	FFQ	Incidence, breast cancer	≥4 vs <1 serving/day	0.87 (0.71-1.07)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, BMI, contraception, educational level, energy Intake, family history of breast cancer, geographic region, HRT use, menopausal status, multivitamin supplement Intake, smoking, vigorous activity
					Incidence, breast cancer, postmenopausal	≥4 vs <1 serving/day	0.76 (0.56-1.04)	
					Incidence, breast cancer, premenopausal	≥4 vs <1 serving/day	0.90 (0.65-1.23)	
					Incidence, breast cancer ER+/PR+	≥4 vs <1 serving/day > 5	0.96 (0.64-1.46)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors
						years		
					Incidence, breast cancer ER-/PR-	≥4 vs <1 serving/day > 5 years	0.79 (0.50-1.24)	
					Incidence, breast cancer ER+/PR-	≥4 vs <1 serving/day > 5 years	1.43 (0.69-2.94)	
Sonestedt, 2008a BRE80192 Sweden	MDCS, Prospective Cohort, Age: 46-75 years, W	544/ 15 773 10.3 years	Cancer registry	7-day food record & FFQ	Incidence, Invasive breast cancer	629 vs 118 g/day	0.78 (0.59-1.03)	Age, age at menopause, alcohol Intake, educational level, exposure assessment, height, household physical activity, Interviewer, menopausal hormone use, parity, physical activity, residual (willet), season of Interview, smoking status, total energy Intake, weight
					Incidence, breast cancer ERα+	per 1 quantile	0.99 (0.92-1.06)	
					Incidence, breast cancer ERβ-	per 1 quantile	0.98 (0.89-1.09)	
					Incidence, breast cancer ERβ+	per 1 quantile	1.00 (0.90-1.10)	
					Incidence, breast cancer ERα+/ERβ+	per 1 quantile	0.98 (0.87-1.09)	
					Incidence, breast cancer ERα+/ERβ-	per 1 quantile	1.00 (0.89-1.12)	
					Incidence, breast cancer ERα-	per 1 quantile	1.03 (0.86-1.24)	
					Incidence, breast cancer, postmenopausal	626 vs 190 g/day	0.78 (0.57-1.05)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors
Olsen, 2003 BRE17890 Denmark	DCH, Prospective Cohort, Age: 50-65 years, W, Postmenopausal	425/ 23 798 4.7 years	Partially histological - over 80%	FFQ	Incidence, breast cancer, postmenopausal	per 100 g/day	1.02 (0.98-1.06)	Age at first child, age-underlying cox models, alcohol, benign breast disease, BMI, duration of HRT use, educational level, HRT use, length of follow-up, parity/pregnancies
					Incidence, breast cancer ER+, postmenopausal	per 100 g/day	1.05 (1.00-1.10)	
					Incidence, breast cancer ER-, postmenopausal	per 100 g/day	0.90 (0.81-0.99)	
Zhang, 1999a BRE13953 USA	NHS, Prospective Cohort, Age: 33-60 years, W, Registered nurses	1 913/ 83 234 14 years	Temp	FFQ-semi-quantitative	Incidence, Invasive breast cancer, postmenopausal	≥5 vs ≤1.9 serving/day	1.03 (0.81-1.31)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, energy Intake , family history, height, HRT use, lenght of follow-up, parity/pregnancies
					Incidence, Invasive breast cancer, premenopausal	≥5 vs ≤1.9 serving/day	0.77 (0.58-1.02)	
Shibata, 1992 BRE80361 USA	Leisure World Cohort, Prospective Cohort, M/W, retirement community, uppermiddle social class	219/ 11 580 70 159 person-years	Community registry	FFQ	Incidence, breast cancer	≥8.3 vs ≤5.8 servings/day	0.87 (0.63-1.21)	Age, smoking status

Table 27 List of studies excluded from the dose-response analysis of fruit and vegetable intake and breast cancer risk

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Emaus, 2013 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Mean age: 50.8 years, W	10 197/ 335 054 11.5 years	Cancer registries, health Insurance records, pathology rec & active follow up	Country-specific dietary questionnaires	Incidence, invasive breast cancer	≥798 vs ≤182 g/day Per 200 g/day	0.90 (0.83-0.97) Ptrend: 0.02 0.99 (0.97-1.01)	Energy intake, saturated fat intake, age at menarche, OC use, age at first full-term pregnancy, menopausal status, HRT use, BMI, BMI x menopausal status, physical activity, smoking status and intensity, alcohol use, alcohol consumption, education level, stratified by age and centre	Excluded, article identified after end date of search
		3 479/			ER+PR+	≥798 vs ≤182 g/day Per 200 g/day	0.86 (0.76-0.99) Ptrend: 0.04 0.99 (0.96-1.03)		Included in the analysis of breast cancer hormone receptor subtype
		1 075/			ER+PR-	≥798 vs ≤182 g/day Per 200 g/day	0.80 (0.62-1.02) Ptrend: 0.04 0.94 (0.88-1.00)		
		1 021/			ER-PR-	≥798 vs ≤182 g/day Per 200 g/day	0.70 (0.54-0.89) Ptrend: <0.01 0.93 (0.87-0.99)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Catsburg, 2014a BRE80536 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	48 840 16.6 years	Cancer registry	FFQ	Incidence, Invasive breast cancer	adhered vs not adhered	0.96 (0.87-1.06)	Age, age at first child birth, age at menarche, alcohol, BMI, energy, family history of breast cancer, history of breast disease, HRT use, menopausal status, oc use, parity, physical activity, red and processed meat, sodium, study center, whole grains	
					Incidence, Invasive breast cancer	adhered vs not adhered	0.92 (0.83-1.01)		
Fung, 2013 BRE80466 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Postmenopausal	792/ 75 929 24 years	Questionnaire, medical records or pathology reports, death certificate, physician, family member	FFQ	Incidence, breast cancer ER-	9.1 vs 3.1 servings/day	0.82 (0.62-1.08)	Age, alcohol, benign breast disease, BMI at age 18 years, diet, energy, height, HRT use, physical activity, smoking, weight change	Not enough studies for analyses of ER- tumors
Fung, 2011 BRE80385 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Postmenopausal	827/ 866 621 26 years	Self-reported/death certificate/pathology reports	FFQ	Incidence, breast cancer ER-	13.4 vs 2.6 serving/day	0.71 (0.55-0.90)	Age, alcohol, benign breast disease, BMI, energy, family history of breast cancer, height, HRT use, mulitivitamin Intake, physical activity, smoking, weight at 18 yrs	Not enough studies for analyses of ER- tumors

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Ravn-Haren, 2006 BRE80151 Denmark	DCH, Nested Case Control, Age: 50-64 years, Postmenopausal	377/ 377 controls	Cancer registry	FFQ	Incidence, breast cancer, postmenopausal	per 100 g/day	1.07 (1.00-1.14)	Age at first child birth, alcohol consumption, benign breast disease, BMI, educational level, HRT use, number of children, parity, selenium Intake, smoking habits	Duplicate, overlap with Olsen, 2003 BRE17890
Mattisson, 2004b BRE16042 Sweden	MDCS, Prospective Cohort, Age: 50- years, W, Postmenopausal	342/ 11 726 11 years	Partially histological - over 80%	7-day record + questionnaire	Incidence, Invasive & In situ breast cancer, postmenopausal	600 vs 210 g/day	0.78 (0.54-1.13)	Age , age at first child, age at menarche, educational level, energy Intake , height, HRT use, Interviewer, leisure time physical activity, other design Issue, other nutritional factors, season of Interview, waist circumference	Duplicate, overlap with Sonestedt, 2008a BRE80192

Figure 28 RR estimates of breast cancer by levels of fruit and vegetable intake

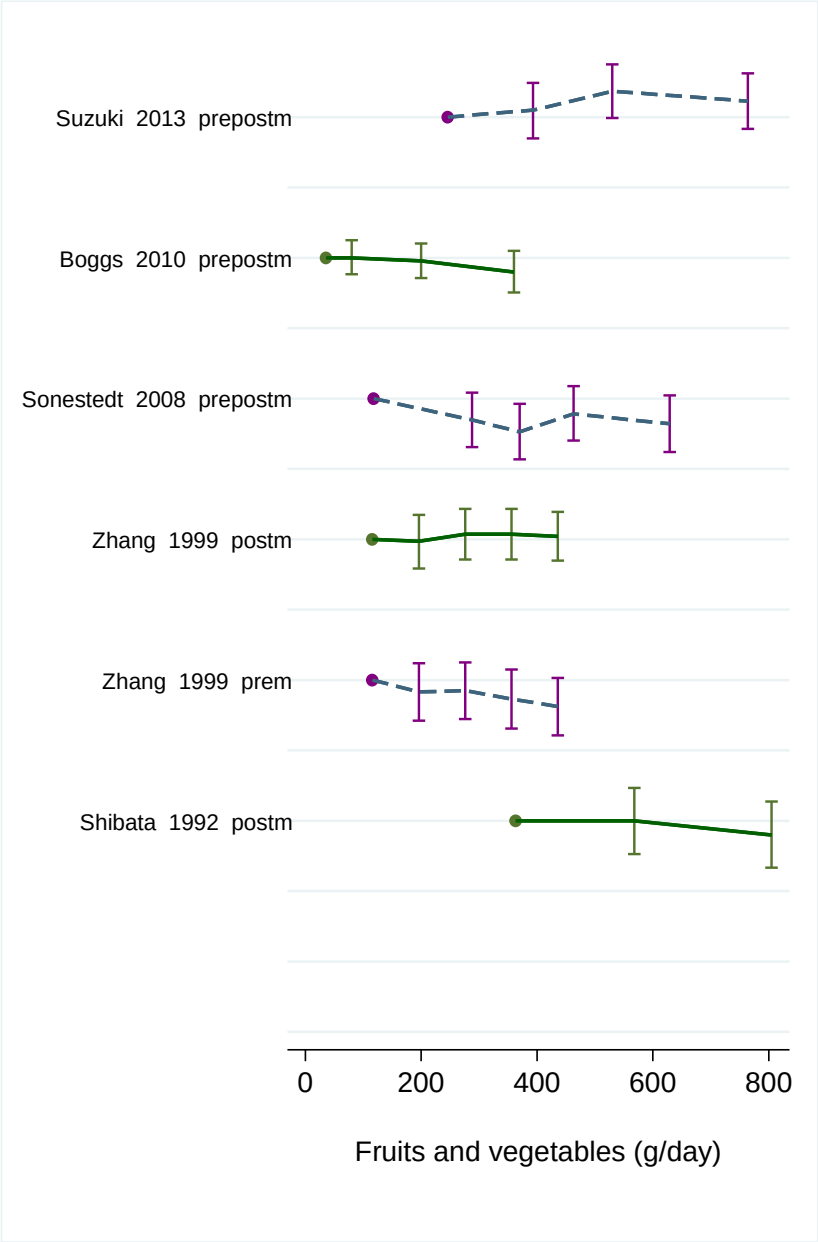


Figure 29 Relative risk of breast cancer for the highest compared with the lowest level of fruit and vegetable intake

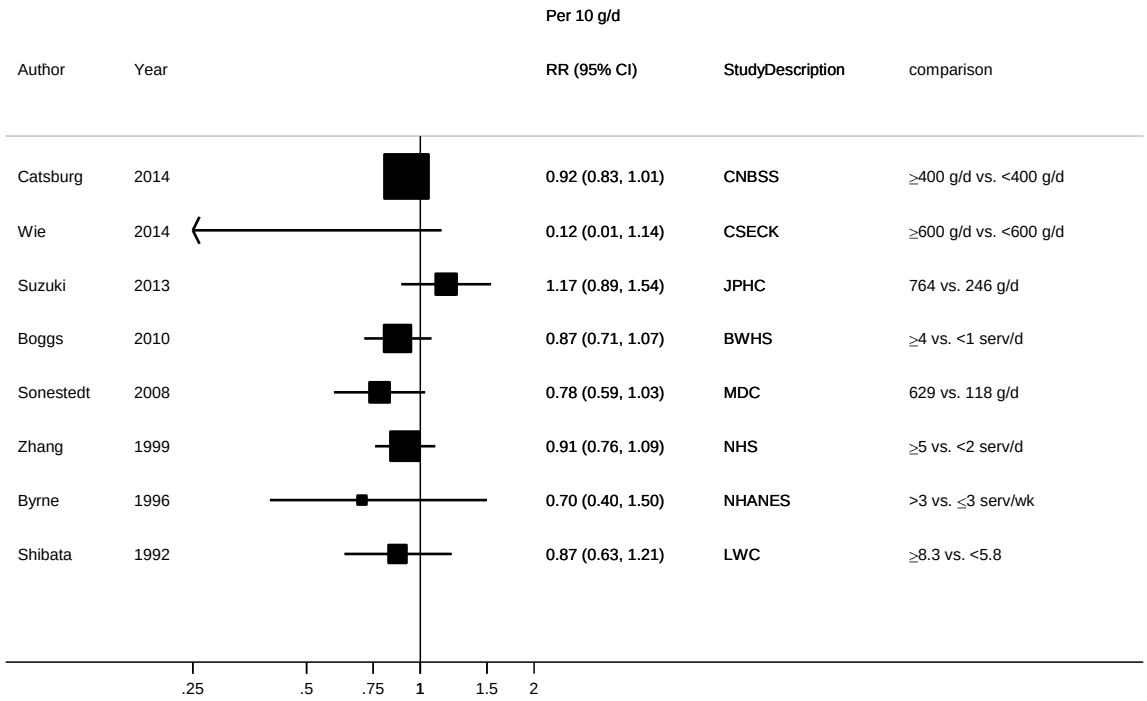


Figure 30 Relative risk of breast cancer for the highest compared with the lowest level of fruit and vegetable intake, stratified by menopausal status

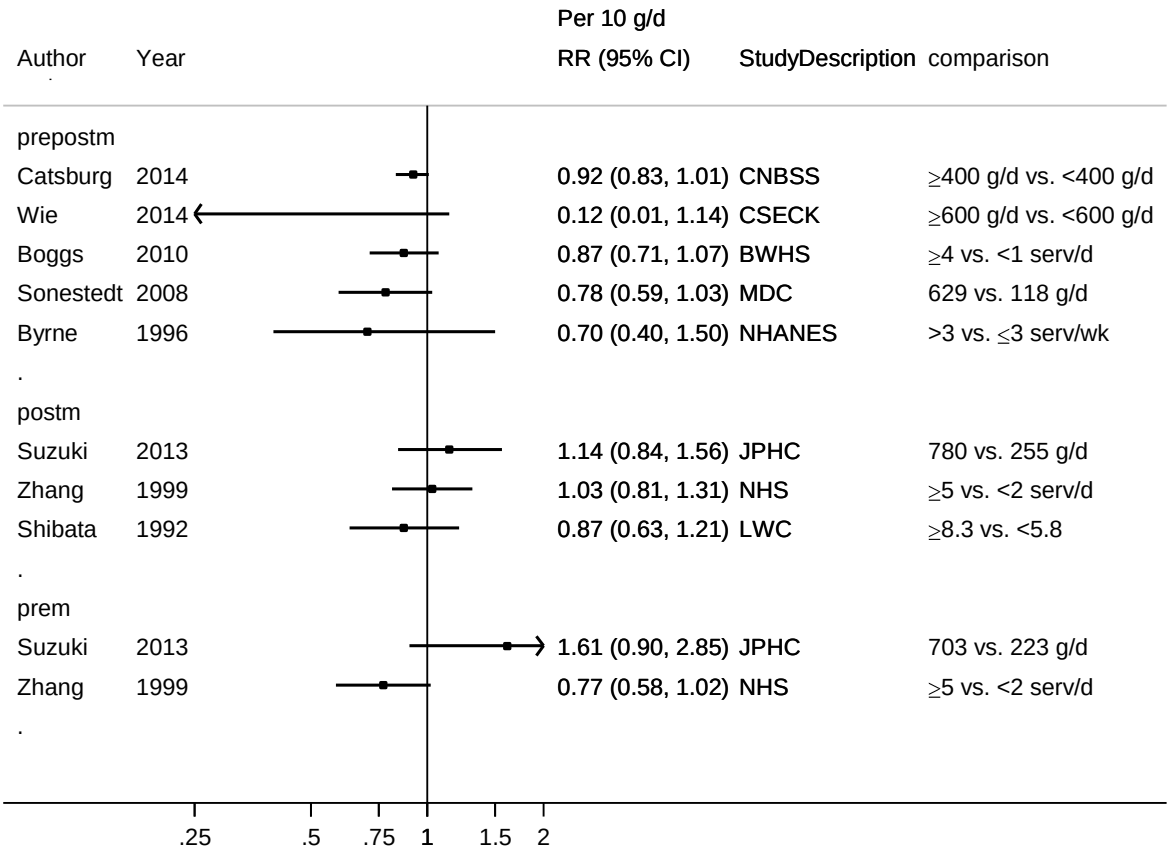


Figure 31 Relative risk of breast cancer for 200 g/day increase in fruit and vegetable intake

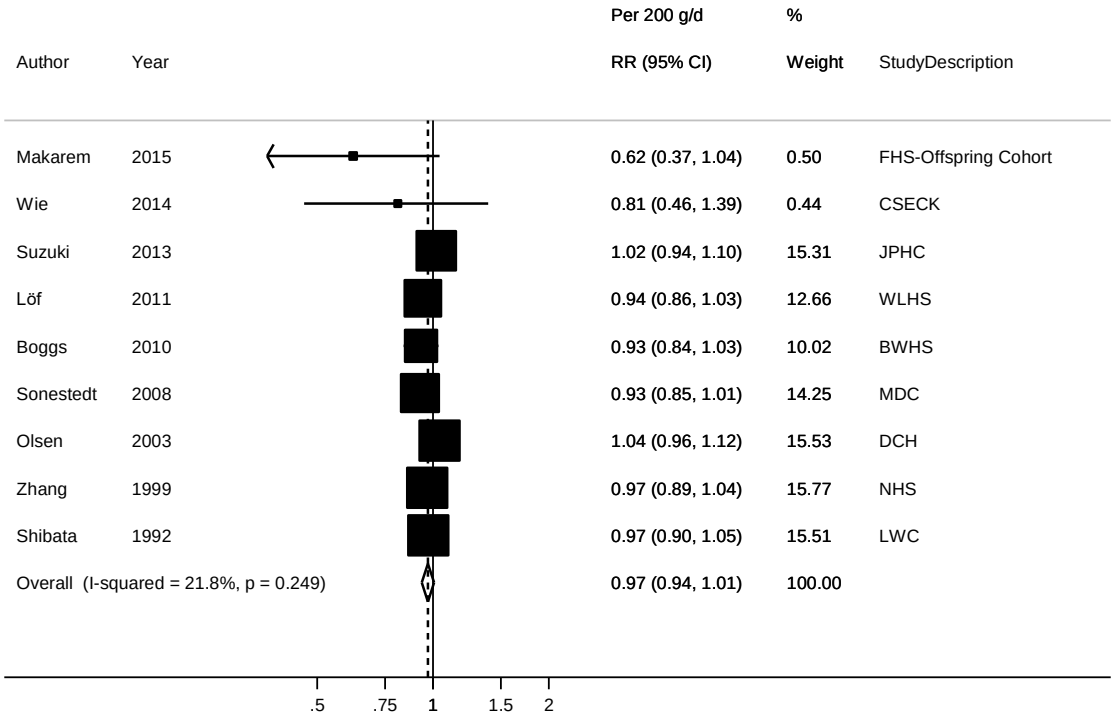


Figure 32 Relative risk of breast cancer for 200 g/day increase in fruit and vegetable intake, stratified by menopausal status

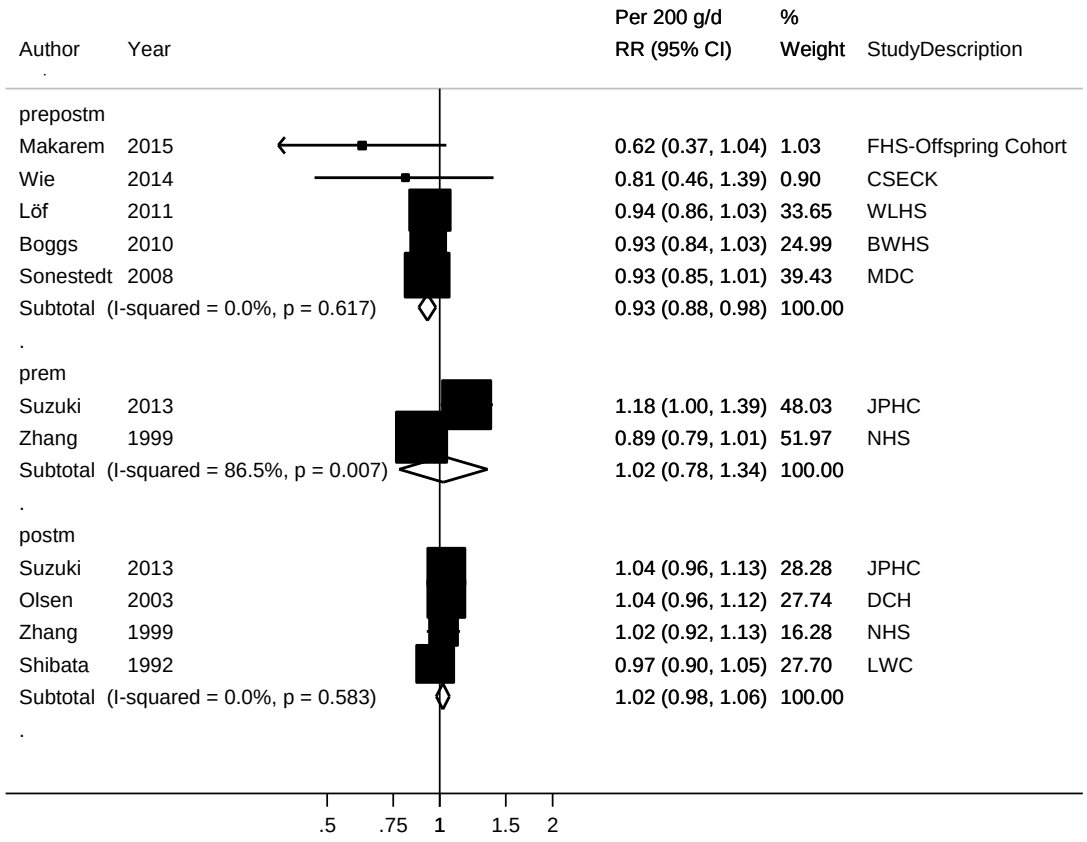
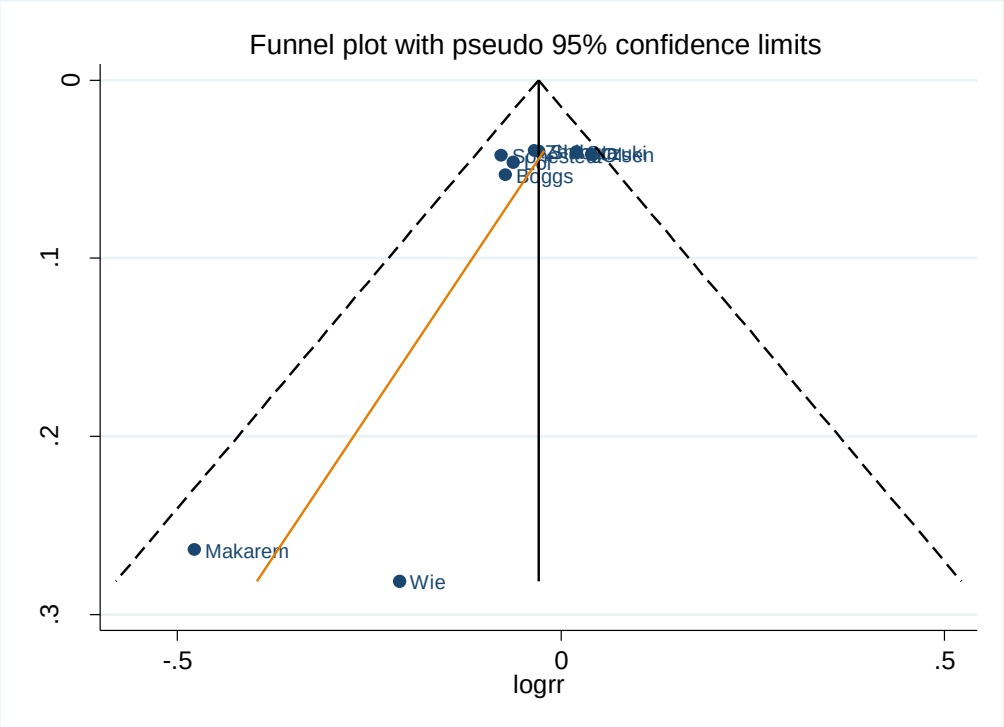
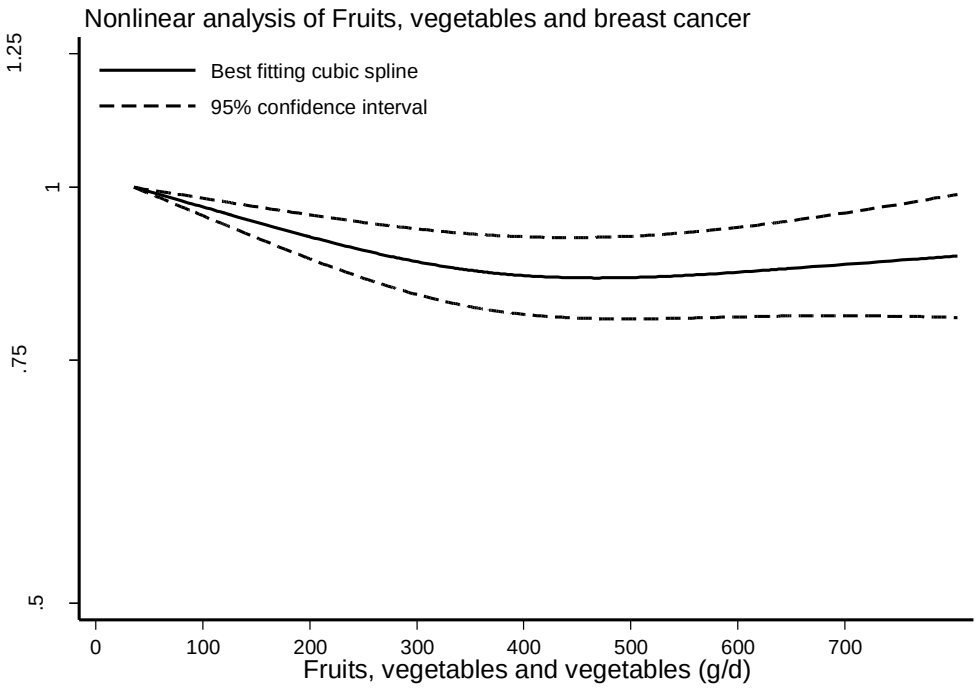


Figure 33 Funnel plot of studies included in the dose response meta-analysis of fruit and vegetable intake and breast cancer



Egger, p=0.09

Figure 34 Fruit and vegetables and breast cancer, nonlinear dose-response analysis



P nonlinearity=0.001

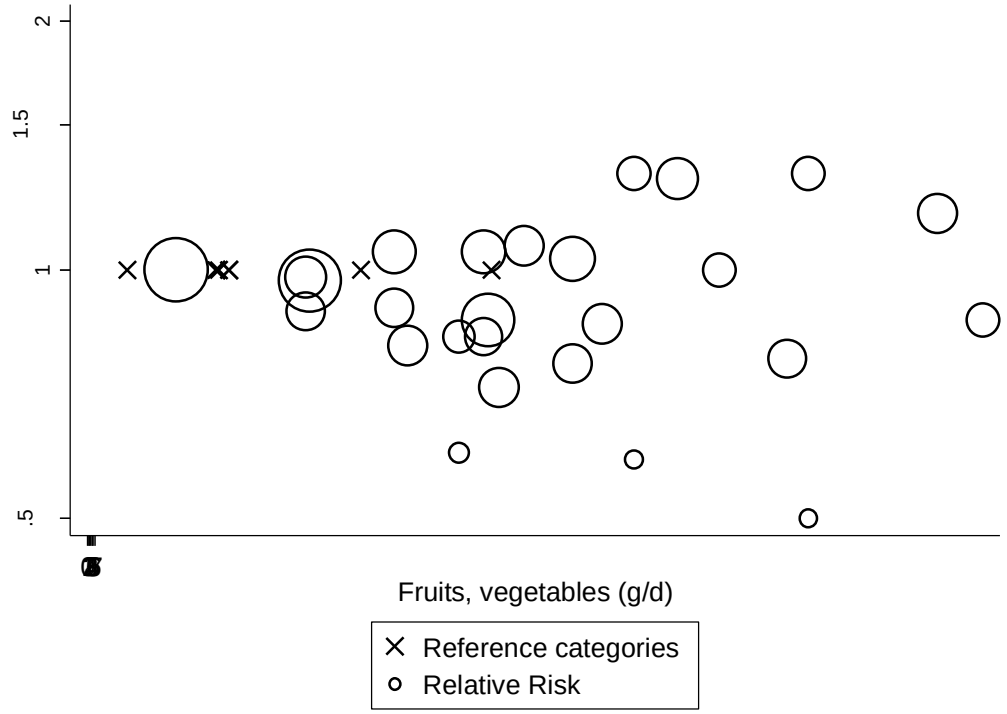
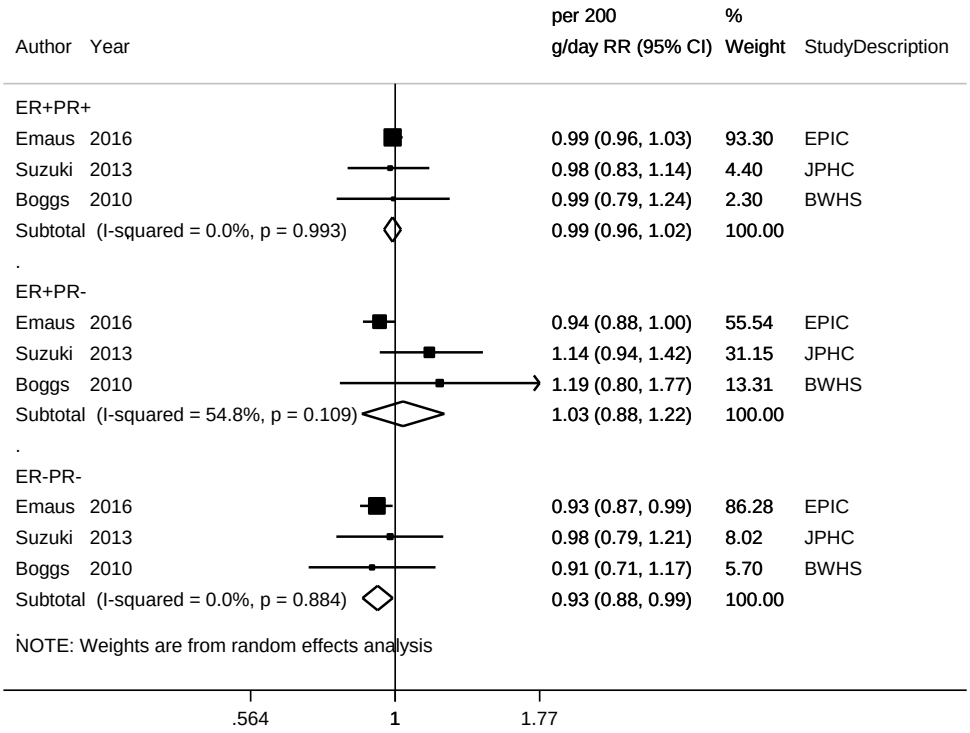


Table 28 Relative risk of breast cancer and fruit and vegetables estimated using non-linear models

Fruit and vegetables (g/day)	RR (95%CI)
36.0	1.00
100	0.95 (0.93-0.97)
200	0.90 (0.86-0.95)
300	0.87 (0.81-0.92)
400	0.85 (0.79-0.91)
500	0.84 (0.78-0.91)
600	0.85 (0.79-0.92)
700	0.86 (0.79-0.95)
800	0.88 (0.79-0.97)

Figure 35 Relative risk of breast cancer for 200 g/day increase in fruit and vegetable intake, stratified by hormone receptor status



2.2.1. Vegetables

Thirteen studies on vegetable intake and breast cancer risk were identified. Eight studies investigated postmenopausal breast cancers, three were on premenopausal breast cancers, and four were on pre- and postmenopausal breast cancers combined. Study characteristics and results for all cancer types are shown in the Table.

Study quality:

Vegetable intake was estimated from food intake assessed by FFQ in all studies. One study used a combination of dietary assessment methods including FFQ, dietary records, and dietary interviews (Buckland, 2013).

Loss to follow-up was low for the studies that reported such data, although some studies did not provide data.

Cancers were identified by record linkages to health registries, cancer registries, mortality registries, or death indexes.

All studies adjusted for at least age, and most of the studies adjusted for most of the established breast cancer risk factors, including: age, parity, age at menarche, age at menopause, physical activity, BMI, and alcohol consumption.

Breast cancer (any)

Twelve studies (24756 cases) were included in the dose-response meta-analysis. The summary RR for a 200 g/d increase in vegetable intake was 0.98 (95% CI: 0.93-1.02) and there was low heterogeneity, I^2=26.5%, $p_{heterogeneity}$=0.18. There was no evidence of small study bias or publication bias with Egger's test, p=0.75. The summary RR ranged from 0.95 (95% CI: 0.92-0.98) when the NIH-AARP Diet and Health Study (George, 2009a) was excluded to 0.99 (95% CI: 0.93-1.05) when the EPIC study (Buckland, 2013) was excluded.

Nonlinear dose-response analysis

There was no indication of a nonlinear association, $p_{nonlinearity}$=0.82 in the overall analysis, however, for postmenopausal breast cancer, there was indication of nonlinearity, $p_{nonlinearity}$=0.006, with a suggestive weak positive association (4-6% increase in the relative risk) from 100 grams/day and above.

Premenopausal breast cancer

Three studies (1635 cases) were included in the dose-response meta-analysis of vegetable intake and premenopausal breast cancer. The summary RR per 200 g/day increase in vegetable intake was 0.96 (95% CI: 0.83-1.11) and there was no heterogeneity, I^2=0%, $p_{heterogeneity}$=0.43.

Postmenopausal breast cancer

Eight studies (10891 cases) were included in the dose-response meta-analysis of vegetable intake and postmenopausal breast cancer. The summary RR per 200 g/d increase in vegetable intake was 1.03 (95% CI: 0.97-1.09), with low heterogeneity, I^2=0.0%, $p_{heterogeneity}$=0.45.

Breast cancer risk by hormone receptor status

Total vegetable consumption was statistically significantly inversely associated with risk of ER− breast cancer (pooled multivariable RR comparing the highest vs lowest quintile = 0.82, 95% CI = 0.74-0.90, ptrend<0.01), but not with the risk of ER+ breast cancer (RR same comparison =1.00, 95% CI=0.94-1.07), PR- cancers (RR =0.97, 95% CI=0.87-1.09), and PR+ cancers (RR=0.99 95% CI= 0.92-1.07) in the Pooling project of cohort studies (Jun, 2013). The pooled multivariable relative risks for ER− breast cancer for a 300g/day increment (approximately three servings/day) in intake was 0.88 (95% CI = 0.81 to 0.95) (Pheterogeneity > 0.34). In continuous increments, total vegetable intake was non-statistically significantly inversely associated with risk of PR− breast cancer. No associations or non-statistically significant positive associations were observed for the risk of ER+ and PR+ breast cancer (data not shown in the publication). When breast cancers were classified simultaneously by ER and PR status, inverse significant associations were observed for ER-PR- and ER-PR+ breast cancers. The pooled multivariable RR comparing the highest vs lowest quintile of vegetable intakes were 0.84, 95% CI = 0.75-0.93 for ER-PR-, ptrend=0.001; 0.68, 95% CI = 0.51-0.90, ptrend=0.04 for ER-PR+; 1.04, 95% CI = 0.89-1.20 for ER+PR- and 1.04, 95% CI = 0.98-1.11 for ER+PR+ breast cancers.

A statistically signficant inverse association with ER-PR- breast cancer (RR per 200 g/day=0.79, 95% CI=0.63-0.98) (I^2=37%, P=0.21) was also observed in the meta-analysis of

three studies that reported results by hormone receptor status (Emaus, 2016, EPIC (identified after the search period); Suzuki, 2013, JPHC; Boggs, 2010, BWHS). Inverse but not significant associations were observed for ER+PR+ breast cancer (RR=0.96, 95% CI=0.81-1.13) (I^2=39%, P=0.19) and ER+PR- breast cancer (RR=0.89, 95% CI=0.79-1.01) (I^2=0%, P=0.39).

The Nurses' Health Study (Fung, 2013) reported a non-significant inverse association with ER-negative breast cancer in postmenopausal women (RR for highest vs lowest intake=0.81, 95% CI=0.61-1.06).

Table 29 Vegetable intake and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	13 studies (22 publications)
Studies included in forest plot of highest compared with lowest intake	Breast cancer: 11 studies Premenopausal: 3 Postmenopausal: 7
Studies included in linear dose-response meta-analysis	Breast cancer: 12 studies Premenopausal: 3 Postmenopausal: 8
Studies included in non-linear dose-response meta-analysis	Breast cancer: 10 studies Premenopausal: not enough studies Postmenopausal: 7

Table 30 Vegetable intake and breast cancer risk. Summary of the linear dose-response meta-analysis in the CUP

	CUP			**2005 SLR***
	Breast cancer (any)	**Premenopausal**	**Postmenopausal**	**Breast cancers (any)**
Increment unit used	200 g/day			100 g/d
Studies (n)	12	3	8	2
Cases (total number)	24756	1635	10891	649
RR (95%CI)	0.98 (0.93-1.02)	0.96 (0.83-1.11)	1.03 (0.97-1.09)	0.95 (0.88-1.03)
Heterogeneity (I^2, p-	26.5%, p=0.18	0%, p=0.43	0%, p=0.45	89.7%, p=NA
P value Egger test	0.75	-	0.004	-

***** One of the studies (Li et al, 2005) included in the 2005 SLR dose-response analysis was previously considered a nested case-control study, but on closer inspection was actually a case-control study and was excluded from the CUP analysis.

Table 31 Vegetable intake and breast cancer risk. Pooling Project of Cohort Studies and not overlapping studies identified in the CUP

	All breast
Increment unit used	High vs. low
Studies (n)	25
Cases (total number)	46743
RR (95%CI)	0.97 (0.91-1.02)
Heterogeneity (I^2, p-	31.2%, p=0.20
P value Egger test	0.72

Stratified analyses

Geographic area	**Asia**	**Europe**	**North-America**
Studies (n)	2	3	6
RR (95%CI)	0.94 (0.82-1.08)	0.95 (0.91-0.99)	1.00 (0.93-1.08)
Heterogeneity (I^2, p- value)	0%, p=0.38	0%, p=0.69	35.0%, p=0.17

Table 32 Vegetable intake and hormone receptor-defined breast cancer risk. Summary of the linear dose-response meta-analysis in the CUP SLR

ER-status	**ER+PR+**	**ER+PR-**	**ER-PR-**
Increment unit used	200 g/day	200 g/day	200 g/day
Studies (n)	3	3	3
Cases	3950	1229	1346
RR (95%CI)	0.96 (0.81-1.13)	0.89 (0.79-1.01)	0.79 (0.63-0.98)
Heterogeneity (I^2, p-value)	39%, 0.19	0%, 0.39	37%, 0.21

Table 33 Vegetables and breast cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Aune et al, 2012	9	16 600	North America, Europe, Asia	Incidence	High vs. low Per 200 g/d	0.99 (0.92-1.06) 1.00 (0.95-1.06)	- -	0.26 0.29
Pooled analyses								
Jung et al, 2013	20	34 526	North America, Europe, Asia	Incidence, ER/PR +/- status	Quintile 5 vs. 1	0.99 (0.95-1.04), all 0.82 (0.74-0.90), ER- 1.04 (0.97-1.11), ER+ 0.94 (0.84-1.03), PR- 1.02 (0.96-1.10), PR+	0.77 <0.001 0.06 0.30 0.45	0.21 0.50 0.04 0.08 0.15
Smith-Warner, 2001a	8 prospective cohort studies (The Nurses' Health Study was divided into 2 studies)	7 377	North America, Canada,The Netherlands, Sweden	Incidence, menopausal status	Per 100g/day Breast cancer Premenopausal breast cancer Postmenopausal breast cancer Quintile 4 vs. 1 Breast cancer	 1.00 (0.97-1.02) 0.99 (0.93-1.06) 1.00 (0.97-1.02) 0.96 (0.89-1.04)	 - - - 0.54	 0.50 0.34 0.31 0.73

Table 34 Vegetable intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Makarem, 2015 BRE80589 USA	FHS-Offspring Cohort, Prospective Cohort, W	124/ 1 602 11.5 years	Death certificate and medical records	Semi-quantitative FFQ	Incidence, breast cancer	per 1 points	0.74 (0.48-1.12)	Age, smoking status
Couto, 2013 BRE80454 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	1 278/ 49 258 16 years	Cancer registry	FFQ	Incidence, breast cancer	per 50 g/day	1.01 (0.95-1.07)	Age at first child birth, age at menarche, alcohol, benign breast disease, beverage Intake, cereal, dairy products consumption, educational level, egg, energy Intake, fish, fruits, height, history of breast cancer, legumes, meat, number of childbirths, potatoes, ratio unsat/sat fat, smoking, sweet products
					Incidence, breast cancer, premenopause	per 50 g/day	1.02 (0.96-1.08)	
					Incidence, breast cancer, postmenopause	per 50 g/day	0.97 (0.89-1.06)	
Buckland, 2013 BRE80433 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	10 225/ 335 062 11 years	Cancer registries, health Insurance records, pathology rec & active follow up	Questionnaire	Incidence, breast cancer	Q 3 vs Q 1	0.93 (0.88-0.98)	Age, age at first child birth, age at menarche, age at menopause, alcohol, BMI, breastfeeding, centre location, cereal, dairy products consumption, educational level, energy, fish, fruits, height, HRT use, legumes, legumes, meat, oil, oral contraceptive history, physical activity, saturated fat, smoking
Suzuki, 2013 BRE80491 Japan	JPHC, Prospective Cohort,	452/ 47 289 10.2 years		FFQ	Incidence, breast cancer	per 100 g/day	0.98 (0.91-1.05)	Age, age at first child birth, age at menarche, alcohol, BMI, BMI at age 20 years, fruits, height,
					Incidence, breast	384 vs 111	1.02 (0.77-1.34)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	W				cancer	g/day		HRT use, Isoflavone, leisure time physical activity, menopausal status, parity, smoking status, study area, vitamin c supplement
					Incidence, breast cancer, postmenopausal	393 vs 114 g/day	1.03 (0.75-1.41)	
					Incidence, breast cancer unknown ER/PR status	per 100 g/day	1.00 (0.91-1.10)	
					Incidence, breast cancer, premenopausal	348 vs 104 g/day	0.95 (0.54-1.69)	
					Incidence, breast cancer ER+/PR+	per 100 g/day	0.89 (0.77-1.04)	
					Incidence, breast cancer ER-/PR-	per 100 g/day	0.93 (0.76-1.13)	
					Incidence, breast cancer ER+/PR-	per 100 g/day	1.04 (0.87-1.25)	
Boggs, 2010a BRE80332 USA	BWHS, Prospective Cohort, Age: 21-69 years, W	1 268/ 51 928 554 528 person-years	Self-report verified by medical record	FFQ	Incidence, breast cancer	≥2 vs <4 serving/week	0.87 (0.73-1.05)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, BMI, contraception, educational level, energy Intake, family history of breast cancer, geographic region, HRT use, menopausal status, multivitamin supplement Intake, parity, smoking, vigorous activity
					Incidence, breast cancer, postmenopausal	≥2 vs <4 serving/week	0.86 (0.65-1.14)	
					Incidence, breast cancer, premenopausal	≥2 vs <4 serving/week	0.82 (0.62-1.08)	
					Incidence, breast cancer ER+/PR+	≥2 vs <4 serving/week	1.41 (0.97-2.04)	
					Incidence, breast	≥2 vs <4	0.57 (0.38-0.85)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					cancer ER-/PR-	serving/week		
					Incidence, breast cancer ER+/PR-	≥2 vs <4 serving/week	1.20 (0.61-2.36)	
Brasky, 2010 BRE80362 USA	VITAL, Prospective Cohort, Age: 50-76 years, W	880/ 35 016	Cancer registry	FFQ	Incidence, breast cancer	≥2.86 vs 0-1.73 servings/day	0.97 (0.82-1.15)	Age
Butler, 2010 BRE80295 Singapore	SCHS, Prospective Cohort, Age: 45-74 years, W	439/ 34 028 10.7 years	Cancer registry	FFQ	Incidence, breast cancer, postmenopause	173.7 vs 51 g/day	0.86 (0.63-1.16)	Age, BMI, dialect group, educational level, energy Intake, family history of cancer, parity, year of Interview
George, 2009a BRE80360 USA	NIH-AARP, Prospective Cohort, Age: 615 years, W, Retired	5 815/ 195 229 8 years	Cancer registry	FFQ	Incidence, breast cancer	1.43-4.38 vs 0-0.56 cup/day	1.08 (1.00-1.18)	Age, alcohol, BMI, educational level, energy Intake, family history, fruits, marital status, menopausal hormone use, physical activity, race, smoking
Zhang, 1999a BRE13953 USA	NHS, Prospective Cohort, Age: 33-60 years, W, Registered nurses	1 913/ 83 234 14 years	Temp	FFQ-semi-quantitative	Incidence, Invasive breast cancer, postmenopausal	≥5 vs ≤1.9 serving/day	1.02 (0.85-1.24)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, energy Intake , family history, height, HRT use, lenght of follow-up, parity/pregnancies
					Incidence, Invasive breast cancer, premenopausal	≥5 vs ≤1.9 serving/day	0.64 (0.43-0.95)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Verhoeven, 1997 BRE12868 Netherlands	NLCS, Case Cohort, Age: 55-69 years, W	519/ 62 573 4.3 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, Invasive breast cancer,	303 vs 108 g/day	0.94 (0.67-1.31)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, energy Intake , family history, parity/pregnancies
Rohan, 1993 BRE17965 Canada	CNBSS, Nested Case Control, Age: 40-59 years, W, Screening Program	518/ 1182 controls 6 years	All histology	Dietary history questionnaire	Incidence, breast cancer,	≥433.1 vs ≤203 g/day	0.86 (0.61-1.23)	Age , age at first child, age at menarche, benign breast disease, educational level, energy Intake , family history, food, menopausal status
Shibata, 1992 BRE80361 USA	Leisure World Cohort, Prospective Cohort, M/W, retirement community, uppermiddle social class	219/ 11 580 70 159 person-years	Community registry	FFQ	Incidence, breast cancer	≥4.8 vs ≤3.1 servings/day	0.96 (0.69-1.34)	Age, smoking status

Table 35 Vegetable intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Emaus, 2013 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Mean age: 50.8 years, W	10 197/ 335 054 11.5 years	Cancer registries, health Insurance records, pathology rec & active follow up	Country-specific dietary questionnaires	Incidence, invasive breast cancer	≥402 vs ≤77 g/day Per 100 g/day	0.86 (0.80-0.94) Ptrend<0.01 0.97 (0.95-0.99)	Energy intake, saturated fat intake, age at menarche, OC use, age at first full-term pregnancy, menopausal status, HRT use, BMI, BMI x menopausal status, physical activity, smoking status and intensity, alcohol use, alcohol consumption, education level, fruit intake, stratified by age and centre	Excluded, article identified after end date of search
		3 479/			ER+PR+	≥402 vs ≤77 g/day Per 100 g/day	0.90 (0.79-1.04) Ptrend: 0.13 0.98 (0.95-1.02)		Included in the analysis of breast cancer hormone receptor subtype
		1 075/			ER+PR-	≥402 vs ≤77 g/day Per 100 g/day	0.81 (0.63-1.05) Ptrend: 0.07 0.93 (0.87-0.99)		
		1 021/			ER-PR-	≥402 vs ≤77 g/day Per 100 g/day	0.76 (0.58-0.98) Ptrend: 0.05 0.92 (0.86-0.99)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Fung, 2013 BRE80466 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Postmenopausal	792/ 75 929 24 years	Questionnaire, medical records or pathology reports, death certificate, physician, family member	FFQ	Incidence, breast cancer ER-	5.6 vs 1.7 servings/day	0.81 (0.61-1.06)	Age, alcohol, benign breast disease, BMI at age 18 years, diet, energy, height, HRT use, physical activity, smoking, weight change	Not enough studies for analyses of ER- tumours
Masala, 2012 BRE80402 Italy	EPIC-Italy, Prospective Cohort, Age: 36-64 years, W	1 072/ 31 510 11.25 years	Cancer registry	FFQ	Incidence, breast cancer	≥264.8 vs ≤107.8 g/day	0.65 (0.53-0.81)	Age at menarche, alcohol, centre location, educational level, energy Intake, height, HRT use, menopausal status, number of children, physical activity, smoking, weight	Duplicate, overlap with Buckland, 2013 BRE80433
Fung, 2011 BRE80385 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Postmenopausal	827/ 866 621 26 years	Self reported/death certificate/pathology reports	FFQ	Incidence, breast cancer ER-	6.5 vs 1.2 serving/day	0.76 (0.60-0.95)	Age, alcohol, benign breast disease, BMI, energy, family history of breast cancer, height, HRT use, multivitamins Intake, physical activity, smoking, weight at 18 yrs	Not enough studies for analyses of ER- tumours
Trichopoulou, 2010 BRE80320 Greece	EPIC-Greece, Prospective Cohort, Age: 20-68 years	240/ 14 807 9.8 years	Medical records and pathology reports	FFQ	Incidence, breast cancer, postmenopausal	per 227 g/day	0.91 (0.70-1.18)	Age, age at first child birth, age at menarche, age at menopause, BMI, educational level, energy Intake, height, HRT use, menopausal status, metabolic equivalents, parity, smoking	Duplicate, overlap with Buckland, 2013 BRE80433
					Incidence, breast cancer, premenopausal	per 227 g/day	0.95 (0.78-1.15)		
					Incidence, breast cancer	per 227 g/day	0.95 (0.82-1.11)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Sonestedt, 2008a BRE80192 Sweden	MDCS, Prospective Cohort, Age: 46-75 years, W	544/ 15 773 10.3 years	Cancer registry	7-day food record & FFQ	Incidence, Invasive breast cancer	312 vs 82 g/day	0.84 (0.64-1.11)	Age, age at menopause, alcohol Intake, educational level, exposure assessment, height, household physical activity, Interviewer, menopausal hormone use, parity, physical activity, residual (willet), season of Interview, smoking status, total energy Intake, weight	Duplicate, overlap with Buckland, 2013 BRE80433
					Incidence, breast cancer ERα+	per 1 quantile	1.01 (0.94-1.09)		
					Incidence, breast cancer ERβ-	per 1 quantile	1.05 (0.95-1.17)		
					Incidence, breast cancer ERβ+	per 1 quantile	0.96 (0.87-1.07)		
					Incidence, breast cancer ERα+/ERβ+	per 1 quantile	0.94 (0.84-1.05)		
					Incidence, breast cancer ERα+/ERβ-	per 1 quantile	1.10 (0.98-1.23)		
					Incidence, breast cancer ERα-	per 1 quantile	0.99 (0.82-1.18)		
Fung, 2006 BRE80107 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Postmenopausal	575/ 121 700 18 years	Medical records	FFQ	Incidence, breast cancer ER-,	≥7 vs ≤1.9 times/week	0.67 (0.53-0.87)	Alcohol, benign breast disease, BMI, BMI, body weight, energy Intake , family history, HRT use, physical activity , smoking habits, supplements	Not enough studies for analyses of ER- tumors

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
van Gils CH, 2005 BRE80167	EPIC, Prospective Cohort, Age: 25-70 years	3 659/ 285 526 5.4 years		Diet questionnaire	Incidence, breast cancer	≥309.1 vs ≤109	0.98 (0.84-1.14)	Age at menarche, alcohol Intake, energy Intake, height, HRT use, menopausal status, oral contraceptive use, parity, physical activity, saturated fat Intake, smoking status, weight	Duplicate, overlap with Buckland, 2013 BRE80433
Fung, 2005 BRE22370 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	71 058 16 years	Medical records + self-reported	FFQ	Incidence, breast cancer ER-, postmenopausal	per 1 serving	0.94 (0.88-0.99)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, energy Intake , family history, height, HRT use, menopausal status, other anthropometric Index, parity/pregnancies, physical activity , smoking habits, supplements	Not enough studies for analyses of ER- tumors
Frazier, 2004 BRE02942 USA	NHS II, Historical Cohort, Age: 34-51 years, W, Registered nurses	361/ 47 355 9 years	All histology	FFQ	Incidence, breast cancer, premenopausal	5.3 vs 1.3 serving/day	1.00 (0.69-1.44)	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, energy Intake , family history, menopausal status, oc use, other anthropometric Index, other design Issue, parity/pregnancies	Adolescent diet

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Olsen, 2003 BRE17890 Denmark	DCH, Prospective Cohort, Age: 50-65 years, W, Postmenopausal	425/ 23 798 4.7 years	Partially histological - over 80%	FFQ	Incidence, breast cancer, postmenopausal	per 100 g/day	0.98 (0.89-1.09)	Age at first child, age-underlying cox models, alcohol, benign breast disease, BMI, duration of HRT use, educational level, HRT use, lenght of follow-up, nutrients, nutrients, parity/pregnancies	Duplicate, overlap with Buckland, 2013 BRE80433
					Incidence, breast cancer ER+, postmenopausal	per 100 g/day	1.01 (0.90-1.13)		
					Incidence, breast cancer ER-, postmenopausal	per 100 g/day	0.92 (0.73-1.16)		

Figure 36 RR estimates of breast cancer by levels of vegetable intake

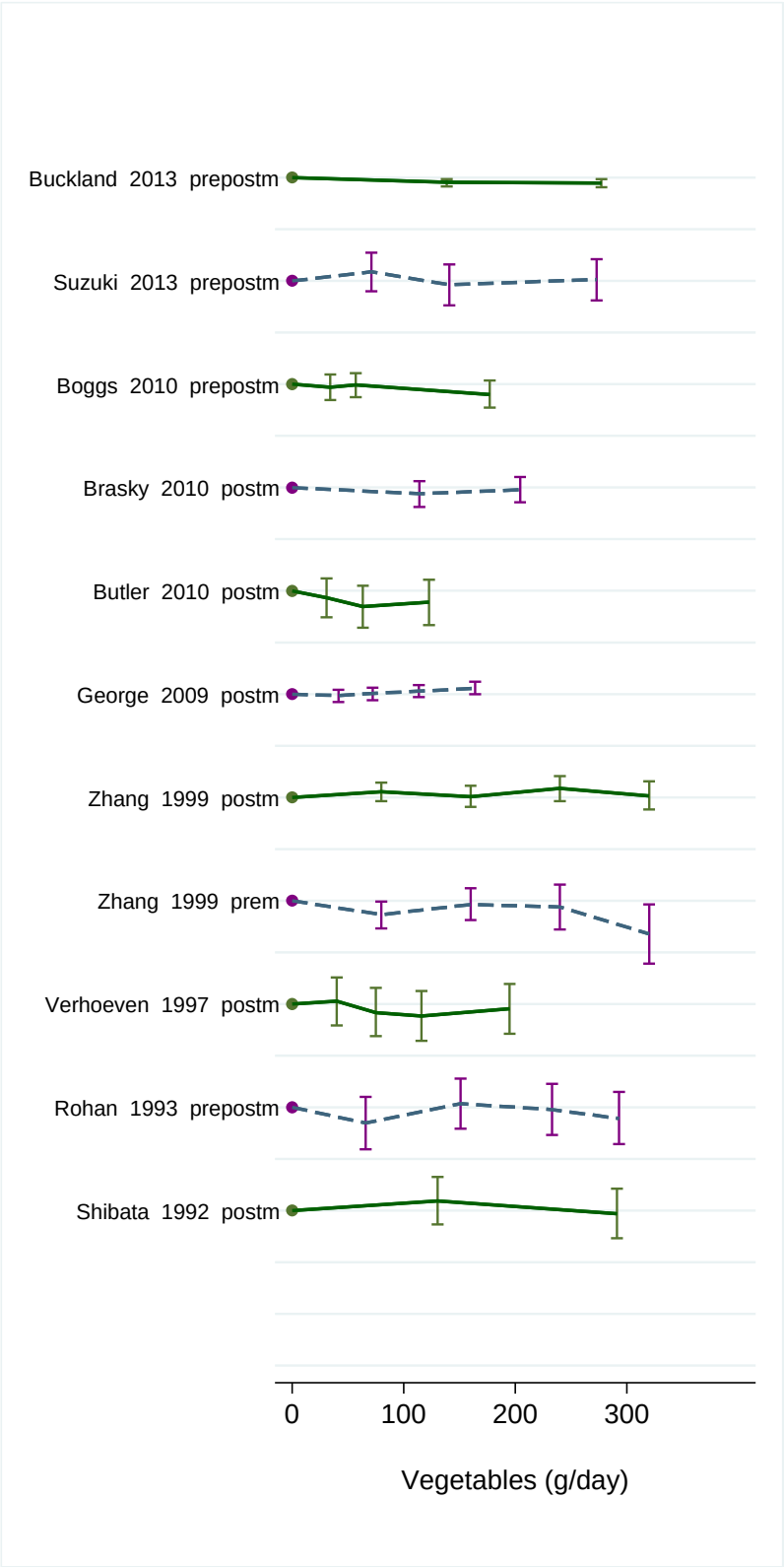


Figure 37 Relative risk of breast cancer for the highest compared with the lowest level of vegetable intake

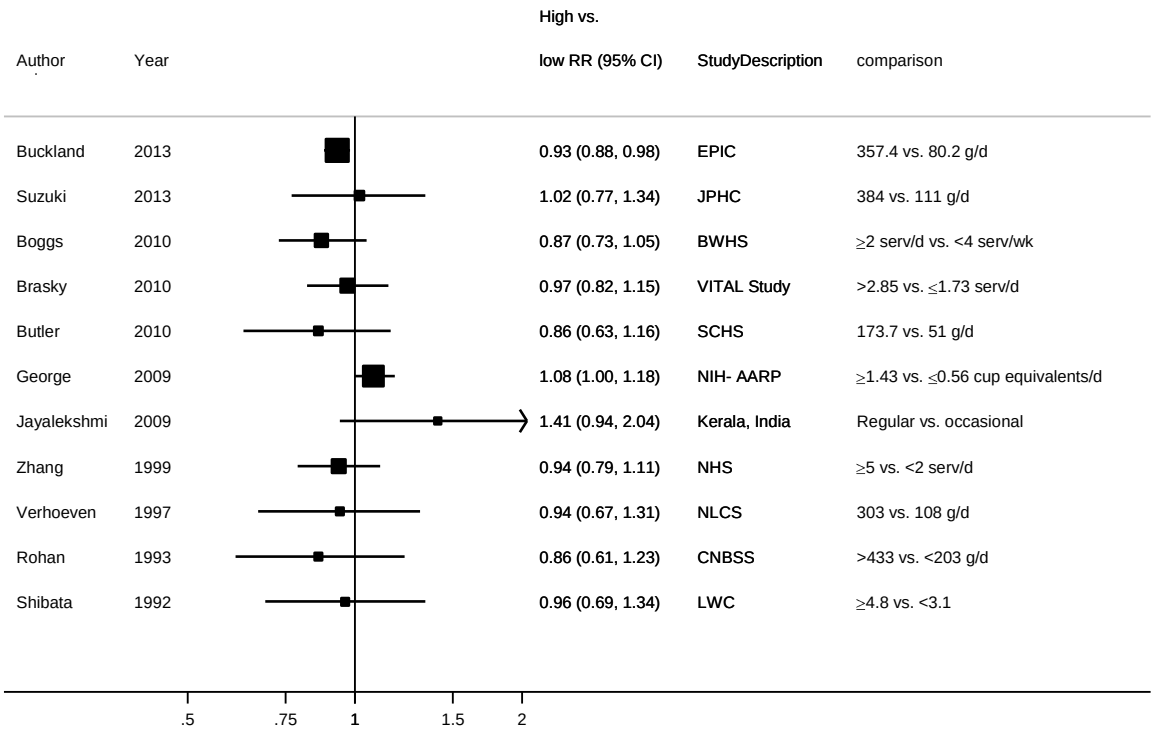


Figure 38 Relative risk of breast cancer for the highest compared with the lowest level of vegetable intake, stratified by menopausal status

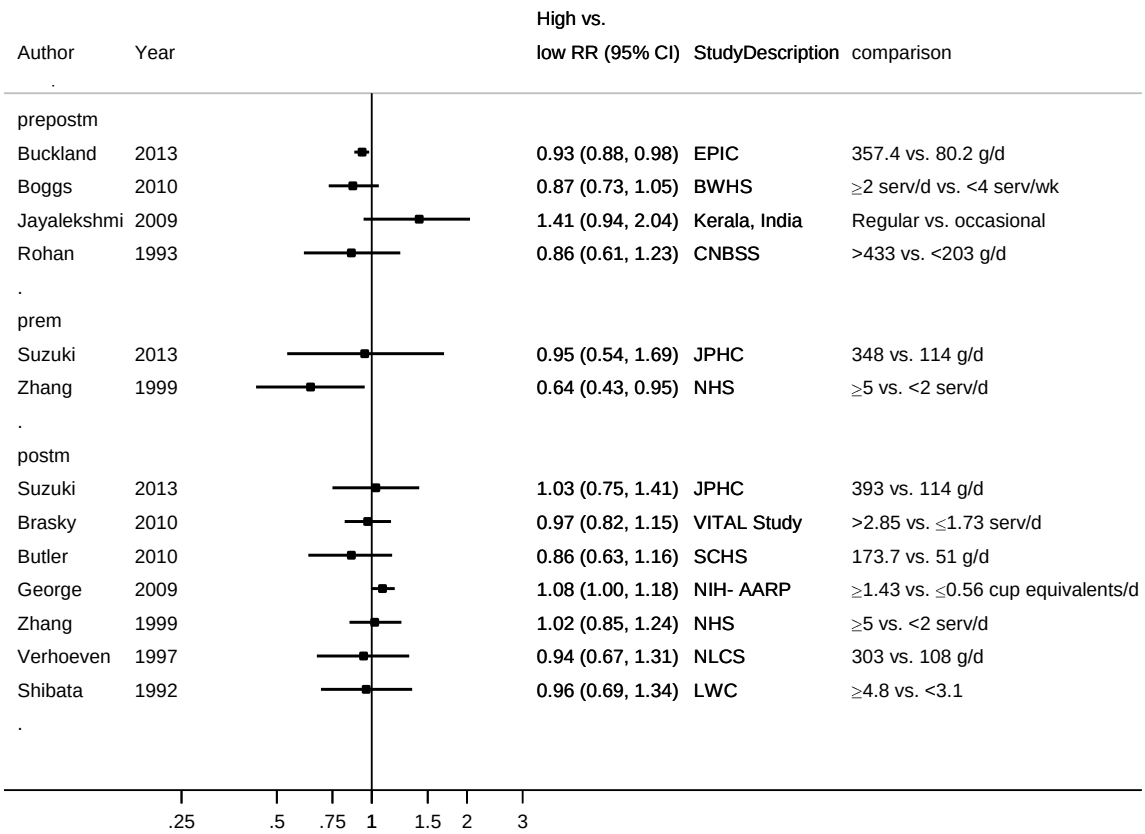


Figure 39 Relative risk of breast cancer for the highest compared with the lowest level of vegetable intake including the Pooling Project of Prospective Studies and not overlapping studies from the CUP

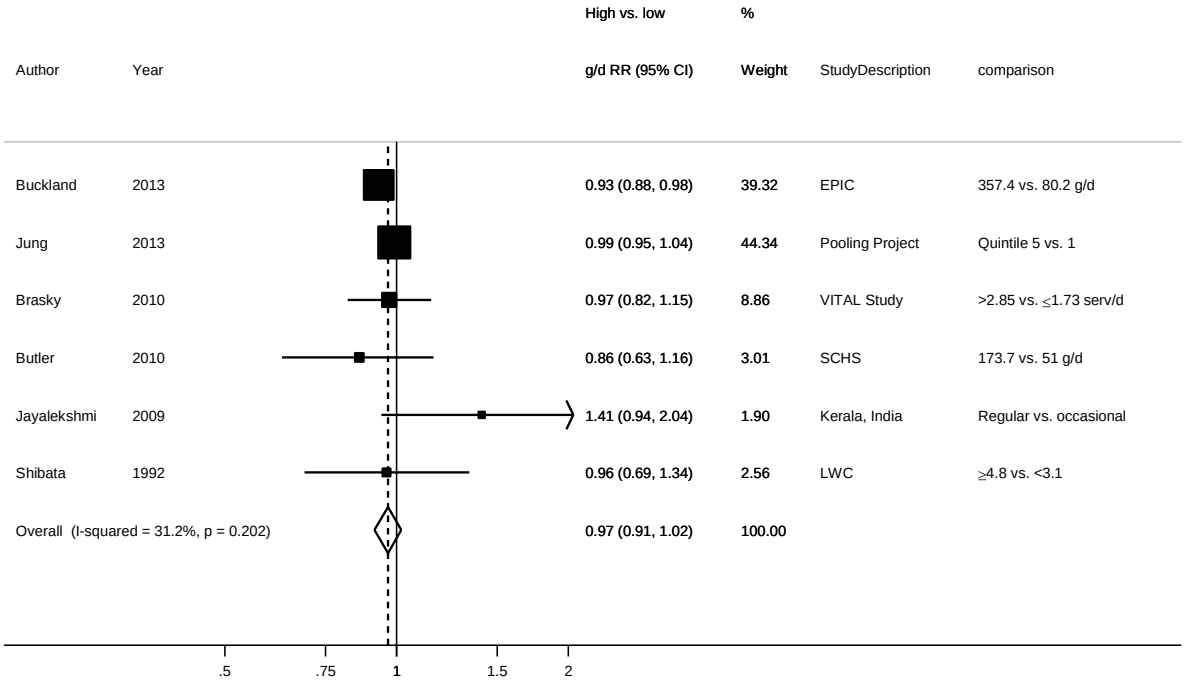


Figure 40 Relative risk of breast cancer for 200 g/day increase in vegetable intake

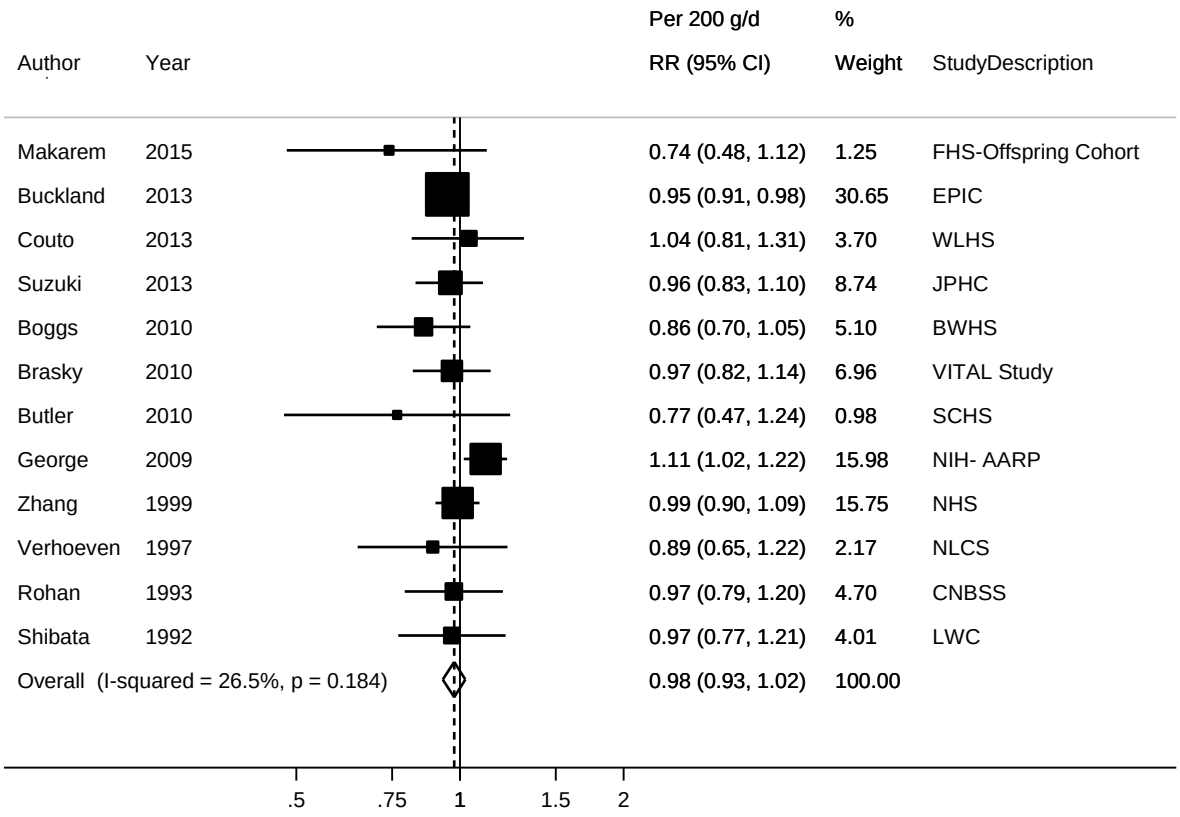


Figure 41 Relative risk of breast cancer for 200 g/day increase in vegetable intake, stratified by menopausal status

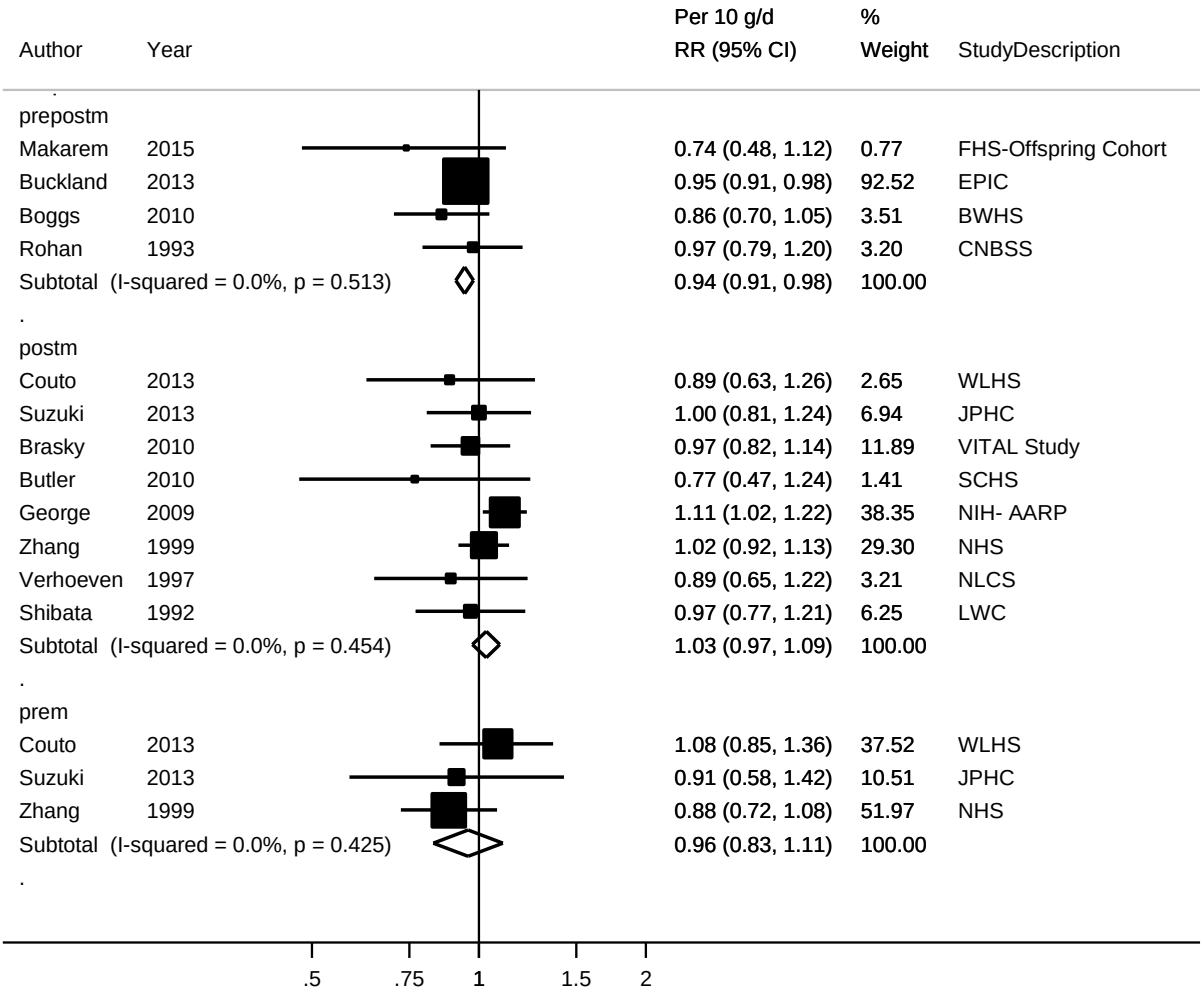


Figure 42 Relative risk of breast cancer for 200 g/day increase in vegetable intake, stratified by geographic location

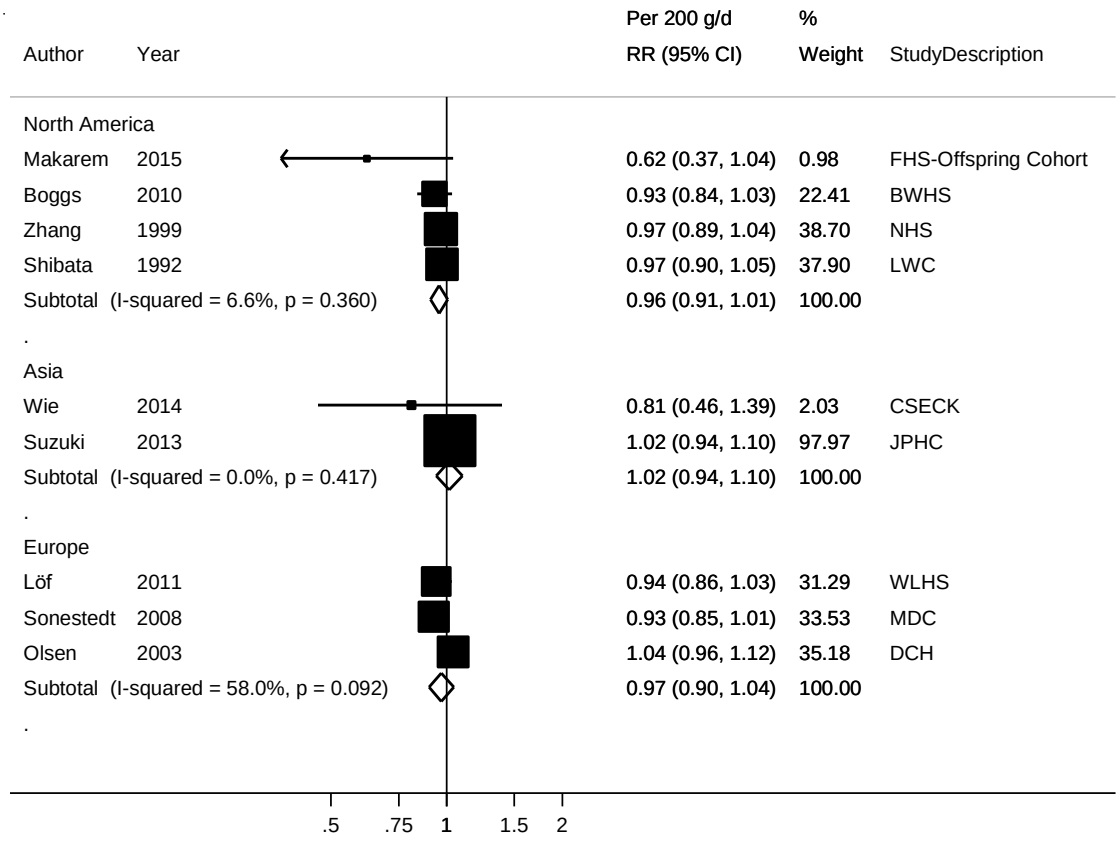


Figure 43 Funnel plot of studies included in the dose response meta-analysis of vegetable intake and breast cancer

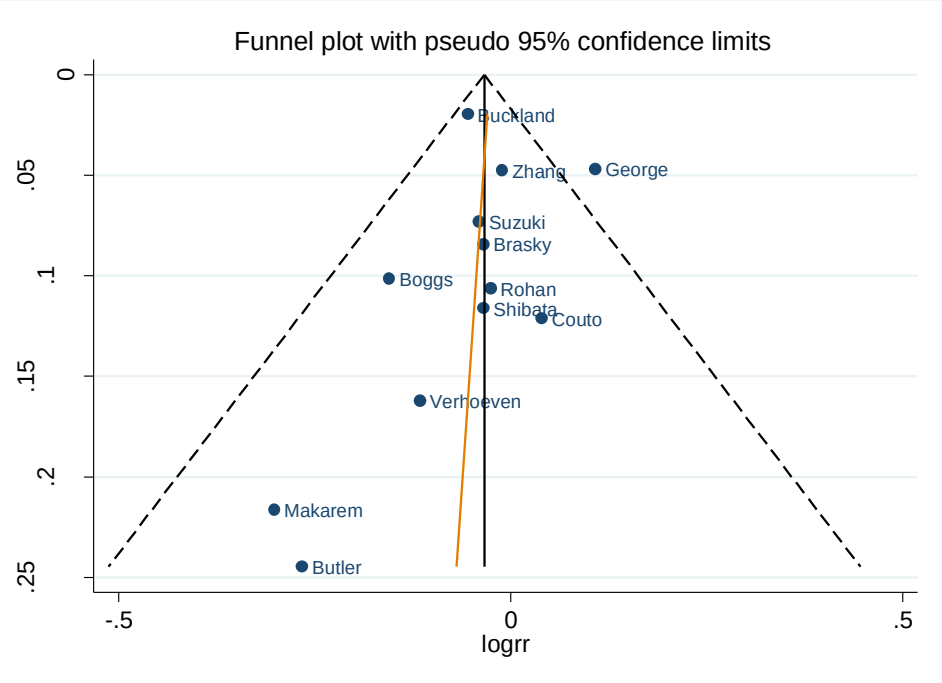
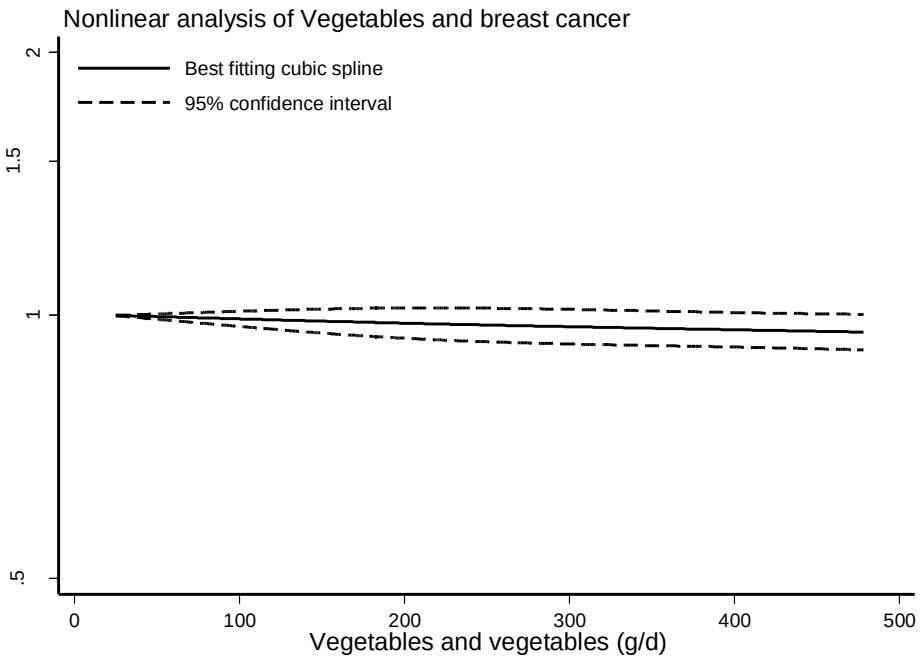


Figure 44 Vegetables and breast cancer, nonlinear dose-response analysis



P nonlinearity=0.82

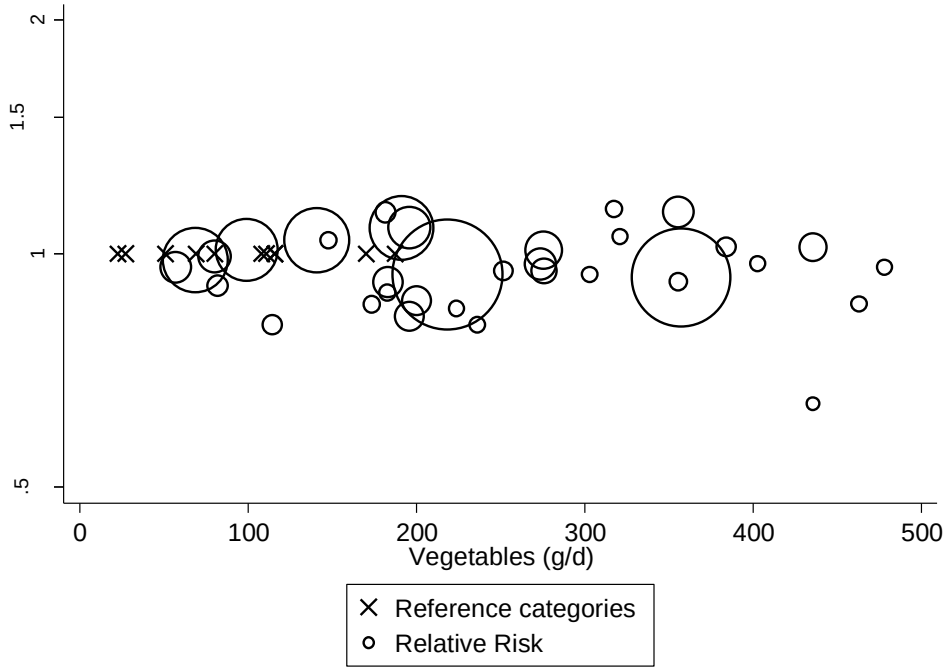
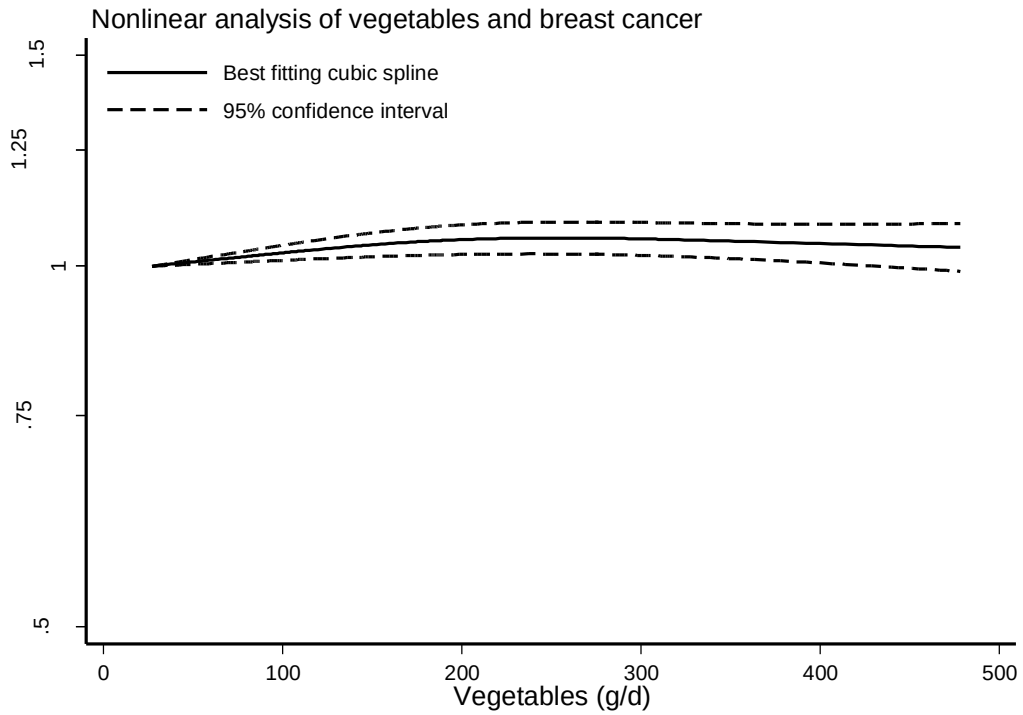


Table 36 Relative risk of breast cancer and vegetables estimated using non-linear models

Vegetables (g/day)	RR (95%CI)
22.9	1.00
100	0.99 (0.96-1.01)
200	0.98 (0.93-1.02)
300	0.97 (0.92-1.02)
400	0.96 (0.91-1.01)
478	0.95 (0.91-1.00)

Figure 45 Vegetables and postmenopausal breast cancer, nonlinear dose-response analysis



P nonlinearity=0.006

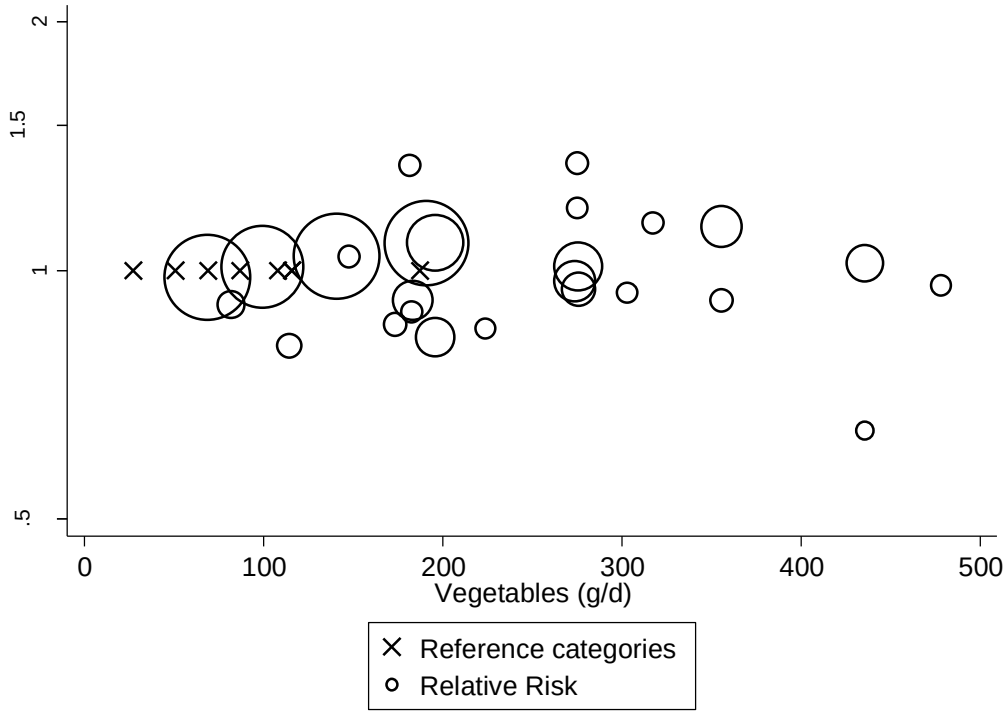
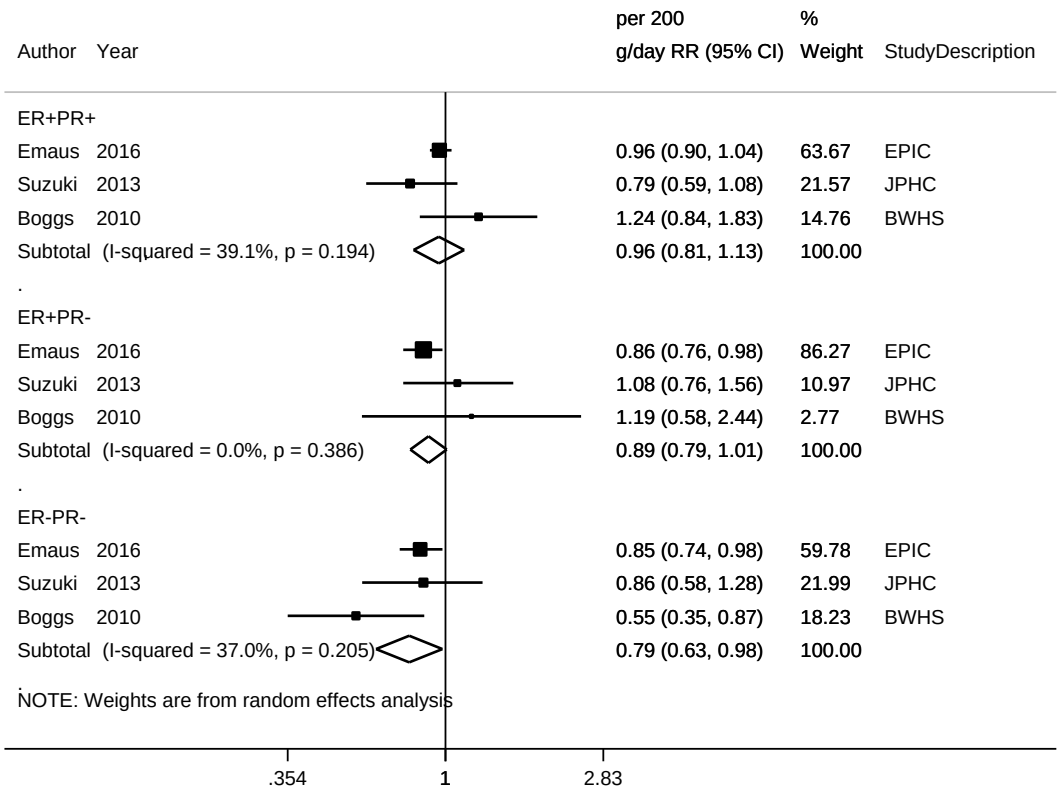


Table 37 Relative risk of postmenopausal breast cancer and vegetables estimated using non-linear models

Vegetables (g/day)	RR (95%CI)
27.2	1.00
100	1.04 (1.02-1.06)
200	1.06 (1.03-1.10)
300	1.06 (1.03-1.10)
400	1.05 (1.01-1.10)
478	1.05 (1.00-1.10)

Figure 46 Relative risk of breast cancer for 200 g/day increase in vegetable intake, stratified by hormone receptor status



2.2.2 Fruits

Fifteen studies on fruit intake and breast cancer risk were identified. Eight studies investigated postmenopausal breast cancers, three were on premenopausal breast cancers, and five were on pre- and postmenopausal breast cancers combined. Study characteristics and results for all cancer types are shown in the Table.

Study quality:

Fruit intake was estimated from food intake assessed by FFQ in all studies. One study used a combination of dietary assessment methods including FFQ, dietary records, and dietary interviews (Buckland, 2013).

Loss to follow-up was low for the studies that reported such data, although some studies did not provide data.

Cancers were identified by record linkages to health registries, cancer registries, mortality registries, or death indexes.

All studies adjusted for at least age, and most of the studies adjusted for most of the established breast cancer risk factors, including: age, parity, age at menarche, age at menopause, physical activity, BMI, and alcohol consumption.

Breast cancer (any)

Eleven studies (25059 cases) were included in the dose-response meta-analysis. The summary RR for a 200 g/d increase in fruit intake was 0.94 (95% CI: 0.90-0.98) and there was low heterogeneity, I^2=31.4%, $p_{heterogeneity}$=0.14. There was some indication of small study bias or publication bias with Egger's test, p=0.07. The summary RR ranged from 0.92 (95% CI: 0.89-0.96) when the EPIC study (Buckland, 2013) was excluded to 0.95 (95% CI: 0.91-0.99) when the NIH-AARP Diet and Health Study (George, 2009a) was excluded.

Nonlinear dose-response analysis

There was no evidence of a nonlinear association, $p_{nonlinearity}$=0.18 in the overall analysis, however, a potential nonlinear association was observed among postmenopausal women, $p_{nonlinearity}$=0.03, with a suggestion of a threshold effect, with significantly reduced risk at intakes of 300 g/d or more.

Premenopausal breast cancer

Three studies (1635 cases) were included in the dose-response meta-analysis of fruit intake and premenopausal breast cancer. The summary RR per 200 g/day increase in fruit intake was 1.00 (95% CI: 0.81-1.23) and there was moderate heterogeneity, I^2=64.1%, $p_{heterogeneity}$=0.06.

Postmenopausal breast cancer

Eight studies (10891 cases) were included in the dose-response meta-analysis of fruit intake and postmenopausal breast cancer. The summary RR per 200 g/d increase in fruit intake was 0.92 (95% CI: 0.87-0.98), with low heterogeneity, I^2=11.3%, $p_{heterogeneity}$=0.34.

Breast cancer risk by hormone receptor status

Total fruit consumption was non-statistically significantly associated with risk of ER− breast cancer (pooled multivariable RR comparing the highest vs lowest quintile = 0.94, 95% CI = 0.85 to 1.04), ER+ breast cancer (RR same comparison =0.99, 95% CI=0.93-1.07), PR- cancers (RR =0.99, 95% CI=0.91-1.06), and PR+ cancers (RR=1.01 95% CI= 0.93-1.10) in the Pooling project of cohort studies (Jun, 2013). The pooled multivariable relative risks for ER− breast cancer for a 300g/day increment (approximately three servings/day) in intake was 0.96 (95% CI = 0.91 to 1.00) (Pheterogeneity > 0.34). Total fruits intake was non-statistically significantly inversely associated with risk of PR− breast cancer. No associations or non-statistically significant positive associations were observed for the risk of ER+ and PR+ breast cancer (data not shown in the publication). Similarly, no significant associations were observed when breast cancers were classified simultaneously by ER and PR status.

One additional study (Emaus, 2016, EPIC), identified after the search period, reported results by hormone receptor subtype. When included in a meta-analysis with two other studies with sufficient data (Suzuki, 2013; Boggs, 2010), statistically non-significant assocations were observed. The summary RRs for a 200 g/d increase in fruit and vegetable intake were 1.01 (95% CI=0.96-1.05) for ER+PR+ breast cancer, 1.06 (95% CI=0.88-1.27) for ER+PR- breast cancer, and 0.97 (95% CI=0.89-1.06) for ER-PR- breast cancer. There was evidence of moderate heterogeneity for ER+PR- (I^2=0%, $p_{heterogeneity}$=0.75; I^2=45.7%, $p_{heterogeneity}$=0.16; I^2=0%, $p_{heterogeneity}$=0.84, respectively).

The Nurses' Health Study (Fung, 2013) reported a non-significant inverse association with ER-negative breast cancer in postmenopausal women (RR for highest vs lowest intake=0.93, 95% CI=0.71-1.21).

Table 38 Fruit intake and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	15 studies (22 publications)
Studies included in forest plot of highest compared with lowest intake	Breast cancer (any): 11 Premenopausal: 3 Postmenopausal: 7
Studies included in linear dose-response meta-analysis	Breast cancer: 12 Premenopausal: 3 Postmenopausal: 8
Studies included in non-linear dose-response meta-analysis	Breast cancer: 11 Premenopausal: not enough studies Postmenopausal: 7

Table 39 Fruit intake and breast cancer risk. Summary of the linear dose-response meta-analysis in the CUP (no dose-response meta-analysis was conducted in the 2005 SLR)

	Breast cancers (any)	**Premenopausal**	**Postmenopausal**
Increment unit used	200 g/day		
Studies (n)	12	3	8
Cases (total number)	25059	1635	10891
RR (95%CI)	0.94 (0.90-0.98)	1.00 (0.81-1.23)	0.92 (0.87-0.98)
Heterogeneity (I^2, p-	0%, p=0.97	64.1%, p=0.06	11.3%, p=0.34
P value Egger test	0.14	-	0.51

Table 40 Fruit intake and breast cancer risk. Pooling Project of Cohort Studies and not overlapping studies identified in the CUP

	Breast cancers (any)
Increment unit used	High vs. low
Studies (n)	25
Cases (total number)	46906
RR (95%CI)	0.98 (0.95-1.01)
Heterogeneity (I^2, p-	0%, p=0.54
P value Egger test	0.18

Stratified analyses

Geographic area	**Asia**	**Europe**	**North-America**
Studies (n)	3	3	6
RR (95%CI)	1.01 (0.92-1.10)	0.95 (0.89-1.03)	0.90 (0.85-0.95)
Heterogeneity (I^2, p- value)	0%, p=0.41	49.0%, p=0.14	0%, p=0.97

Table 41 Fruit intake and hormone receptor-defined breast cancer risk. Summary of the linear dose-response meta-analysis in the CUP SLR

ER-status	**ER+PR+**	**ER+PR-**	**ER-PR-**
Increment unit used	200 g/day	200 g/day	200 g/day
Studies (n)	3	3	3
Cases	3950	1229	1346
RR (95%CI)	1.01 (0.96-1.05)	1.06 (0.88-1.27)	0.97 (0.89-1.06)
Heterogeneity (I^2, p-value)	0%, 0.75	46%, 0.16	0%, 0.83

Table 42 Fruits and breast cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Aune et al, 2012	10	16763	North America, Europe, Asia	Incidence	High vs. low Per 200 g/d	0.92 (0.86-0.98) 0.94 (0.89-1.00)	- -	0.36 0.10
Pooled analyses								
Jung et al, 2013	20	34526	North America, Europe, Asia	Incidence, ER/PR +/- status	Quintile 5 vs. 1	0.99 (0.95-1.03), all 0.94 (0.85-1.04), ER- 0.99 (0.93-1.07), ER+ 0.98 (0.91-1.06), PR- 1.01 (0.93-1.10), PR+	0.36 0.13 0.57 0.49 0.97	0.20 0.65 0.02 0.50 0.004
Smith-Warner, 2001a	8 prospective cohort studies (The Nurses' Health Study was divided into 2 studies)	7377	North America, Canada,The Netherlands, Sweden	Incidence, menopausal status	Per 100g/day Breast cancer Premenopausal breast cancer Postmenopausal breast cancer Quintile 4 vs. 1 Breast cancer	 0.99 (0.98-1.00) 0.98 (0.94-1.02) 0.99 (0.98-1.01) 0.93 (0.86-1.00)	 - - - 0.08	 0.90 0.83 0.89 0.94

Table 43 Fruit intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Buckland, 2013 BRE80433 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	10 225/ 335 062 11 years	Cancer registries, health Insurance records, pathology rec & active follow up	Questionnaire	Incidence, breast cancer	Q 3 vs Q 1	0.99 (0.94-1.05)	Age, age at first child birth, age at menarche, age at menopause, alcohol, BMI, breastfeeding, centre location, cereal, dairy products consumption, educational level, energy, fish, height, HRT use, legumes, legumes, meat, oil, oral contraceptive history, physical activity, saturated fat, smoking, vegetables
Suzuki, 2013 BRE80491 Japan	JPHC, Prospective Cohort, W	452/ 47 289 10.2 years		FFQ	Incidence, breast cancer	444 vs 83 g/day	1.28 (0.89-1.85)	Age, age at first child birth, age at menarche, alcohol, BMI, BMI at age 20 years, height, HRT use, Isoflavone, leisure time physical activity, menopausal status, parity, smoking status, study area, vegetable, vitamin c supplement
					Incidence, breast cancer	per 100 g/day	1.02 (0.94-1.10)	
					Incidence, breast cancer, postmenopausal	275 vs 87 g/day	1.19 (0.84-1.67)	
					Incidence, breast cancer unknown ER/PR status	per 100 g/day	0.99 (0.91-1.06)	
					Incidence, breast cancer, premenopausal	412 vs 72 g/day	2.32 (1.23-4.38)	
					Incidence, breast cancer ER+/PR+	per 100 g/day	1.04 (0.94-1.15)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					Incidence, breast cancer ER-/PR-	per 100 g/day	1.02 (0.88-1.18)	
					Incidence, breast cancer ER+/PR-	per 100 g/day	1.12 (0.99-1.26)	
Couto, 2013 BRE80454 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	1 278/ 49 258 16 years	Cancer registry	FFQ	Incidence, breast cancer	per 120 gday	0.95 (0.89-1.00)	Age at first child birth, age at menarche, alcohol, benign breast disease, beverage Intake, cereal, dairy products consumption, educational level, egg, energy Intake, fish, height, history of breast cancer, legumes, meat, number of childbirths, potatoes, ratio unsat/sat fat, smoking, sweet products, vegetable
					Incidence, breast cancer, premenopause	per 120 gday	0.95 (0.89-1.01)	
					Incidence, breast cancer, postmenopause	per 120 gday	0.97 (0.89-1.06)	
Boggs, 2010a BRE80332 USA	BWHS, Prospective Cohort, Age: 21-69 years, W	1 268/ 51 928 554 528 person-years	Self report verified by medical record	FFQ	Incidence, breast cancer	≥2 vs <2 serving/week	0.91 (0.74-1.11)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, BMI, contraception, educational level, energy Intake, family history of breast cancer, geographic region, HRT use, menopausal status, multivitamin supplement Intake, smoking, vigorous activity
					Incidence, breast cancer, postmenopausal	≥2 vs <2 serving/week	0.86 (0.63-1.18)	
					Incidence, breast cancer, premenopausal	≥2 vs <2 serving/week	1.00 (0.74-1.35)	
					Incidence, breast cancer ER+/PR+	≥2 vs <2 serving/week	1.02 (0.69-1.50)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					Incidence, breast cancer ER-/PR-	≥2 vs <2 serving/week	1.04 (0.67-1.61)	
					Incidence, breast cancer ER+/PR-	≥2 vs <2 serving/week	0.84 (0.40-1.76)	
Brasky, 2010 BRE80362 USA	VITAL, Prospective Cohort, Age: 50-76 years, W	880/ 35 016	Cancer registry	FFQ	Incidence, breast cancer	≥2.15 vs 0-1.04 servings/day	0.86 (0.73-1.02)	Age
Butler, 2010 BRE80295 Singapore	SCHS, Prospective Cohort, Age: 45-74 years, W	439/ 34 028 10.7 years	Cancer registry	FFQ	Incidence, breast cancer, postmenopause	357 vs 39 g/day	1.03 (0.77-1.38)	Age, BMI, dialect group, educational level, energy Intake, family history of cancer, parity, year of Interview
George, 2009a BRE80360 USA	NIH-AARP, Prospective Cohort, Age: 615 years, W, Retired	5 815/ 195 229 8 years	Cancer registry	FFQ	Incidence, breast cancer	1.9-5.58 vs 0-0.6 cup/day	0.91 (0.84-1.00)	Age, alcohol, BMI, educational level, energy Intake, family history, marital status, menopausal hormone use, physical activity, race, smoking, vegetables
Key, 1999 BRE04758 Japan	LSS, 1969, Prospective Cohort, W	427/ 34 759 24 years	Partially histological - over 80%	Questionnaire	Incidence, breast cancer,	≥5 vs ≤1 times/week	0.95 (0.71-1.27)	Age , calendar year, other factors , other factors , place of residence
Zhang, 1999a BRE13953	NHS, Prospective	784/ 83 234	Temp	FFQ-semi-quantitative	Incidence, Invasive breast	≥5 vs ≤1.9 serving/day	0.74 (0.45-1.24)	Age, length of follow-up, total energy intake, parity,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
USA	Cohort, Age: 33-60 years, W, Registered nurses	14 years			cancer, premenopausal			age at first birth, age at menarche, history of breast cancer in mother or a sister, history of benign breast disease, alcohol intake, BMI at age 18 years, weight change from age 18 years, height
Verhoeven, 1997 BRE12868 Netherlands	NLCS, Case Cohort, Age: 55-69 years, W	519/ 62 573 4.3 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, Invasive breast cancer,	343.1 vs 64.9 g/day	0.76 (0.54-1.08)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, energy Intake , family history, parity/pregnancies
Rohan, 1993 BRE17965 Canada	CNBSS, Nested Case Control, Age: 40-59 years, W, Screening Program	518/ 1182 controls 6 years	All histology	Dietary history questionnaire	Incidence, breast cancer,	≥491.1 vs ≤189 g/day	0.81 (0.57-1.14)	Age , age at first child, age at menarche, benign breast disease, educational level, energy Intake , family history, food, menopausal status
Shibata, 1992 BRE80361 USA	Leisure World Cohort, Prospective Cohort, M/W, retirement community, uppermiddle social class	219/ 11 580 70 159 person-years	Community registry	FFQ	Incidence, breast cancer	≥3.7 vs ≤2.3 servings/day	0.82 (0.60-1.12)	Age, smoking status

Table 44 Fruit intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Emaus, 2013 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Mean age: 50.8 years, W	10 197/ 335 054 11.5 years	Cancer registries, health Insurance records, pathology rec & active follow up	Country-specific dietary questionnaires	Incidence, invasive breast cancer	≥460 vs ≤63 g/day Per 100 g/day	1.01 (0.94-1.09) Ptrend: 0.70 1.01 (0.99-1.02)	Energy intake, saturated fat intake, age at menarche, OC use, age at first full-term pregnancy, menopausal status, HRT use, BMI, BMI x menopausal status, physical activity, smoking status and intensity, alcohol use, alcohol consumption, education level, vegetable intake, stratified by age and centre	Excluded, article identified after end date of search
		3 479/			ER+PR+	≥460 vs ≤63 g/day Per 100 g/day	0.98 (0.86-1.10) Ptrend: 0.70 1.00 (0.98-1.03)		Included in the analysis of breast cancer hormone receptor subtype
		1 075/			ER+PR-	≥460 vs ≤63 g/day Per 100 g/day	0.91 (0.73-1.14) Ptrend: 0.50 0.99 (0.95-1.03)		
		1 021/			ER-PR-	≥460 vs ≤63 g/day Per 100 g/day	0.92 (0.73-1.16) Ptrend: 0.35 0.98 (0.94-1.03)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Fung, 2013 BRE80466 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Postmenopausal	792/ 75 929 24 years	Questionnaire, medical records or pathology reports, death certificate, physician, family member	FFQ	Incidence, breast cancer ER-	3.9 vs 0.9 servings/day	0.93 (0.71-1.21)	Age, alcohol, benign breast disease, BMI at age 18 years, diet, energy, height, HRT use, physical activity, smoking, weight change	Not enough studies for analysis of ER- tumors
Masala, 2012 BRE80402 Italy	EPIC-Italy, Prospective Cohort, Age: 36-64 years, W	1 072/ 31 510 11.25 years	Cancer registry	FFQ	Incidence, breast cancer	≥476.8 vs ≤195.3 g/day	0.86 (0.70-1.05)	Age at menarche, alcohol, centre location, educational level, energy Intake, height, HRT use, menopausal status, number of children, physical activity, smoking, weight	Overlap with Buckland, 2013 BRE80433
Trichopoulou, 2010 BRE80320 Greece	EPIC-Greece, Prospective Cohort, Age: 20-68 years	240/ 14 807 9.8 years	Medical records and pathology reports	FFQ	Incidence, breast cancer	per 204 g/day	1.02 (0.89-1.17)	Age, age at first child birth, age at menarche, age at menopause, BMI, educational level, energy Intake, height, HRT use, menopausal status, metabolic equivalents, parity, smoking	Overlap with Buckland, 2013 BRE80433
					Incidence, breast cancer, postmenopausal	per 204 g/day	1.07 (0.85-1.33)		
					Incidence, breast cancer, premenopausal	per 204 g/day	1.00 (0.84-1.18)		
Sonestedt, 2008a BRE80192 Sweden	MDCS, Prospective Cohort, Age: 46-75 years,	544/ 15 773 10.3 years	Cancer registry	7-day food record & FFQ	Incidence, Invasive breast cancer	364 vs 70 g/day	0.93 (0.70-1.23)	Age, age at menopause, alcohol Intake, educational level, exposure assessment, height, household	Overlap with Buckland, 2013 BRE80433
					Incidence, breast cancer ERα+	per 1 quantile	0.98 (0.91-1.05)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	W				Incidence, breast cancer ERβ-	per 1 quantile	0.95 (0.86-1.05)	physical activity, Interviewer, menopausal hormone use, parity, physical activity, residual (willet), season of Interview, smoking status, total energy Intake, weight	
					Incidence, breast cancer ERβ+	per 1 quantile	1.03 (0.92-1.14)		
					Incidence, breast cancer ERα+/ERβ+	per 1 quantile	1.00 (0.90-1.24)		
					Incidence, breast cancer ERα+/ERβ-	per 1 quantile	0.96 (0.86-1.07)		
					Incidence, breast cancer ERα-	per 1 quantile	1.07 (0.89-1.28)		
van Gils CH, 2005 BRE80167	EPIC, Prospective Cohort, Age: 25-70 years	3 659/ 285 526 5.4 years		Diet questionnaire	Incidence, breast cancer	≥309.1 vs ≤109	1.09 (0.94-1.25)	Age at menarche, alcohol Intake, energy Intake, height, HRT use, menopausal status, oral contraceptive use, parity, physical activity, saturated fat Intake, smoking status, weight	Overlap with Buckland, 2013 BRE80433
Fung, 2005 BRE22370 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	71 058 16 years	Medical records + self-reported	FFQ	Incidence, breast cancer ER-, postmenopausal	per 1 serving	0.88 (0.80-0.97)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, energy Intake , family history, height, HRT use, menopausal status, other anthropometric Index, parity/pregnancies,	Not enough studies for analysis of ER- tumors

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								physical activity , smoking habits, supplements	
Frazier, 2004 BRE02942 USA	NHS II, Historical Cohort, Age: 34-51 years, W, Registered nurses	361/ 47 355 9 years	All histology	FFQ	Incidence, breast cancer, premenopausal	4.1 vs 0.7 serving/day	0.75 (0.53-1.07)	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, energy Intake , family history, menopausal status, oc use, other anthropometric Index, other design Issue, parity/pregnancies	Adolescent diet
Sauvaget, 2003 BRE20841 Japan	LSS, 1969, Prospective Cohort, Age: 34-103 years, W, Atomic bomb survivors	76/ 23 667 16 years	Partially histological - over 80%	FFQ	Mortality, breast cancer,	≥1 vs ≤1 times/week	0.91 (0.48-1.72)	Age , alcohol, BMI, educational level, other specified factor, place of residence, smoking habits	Mortality as outcome
Olsen, 2003 BRE17890 Denmark	DCH, Prospective Cohort, Age: 50-65 years, W, Postmenopausal	425/ 23 798 4.7 years	Partially histological - over 80%	FFQ	Incidence, breast cancer, postmenopausal	per 100 g/day	1.05 (0.98-1.11)	Age at first child, age-underlying cox models, alcohol, benign breast disease, BMI, duration of HRT use, educational level, HRT use, lenght of follow-up, nutrients, nutrients, parity/pregnancies	Overlap with Buckland, 2013 BRE80433
					Incidence, breast cancer ER+, postmenopausal	per 100 g/day	1.07 (1.00-1.15)		
					Incidence, breast cancer ER-, postmenopausal	per 100 g/day	0.92 (0.79-1.08)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Key, 1996 BRE15654 UK	UK Cohort of Vegetarians and Other Health Conscious People, 1973, Prospective Cohort, Age: 16-79 years, W, Vegetarian and health conscious people	6 435 16.8 years	Death certificate	Questionnaire	Mortality, breast cancer,	daily consumption vs less than daily consumption	0.74 (0.41-1.32)	Age , smoking habits	Mortality as outcome

Figure 47 RR estimates of breast cancer by levels of fruit intake

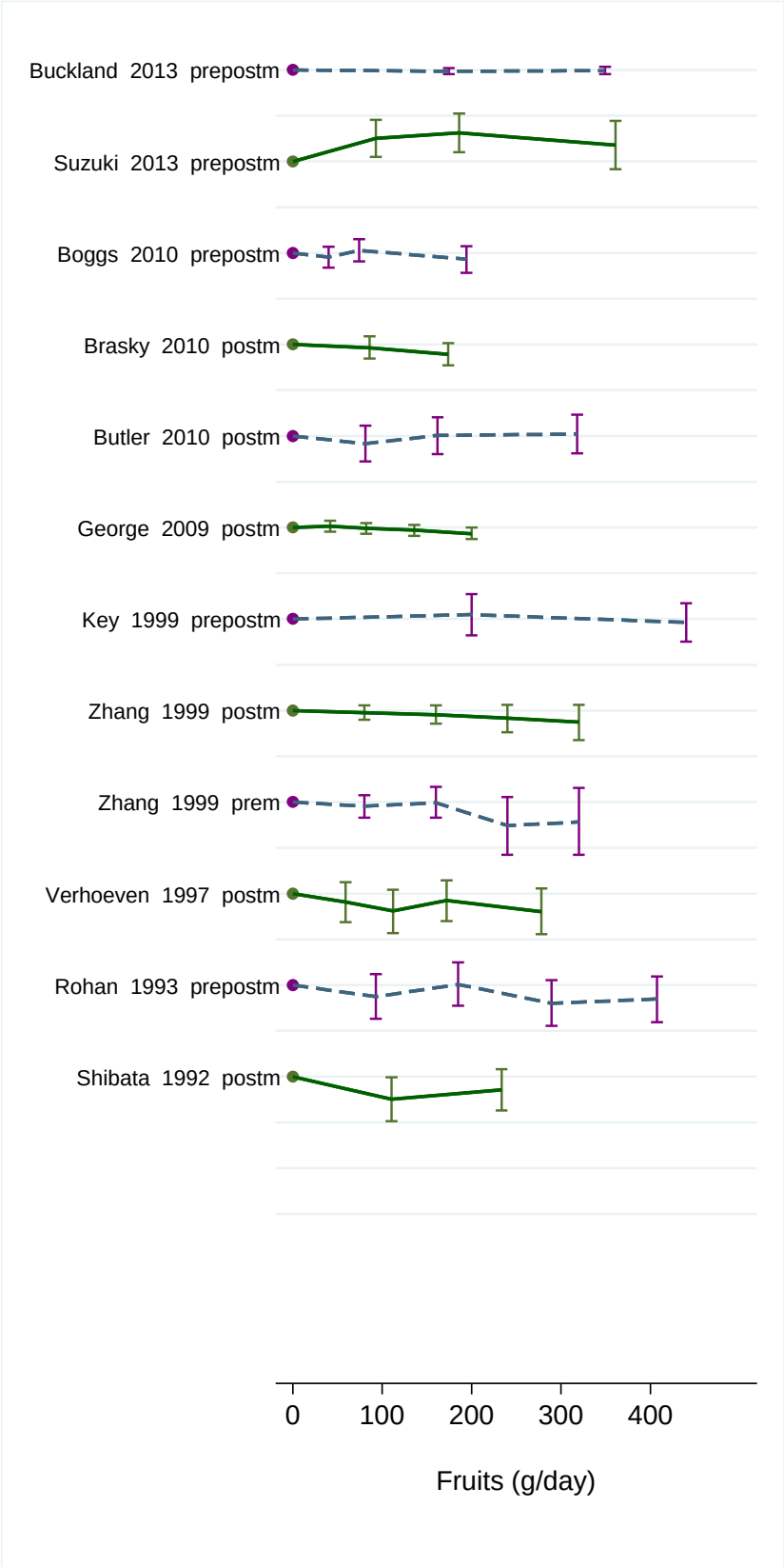


Figure 48 Relative risk of breast cancer for the highest compared with the lowest level of fruit intake

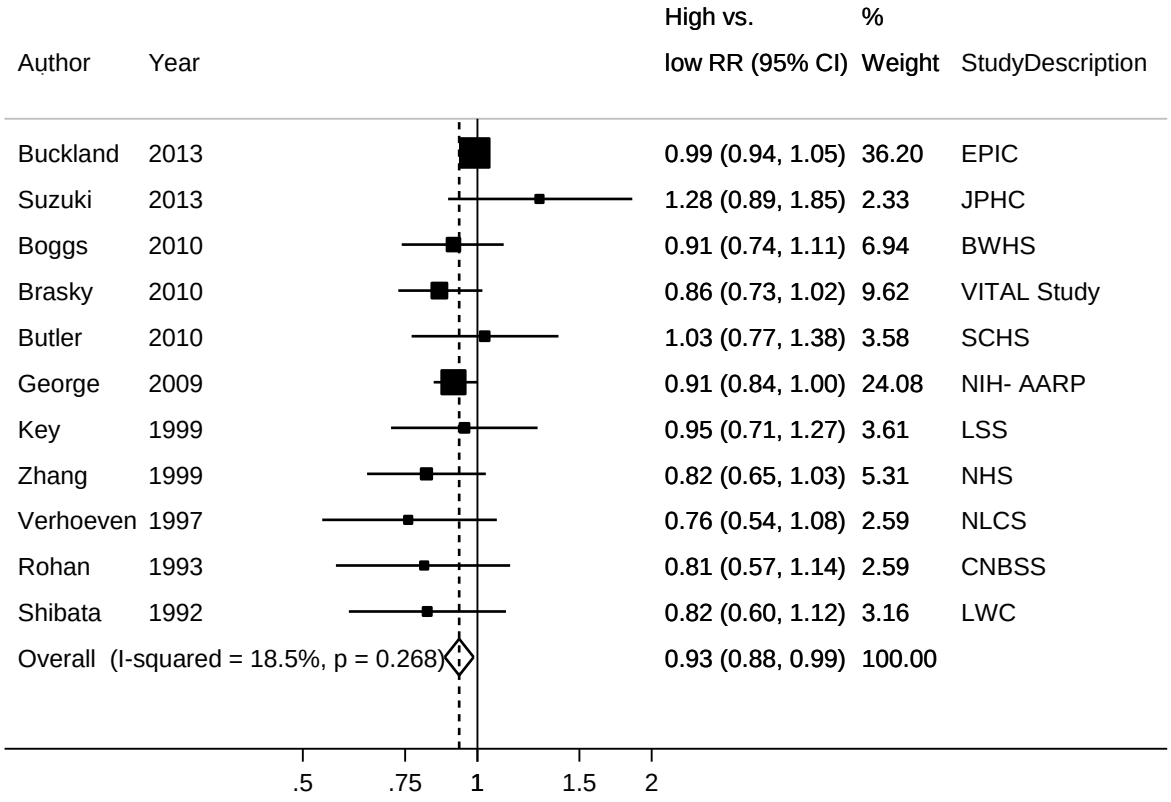


Figure 49 Relative risk of breast cancer for the highest compared with the lowest level of fruit intake, stratified by menopausal status

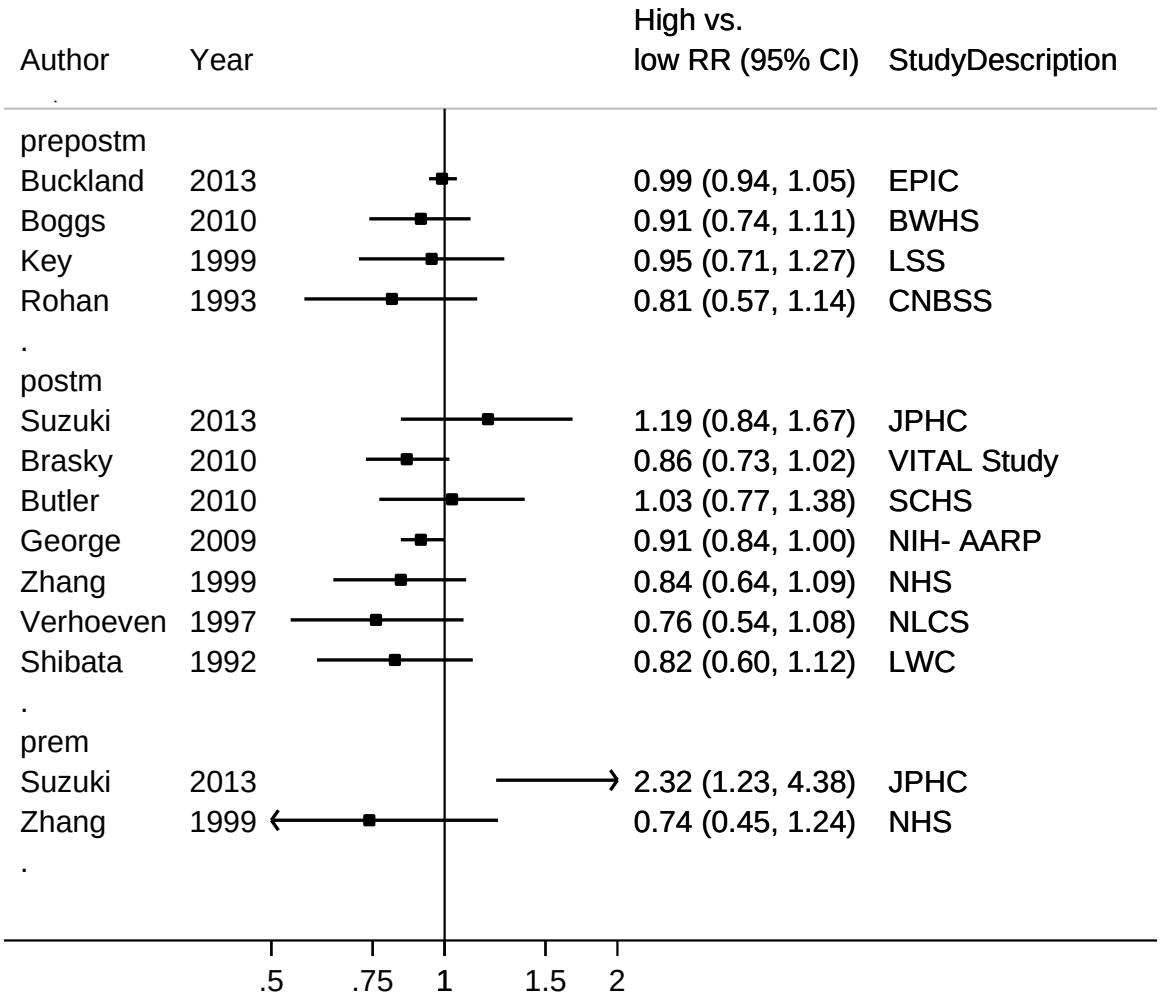


Figure 50 Relative risk of breast cancer for high vs. low fruit intake, including the Pooling Project and non-overlapping studies from the CUP

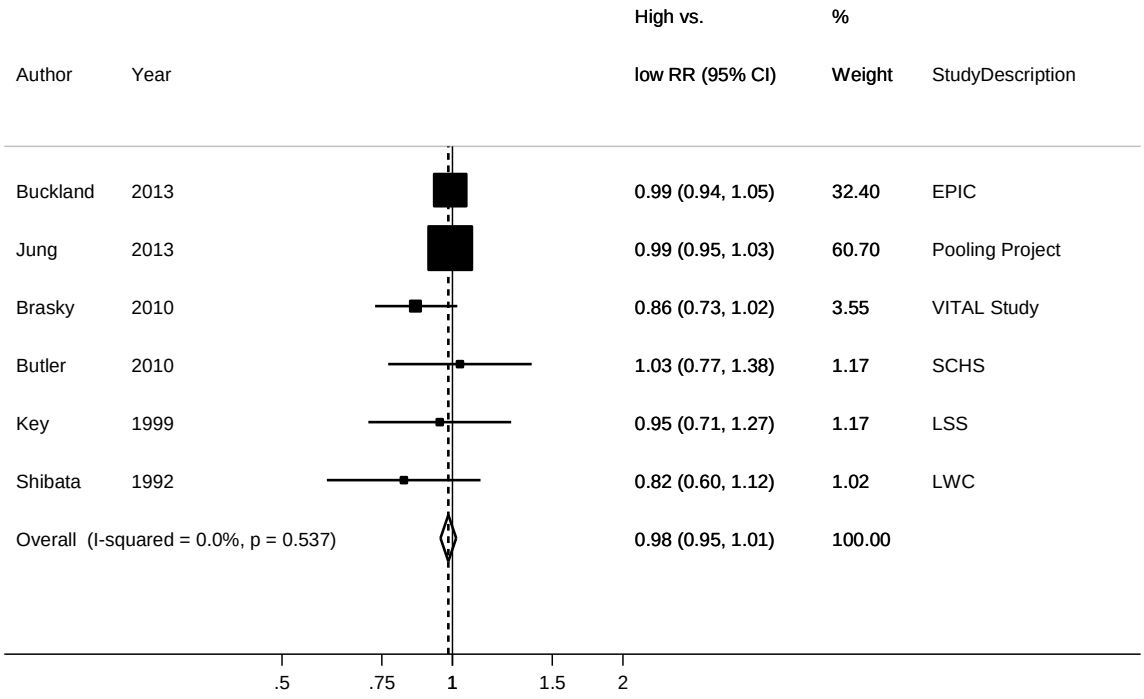


Figure 51 Relative risk of breast cancer for 200 g/day increase in fruit intake

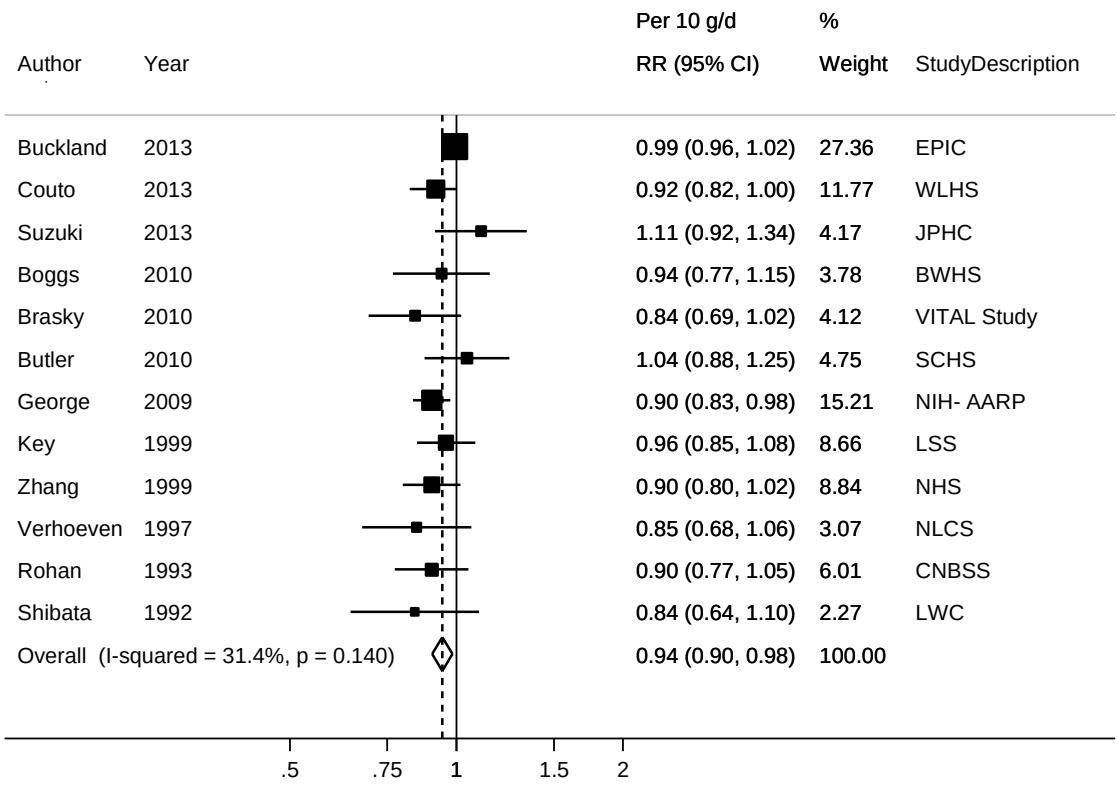


Figure 52 Relative risk of breast cancer for 200 g/day increase in fruit intake, stratified by menopausal status

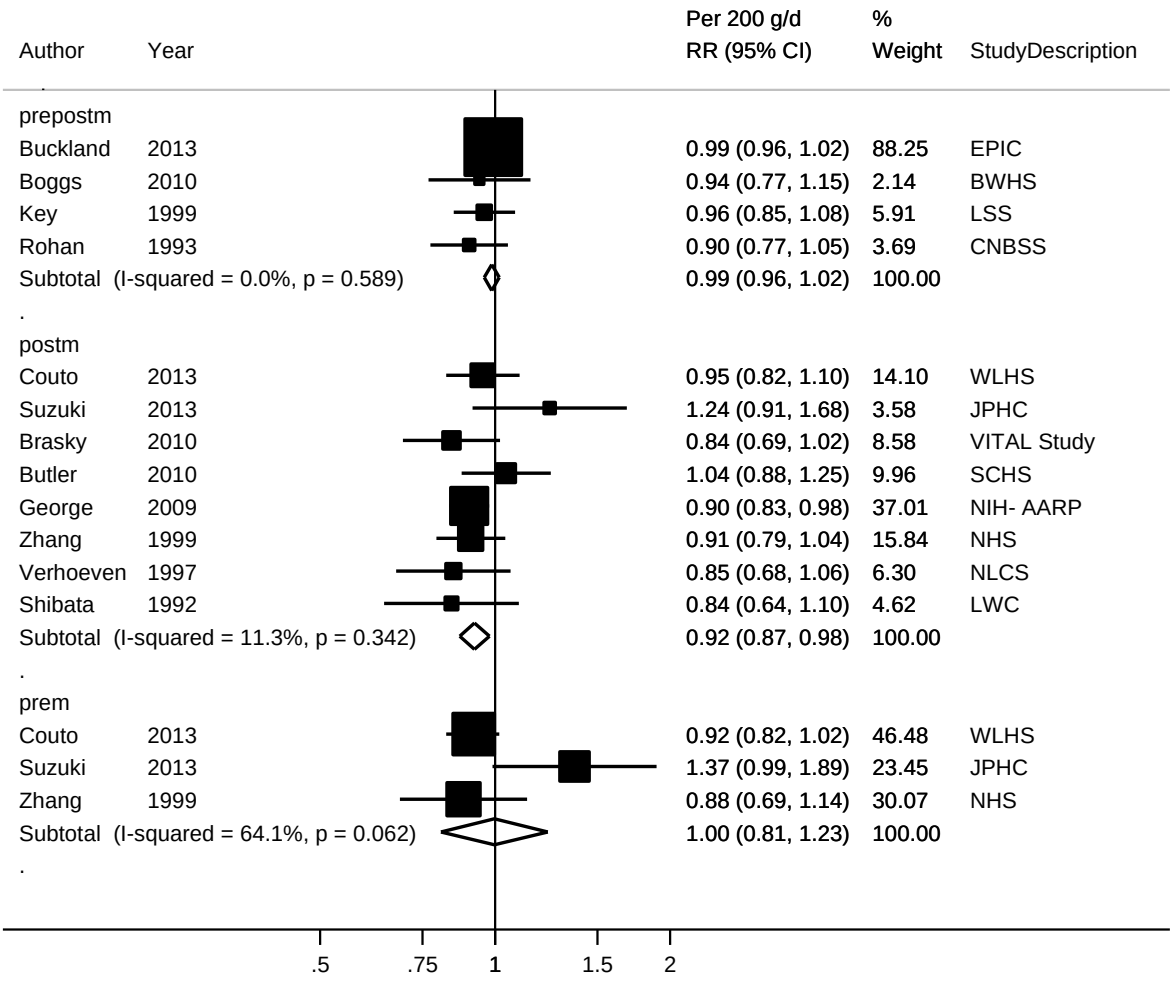


Figure 53 Relative risk of breast cancer for 200 g/day increase in fruit intake, stratified by geographic location

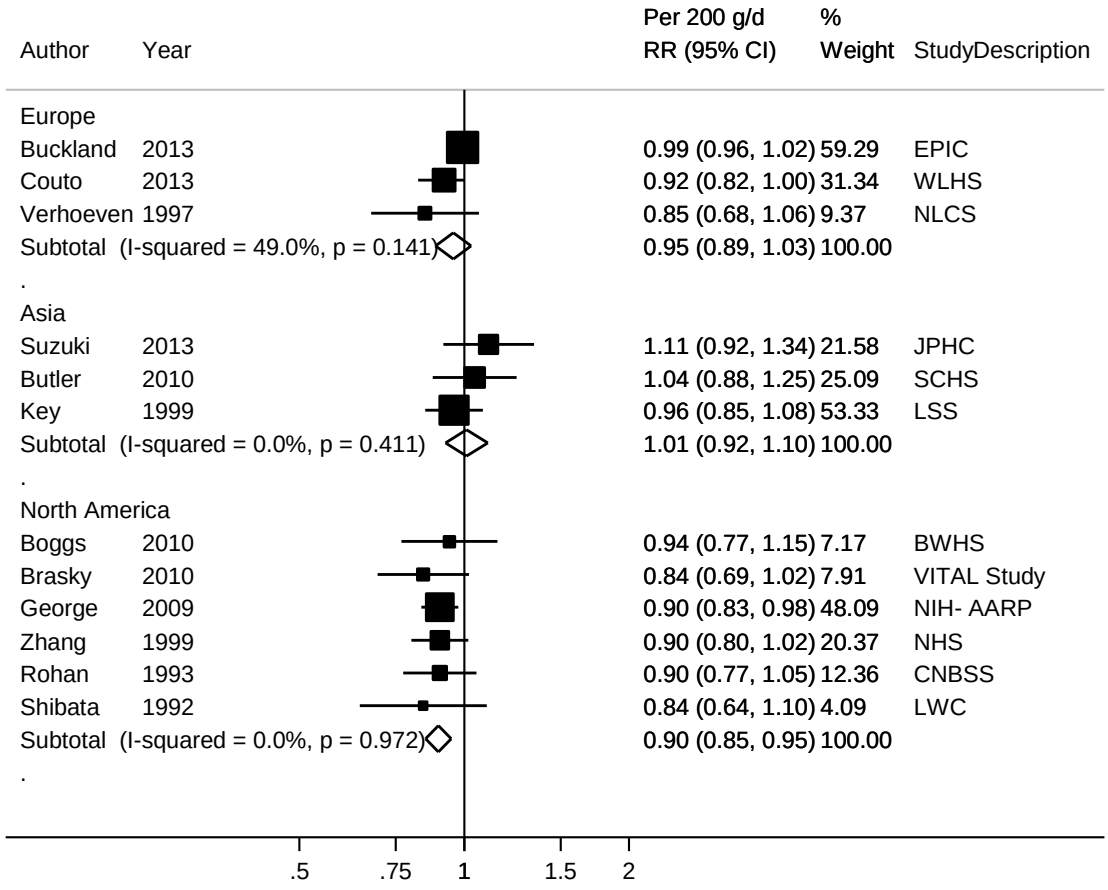
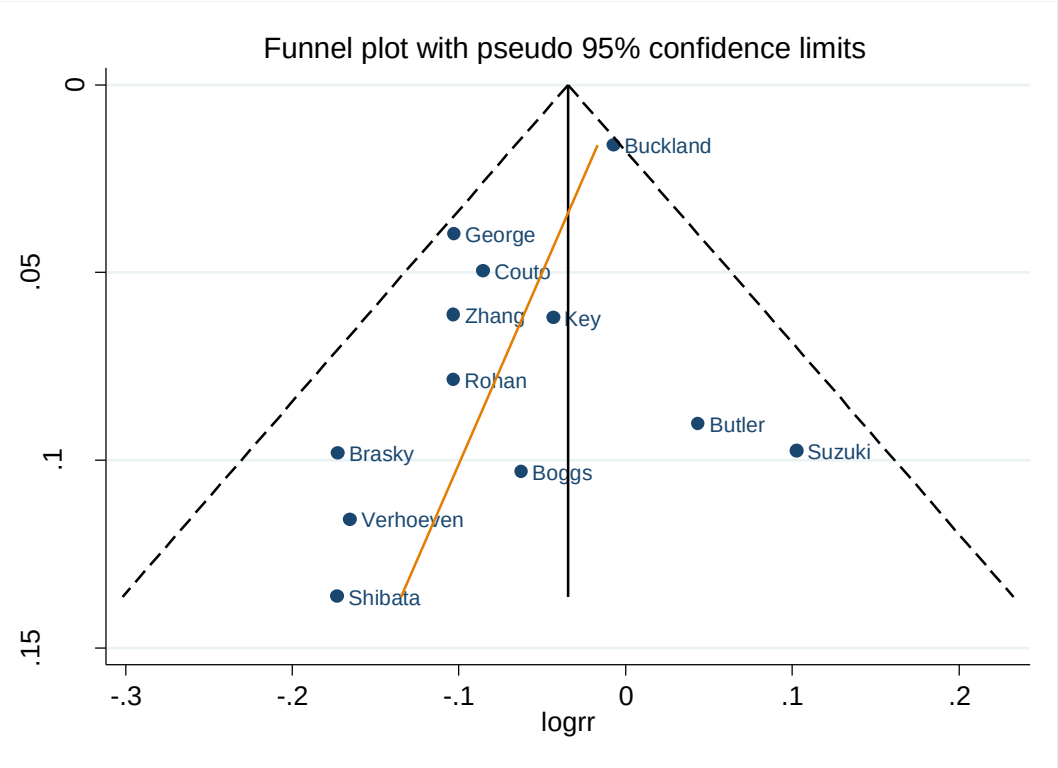
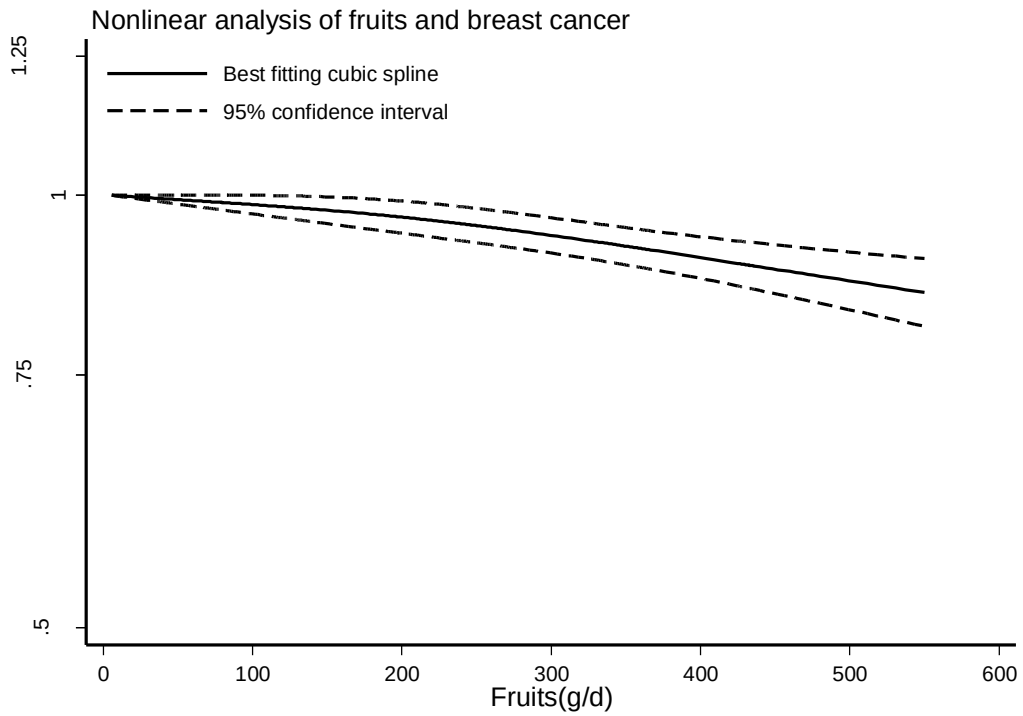


Figure 54 Funnel plot of studies included in the dose response meta-analysis of fruit intake and breast cancer



Egger, p=0.07

Figure 55 Fruits and breast cancer, nonlinear dose-response analysis



P nonlinearity=0.18

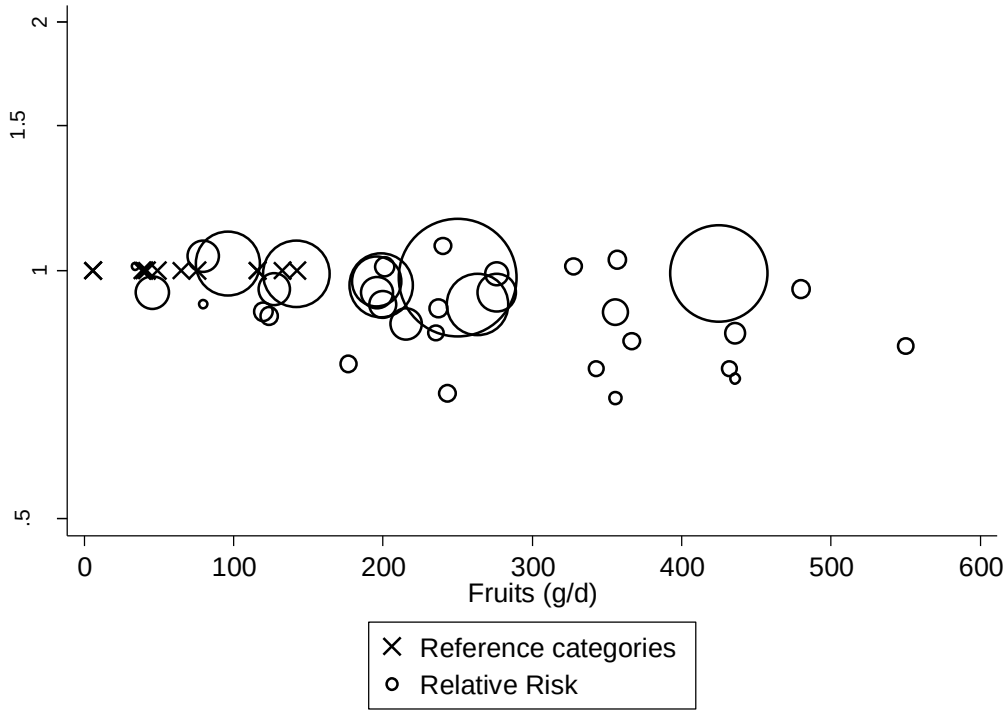
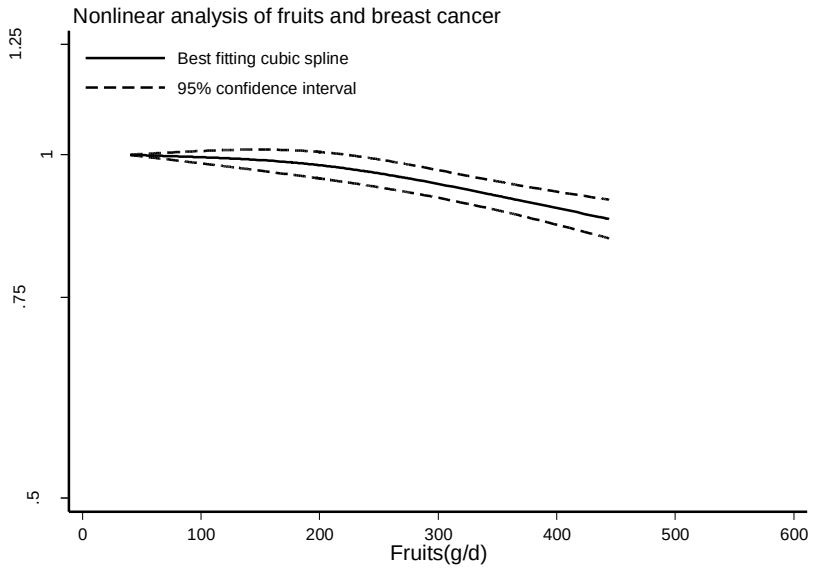


Table 45 Relative risk of breast cancer and fruits estimated using non-linear models

Fruits (g/day)	RR (95%CI)
5.7	1.00
100	0.98 (0.97-1.00)
200	0.96 (0.94-0.99)
300	0.94 (0.91-0.96)
400	0.90 (0.87-0.94)
500	0.87 (0.83-0.91)
550	0.86 (0.81-0.90)

Figure 56 Fruits and postmenopausal breast cancer, nonlinear dose-response analysis



P nonlinearity=0.03

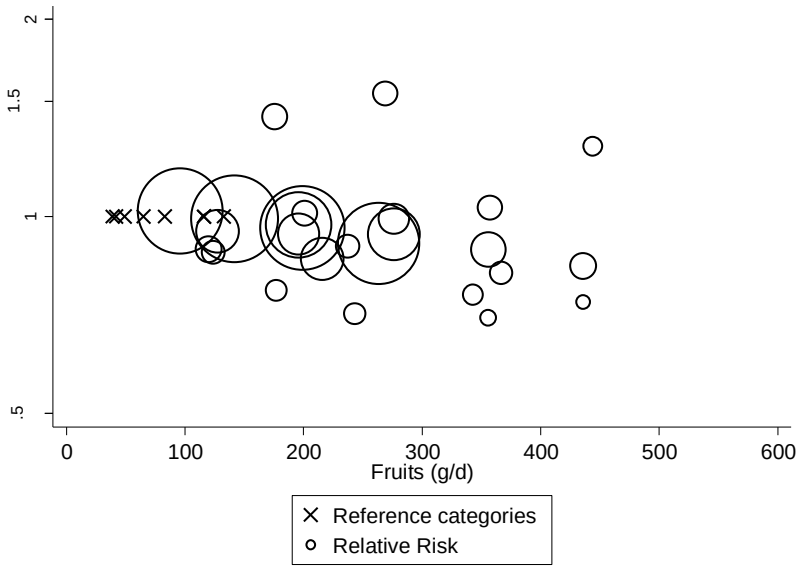
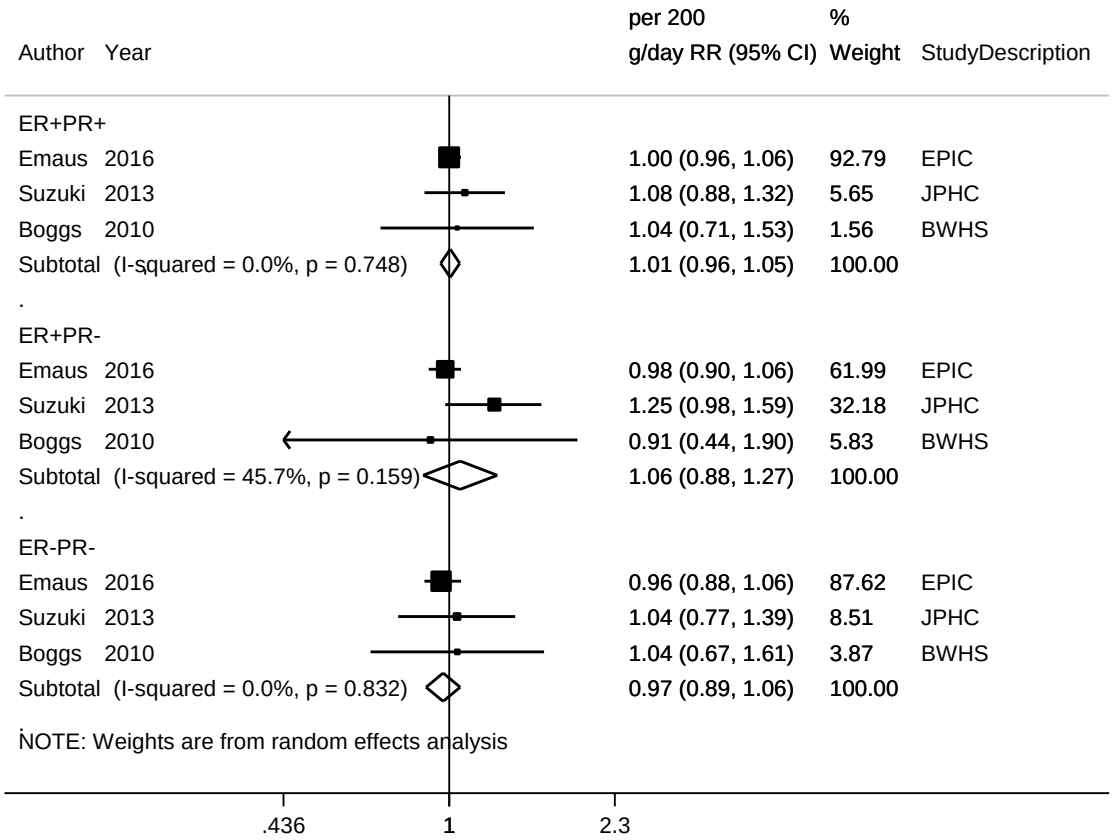


Table 46 Relative risk of postmenopausal breast cancer and fruits estimated using non-linear models

Fruits (g/day)	RR (95%CI)
39	1.00
100	0.99 (0.97-1.01)
200	0.98 (0.94-1.01)
300	0.94 (0.91-0.97)
400	0.90 (0.86-0.93)
444	0.88 (0.84-0.91)

Figure 57 Relative risk of breast cancer for 200 g/day increase in fruit intake, stratified by hormone receptor status



2.3.1 Soy products

Cohort studies

Overall summary

Six publications from five cohorts were detected that reported data on soy products (the studies included one or a combination of the following products: miso soup, tofu, deep-fried tofu, fried bean curd, dried bean curd, fermented bean curd, fermented soy beans, houba-miso, soymilk, boiled soy beans, dim sum) in relation to breast cancer. One meta-analysis was identified and no pooled analysis was identified.

Dose response meta-analyses were not conducted due to inadequate categorisation of soy products intake in some of the studies.

Breast cancer (any)

Five publications from four cohorts were identified (Wada, 2013; Nishio, 2007; Li, 2005; Shannon, 2005; Yamamoto, 2003). None of the studies reported significant association between soy products and breast cancer.

The JACC and BSE studies (Nishio, 2007; Shannon, 2005) reported non-significant positive associations, while the TCCJ study and a Japanese prospective cohort showed non-significant inverse associations with higher consumption of soy products (Wada, 2013, Yamamoto, 2003). Li et al. (2005) using the BSE cohort reported no association between soy products consumption and breast cancer.

Postmenopausal breast cancer

Three publications were identified (Wada, 2013, Butler, 2010, Nishio, 2007). In all three studies a non-significant inverse association was found between postmenopausal breast cancer and higher soy products consumption.

Premenopausal breast cancer

One study was identified (Wada 2013) and it reported a non-significant slightly positive association between higher consumption of soy product and premenopausal breast cancer.

Table 47 Soy products intake and breast cancer risk. Results of meta-analyses of studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Chen, 2014	Total: 35 studies Postmenopausal: 31 studies (12 cohort or nested case-control studies, 19 case-control studies) Premenopausal: 30 studies (10 cohort or nested case-control studies, 20 case-control studies)	11 premenopausal 13 postmenopausal	Asian and Western countries	Premenopausal BC Postmenopausal BC	Highest vs lowest soy bean/ soy products	0.64 (0.49-0.80) 0.72 (0.48-0.97)		66.5% 0.001 91.4% 0.000

2.3.1.1 Miso soup

Cohort studies

Summary

Four publications from three cohorts were detected that reported results in miso soup consumption in relation to breast cancer.

Dose response meta-analyses were not conducted due to insufficient number of studies.

Breast cancer (any)

Three cohorts (four publications) were identified. From the three studies reporting results on miso soup intake and breast cancer incidence risk, the JACC study did not find an association (Nishio, 2007), the JPHC study revealed a non-significant inverse association (Yamamoto, 2003) while a study on atomic bomb survivors in Japan found a non-significant positive association (Key, 1999).

Furthermore, the JACC study presented a non-significant decreased risk for breast cancer mortality with higher consumption of miso soup (Iso, 2007).

Postmenopausal breast cancer

One study was identified (Nishio, 2007) reporting results on postmenopausal breast cancer and miso soup consumption. The JACC study reported a non-significant inverse association with higher consumption of miso soups compared to lower consumption.

2.3.1.5 Tofu

Cohort studies

Summary

Five publications from three cohorts were found on tofu consumption and breast cancer.

Dose response meta-analyses were not conducted due to insufficient number of studies.

Breast cancer (any)

Three cohorts (five publications) were identified. Two of those studies reported results on tofu consumption in relation to breast cancer incidence. The JACC study found a non-significant positive association (Nishio, 2007), while the Radiation Effects Research Foundation's Life Span study reported a non-significant reverse association (Key, 1999). Furthermore, the JACC study reported a significant positive association between tofu consumption and breast cancer mortality risk (Iso, 2007).

In addition, two nested case-control studies reported results from the BSE trial (Li, 2005, Shannon, 2005). Both of them reported a non-significant inverse association between consumption of fermented bean curd and breast cancer incidence.

Postmenopausal breast cancer

One study was identified that reported data on tofu consumption and postmenopausal breast cancer (Nishio, 2007). The JACC study reported a non-significant positive association of

postmenopausal breast cancer incidence with higher consumption of tofu compared to lower consumption.

2.5.1 Red and processed meat

Cohort studies

Overall summary

Eleven publications on red meat intake and breast cancer risk were identified, including a pooled analysis of eight cohort studies. The results of recent updates of some cohorts included in the Pooling project are similar to the results of the Pooling project that was selected for analysis.

The study characteristics and results are shown in inclusion and exclusion tables in this section.

Study quality:

Total red meat was assessed by FFQ in all studies except two studies (Wie, 2014; Sonestedt, 2008b) in which diet was assessed through 3- and 7-day records respectively. Two studies (CNBSS and SMC) were based in participants in mammography studies. Cancer outcome was confirmed using medical notes, death records or through cancer registries. Loss to follow-up was low in general.

Most studies adjusted results at least for age, total energy intake, BMI and some reproductive factors (or tested for their effect in the models). The analyses were not adjusted for reproductive factors in a Korean study (Wie, 2014) that reported inverse non-significant association of total red meat intake and breast cancer risk, and in the analysis of the NIH-AARP (Kabat, 2007). In the NIH-AARP, both red meat and processed meats were not associated with breast cancer in other analyses that adjusted for hormone-related factors and other main potential confounders (see Kabat, 2007 in sections on red meat and processed meat).

Main results:

Breast cancer (any)

Ten studies (13 280 cases) were included in the dose-response meta-analysis. No significant association of total red meat intake with breast cancer was observed.

Larsson, 2009a was the only study reporting RRs by hormone receptor status. Total red meat intake was non-significantly associated with risk of ER+/PR- breast cancer (inverse relationship) and ER-/PR- and ER+/PR+ tumours (positive relationship).

No heterogeneity was observed.

Sensitivity analyses:

Sensitivity analysis was not conducted due to low number of studies.

Premenopausal breast cancer

No analysis was conducted. The Pooling reported no significant association (inverse, 5 cohorts, no evidence of heterogeneity).

Postmenopausal breast cancer

Nine studies were included in the dose-response meta-analysis. Total red meat intake was not associated with postmenopausal breast cancer.

Wu, 2010 (NHS I) reported non-significant inverse association for ER+/PR+ and non-significant positive association for ER-/PR- postmenopausal breast cancer. Ferrucci, 2009 reported significant positive association for ER+/PR+ postmenopausal breast cancer.

Table 48 Total red meat intake and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	13 (11 publications)
Studies included in forest plot of highest compared with lowest exposure	Breast cancer: 10 (3 publications) Premenopausal: 2 (2 publications) Postmenopausal: 4 (4 publications)
Studies included in linear dose-response meta-analysis	Breast cancer: 10 (3 publications) Premenopausal: 5 (1 publication) Postmenopausal: 9 (2 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 49 Total red meat intake and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	5 times/month	100 g/day
Breast cancer		
Studies (n)	3*	10
Cases (total number)	607	13 280
RR (95%CI)	1.02 (0.98-1.07)	0.99 (0.94-1.04)
Heterogeneity (I^2, p-value)	74%	0%, 0.67
P value Egger test	-	-
CUP		
	Premenopausal	Postmenopausal
Studies (n)	5**	9
Cases	-	**
RR (95%CI)	0.94 (0.87-1.02)	1.00 (0.88-1.13)
Heterogeneity (I^2, p-value)	0.58	25.5%, 0.25
P value Egger test	-	-

*None of the studies are included in the CUP analysis: two were on fresh meat and the other on meat meals

**The number of cases was not reported in the Pooling project (Missmer, 2002)

Table 50 Total red meat and breast cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Guo, 2015*	11 studies*		USA, UK, Europe	Incidence, breast cancer	Per 120 g/day	1.11 (1.05-1.16)		p>0.1
	14 studies**				Highest vs lowest	1.10 (1.02-1.19)		62%, p=0.001
	5 studies			Incidence, premenopausal breast cancer	Highest vs lowest	1.08 (0.95-1.22)		31%, p=0.22
	6 studies			Incidence, postmenopausal breast cancer		1.20 (1.00-1.44)		57%, p=0.04

*Guo 2015 included studies on total red meat and unprocessed red meats. In the highest vs lowest analysis, the Pooling project (Missmer, 2002) was included but also some of its component.

Table 51 Total red meat intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Wie, 2014 BRE80609 Korea	CSECK, Prospective Cohort, Age: 48.4 years (controls), W	29/ 3 486 7 years	Korean Central Cancer Registry, Electronic Medical Record of the National Cancer Centre	Three day food record	Incidence, breast cancer	≥43 vs <43 g/day	0.53 (0.14-1.97)	Age, energy intake, BMI, physical activity, smoking, alcohol use, income, education, marital status	
						per 50 g/day	0.85 (0.42-1.72)		RR rescaled for an increment of 100g
Ferrucci, 2009 BRE80234 USA Result Number:454835	PLCO, Prospective Cohort, Age: 55-74 years, W, postmenopausal	1 205/ 52 158 5.5 years	Self-report verified by medical record	Validated FFQ	Incidence, breast cancer postmenopausal	52.8 vs 9.4 g/1000 kcal/day	1.23 (1.00-1.51)	Age, age at first live birth, age at menarche, age at menopause, alcohol consumption, BMI, benign breast disease, educational level, ethnicity/race, family history of cancer, fat intake, HRT use, mammography, randomization group, study canter, total caloric intake	Intakes in g/1000kcal/day converted to g/day using average energy intake per each quantile, mid-points of exposure quantiles
		259/			Postmenopausal ER+/PR+		1.59 (1.03-2.48)		Analysis by ER/PR status was not conducted
Cross, 2007 BRE80448 USA Result Number:478045	NIH- AARP, Prospective Cohort, Age: 50-71 years, W, Retired	5 872/ 199 312 6.8 years	Cancer registry and National Death Index	Validated 124-item FFQ	Incidence, breast cancer	62.7 vs 9.8 g/1000 kcal	1.02 (0.93-1.12)	Age, BMI, education level, family history of cancer, fruit and vegetable consumption, marital status, race,	Distribution of person-years by exposure quantiles, intakes in g/1000kcal converted to

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								smoking status, alcohol intake, frequency of vigorous physical activity, total energy intake	g/day using average energy intake per quantile
Missmer, 2002 Pooled analysis		7 379/351 041			Incidence, breast cancer	Q4 vs Q1	0.94 (0.87-1.02)	Age at menarche, parity, age at first birth, oral contraceptive use, history of benign breast disease, family history of breast cancer, menopausal status, BMI, HRT use, smoking status, education, height, alcohol intake, total energy intake	
						per 100g/day	0.98 (0.93-1.04)		
					Premenopausal		0.97 (0.79-1.20)		
					Postmenopausal		0.97 (0.91-1.03)		
USA, Canada	AHS	160/15 172							
Canada	CNBSS	419/56 837							
USA	IWHS	1 130/34 406							
Netherlands	NLCS	937/62 377							
USA	NYS	367/18 475							
USA	NYU	385/13 261							
USA	NHS (1980-1986)	1 023/89 046							
USA	NHS (1986-1996)	1 638/68 817							
Sweden	SMC	1 320/61 467							

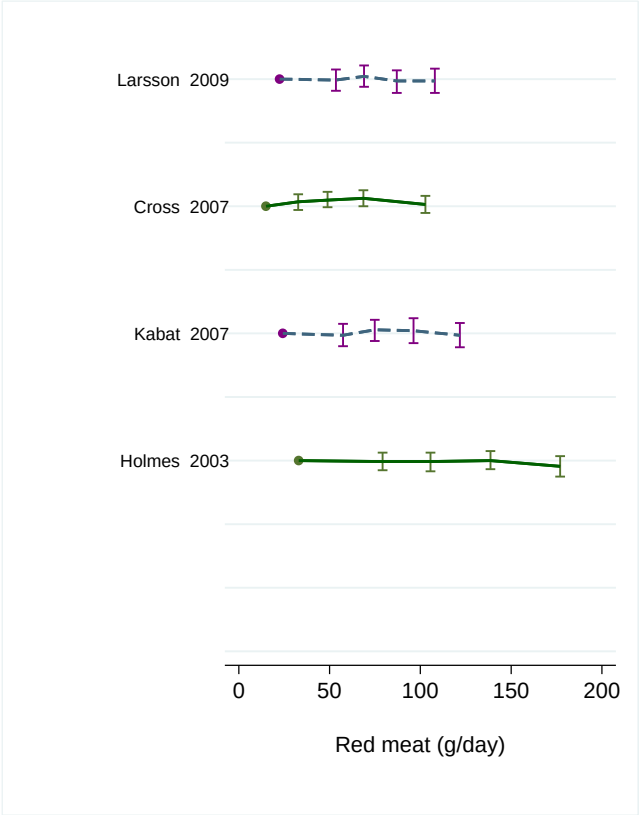
Table 52 Total red meat intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Lee, 2013 BRE80559 USA Result Number:497605	NHS I, Nested Case Control, Age: 64.00years, W, postmenopausal women	1 057/ 2 105		FFQ	Incidence, breast cancer postmenopausal	1.5 vs 0.6 servings/day	1.06 (0.83-1.36)	Age, age at menarche, BMI at age 18 years, benign breast disease, family history of breast cancer, smoking status, weight gain since 18, alcohol intake, parity and age at first birth, postmenopausal hormone use, total energy	Included in Pooling project (Missmer, 2002)
Wu, 2010 BRE80290 USA Result Number:458834	NHS I, Prospective Cohort, Age: 30-55 years, W, postmenopausal women	2 317/ 54 440 10 years	Self-reported, next of kin, postal service, National Death Index, hospital records	Validated semi-quantitative FFQ	Incidence, breast cancer postmenopausal	Q5 vs Q1	0.95 (0.83-1.09)	Age, age at first birth, age at menarche, alcohol consumption, BMI, benign breast disease, energy intake, family history of cancer, height, parity, physical activity, smoking status, weight, postmenopausal hormone use	Included in Pooling project (Missmer, 2002)
		1 174/			ER+/PR+		0.91 (0.75-1.10)		Analysis by ER status was not conducted
		295/			ER-/PR-		1.05 (0.72-1.53)		
Larsson, 2009a BRE80252	SMC, Prospective	2 952/ 61 433	Cancer registry	Validated FFQ	Incidence, breast cancer	≥98 vs <46 g/day	0.98 (0.86-1.12)	Age, age at first birth, age at	Included in Pooling

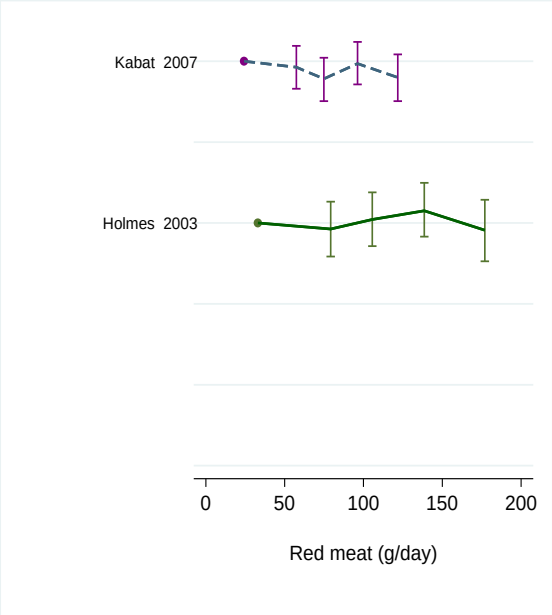
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Sweden Result Number:455595	Cohort, W	17.4 years						menarche, age at menopause, alcohol consumption, BMI, calendar year of follow-up, educational level, family history of cancer, HRT use, height, oral contraceptive use, parity, total caloric intake	Project (Missmer, 2002)
		1 286/			ER+/PR+		1.10 (0.90-1.34)		
		417/			ER+/PR-		0.86 (0.60-1.23)		
		266/			ER-/PR-		1.12 (0.70-1.79)		
Sonestedt, 2008b BRE80196 Sweden Result Number:445645	MDC, Prospective Cohort, Age: 50- years, W, Postmenopausal	430/ 11 699 10.4 years	Cancer registry	7-day food record & FFQ	Incidence, breast cancer, postmenopausal	Q5 vs Q1	1.12 (0.83-1.50)	Age, energy intake, exposure assessment, season of year	Excluded, only two levels of exposure
Kabat, 2007 BRE80138 Canada Result Number:442983	CNBSS, Prospective Cohort, Age: 40-59 years, W, Screening Program	2 491/ 48 662 16.4 years	Cancer registry	FFQ	Incidence, breast cancer	≥108.99 vs <48.49 g/day	0.98 (0.86-1.12)	Age, age at menarche, alcohol intake, BMI, benign breast disease, educational level, energy intake, family history of cancer, HRT use, menopausal status, oral contraceptive use, parity, randomization group, study centre	Included in Pooling project (Missmer, 2002)
		1 171/			Incidence, breast cancer, premenopausal		0.87 (0.71-1.06)		
		993/			Incidence, breast cancer, postmenopausal		1.08 (0.88-1.34)		
Holmes, 2003	NHS I,		Self-reported,	Validated	Incidence,	≥1.32 vs ≤0.55	0.94 (0.84-1.05)	Age, age at first	Included in

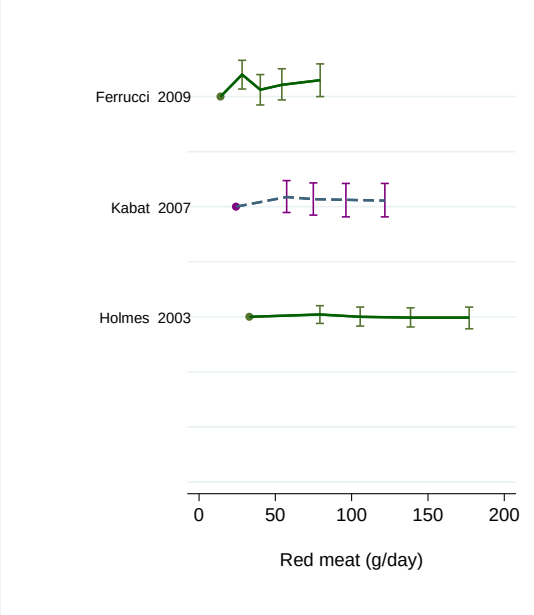
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
BRE15400 USA Result Number:81074	Prospective Cohort, Age: 30-55 years, W, Registered nurses	4 107 88 647 18 years	death certificate, pathology reports	semi-quantitative FFQ	breast cancer	serving/day		pregnancy/child, age at menarche, age at menopause, alcohol, BMI, benign breast disease, energy intake, family history, HRT use, height, menopausal status, other anthropometric index, other design issue, other menstrual characteristics, parity/pregnancies, weight change since 18, BMI at age 18	Pooling project (Missmer, 2002)
		854/			Premenopausal		0.94 (0.72-1.22)		
		2 936/			Postmenopausal		0.99 (0.86-1.13)		
Gertig, 1999 BRE03215 USA Result Number:78663	NHS I, Nested Case Control, Age: 58.00years, W, Registered nurses	455/ 917 8 years	Self-report verified by medical record	Semi-quantitative FFQ	Incidence, breast cancer	>1.0 vs ≤0.5 serving/day	0.90 (0.60-1.30)	Age at first pregnancy/child, age at menarche, BMI, benign breast disease, family history, parity/pregnancies	Included in Pooling project (Missmer, 2002)

Figure 58 RR estimates of breast cancer by levels of total red meat intake.Breast cancer



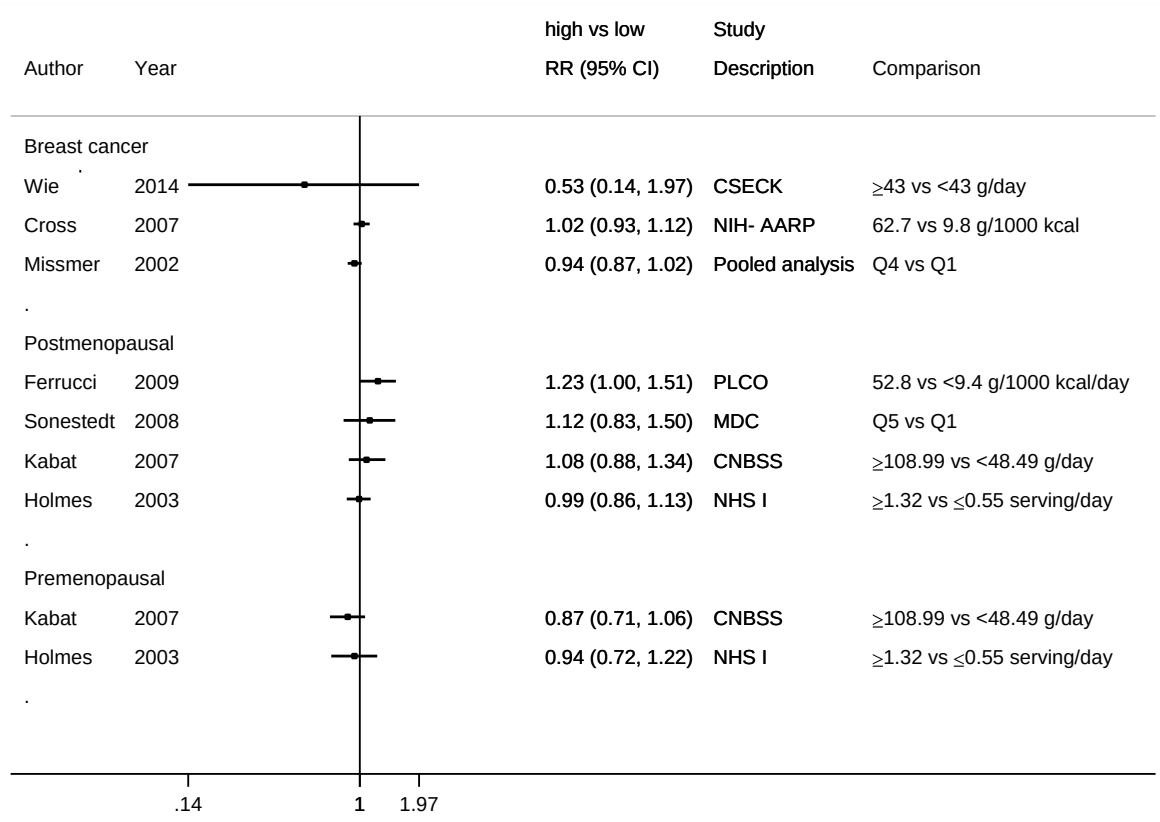
Premenopausal **Postmenopausal**





Note: The Pooling project is not included in any figure (Missmer, 2002)

Figure 59 RR (95% CI) of breast cancer for the highest compared with the lowest level of total red meat intake



Note: The Pooling project (Missmer, 2002) is not included in the figure for post- and premenopausal breast cancers

Figure 60 RR (95% CI) of breast cancer for the highest compared with the lowest level of total red meat intake by hormone receptor status

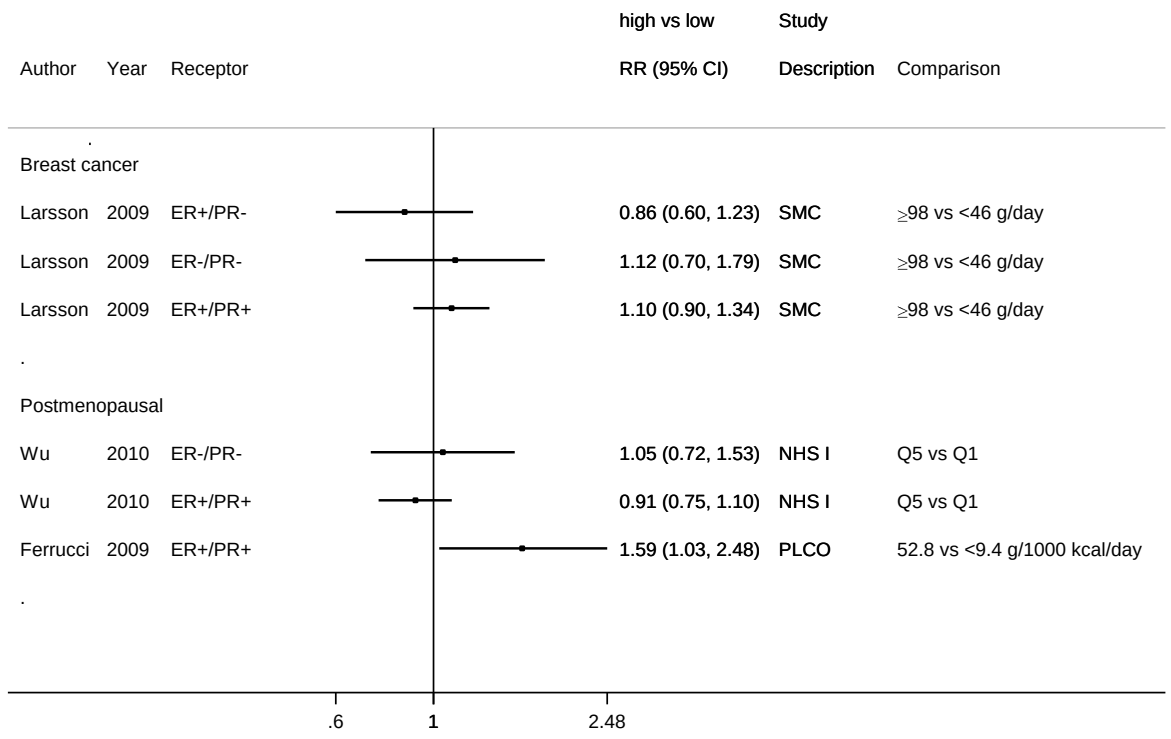


Figure 61 Relative risk of breast cancer for 100 g/day increase of total red meat intake

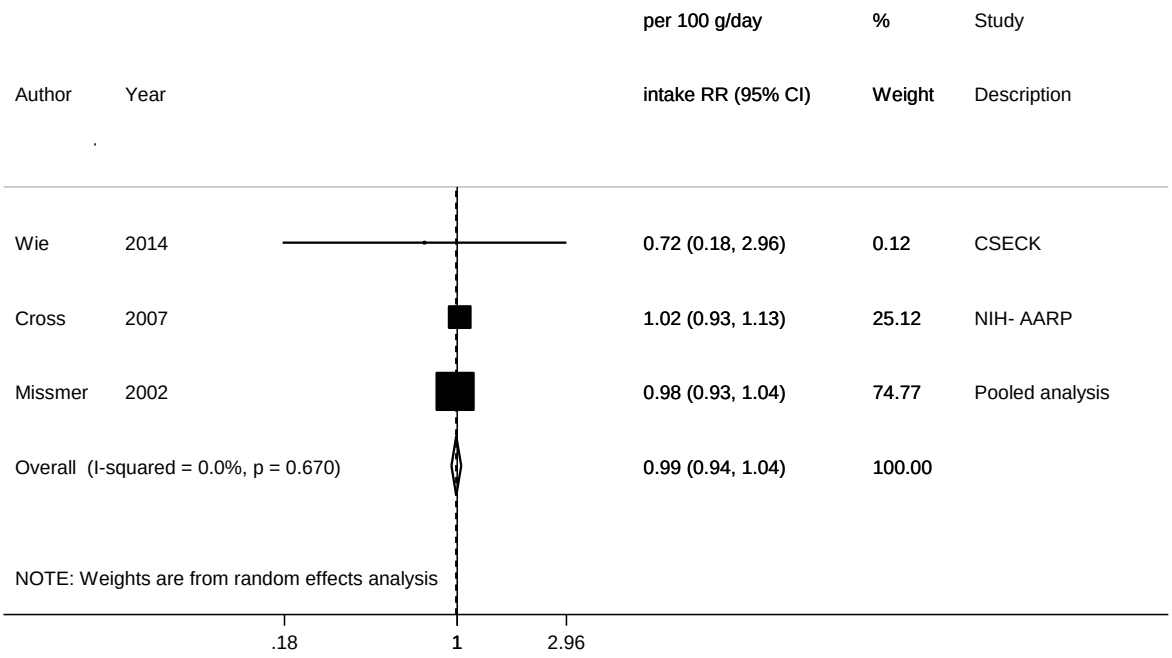
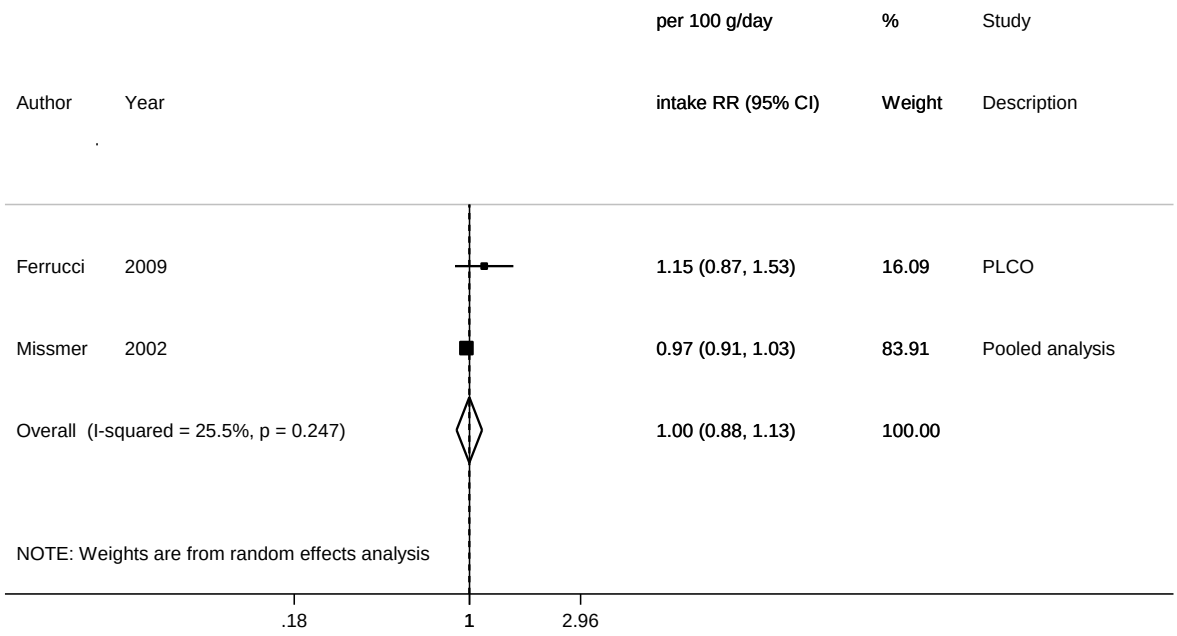


Figure 62 Relative risk of postmenopausal breast cancer for 100 g/day increase of total red meat intake



2.5.1.2 Processed meat

Cohort studies

Overall summary

Nineteen publications on processed meat intake and breast cancer risk were identified, including a pooled analysis of seven cohort studies. From these, two publications were excluded because were superseded by other publications, and one publication was on a cohort included in the pooled analysis. Two studies on breast cancer (Wie, 2014; Li, 2005) on breast cancer (all), and one on premenopausal breast cancer (Cho, 2006) were excluded from the analysis.

The study characteristics and results are shown in a table in this section.

Study quality

Processed meat was assessed by FFQ in all studies except one (Pouchieu, 2014) in which diet was assessed through repeated 24 h recall during follow-up.

One study on African-American women included some participants aged less than 21 years at baseline. The small Chinese cohort (excluded from the analysis) was based in a trial on breast self- examination (Li, 2005); among studies in the Pooling project, two studies were based in mammography screening studies, but there was no heterogeneity across studies (p het=0.99) (Missmer, 2002). A French study (Pouchieu, 2014) is a follow-up of a trial on antioxidants supplementation but no significant interaction with treatment was observed.

Loss to follow-up was low in general. In the French study (Pouchieu, 2014) loss to follow-up was only 2.8% but mainly premenopausal women.

In the studies, cancer outcome was confirmed using medical notes, death records or through cancer registries.

All studies adjusted results at least for age, total energy intake, BMI and some reproductive factors (or tested for their effect in the models). Only two studies (Taylor et al, 2007; Lin, 2005) did not adjust (or tested as a covariate) for alcohol intake.

Main results:

Breast cancer (any)

Thirteen studies (22 735 cases) (seven publications) were included in the dose-response meta-analysis. No significant association was observed.

Two studies were excluded from the analysis. A Korean study (Wie, 2014) with only 29 cases in the analysis and a Chinese study (Li, 2005) in which processed meat intake was too low (top intake was more than 16 times/year). The study reported non-significant positive relationships.

High heterogeneity was observed. There was no evidence of a significant publication or small study bias.

Sensitivity analyses:

In influence analysis, the summary RR ranged from 1.01 (95% CI=0.92-1.10) when Taylor, 2007 (12% weight) was omitted to 1.14 (95% CI=0.99-1.32) when pooled analysis (Missmer, 2002) (23% weight) was omitted.

The low number of studies did not allow formal exploration of heterogeneity. Two studies reported positive strong significant associations (see funnel and forest plots). One was a follow-up of a trial on antioxidants supplementation from France (Pouchieu, 2014). Antioxidant treatment did not influence the association. The other was a large UK study (Taylor, 2007).

Premenopausal breast cancer

Summary

Main results:

Four studies (3 409 cases) were included in the dose-response meta-analysis. No significant association was observed. There was low heterogeneity and no significant evidence of publication or small study bias

One study (Cho, 2006) investigated types of processed meats and was excluded from the analysis. Intakes of bacon, hot dogs and other processed meats were not associated to risk of premenopausal breast cancer. Positive associations were observed for ER+/PR+ tumours, but not for ER-/PR- breast cancer. In the Pooling project (7 cohorts) processed meat intake was not related to breast cancer risk. There was no effect modification by menopausal status (data not shown) (Missmer, 2002).

Sensitivity analyses:

In influence analysis, the summary RR ranged from 0.97 (95% CI=0.84-1.12) when Taylor, 2007 (16% weight) was omitted to 1.07 (95% CI=0.88-1.29) when Holmes, 2003 (15% weight) was omitted.

Postmenopausal breast cancer

Thirteen studies (13 708 cases) were included in the dose-response meta-analysis. No significant association was observed. There was moderate heterogeneity and no significant evidence of publication or small study bias.

In the Pooling project (7 cohorts) processed meat intake was not related to breast cancer risk. There was no effect modification by menopausal status (data not shown) (Missmer, 2002).

Dose-response meta-analysis by hormonal status was not conducted due to low number of studies. Fung, 2005 reported non-significantly positive association for postmenopausal breast cancer ER-. Wu, 2010 reported non-significantly positive association for postmenopausal ER+/PR+ breast cancer and non-significantly inverse association for postmenopausal ER-/PR- breast cancer.

Sensitivity analyses:

The summary RR ranged from 1.08 (95% CI=0.97-1.19) when Taylor, 2007 (11% weight) was omitted to 1.17 (95% CI=1.02-1.35) when Holmes, 2003 (17% weight) was omitted.

Two studies reported positive strong significant associations (see funnel and forest plots). One was a nested case-control in a Danish cohort (Egeberg, 2008). The association of processed meat and postmenopausal breast cancer was confined to intermediate/fast N-acetyl transferase 2 acetylators. The other was a large UK study (Taylor, 2007).

Nonlinear dose-response meta-analysis:

There was no evidence of non-linear relationship (p=0.93).

Table 53 Processed meat intake and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	23 (19 publications)
Studies included in forest plot of highest compared with lowest exposure	Breast cancer: 9 (9 publications) Premenopausal: 4 (4 publications) Postmenopausal: 8 (10 publications)
Studies included in linear dose-response meta-analysis	Breast cancer: 13 (7 publications) Premenopausal: 4 (4 publications) Postmenopausal: 8 (8 publications)
Studies included in non-linear dose-response meta-analysis	Breast cancer: 6 (6 publications) Premenopausal: not enough studies Postmenopausal: 7 (7 publications)

Table 54 Processed meat intake and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	CUP
Increment unit used	20 g/day	50 g/day
All studies		
Studies (n)	2	13
Cases (total number)	684	22 735
RR (95%CI)	1.04 (0.91-1.20)	1.08 (0.96-1.22)
Heterogeneity (I^2, p-value)	-	72%, 0.002
P value Egger test	-	0.24
CUP		
	Premenopausal	Postmenopausal
Studies (n)	4	8
Cases	3 409	13 708
RR (95%CI)	1.02 (0.84-1.24)	1.13 (0.99-1.29)
Heterogeneity (I^2, p-value)	31%, 0.23	47%, 0.07
P value Egger test	0.85	0.82

Stratified analyses

Geographic area	**Asia**	**Europe**	**North-America**
	Breast cancer		
Studies (n)	-	4	3
RR (95%CI)	-	1.31 (0.93-1.84)	0.97 (0.83-1.14)
Heterogeneity (I^2, p- value)	-	80%, 0.002	50%, 0.14
	Premenopausal		
Studies (n)	-	2	3
RR (95%CI)	-	1.14 (0.80-1.62)	0.90 (0.67-1.21)
Heterogeneity (I^2, p- value)	-	62%, 0.10	0%, 0.34
	Postmenopausal		
Studies (n)	-	4	4
RR (95%CI)	-	1.31 (1.00-1.71)	1.00 (0.87-1.14)
Heterogeneity (I^2, p- value)	-	64%, 0.04	0%, 0.71

Table 55 Processed meat and breast cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Guo, 2015	7*		USA, UK, Europe	Incidence, breast cancer	Per 50g/day	1.09 (1.03-1.16)		>0.1
	12				Highest vs lowest	1.08 (1.01-1.15)		58.3%, <0.006
	3			Incidence, premenopausal breast cancer	Highest vs lowest	1.03 (0.89-1.18)		20.4%, 0.29
	4			Incidence, postmenopausal breast cancer		1.23 (0.98-1.55)		60.4%, 0.06

*Comparison with dose-response analysis in the CUP:

Guo, 2015 included in the analysis of all breast cancers four studies excluded from the CUP: a Chinese study where top intake was more than 16 times/ year and not comparable to the other studies (Li, 2005), a study in premenopausal breast cancer that investigated processed meat types (Cho, 2006) and two studies in postmenopausal breast cancer (Egeberg, 2008; Ferrucci, 2009).

The CUP included the Pooling Project of cohort studies (Missmer, 2002) that was not included in Guo, 2015.

Table 56 Processed meat intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Pouchieu, 2014 BRE80553 France	SU.VI.MAX, Prospective Cohort, W	190/ 4 684 11.3 years	Self-report verified by medical record	24 hour dietary recall	Incidence, breast cancer	>43.6 vs <16.4 g/day	1.45 (0.92-2.27) Ptrend:0.03	Age, BMI, educational level, family history of breast cancer, fat intake, height, intervention group, menopausal status, number of live births, physical activity, red meat intake, smoking status, alcohol intake, non-alcohol energy, use of HRT	Distribution of cases, person-years by exposure quantiles, mid-points of exposure quantiles
Genkinger, 2013 BRE80446 USA	BWHS, Prospective Cohort, Age: 21-69 years, African-American women	1 268/ 56 062 12 years	Cancer registry and national death index	68-item FFQ in 1995 and 85-item FFQ in 2001	Incidence, breast cancer	≥200 vs <100 g/week	0.99 (0.82-1.20)	Age at first birth, age at menarche, age at menopause, BMI, energy intake, family history of breast cancer, HRT use, parity, alcohol, education, oral contraceptive history, smoking, vigorous physical activity, menopausal status	Mid-points of exposure quantiles, g/week converted to g/ day
		573/			Premenopausal		0.92 (0.72-1.18)		
		520/			Postmenopausal		0.93 (0.69-1.27)		
Ferrucci, 2009 BRE80234 USA	PLCO, Prospective Cohort, Age: 55-74 years, Postmenopausal women	1 205/ 52 158 5.5 years	Self-report verified by medical record	Validated FFQ	Incidence, breast cancer postmenopausal	>11.7-124.1 vs ≤2.4 g/1000 kcal/day	1.12 (0.92-1.36)	Age, age at first live birth, age at menarche, age at menopause, alcohol consumption, BMI, benign breast disease, educational	Intakes in g/1000kcal converted to g/day using average energy intake

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								level, ethnicity/race, HRT use, family history of cancer, fat intake, mammography, randomization group, study centre, total caloric intake	of the whole cohort, mid-points of exposure quantiles
Kabat, 2009a BRE80240 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, Postmenopausal women	3 818/ 120 755 8 years	Cancer registry and death records	Validated 124-item FFQ	Incidence, breast cancer, postmenopausal	>12.6 vs <2.2 g/1000 kcal/day	1.00 (0.90-1.12)	Age, age at first live birth, age at menarche, age at menopause, alcohol intake, BMI, breast biopsies, educational level, family history of cancer, HRT use, height, physical activity, race, saturated fat intake, smoking habits, total energy intake, non-processed meat	Intakes in g/1000kcal converted to g/day using average energy intake per each quantile, mid-points of exposure quantiles
Pala, 2009 BRE80268 Europe	EPIC, Prospective Cohort, Age: 25-70 years, W	7 119/ 319 826 8.8 years	Multiple methods	Country-specific validated food questionnaires	Incidence, breast cancer	56.5 vs 1.7 g/day	1.10 (1.00-1.20) Ptrend:0.07	Age, alcohol intake, center, educational level, energy intake, height, smoking habits, weight, menopausal status	Distribution of person-years by exposure quantiles, RR rescaled for an increment of 50 g
						per 40 g/day	1.01 (0.96-1.05)		
		1 699/			Premenopausal	56.5 vs 1.7 g/day	0.99 (0.82-1.19)		
		3 673/			Postmenopausal		1.13 (1.00-1.28) Ptrend:0.06		
Egeberg, 2008 BRE80153	DCH, Nested Case	378/ 24 697	Cancer registry	Validated 192-item FFQ	Incidence, breast cancer,	>45 vs <20 g/day	1.59 (1.02-2.47)	Age, age at first birth, alcohol consumption,	RR rescaled for an

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Denmark	Control, Age: 50-64 years, Postmenopausal women	4.2 years			postmenopausal	per 25 g/day	1.23 (1.04-1.45)	BMI, educational level, HRT use, parity	increment of 50 g
Cross, 2007 BRE80448 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, W, Retired	5 872/ 494 036 6.8 years	Cancer registry and National Death Index	Validated 124-item FFQ	Incidence, breast cancer	22.6 vs 1.6 g/1000 kcal/day	1.03 (0.94-1.12)	Age, BMI, education level, family history of cancer, fruit and vegetable consumption, marital status, race, smoking status, alcohol intake, frequency of vigorous physical activity, total energy intake	Distribution of person-years by exposure quantiles, intakes in g/1000kcal converted to g/day using average energy intake per quantile
Taylor, 2007 BRE80008 UK	UKWCS, 1993, Prospective Cohort, Age: 35-69 years, W	678/ 33 725 8 years	NHS central registry	Validated 217-item FFQ	Incidence, breast cancer	>20 g/day vs none	1.39 (1.09-1.78) Ptrend:<0.001	Additionally adjusted for menopausal status	RR rescaled for an increment of 50 g
						per 50 g/day	1.59 (1.22-2.06)		
		283/			Premenopausal	>20 g/day vs none	1.20 (0.85-1.70) Ptrend:0.09	Age, energy intake, menopausal status, BMI, physical activity, smoking status, HRT use, OCP use, parity, total fruit and vegetable intake	
						per 50 g/day	1.45 (0.95-2.23)		
		395/			Postmenopausal	>20 g/day vs none	1.64 (1.14-2.37) Ptrend:0.003		
						per 50 g/day	1.64 (1.19-2.27)		
Fung, 2005 BRE22370 USA	NHS I, Prospective Cohort, Age: 30-55 years,	512/ 71 058 16 years	Self-reported, next of kin, postal service, National Death	Validated semi-quantitative FFQ	Incidence, breast cancer ER-, postmenopausal	per 1 serving/day	1.03 (0.79-1.33)	Age, age at first pregnancy/child, age at menarche, age at menopause, alcohol,	Analysis by ER- status in postmenopausal women

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	W, Registered nurses		Index, hospital records					BMI, benign breast disease, energy intake, family history, HRT use, height, menopausal status, other anthropometric index, parity/pregnancies, physical activity, smoking habits, supplements	was not conducted
van der Hel, 2004 BRE12728 Denmark	MPCDRF, Nested Case Control, Age: 20-59 years, W	229/ 493 10 years maximum	The Netherlands Cancer Registry, regional cancer registers	Validated semi-quantitative FFQ	Incidence, breast cancer	≥35 vs <20 g/day	1.08 (0.60-1.70)	Age, energy intake, menopausal status, place of residence, smoking, alcohol, age at menarche, BMI	
Holmes, 2003 BRE15400 USA	NHS I, Prospective Cohort, Age: 30-55 years, W, Registered nurses	4107/ 88 647 18 years	Self-reported, next of kin, postal service, National Death Index, hospital records	Validated semi-quantitative FFQ	Incidence, breast cancer	≥0.46 vs ≤0.1 serving/day	0.94 (0.85-1.05)	Age, total energy intake, alcohol intake, parity and age at first birth, BMI at age 18, weight change since age 18, height, family history of breast cancer, history of benign breast disease, age at menarche, menopausal status, age at menopause, HRT use, duration of menopause	Distribution of person-years by exposure quantiles, standard serving size of 50g was used, mid-points of exposure quantiles
		854/ 53 952			Premenopausal		0.86 (0.67-1.09)		
		2 936/ 76 152			Postmenopausal		1.00 (0.88-1.13)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Missmer, 2002 Pooled analysis		7 379/351 041			Incidence, breast cancer	per 10g/day	0.98 (0.96-1.00)	Age at menarche, parity, age at first birth, oral contraceptive use, history of benign breast disease, family history of breast cancer, menopausal status, BMI, HRT use, smoking status, education, height, alcohol intake, total energy intake	RR rescaled for an increment of 50 g
Canada	CNBSS	419/56 837							
USA	IWHS	1 130/34 406							
Netherlands	NLCS	937/62 377							
USA	NYS	367/18 475							
USA	NYU	385/13 261							
USA	NHS (1980-1986)	1 023/89 046							
USA	NHS (1986-1996)	1 638/68 817							
Sweden	SMC	1 320/61 467							
Voorrips, 2002 BRE13011 Netherlands	NLCS, Case Cohort, Age: 55-69 years, Postmenopausal women	783/ 62 573 6.3 years	Record linkage with regional cancer registries and the national database of pathology reports	Validated 150-item FFQ	Incidence, breast cancer postmenopausal	13 vs 0 g/day	0.93 (0.67-1.29)	Age, age at first pregnancy/child, age at menarche, age at menopause, alcohol, BMI, benign breast disease, benign breast disease, educational level, energy intake, family history, oral contraceptive use, parity/pregnancies, smoking habits	

Table 57 Processed meat intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Wie, 2014 BRE80609 Korea	CSECK, Prospective Cohort, Age: 48.4 years (controls), W	29/3486 7 years	Korean Central Cancer Registry, Electronic Medical Record of the National Cancer Centre	Three day food record	Incidence, breast cancer	per 10 g/day	1.48 (0.66-3.32)	Age, energy, BMI, physical activity, smoking, alcohol use, income, education, marital status	Excluded, wide 95% CI: 7.1 (0.13-403.4) per 50g/day
Wu, 2010 BRE80290 USA	NHS I, Prospective Cohort, Age: 30-55 years, W, postmenopausal women	2 317/ 54 440 10 years	Self-reported, next of kin, postal service, National Death Index, hospital records	Validated semi-quantitative FFQ	Incidence, breast cancer postmenopausal	Q5 vs Q1	0.98 (0.86-1.12)	Age, age at first birth, age at menarche, alcohol consumption, BMI, history of benign breast disease, energy intake, family history of cancer, height, parity, physical activity, smoking status, weight change, HRT use	Superseded by Holmes, 2003
		1 174/			ER+/PR+		1.06 (0.87-1.28)		Analysis was not conducted by ER/PR status (only one study), intake was not quantified
		295/			ER-/PR-		0.90 (0.61-1.31)		
Larsson, 2009a BRE80252 Sweden	SMC, Prospective Cohort, W	2 952/ 61 433 17.4 years	Cancer registry	Validated 67(at baseline) and 96-item (in 1997) FFQ	Incidence, breast cancer	Q5 vs Q1	1.08 (0.96-1.22)	Age, age at first birth, age at menarche, age at menopause, alcohol consumption, BMI, calendar year of follow-up, educational level,	Excluded, two exposure categories only

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								family history of cancer, HRT use, height, oral contraceptive use, parity, total caloric intake	
Cho, 2006 BRE80034 USA	NHS II, Prospective Cohort, Age: 26-46 years, W, Premenopausal	1 021/ 90 659 12 years	Self-report verified by medical record	FFQ-semi-quantitative	Incidence, breast cancer, premenopausal	>3 servings/week vs <1 serving/month of sausages, salami, bologna	1.28 (0.87-1.88)		Excluded, exposure is by types of processed meats
		512/			ER+/PR+		2.34 (1.47-3.71)		
		167/			ER-/PR-		0.79 (0.24-2.61)		
Li, 2005 BRE23123 China	Shanghai BSE, Nested Case Control, W	130/ 1200	Biopsy	Validated 99-item FFQ	Incidence, breast cancer	>16 vs ≤4 times/year	1.20 (0.60-2.10)	Age, energy, year of interview	Excluded, extremely low processed meat intake
Gertig, 1999 BRE03215 USA	NHS I, Nested Case Control, Age: 58.00 years, W, Registered nurses	455/ 917	Self-report confirmed by medical records	Validated semi-quantitative FFQ	Incidence, breast cancer	>0.50 vs ≤0.14 serving/day	1.00 (0.70-1.50)	Age at first pregnancy/child, age at menarche, BMI, benign breast disease, family history, parity/pregnancies	Superseded by Holmes, 2003

Figure 63 RR estimates of breast cancer by levels of processed meat intake

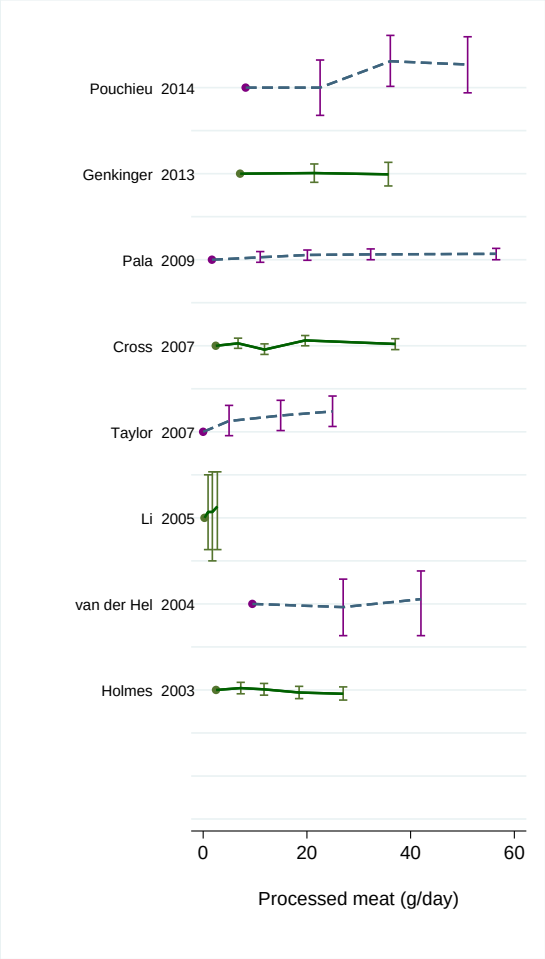


Figure 64 RR estimates of premenopausal breast cancer by levels of processed meat intake

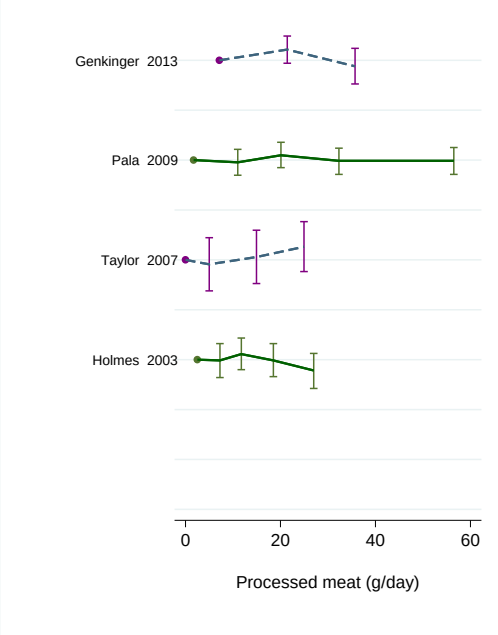


Figure 65 RR estimates of postmenopausal breast cancer by levels of processed meat intake

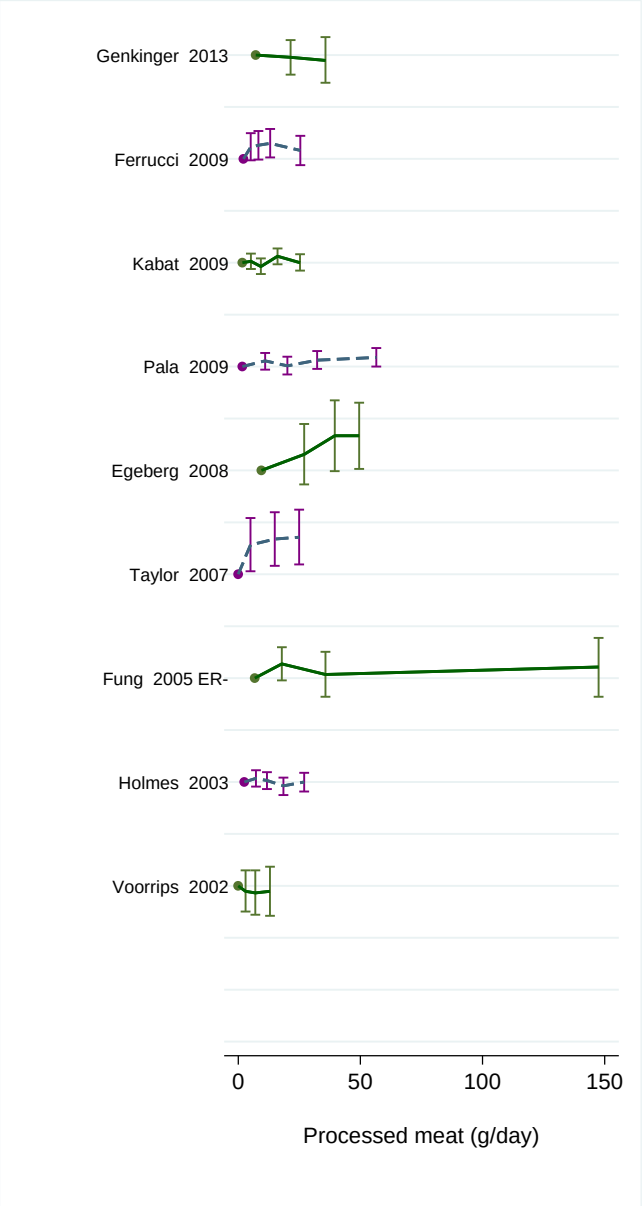
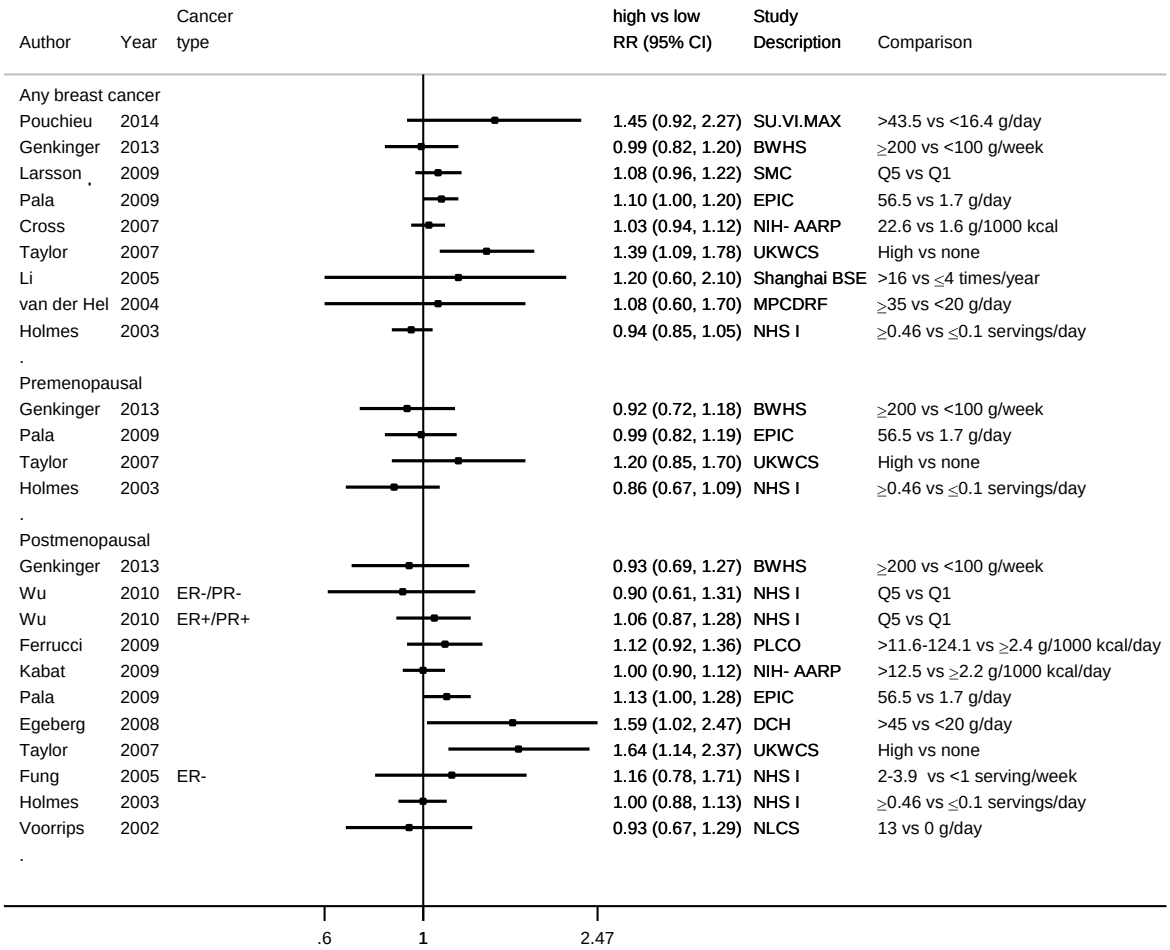


Figure 66 RR (95% CI) of breast cancer for the highest compared with the lowest level of processed meat intake



Note: only two studies (Wu, 2010; Fung, 2005) reported results by hormone receptor status.

Figure 67 Relative risk of breast cancer for 50g/day increase of processed meat intake

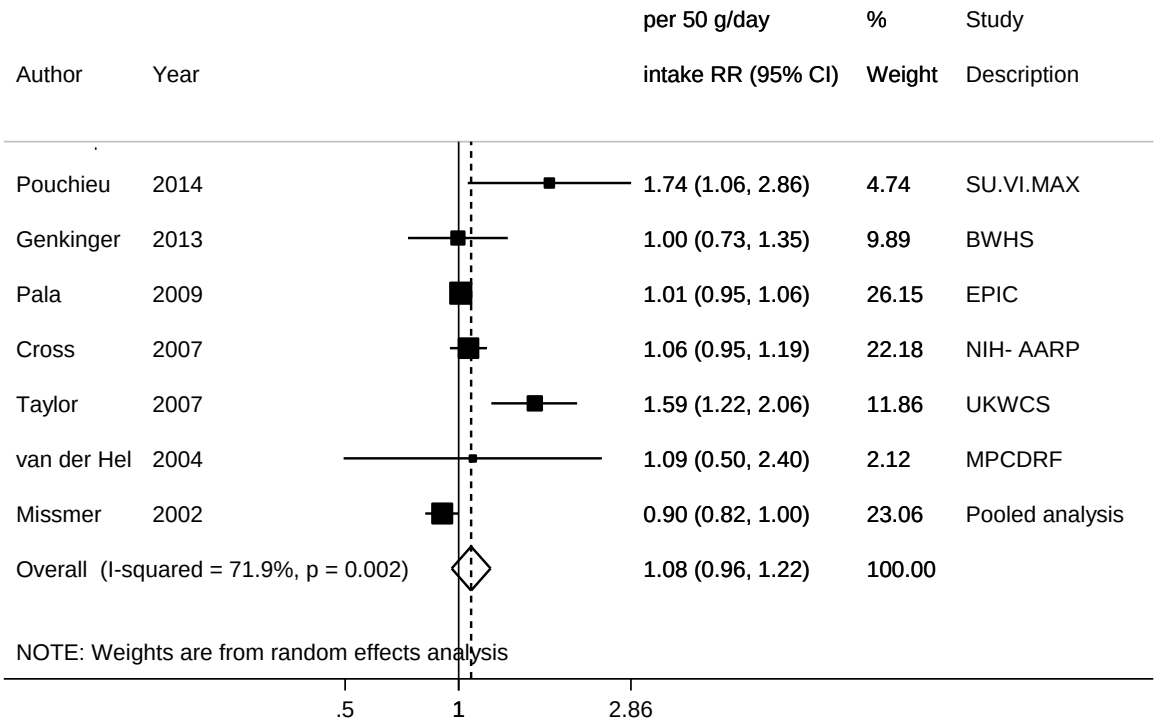


Figure 68 Relative risk of premenopausal breast cancer for 50g/day increase of processed meat intake

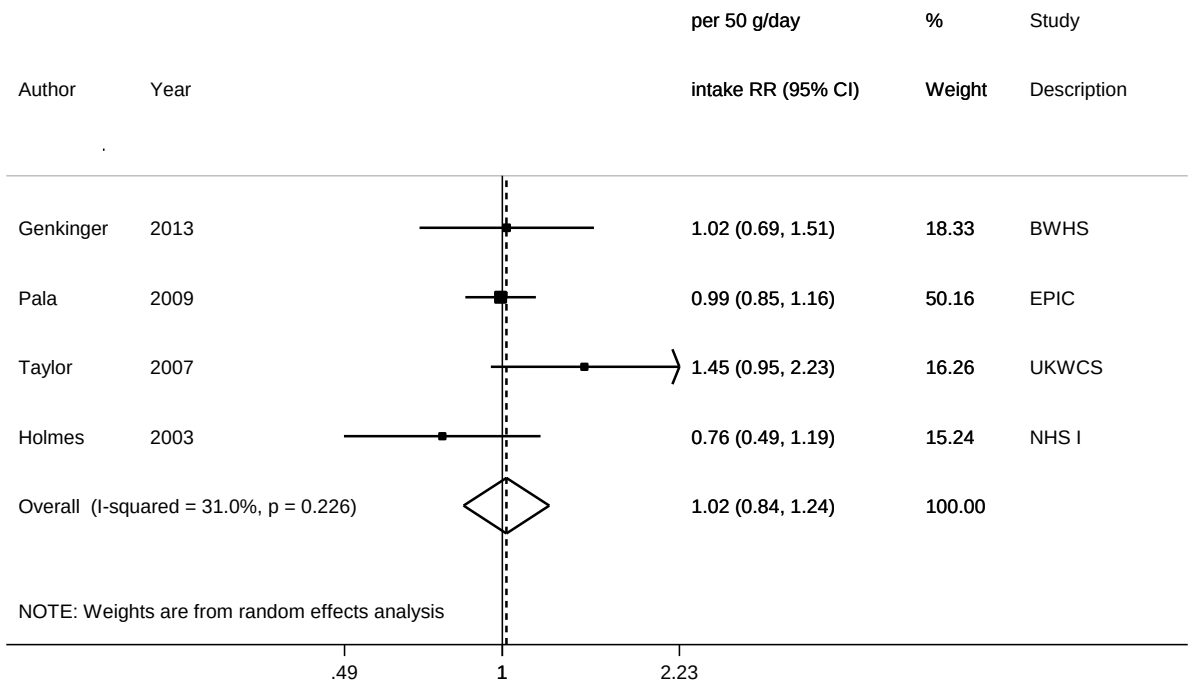


Figure 69 Relative risk of postmenopausal breast cancer for 50g/day increase of processed meat intake

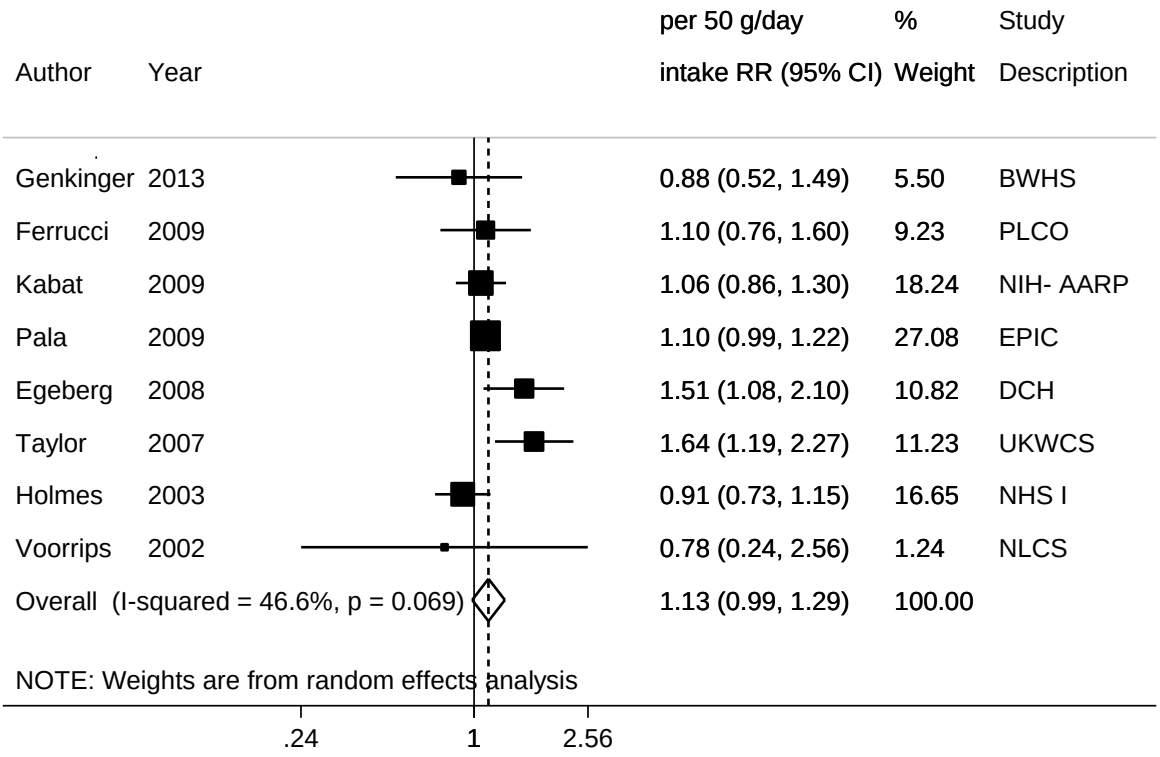
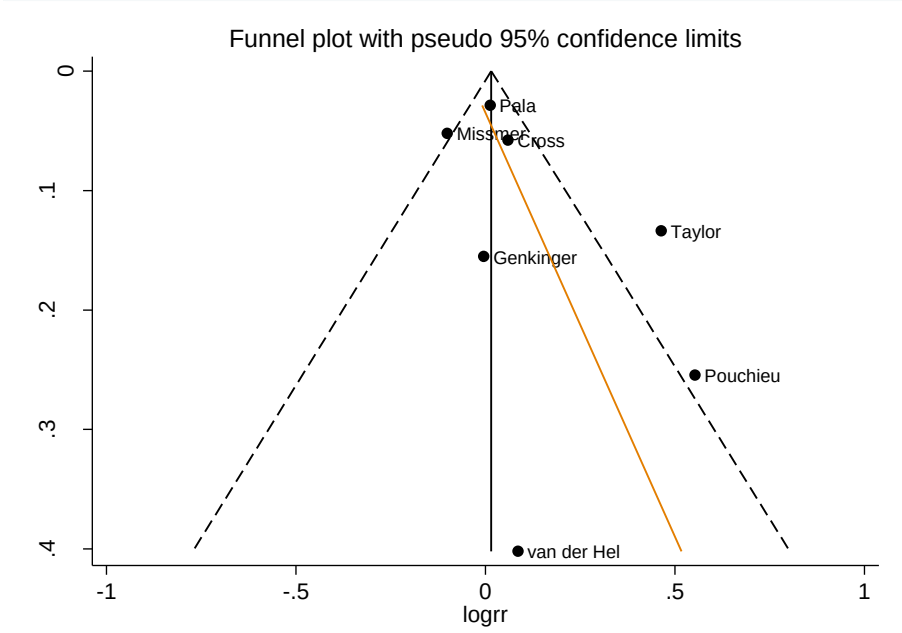
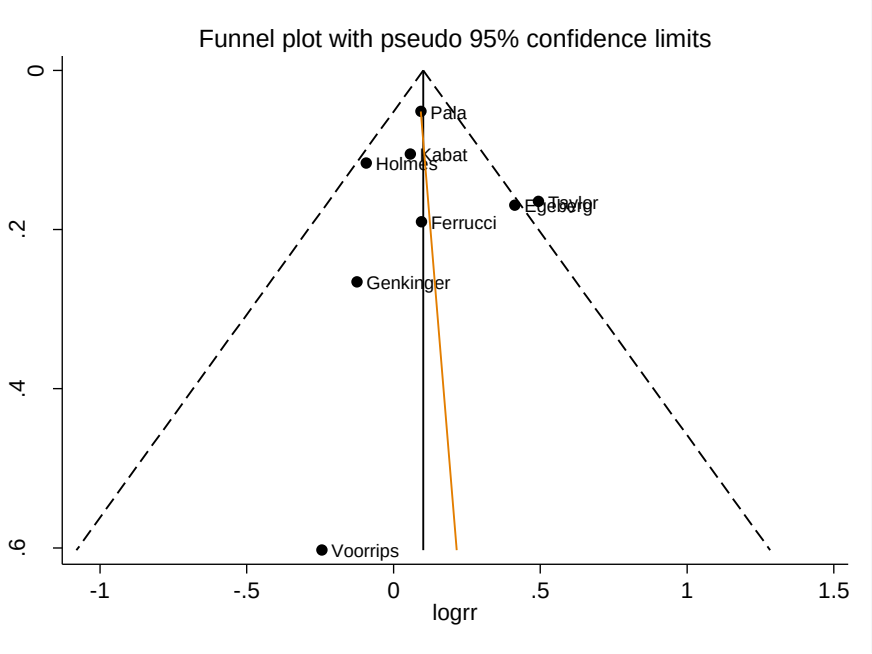


Figure 70 Funnel plot of studies included in the dose response meta-analysis of processed meat and breast cancer



Egger's test P=0.24

Figure 71 Funnel plot of studies included in the dose response meta-analysis of processed meat and postmenopausal breast cancer



Egger's test P=0.82

Figure 72 Relative risk of breast cancer for 50g/day of processed meat intake, by geographic location

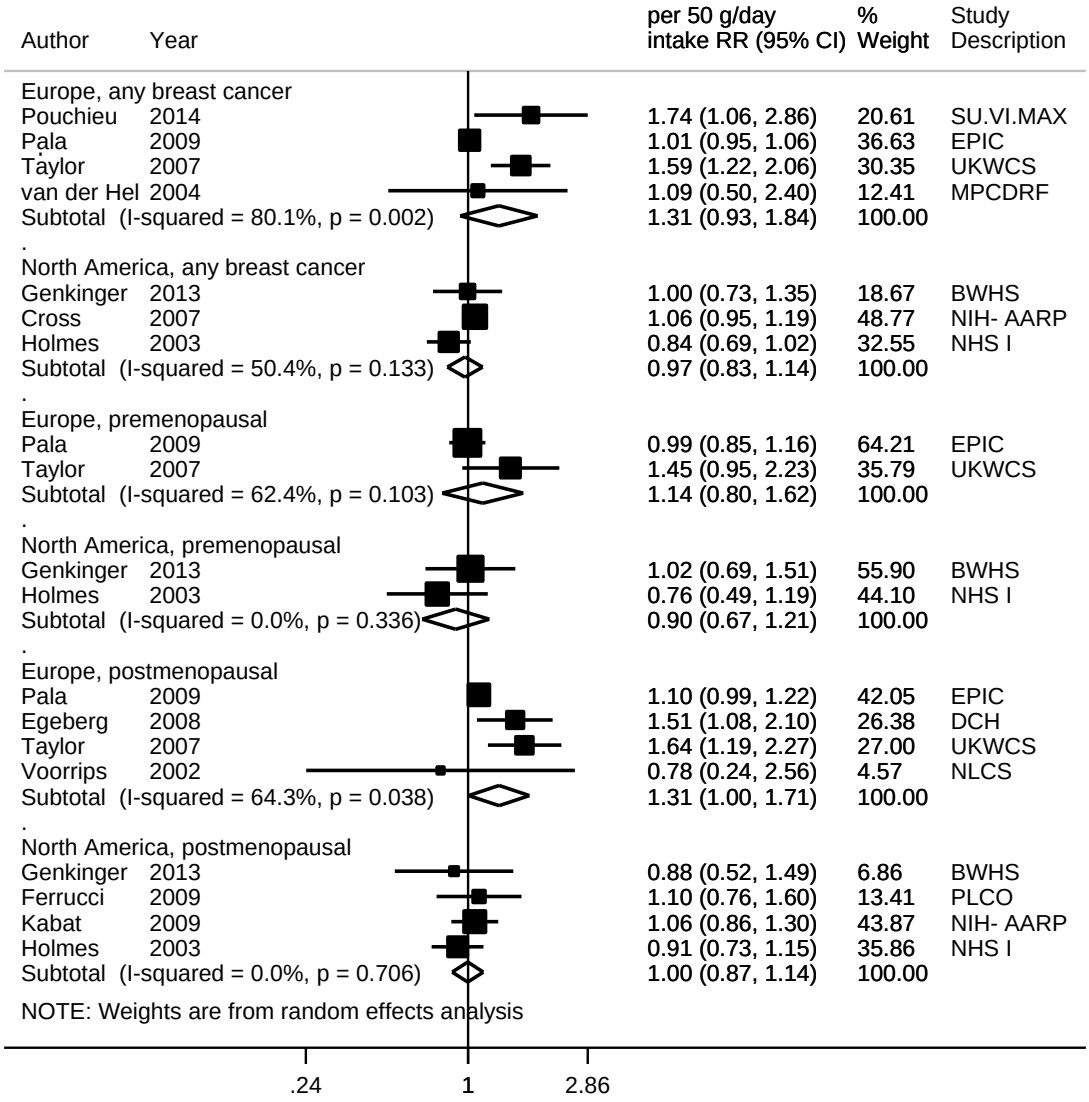
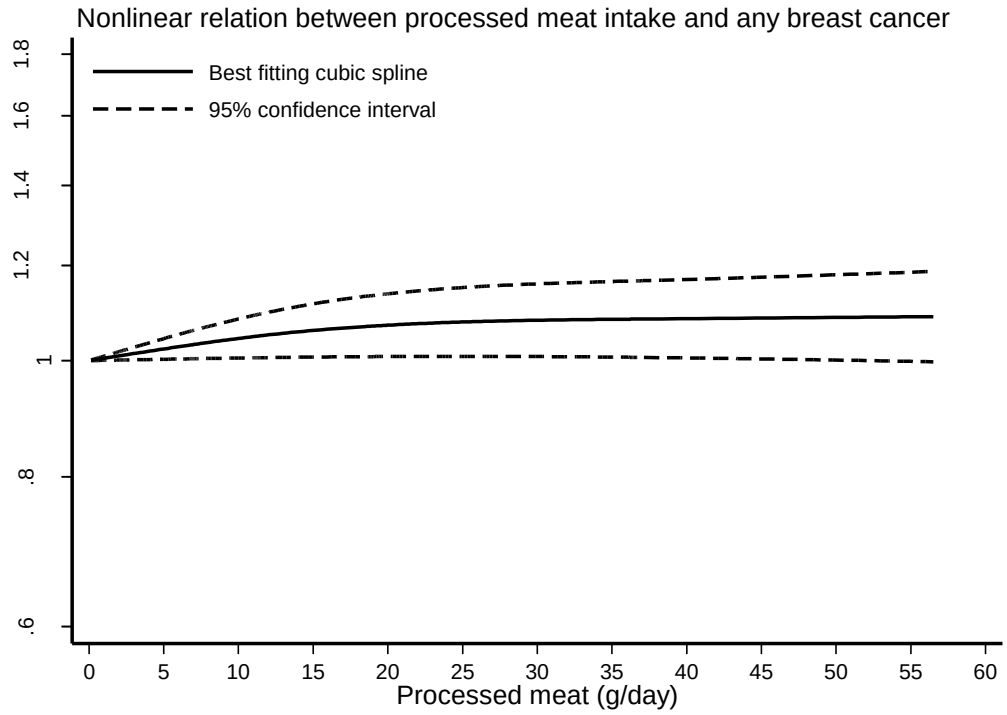


Figure 73 Nonlinear dose-response meta-analysis of processed meat and breast cancer



P nonlinear =0.04

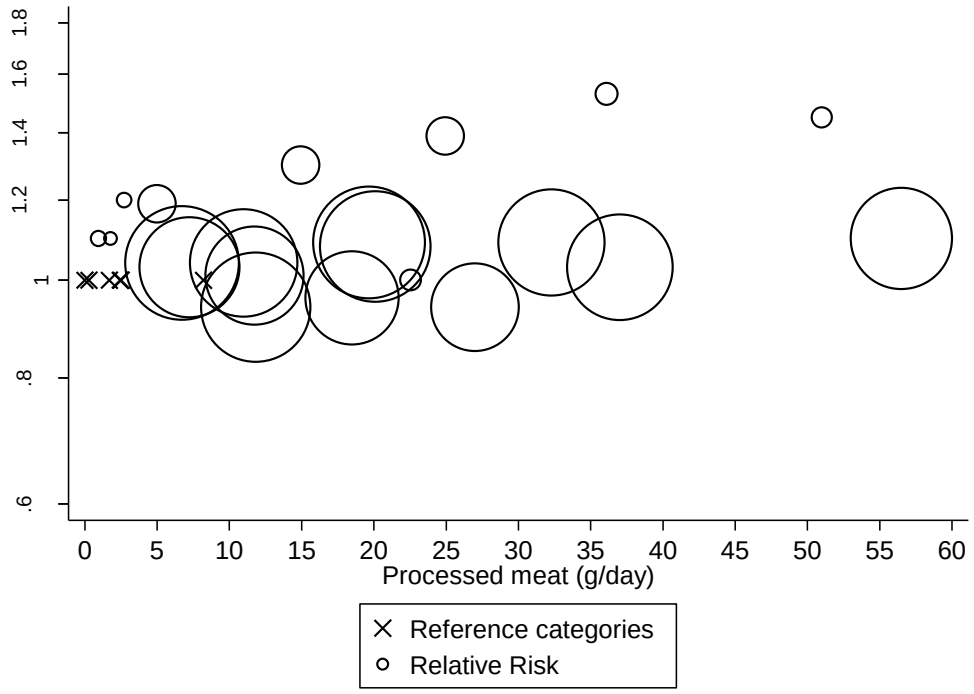
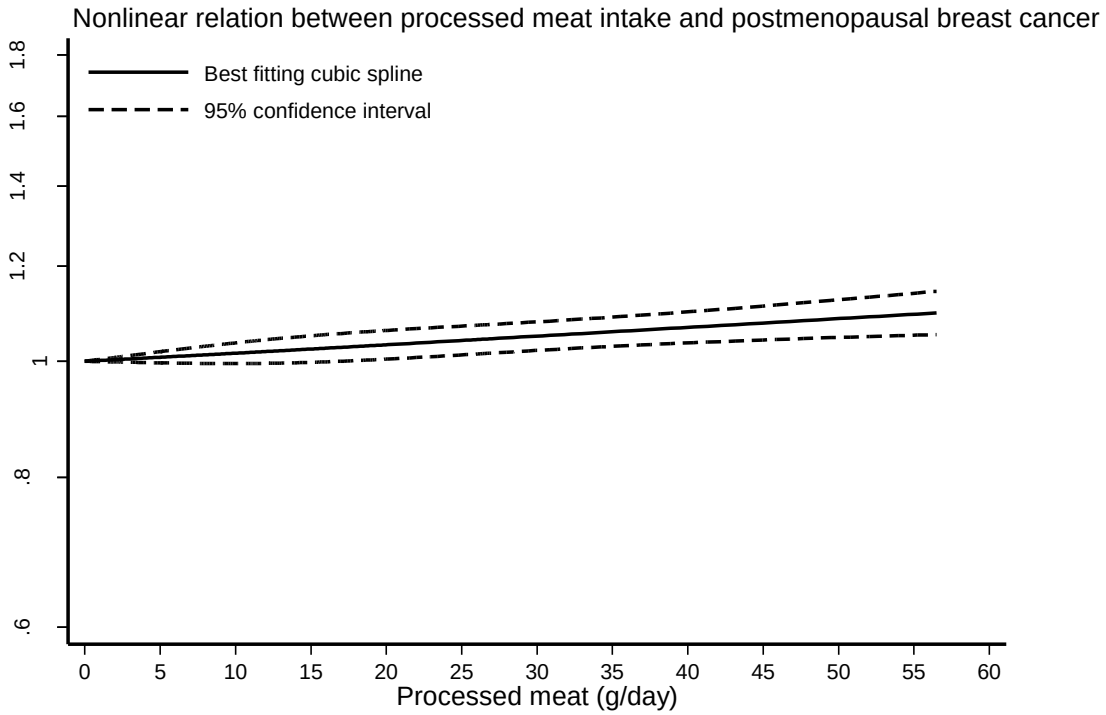
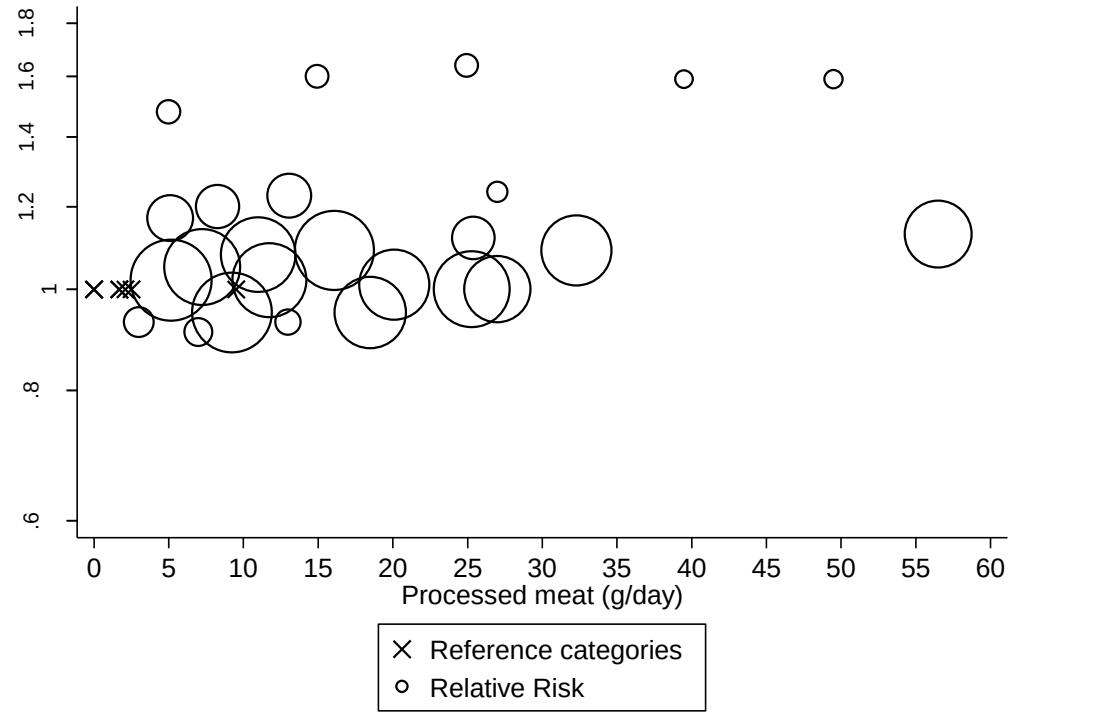


Figure 74 Nonlinear dose-response meta-analysis of processed meat and postmenopausal breast cancer



P nonlinear =0.93



2.5.1.3 Red meat

Cohort studies

Overall summary

Twelve studies (12 publications) on red meat (unprocessed) and breast cancer had been identified. Nine studies investigated all breast cancers, and from these, three studies investigated pre- and postmenopausal cancers. One study was on postmenopausal breast cancers and one study was on estrogen receptor negative postmenopausal breast cancer. The study characteristics and results for all cancer types are showed in the same Table in this section.

One additional study on meat intake during adolescence is also in the Table.

Study quality:

Red meat was assessed by FFQ in all studies except one (Pouchieu, 2014) in which diet was assessed through repeated 24 h recall during follow-up. It is unclear if the group of red meat included processed red meat in two American studies showing no association of red meat and breast cancer risk (Genginker, 2013; Kabat, 2009a). Both studies are included in this section. In the Danish study, offal was included in the definition of red meats.

One study on African-American women included some participants aged less than 21 years at baseline. The small Chinese cohort was based in a trial on breast self- examination (Li, 2005) and the Swedish cohort was based in a mammography screening study (Larsson, 2009a). A French study (Pouchieu, 2014) is a follow-up of a trial on antioxidants supplementation. No significant interaction with treatment was observed.

Loss to follow-up was low in general. In the French study (Pouchieu, 2014) loss to follow-up was only 2.8% but mainly premenopausal women.

In the studies, cancer outcome was confirmed using medical notes, death records or through cancer registries.

All studies adjusted results at least for age, total energy intake, BMI and some reproductive factors (or tested for their effect in the models). Only two studies (Taylor et al, 2007; Lin, 2005) did not adjust (or tested as a covariate) for alcohol intake.

Two studies had very low statistical power (less than 200 cases) (Pouchieu, 2014; Li, 2005).

Main results:

Breast cancer (any)

Two studies were excluded from the dose-response meta-analysis (Larsson, 2009a; Mills, 1989). In the Adventists Health Study (Mills, 1989), total intake of unprocessed red meat was not investigated. Consuming beef hamburger, beef steak, other beef or veal, or pork were each unrelated to breast cancer risk when compared to no consumption (Mills, 1989). In the cohort of Swedish women mainly postmenopausal (Larsson, 2009a) red meat was not related to breast cancer risk.

Six studies (9 614 cases) were included in the dose-response meta-analysis. A significant 12% increase of breast cancer risk was observed for 100 g/d increment of red meat intake. There was low heterogeneity (13.7%) and no significant evidence of publication or small study bias. One study showing no significant association (EPIC, Pala, 2009) had 59% weight in the analysis.

Sensitivity and stratified analyses:

In influence analysis, the summary RR ranged from 1.07 (95% CI=0.99-1.16) when a UK study was omitted (Taylor, 2007, 26% weight) to 1.21 (95% CI=1.05-1.39) when the cohort of Black American women was omitted (Genkinger, 2013, 9.3% weight).

Nonlinear dose-response meta-analysis:

There was no evidence of non-linear association (p=0.26).

Published meta-analysis:

No published meta-analysis or pooled study was identified.

Premenopausal breast cancer

The three studies identified (2 555 cases) were included in the dose-response meta-analysis. Red meat was not significantly associated with premenopausal breast cancer. Low heterogeneity was observed and there was no evidence of publication or small study bias. However, the number of studies was too small. Nonlinear dose-response was not explored as data was scarce.

Postmenopausal breast cancer

Five studies (8 784 cases) were included in the dose-response meta-analysis. No significant association was observed.

There was moderate heterogeneity (45.25%) across studies. No significant publication or small study bias was detected in the limited number of studies available. The two smaller studies reported the most discordant estimates of association (Genginker 2013; Egeberg, 2008). The study in Black American women (Genginker, 2015) reported a non-significant inverse association of red meat intake and postmenopausal breast cancer risk. Measurement of dietary intake was updated once during the 12 years of follow-up. The association did not differ by receptor status. The study was adjusted by main potential confounders. In the Danish study (Egeberg, 2008), a strong significant positive association was observed. In this nested case-control (378 cases), the association was confined to participants with as intermediate/fast NAT2 acetylators phenotype (Pinteraction=0.04).

One study (Fung, 2005) not included in the dose-response meta-analysis reported non-significant positive association of red meat intake and risk of postmenopausal ER- breast cancer.

Sensitivity analyses:

In influence analysis, the summary RR ranged from 1.07 (95% CI=0.92-1.23) when Taylor, 2007 (21.1% weight) was omitted to 1.15 (95% CI=0.94-1.41) when Kabat, 2009a (31.7% weight) was omitted.

Nonlinear dose-response meta-analysis:

There was evidence of a non-linear association (p<0.0001). The risk increases with intakes up to approximately 60.6 g/day and decreases thereafter. The significant association was driven by two studies (Egeberg, 2008; Taylor, 2007).

No published meta-analysis or pooled study was identified.

Table 58 Red meat (unprocessed) intake and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	11
Studies included in forest plot of highest compared with lowest intake	Breast cancer (any): 7 Premenopausal: 3
Studies included in linear dose-response meta-analysis	Breast cancer: 6 Premenopausal: 3
Studies included in non-linear dose-response meta-analysis	Breast cancer: 5 Premenopausal: not enough studies

Table 59 Red meat (unprocessed) and breast cancer risk. Summary of the linear dose-response meta-analysis in the CUP (no dose-response meta-analysis was conducted in the 2005 SLR)

	Breast cancers (any)	**Premenopausal**	**Postmenopausal**
Increment unit used	100 g/day		
Studies (n)	6	3	5
Cases (total number)	9 614	2 555	8 784
RR (95%CI)	1.12 (1.01-1.24)	1.04 (0.84-1.29)	1.11 (0.97-1.27)
Heterogeneity (I^2, p-	14%, 0.33	47%, 0.15	45%, 0.12
P value Egger test	0.22	-	0.70

Stratified analyses

Geographic area	**Asia**	**Europe**	**North-America**
	Breast cancer		
Studies (n)	1	4	1
RR (95%CI)	1.36 (0.68-2.73)	1.16 (1.01-1.33)	0.96 (0.70-1.31)
Heterogeneity (I^2, p- value)	-	36%, 0.20	-
	Premenopausal		
Studies (n)	-	2	1
RR (95%CI)	-	1.07 (0.79-1.46)	0.97 (0.64-1.45)
Heterogeneity (I^2, p- value)	-	73%, 0.06	-
	Postmenopausal		
Studies (n)	-	3	2
RR (95%CI)	-	1.20 (1.00-1.46)	0.97 (0.75-1.25)
Heterogeneity (I^2, p- value)	-	49%, 0.14	32.5%, 0.22

Table 60 Red meat intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Pouchieu, 2014 BRE80553 France Result Number:497437	SU.VI.MAX, Prospective Cohort, W	190/ 4 684 11.3 years	Self-report verified by medical record	24 hour dietary recall	Incidence, breast cancer	≥63.8 vs ≤24.9 g/day	1.19 (0.79-1.80)	Age, BMI, educational level, family history of breast cancer, intake of fat, processed meat, height, intervention group, menopausal status, number of live births, physical activity, smoking status, alcohol intake, non-alcohol energy, HRT	Distribution of cases, person-years by exposure quantiles, mid-points of exposure quantiles
Genkinger, 2013 BRE80446 USA Result Number:477725	BWHS, Prospective Cohort, Age: 21-69 years, W	1 268/ 56 062 12 years	Cancer registry and National Death Index	68-item FFQ in 1995 and 85-item FFQ in 2001	Incidence, breast cancer	≥400 vs 100 g/week	1.02 (0.83-1.24)	Age at first birth, age at menarche, age at menopause, BMI, energy intake, family history of breast cancer, HRT use, menopausal status, parity, alcohol, education, oral contraceptive history,	Mid-points of exposure quantiles, g/week converted to g/ day
		573/			Premenopausal		1.01 (0.78-1.30)		
		520/			Postmenopausal		0.86 (0.62-1.20)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								smoking, vigorous physical activity	
Kabat, 2009a BRE80240 USA Result Number:455075	NIH- AARP, Prospective Cohort, Age: 50-71 years, W, Postmenopausal women	3 818/ 120 755 8 years	Cancer registry and death records	Validated 124-item FFQ	Incidence, breast cancer, postmenopausal	≥43.7 vs ≤13 g/1000 kcal/day	1.05 (0.93-1.18)	Age, age at first live birth, age at menarche, age at menopause, alcohol intake, BMI, educational level, family history of cancer, HRT use, height, physical activity, race, saturated fat intake, smoking habits, total energy intake, white meat	Intakes in g/1000kcal/day converted to g/day using average energy intake per each quantile, mid-points of exposure quantiles
Pala, 2009 BRE80268 Europe Result Number:457093	EPIC, Prospective Cohort, Age: 25-70 years, W	7 119/ 319 826 8.8 years	Multiple methods	Country-specific validated food questionnaires	Incidence, breast cancer	84.6 vs 1.4 g/day	1.06 (0.98-1.14)	Age, centre, educational level, energy intake, height, menopausal status, smoking habits, weight	Distribution of person-years by exposure quantiles, RR rescaled for an increment of 100 g
					Observed	per 150 g/day	1.08 (0.97-1.21)		
					Calibrated		1.23 (0.97-1.57)		
		1 699/ 319 826 8.8 years			Premenopausal	84.6 vs 1.4 g/day	0.94 (0.80-1.10)	Additionally adjusted for alcohol intake.	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		3 673/ 319 826 8.8 years			Postmenopausal	84.6 vs 1.4 g/day	1.05 (0.94-1.18)	Hormonal related factors did not influence the results	
Egeberg, 2008 BRE80153 Denmark Result Number:443292	DCH, Nested Case Control, Age: 50-64 years, W, Postmenopausal women	378/ 24 697 4.2 years	Cancer registry	FFQ	Incidence, breast cancer postmenopausal	>80 vs <50 g/day	1.65 (1.09-2.50)	Age, age at first birth, alcohol consumption, BMI, educational level, HRT use, parity	Mid-points of exposure quantiles
						per 25 g/day	1.15 (1.01-1.31)		
Taylor, 2007 BRE80008 UK Result Number:223772	UKWCS, 1993, Prospective Cohort, Age: 35-69 years, W	678/ 33 725 8 years	NHS central registry	Validated 217-item FFQ	Incidence, breast cancer	≥57 vs ≤0 g/day	1.41 (1.11-1.81)	Age, BMI, energy intake, HRT use, menopausal status, oral contraceptive use, parity/pregnancies, physical activity, smoking habits, total fruit and vegetable intake	RR rescaled for an increment of 100 g/day
						per 50 g/day	1.12 (1.03-1.22)		
		395/ 33 725 8 years			Premenopausal	≥57 vs ≤0 g/day	1.32 (0.93-1.88)		
						per 50 g/day	1.13 (0.99-1.29)		
		283/ 33 725 8 years			Postmenopausal	≥57 vs ≤0 g/day	1.56 (1.09-2.23)		
						per 50 g/day	1.12 (1.01-1.26)		
						per 1 serving	1.06 (0.84-1.35)		
Li, 2005 BRE23123 China Result Number:79763	Shanghai BSE, Nested Case Control, W	130/ 1200	Biopsy	Validated 99-item FFQ	Incidence, breast cancer	>302 vs <148 times/year	1.30 (0.70-2.50)	Age, energy, year of interview	Mid-points of exposure quantiles, intake in times/year converted to g/day

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
van der Hel, 2004 BRE12728 Denmark Result Number:79231	MPCDRF, Nested Case Control, Age: 20-59 years, W	229/ 493 10 years maximum	The Netherlands Cancer Registry, regional cancer registers	Validated semi-quantitative FFQ	Incidence, breast cancer	≥45 vs ≤30 g/day	1.32 (0.84-2.08)	Age, energy intake), menopausal status, place of residence, smoking, alcohol, age at menarche, BMI	Mid-points of exposure quantiles

Table 61 Red meat intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Farvid, 2015a BRE80545 USA Result Number:496960	NHS II, Prospective Cohort, Age: 24-43 years, W, Registered nurses	1 132/ 44 231 13 years	Biennial questionnaires or via death certificate and confirmed by medical record by a pathologist	Validated FFQ	Incidence, breast cancer	1.5 vs 0.49 servings/day	1.17 (0.95-1.43)	Additionally adjusted for hormone use, menopausal status, age at menopause	Excluded, intake during adolescence
		546/			Premenopausal		1.22 (0.90-1.66)	Age, age at menarche, BMI at age 18 years, family history of breast cancer, height, oral contraceptive use, race, weight gain since 18,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								adolescent alcohol intake, adolescent energy intake, alcohol intake, history of benign breast disease, parity and age at first birth, smoking	
		483/			Postmenopausal		1.09 (0.80-1.48)	Additionally adjusted for postmenopausal hormone use, age at menopause	
Larsson, 2009a BRE80252 Sweden Result Number:455607	SMC, Prospective Cohort, W	2 952/ 61 433 17.4 years	Cancer registry	Validated 67-item (at baseline) and 96-item (in 1997) FFQ	Incidence, breast cancer	Q5 vs Q1	0.90 (0.79-1.03)	Age, age at first birth, age at menarche, age at menopause, alcohol consumption, BMI, calendar year of follow-up, educational level, family history of cancer, HRT use, height, oral contraceptive use, parity, total caloric intake	Excluded, only two categories of exposure

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Fung, 2005 BRE22370 USA Result Number:84796	NHS I, Prospective Cohort, Age: 30-55 years, W, Registered nurses	512/ 71 058 16 years	Self-reported, next of kin, postal service, National Death Index, hospital records	Validated semi-quantitative FFQ	Incidence, breast cancer ER-, postmenopausal	2-3.9 servings/day vs <1/week	1.62 (0.78-3.35)	Age, age at first pregnancy/child, age at menarche, age at menopause, alcohol, BMI, benign breast disease, energy intake, family history, HRT use, height, menopausal status, other anthropometric index, parity/pregnancies, physical activity, smoking habits, supplements	Analysis by ER-status in postmenopausal women was not conducted
Mills, 1989 BRE17837 USA Result Number:82232	AHS, Prospective Cohort, Age: 25-99 years, W, Adventists	209/ 20 341 6 years	By mail	FFQ	Incidence, breast cancer	≥1 vs 0 times/week	1.06 (0.71-1.58)	Age, age at first pregnancy/child, age at menarche, BMI, benign breast disease, educational level, family history	Excluded, exposure defined as "other beef/veal"

Figure 75 RR estimates of breast cancer by levels of red meat intake

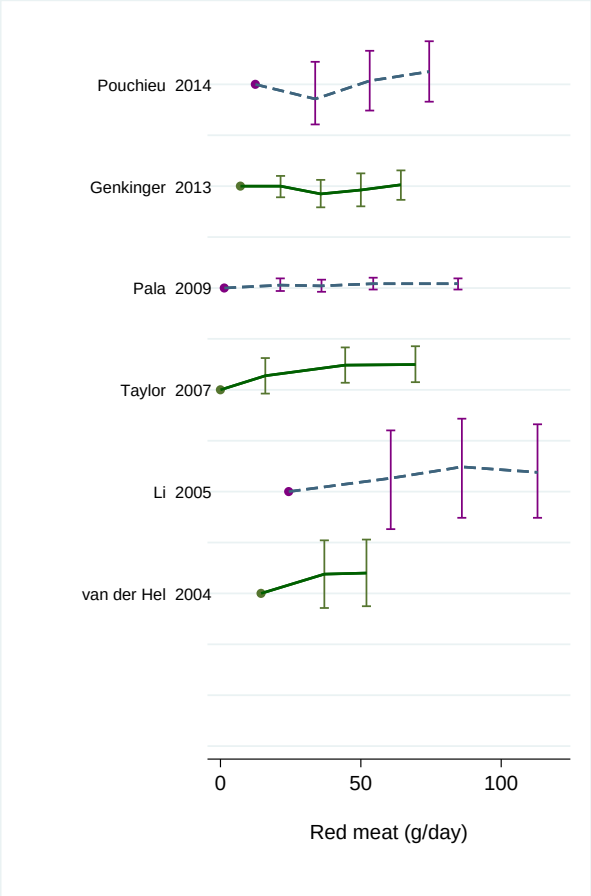


Figure 76 RR estimates of premenopausal breast cancer by levels of red meat intake

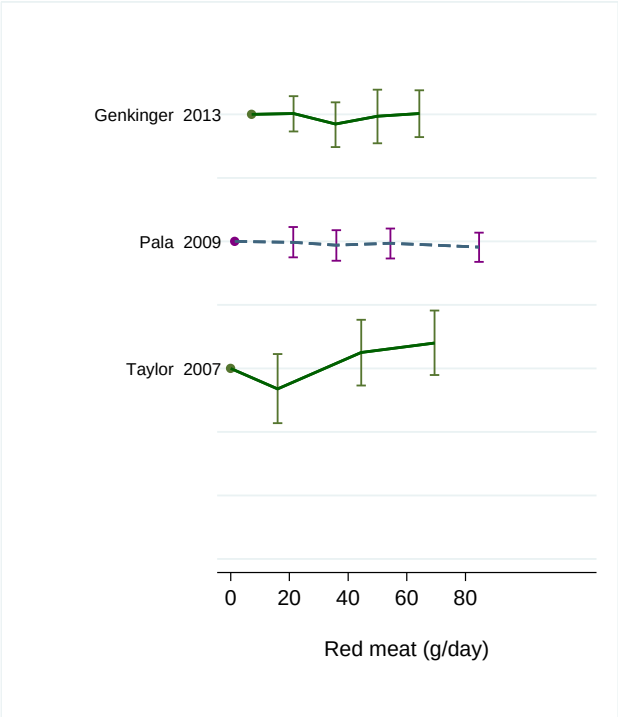


Figure 77 RR estimates of postmenopausal breast cancer by levels of red meat intake

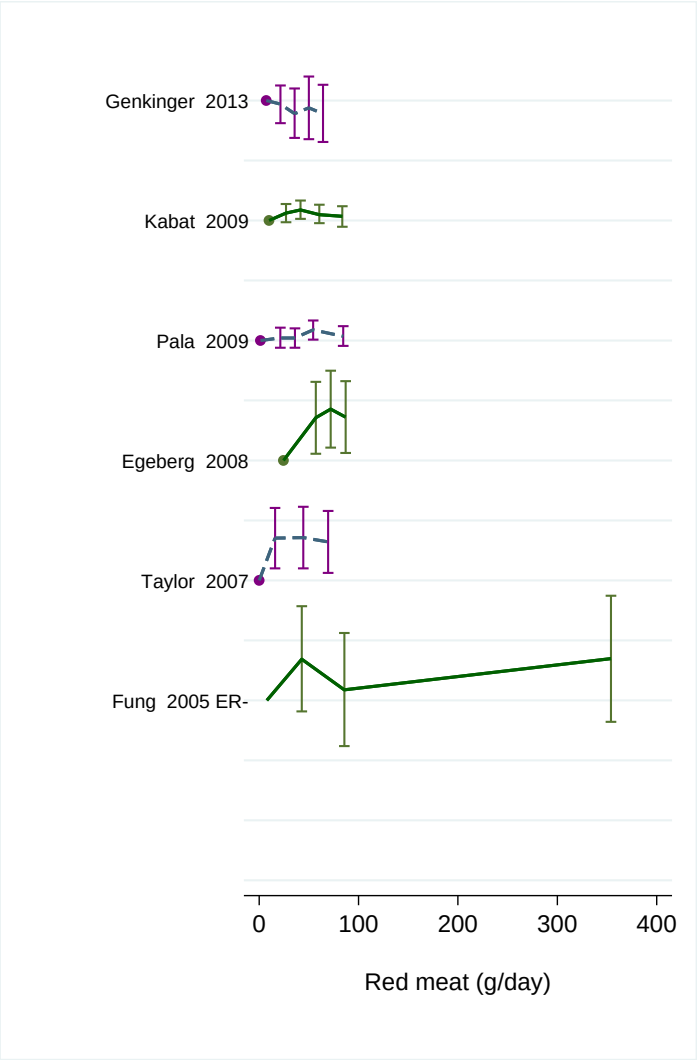
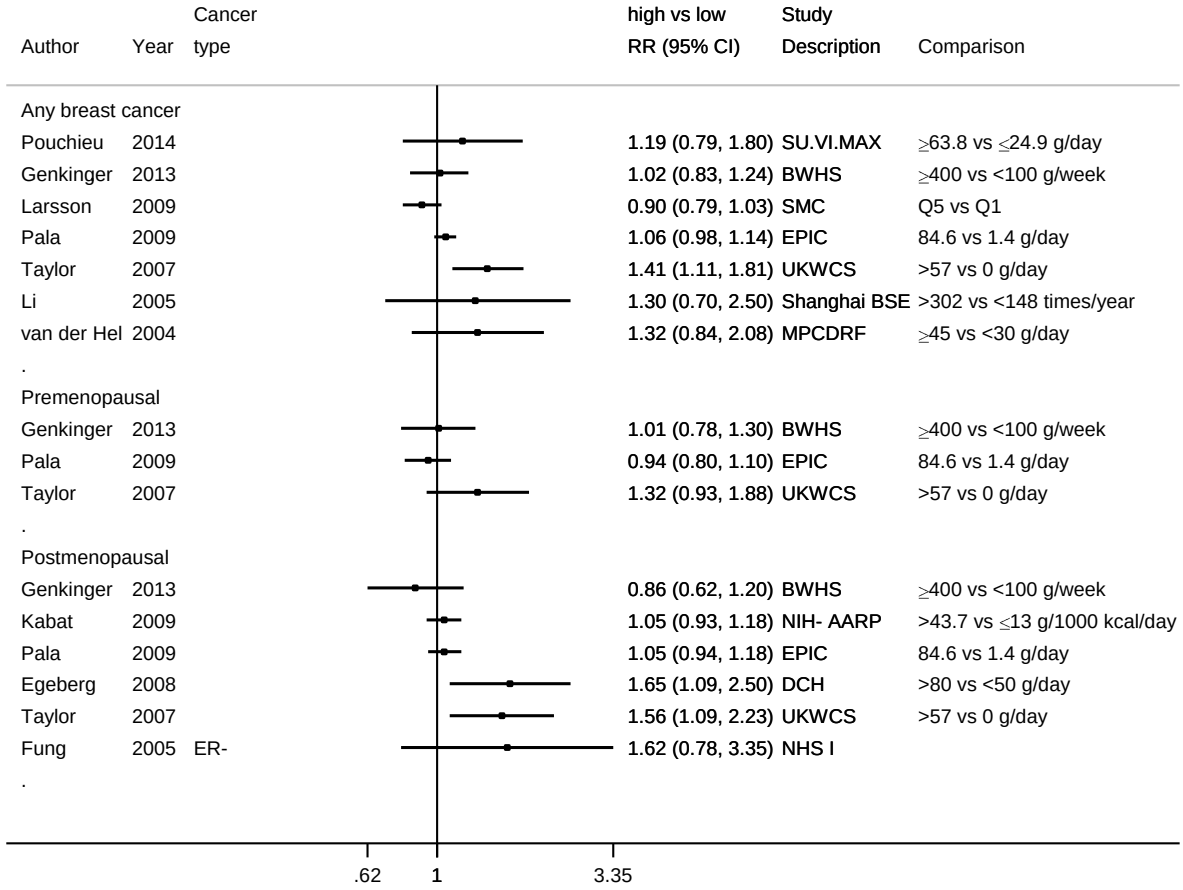


Figure 78 RR (95% CI) of breast cancer (any and by menopausal status) for the highest compared with the lowest level of red meat intake



Note: only one study (Fung, 2005) reported results by hormone receptor status.

Figure 79 Relative risk of breast cancer for 100g/day increase of red meat intake

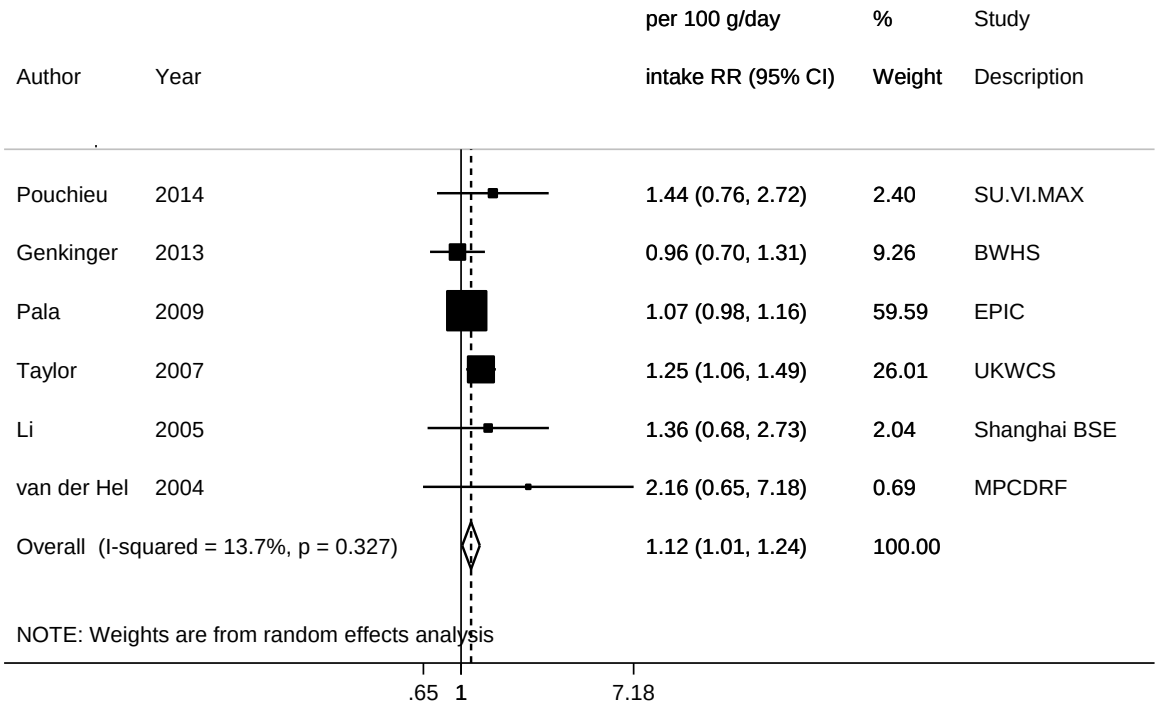


Figure 80 Relative risk of premenopausal breast cancer for 100g/day increase of red meat intake

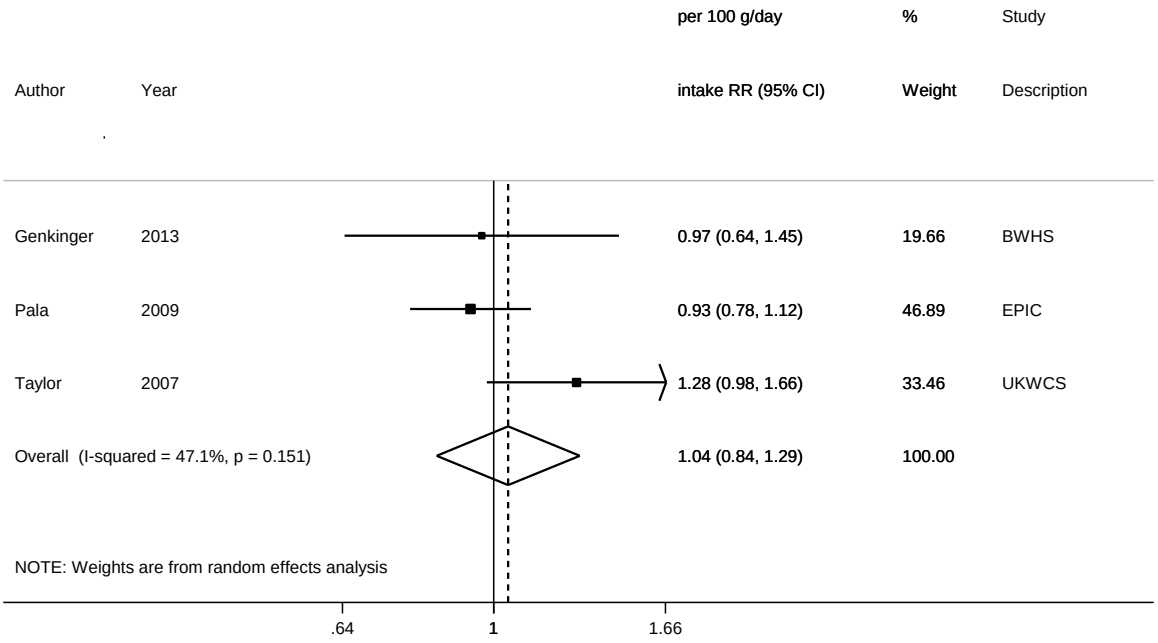


Figure 81 Relative risk of postmenopausal breast cancer for 100g/day increase of red meat intake

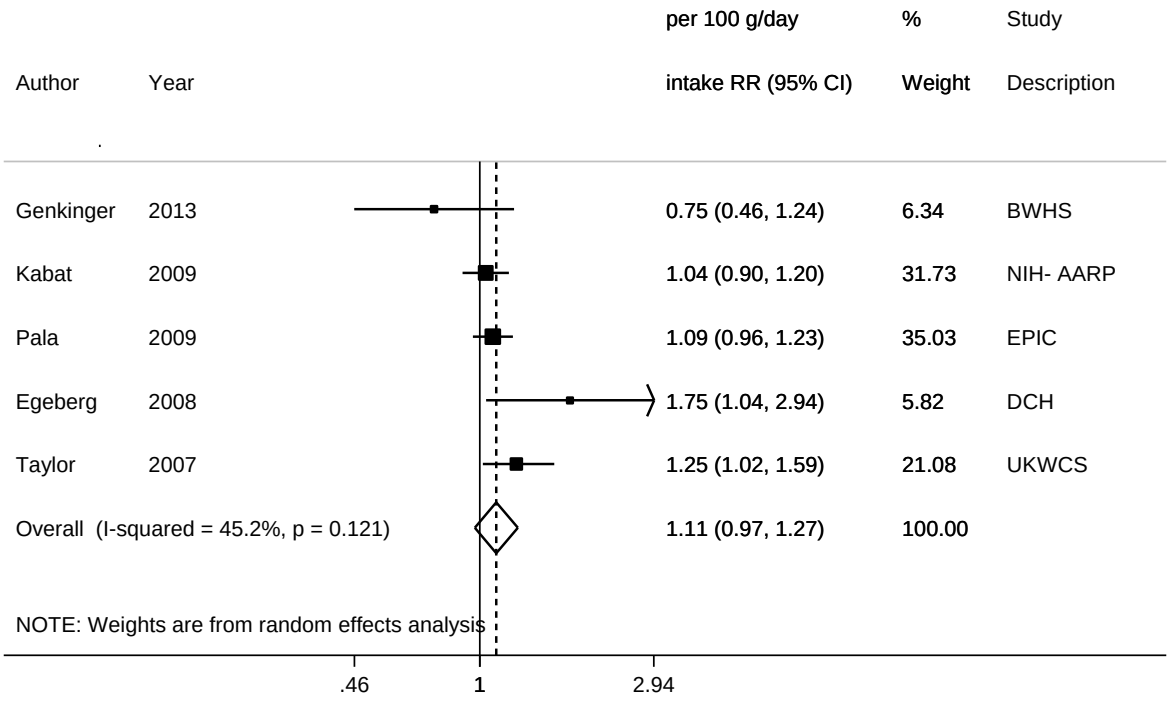
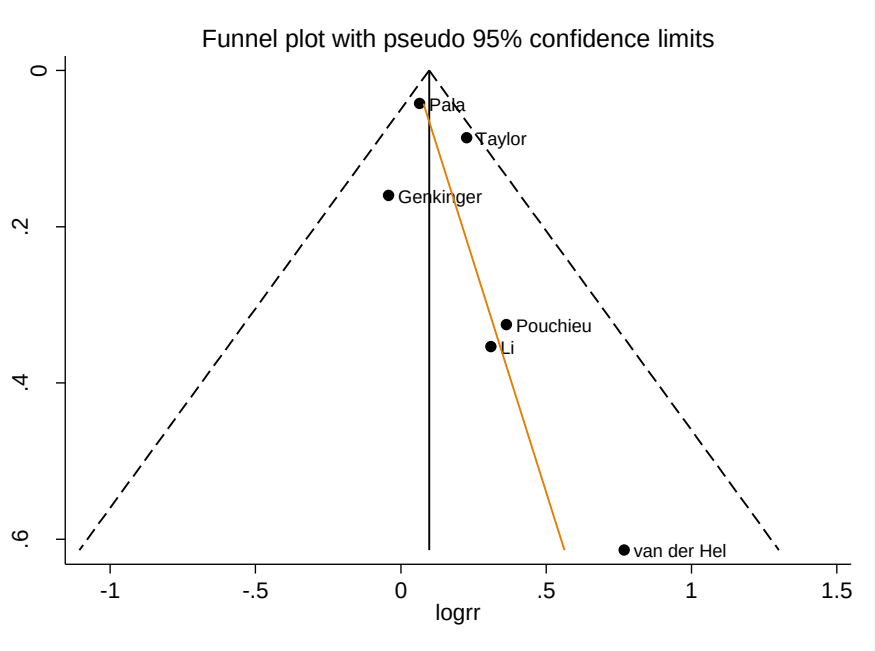
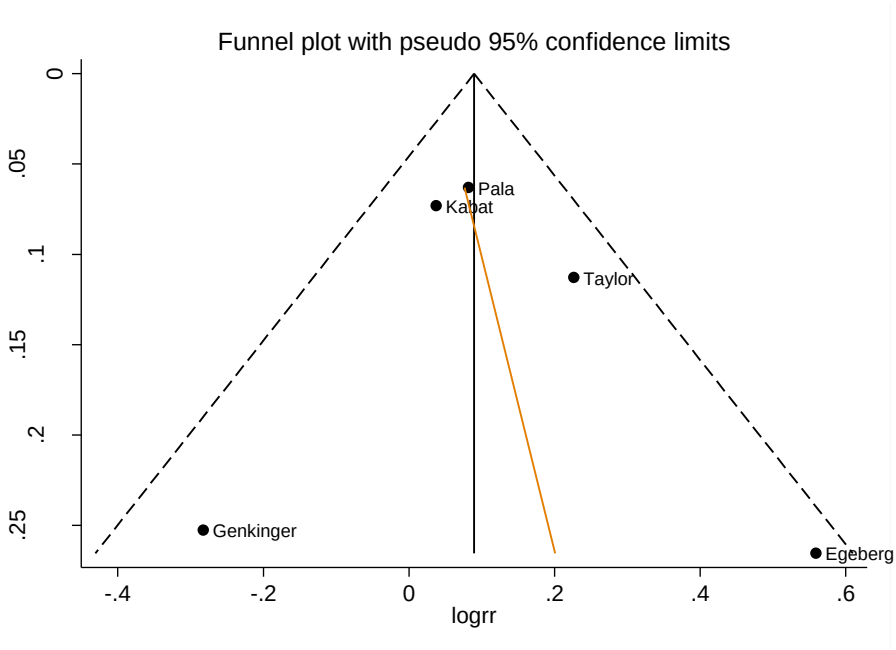


Figure 82 Funnel plot of studies included in the dose response meta-analysis of red meat intake and breast cancer



Egger's test P=0.22

Figure 83 Funnel plot of studies included in the dose response meta-analysis of red meat intake and postmenopausal breast cancer



Egger's test P=0.70

Figure 84 Relative risk of breast cancer for 100 g/day of red meat intake, by geographic location

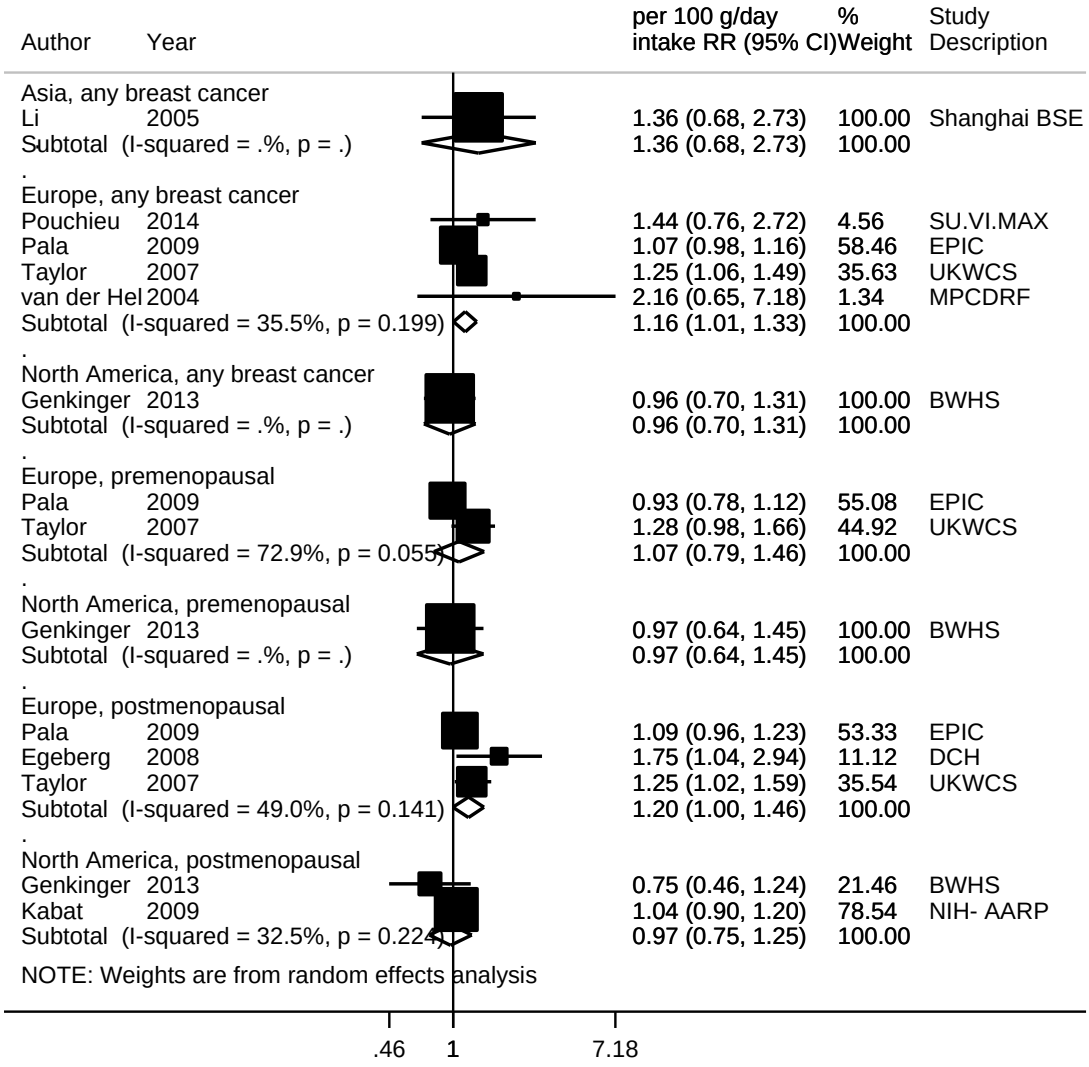
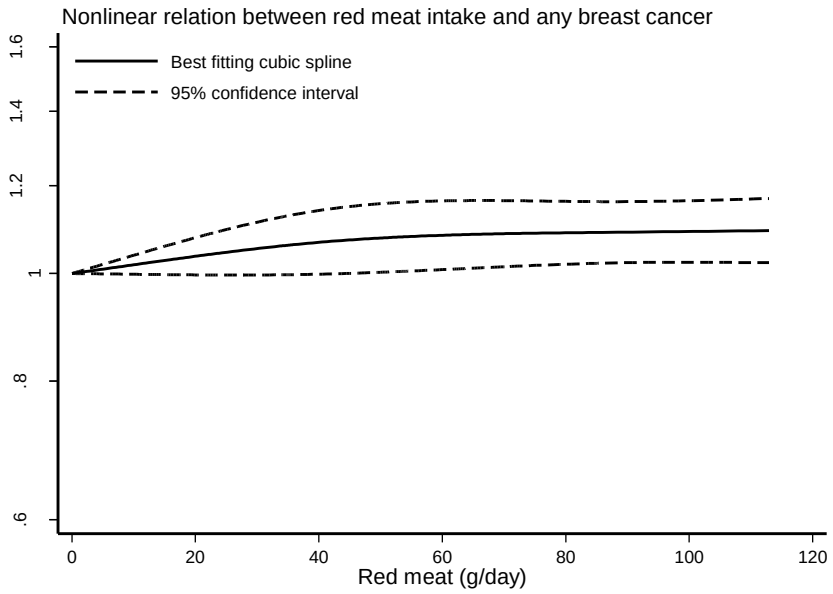


Figure 85 Nonlinear dose-response meta-analysis of red meat and breast cancer



P nonlinearity =0.26

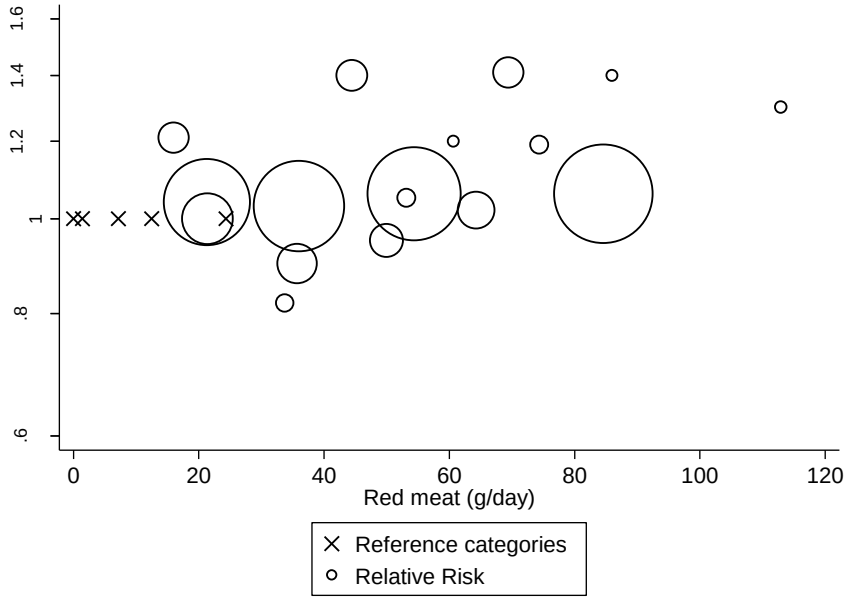
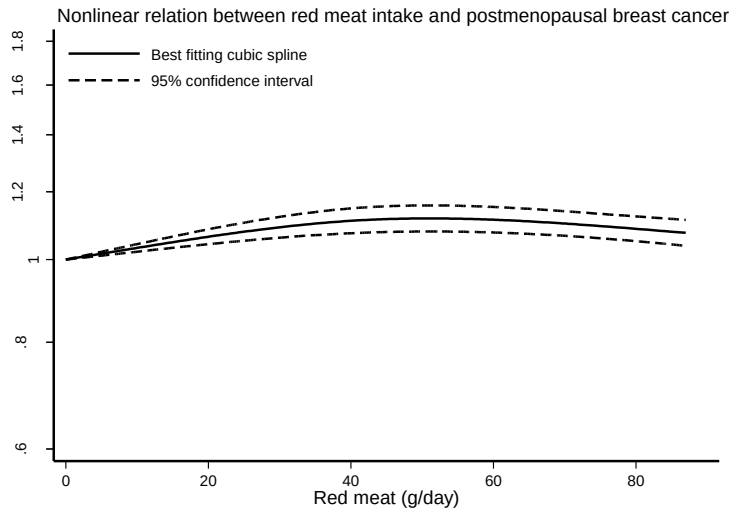


Table 62 Relative risk of breast cancer and red meat estimated using non-linear models

Red meat (g/day)	RR (95%CI)
0	1.00
7.1	1.01 (1.00-1.03)
21.3	1.04 (1.00-1.08)
36	1.06 (1.00-1.13)
54.4	1.08 (1.00-1.16)
60.7	1.08 (1.01-1.16)
84.6	1.09 (1.02-1.16)
112.9	1.09 (1.02-1.16)

Figure 86 Nonlinear dose-response meta-analysis of red meat and postmenopausal breast cancer



P nonlinearity <0.0001

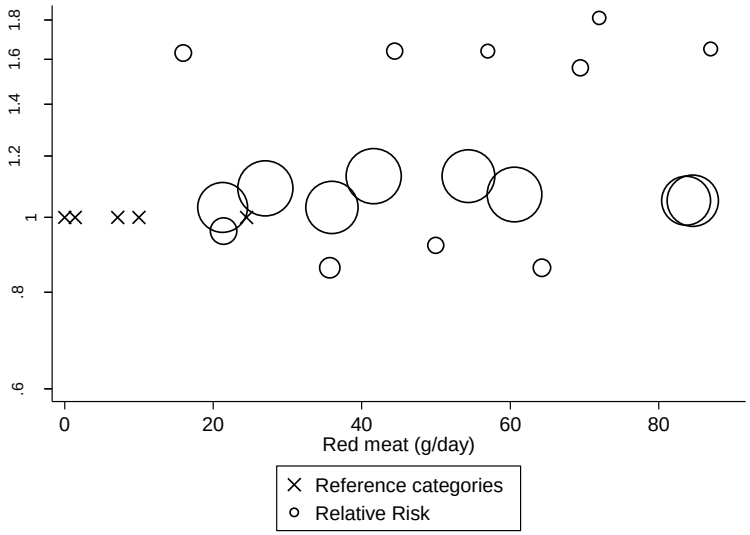


Table 63 Relative risk of postmenopausal breast cancer and red meat estimated using non-linear models

Processed meat(g/day)	RR (95%CI)
0	1.00
7.1	1.02 (1.02-1.03)
21.3	1.07 (1.04-1.09)
35.7	1.10 (1.07-1.14)
50	1.12 (1.08-1.16)
57	1.12 (1.08-1.15)
60.6	1.11 (1.08-1.15)
72	1.10 (1.06-1.14)
84.6	1.08 (1.04-1.12)
87	1.07 (1.04-1.11)

2.5.1.4 Poultry

Cohort studies

Overall summary

Twelve studies (11 publications) on poultry intake and breast cancer risk were identified, including a pooled analysis of seven cohort studies.

One study was excluded from the dose-response meta-analysis (Li, 2005). In this study, poultry intake was not associated with breast cancer risk.

Study quality:

Diet was assessed using FFQ in all studies apart one centre in EPIC that used diet history (Pala, 2009). Two studies (CNBSS and SMC) recruited participants in breast cancer screening programs (Missmer, 2002). Cancer cases were identified by record linkage to cancer and death registries, and self-report verified by medical records, in most studies, multiple methods were used in the EPIC study. Loss to follow-up was low in general.

Main results:

Breast cancer (any)

Nine studies (15 176 cases, three publications) were included in the dose-response meta-analysis. No significant association of poultry intake with breast cancer was observed. Two studies reporting no association were excluded from the analyses (Sonestedt, 2008b; Li, 2005).

No heterogeneity was observed. The number of publications was too small to investigate publication or small study bias.

Stratified analysis was not conducted due to low number of publications (one publication was the Pooling project of cohort studies).

Premenopausal breast cancer

Three studies (2 836 cases) were included in the dose-response meta-analysis. No significant association of poultry intake with premenopausal breast cancer was observed. Low heterogeneity was observed.

Sensitivity analyses:

Sensitivity and stratified analyses were not conducted due to low number of studies.

Postmenopausal breast cancer

Four studies (14 468 cases) were included in the dose-response meta-analysis. No significant association was observed.

Only one study reported results by hormonal status. Fung, 2005 reported non-significantly inverse association for postmenopausal ER- breast cancer.

No heterogeneity was observed. There was no evidence of a significant publication or small study bias (p=0.38).

Sensitivity analyses:

The summary RR did not change materially when each study was omitted in turn in influence analysis.

Nonlinear dose-response meta-analysis was not conducted due to low number of studies.

Table 64 Poultry intake and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	13 (11 publications)
Studies included in forest plot of highest compared with lowest exposure	Breast cancer: 6 (6 publications) Premenopausal: 3 (3 publications) Postmenopausal: 5 (6 publications)
Studies included in linear dose-response meta-analysis	Breast cancer: 9 (3 publications) Premenopausal: 3 (3 publications) Postmenopausal: 4 (4 publications)
Studies included in non-linear dose-response meta-analysis	Breast cancer: not enough studies Premenopausal: not enough studies Postmenopausal: 5 (5 publications)

Table 65 Poultry intake and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	CUP
Increment unit used	-	100 g/day
Breast cancer		
Studies (n)	-	9
Cases (total number)	-	15 176
RR (95%CI)	-	1.05 (0.98-1.12)
Heterogeneity (I^2, p-value)	-	0%, 0.67
P value Egger test	-	-
CUP		
	Premenopausal	Postmenopausal
Studies (n)	3	4
Cases	2 836	14 468
RR (95%CI)	1.12 (0.87-1.43)	1.01 (0.94-1.09)
Heterogeneity (I^2, p-value)	1.7%, 0.36	0%, 0.76
P value Egger test	-	0.38

Stratified analyses

Geographic area	**Asia**	**Europe**	**North-America**
	Postmenopausal		
Studies (n)	-	2	2
RR (95%CI)	-	1.11 (0.91-1.35)	0.99 (0.91-1.08)
Heterogeneity (I^2, p- value)	-	0%, 0.66	0%, 0.76

Table 66 Poultry intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Daniel, 2011 BRE80386 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W, Postmenopausal	7 181/ 492 186 9.1 years	Cancer registry	FFQ	Incidence, breast cancer postmenopausal	51.2 vs 5.3 g/1000 kcal	0.98 (0.90-1.06) Ptrend:0.92	Age, sex, alcohol, BMI, educational level, family history of cancer, fish intake, HRT use, marital history, race, red meat intake, smoking, total energy, vigorous activity	Intake in g/1000kcal converted to intake in g using energy intake per quantile of the whole cohort, person years per quantile
Pala, 2009 BRE80268 Europe	EPIC, Prospective Cohort, Age: 25-70 years, W	7 119/ 319 826 8.8 years	Multiple methods	Country-specific validated food questionnaires	Incidence, breast cancer	46.1 vs 0 g/day	1.02 (0.95-1.11) Ptrend:0.50	Age, centre location, educational level, energy intake, height, menopausal status, smoking habits, weight	
						per 150 g	1.04 (0.85-1.26)		RR rescaled for an increment of 100g/day
		1 699/ 114 812			Premenopausal	46.1 vs 0 g/day	0.98 (0.83-1.16) Ptrend:0.83	Additionally adjusted for alcohol intake	
		3 673/ 135 529			Postmenopausal	46.1 vs 0 g/day	1.05 (0.94-1.17) Ptrend:0.29		
Taylor, 2007 BRE80008 UK	UKWCS, Prospective Cohort, Age: 35-69	678/ 34 403 8 years	NHS central registry	FFQ	Incidence, breast cancer	>23 vs 0 g/day	1.22 (0.95-1.56)	Age, BMI, energy intake, HRT use, menopausal	RR rescaled for an increment of 100g/day
						per 50 g/day	1.11 (0.92-1.34)		
		283/			Premenopausal	>23 vs 0 g/day	1.15 (0.82-1.61)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
	years, W	15 947 8 years				per 50 g/day	1.28 (0.93-1.75)	status, oral contraceptive use, parity/pregnancies, physical activity, smoking habits, total fruit and vegetable intake	
		395/ 17 778 8 years			Postmenopausal	>23 vs 0 g/day	1.30 (0.89-1.89)		
						per 50 g/day	1.00 (0.78-1.28)		
Holmes, 2003 BRE15400 USA	NHS I, Prospective Cohort, Age: 30-55 years, W, Registered nurses	4 107 88 647 18 years	Self-reported, death certificate, pathology reports	Validated semi-quantitative FFQ	Incidence, invasive breast cancer	≥0.46 vs ≤0.17 servings/day	1.01 (0.91-1.11) Ptrend:0.69	Age, age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, energy intake, family history, height, HRT use, menopausal status, other anthropometric index, other design issue, other menstrual characteristics, parity/pregnancies	Servings/day converted to g day using 120g standard portion size, midpoints of exposure categories, person years and cases per quantile
		854/ 53 952 18 years			Premenopausal		1.08 (0.85-1.37) Ptrend:0.65		
		2 936/ 76 152 18 years			Postmenopausal		1.00 (0.89-1.12) Ptrend:0.97		
Missmer, 2002 Pooled analysis		7 015/401413			Incidence, breast cancer	per 100g/day	1.05 (0.96-1.13)	Age at menarche, parity, age at first birth, oral contraceptive use,	
USA, Canada	AHS	160/15 172							

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Canada	CNBSS	419/56 837						history of benign breast disease, family history of breast cancer, menopausal status, BMI, HRT use, smoking status, education, height, alcohol intake, total energy intake	
USA	IWHS	1 130/34 406							
Netherlands	NLCS	937/62 377							
USA	NYUWHS	388/13261							
USA	NHS (1980-1986)	1 023/89 046							
USA	NHS (1986-1996)	1 638/68 817							
Sweden	SMC	1 320/61 467							
Mills, 1989 BRE17837 USA Result Number:82235	AHS, Prospective Cohort, Age: 25-99 years, W, Adventist	207/ 20 341 6 years	Medical records	FFQ	Incidence, breast cancer	≥1 vs ≤0 times/week	1.43 (0.94-2.13) Ptrend:0.22	Age, age at first child, age at menarche, benign breast disease, BMI, educational level, family history	Times/day converted to g day using 120g standard portion size, midpoints of exposure categories, controls per quantile

Table 67 Poultry intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

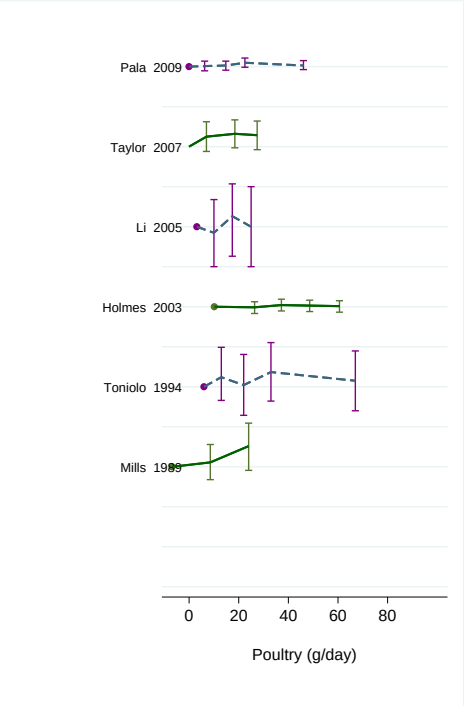
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Egeberg, 2008 BRE80153	DCH, Nested Case	378/ 378	Cancer registry	FFQ	Incidence, breast cancer,	>25 vs <10 g/day	1.33 (0.85-2.07) Ptrend:0.73	Age, age at first child birth, alcohol	Superseded by Pala, 2009

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Denmark	Control, Age: 50-64 years, W, Postmenopausal				postmenopausal	per 25 g/day	1.04 (0.84-1.28)	consumption, BMI, educational level, HRT use, parity	
Sonestedt, 2008b BRE80196 Sweden	MDC, Prospective Cohort, Age: 50- years, W, Postmenopausal	430/ 11 699 10.4 years	Cancer registry	7-day food record & FFQ	Incidence, invasive breast cancer, postmenopausal	Q5 vs Q1	1.00 (0.74-1.34)	Age, energy intake, exposure assessment, season of year	Superseded by Pala, 2009
Fung, 2005 BRE22370 USA	NHS I, Prospective Cohort, Age: 30-55 years, W, Registered nurses	512 71 058 16 years	Self-reported, next of kin, postal service, National Death Index, hospital records	Validated semi-quantitative FFQ	Incidence, breast cancer ER-, postmenopausal	per 1 serving/day	0.87 (0.60-1.28)	Age, age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, energy intake, family history, height, HRT use, menopausal status, other anthropometric index, parity/pregnancies, physical activity, smoking habits, supplements	Superseded by Holmes, 2003
Li, 2005 BRE23123 China	Shanghai BSE, Nested Case Control, W	130/ 1200	Biopsy	Validated 99-item FFQ	Incidence, breast cancer	>64 vs <20 times/year	1.00 (0.50-2.00) Ptrend:0.7	Age, energy, year of interview	Excluded, very low intake

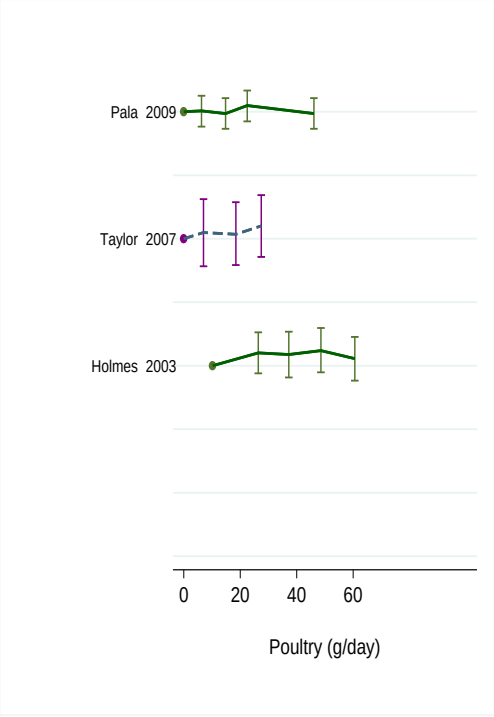
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Toniolo, 1994 BRE12398 USA Result Number:83725	NYUWHS, Nested Case Control, Age: 35-65 years, W	180/ 1009 7 years	Medical records	71-item semi-quantitative FFQ	Incidence, invasive breast cancer	67 vs 6 g/day	1.11 (0.66-1.86) Ptrend:0.62	Matched by age, menopausal status, date of enrolment, number and dates of blood donations, day of menstrual cycle at enrolment, height, Quatelet index, age at menarche, age at first full-term pregnancies, first-degree family history of breast cancer, history of benign breast conditions, race, and religion, energy intake	Included in Pooling project (Missmer, 2002), used in the highest vs lowest analysis only

Figure 87 RR estimates of breast cancer by levels of poultry intake

Breast cancer



Premenopausal



Postmenopausal

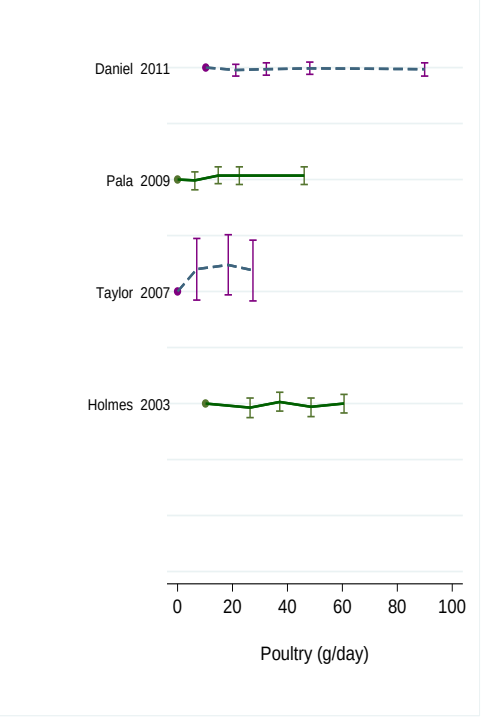
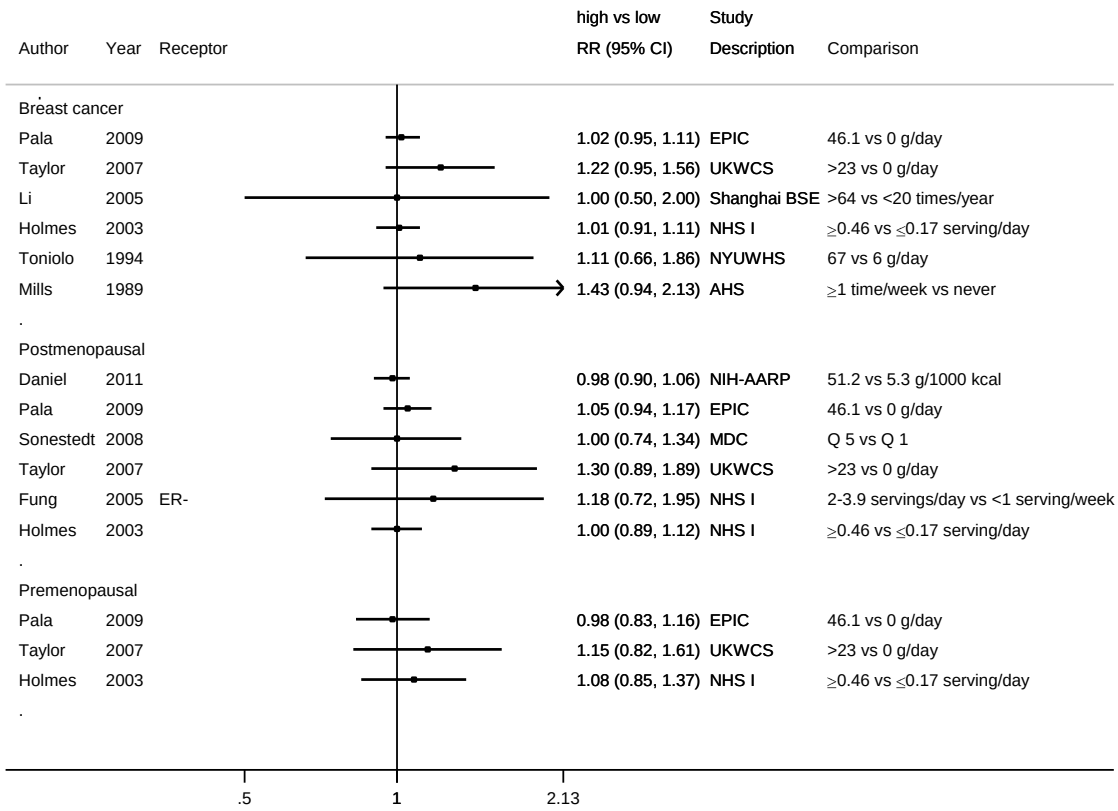


Figure 88 RR (95% CI) of breast cancer for the highest compared with the lowest level of poultry intake



Note: only one study (Fung, 2005) reported results by hormone receptor status.

Figure 89 Relative risk of breast cancer for 100g/day increase of poultry intake

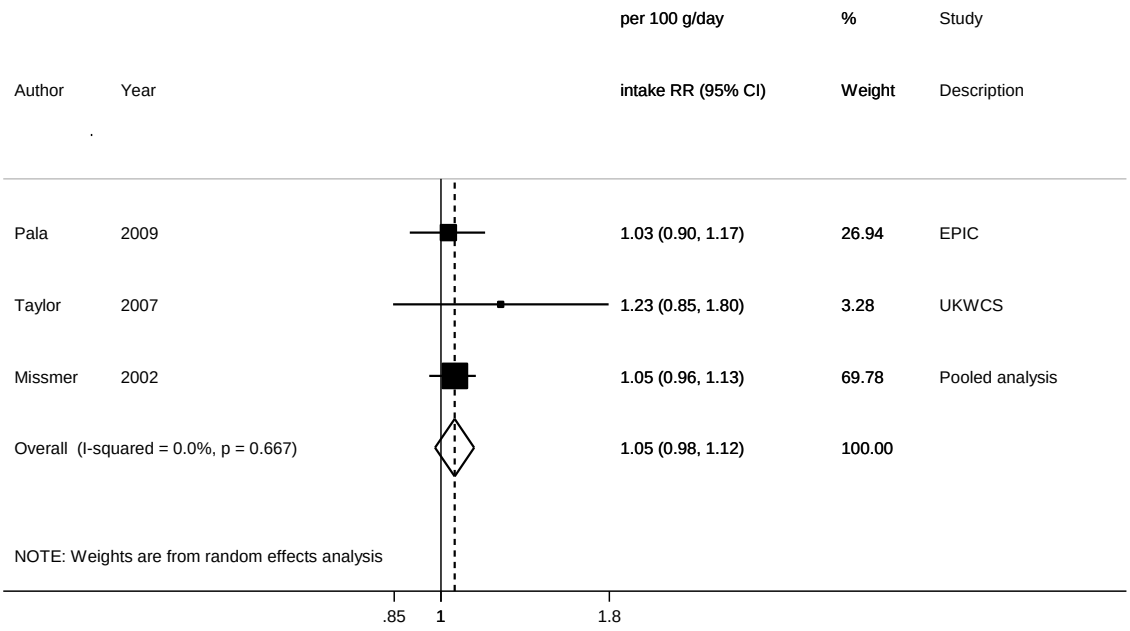


Figure 90 Relative risk of premenopausal breast cancer for 100g/day increase of poultry intake

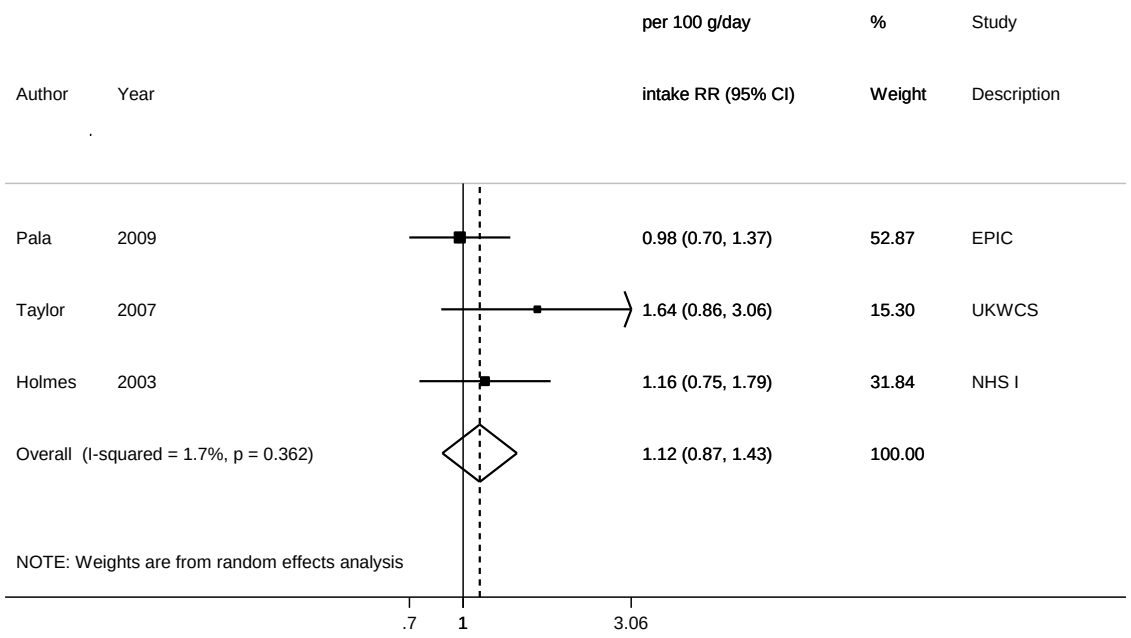


Figure 91 Relative risk of postmenopausal breast cancer for 100g/day increase of poultry intake

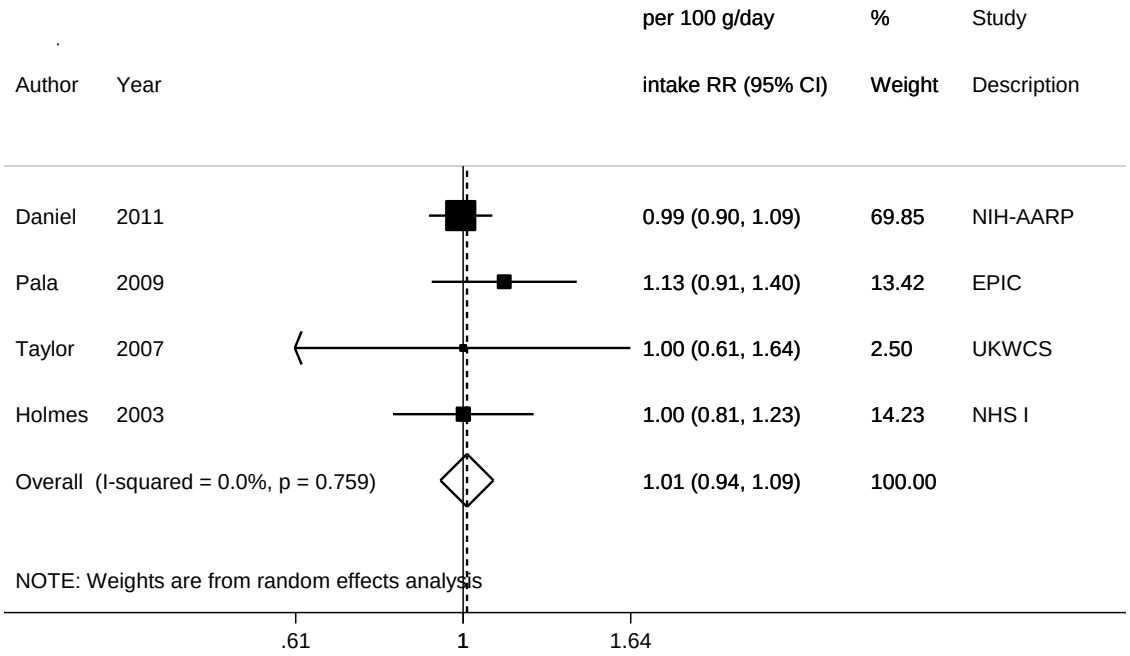
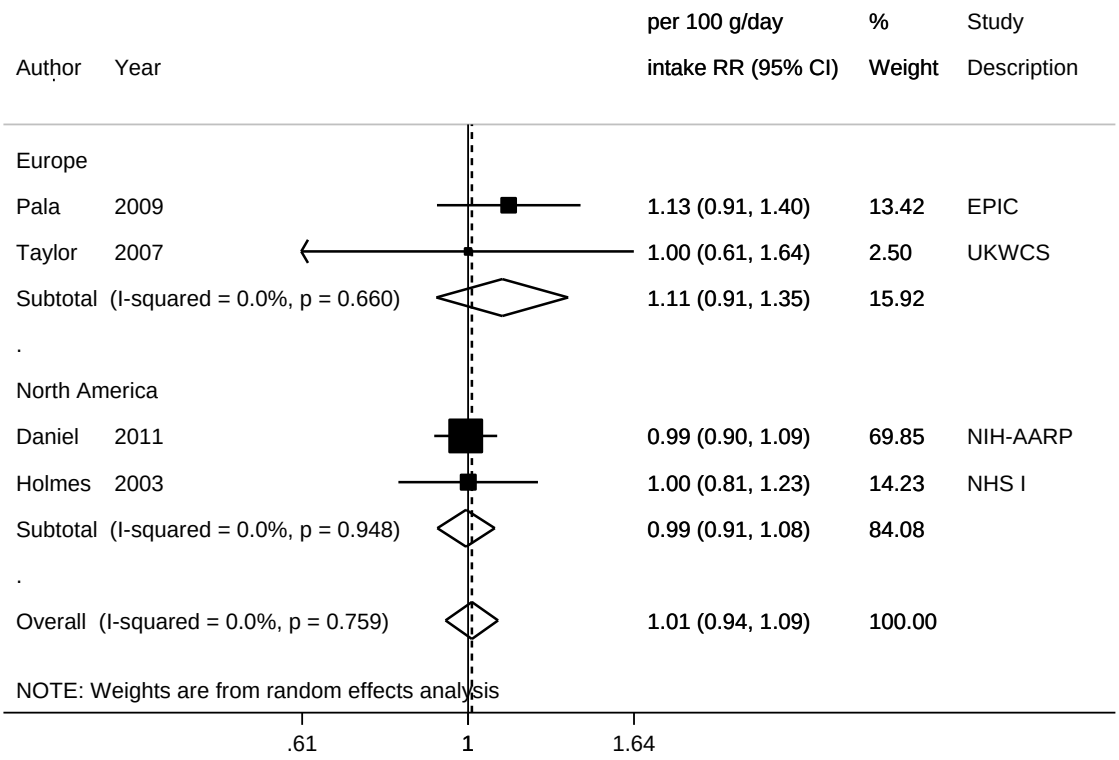


Figure 92 Relative risk of postmenopausal breast cancer for 100g/day increase of poultry intake, by geographic location



2.5.2 Total fish

Cohort studies

Overall summary

Twenty four publications (22 studies) on total fish intake and breast cancer risk were identified, including a pooled analysis of eight cohort studies.

No published meta-analysis was identified.

Study quality:

Fish intake was assessed using FFQ in most studies apart from Engeset, 2006 (EPIC) where diet history was used in some of the participating cohorts.
In most studies, cancer cases were identified by record linkage to registries of cancerand mortality; active follow-up was used in some cohorts in which cancer diagnosis was validated through clinical or pathological records. Loss to follow-up was low in most studies.

Most studies adjusted for main risk factors, including age, anthropometric and reproductive factors, alcohol intake, smoking and physical activity. One of the studies included in the meta-analysis for breast cancer (any) (Key, 1990) was not adjusted by main risk factors (see Table of main characteristics of studies). The studies included in the meta-analyses on premenopausal and postmenopausal breast cancer were adjusted for major risk factors including BMI, alcohol intake and reproductive factors.

Breast cancer (any)

16 studies (16 708 cases) (9 publications) were included in the dose-response meta-analysis. No significant association was observed.

Four studies were excluded from the dose-response meta-analysis. Two studies reported non-significant positive association (Li, 2015; Vatten, 1990a), one study reported non-significant inverse association (Iso, 2007 (mortality) and one study reported no association with risk of any breast cancer (Buckland, 2013).

Low heterogeneity was observed for breast cancer. There was no evidence of a significant publication or small study bias.

Sensitivity analyses:

The summary RR ranged from 0.98 (95% CI=0.86-1.12) when Engeset, 2006 (38.5% weight) was omitted to 1.04 (95% CI=0.95-1.14) when Cade, 2010 (6.4% weight) was omitted.

Premenopausal breast cancer

Summary

Main results:

Six studies (3 993 cases) were included in the dose-response meta-analysis. No significant association was observed with premenopausal breast cancer.

In the two studies excluded from the dose-response meta-analysis, fish intake was non-significantly inversely associated with premenopausal breast cancer risk (Buckland, 2013; Gago-Dominguez, 2003). The Pooling Prject of cohort study (Missmer, 2002) did not provide data to be included in the meta-analysis. The authors reported that the lack of association with fish intake was observed for both pre- and postmenopausal breast cancer (data not shown in the publication).

No heterogeneity was observed. There was no evidence of a significant publication or small study bias.

The summary RR ranged from 0.94 (95% CI=0.75-1.17) when Engeset, 2006 (38.7% weight) was omitted to 1.07 (95% CI=0.89-1.29) when Cade, 2010 (8.1% weight) was omitted.

Postmenopausal breast cancer

Summary

Main results:

Seven studies (16 123 cases) were included in the dose-response meta-analysis. No significant association was observed with postmenopausal breast cancer.

Four studies were excluded from the dose-response meta-analysis. Two studies reported non-significant inverse (Sonestedt, 2008b; Gago-Dominguez, 2003) and two studies non-significant positive association (Li, 2015; Ferrucci, 2009) for postmenopausal breast cancer. The Pooling Prject of cohort study (Missmer, 2002) did not provide data to be included in the meta-analysis. The authors reported that the lack of association with fish intake was observed for both pre- and postmenopausal breast cancer (data not shown in the publication).

No heterogeneity was observed. There was no evidence of a significant publication or small study bias.

Two studies reported results by tumour hormone receptor status (Fung, 2005; Stripp, 2003). In the NHS cohort (Fung, 2005), fish inatke was non-significantly inversely associated with postmenopausal ER- breast cancer (RR for one serving/day increment=0.92; 95% CI=0.66-1.30; p-trend=0.64). No data for ER+ was shown in the paper. In the DCH study (Stripp, 2003), fish intake was not associated with ER- brast cancer risk (RR for 25g/day increment= 1.00; 95% CI=0.81-1.24; 91 cases) and it was significantly positively associated with ER+ postmenopausal breast cancer (RR for 25g/day increment= 1.14; 95% CI=1.03-1.26; 303 cases).

Sensitivity analyses:

The summary RR ranged from 1.05 (95% CI=0.91-1.21) when Engeset, 2006 (46.5% weight) was omitted to 1.09 (95% CI=0.98-1.21) when Folsom, 2004 (8.5% weight) was omitted.

Table 68 Total fish intake and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	24 (22 publications)
Studies included in forest plot of highest compared with lowest exposure	Breast cancer: 9 (9 publications) Premenopausal: 6 (6 publications) Postmenopausal: 9 (9 publications)
Studies included in linear dose-response meta-analysis	Breast cancer: 16 (9 publications) Premenopausal: 6 (6 publications) Postmenopausal: 7 (7 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies with available data

Table 69 Total fish intake and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	-	100 g/day
All studies		
Studies (n)	-	16
Cases (total number)	-	15 973
RR (95%CI)	-	1.02 (0.92-1.12)
Heterogeneity (I^2, p-value)	-	14%, 0.32
P value Egger test	-	0.31
	Premenopausal	Postmenopausal
Studies (n)	6	7
Cases	3 993	16 123
RR (95%CI)	1.02 (0.86-1.22)	1.07 (0.97-1.19)
Heterogeneity (I^2, p-value)	0%, 0.46	0%, 0.96
P value Egger test	0.13	0.39

Other stratified analyses

Geographic area	**Asia**	**Europe**	**North-America**
	Breast cancer		
Studies (n)	3	3	3
RR (95%CI)	0.94 (0.56-1.54)	0.99 (0.82-1.18)	1.09 (0.90-1.31)
Heterogeneity (I^2, p- value)	60%, 0.08	32%, 0.23	0%, 0.81
	Premenopausal		
Studies (n)	-	3	3
RR (95%CI)	-	0.96 (0.69-1.34)	1.02 (0.74-1.39)

Heterogeneity (I^2, p- value)	-	52%, 0.13	0%, 0.76
	Postmenopausal		
Studies (n)	-	3	4
RR (95%CI)	-	1.09 (0.95-1.25)	1.06 (0.91-1.23)
Heterogeneity (I^2, p- value)	-	0%, 0.90	0%, 0.76

Table 70 Total fish intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Couto, 2013 BRE80454 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	1 278/ 49 258 16 years	Cancer registry	FFQ	Incidence, breast cancer	Per 15 g/day	0.98 (0.93-1.04)	Age at first child birth, age at menarche, BMI, alcohol, benign breast disease, beverage intake, cereal, dairy products consumption, educational level, egg, energy intake, fruits intake, height, history of breast cancer, legumes, meat, number of childbirths, potatoes, ratio unsaturated/saturated fat, smoking, sweet products, vegetable	RR rescaled for an increment used
		736/			Premenopausal		1.00 (0.94-1.05)		
		448/			Postmenopausal		1.01 (0.93-1.09)		
Genkinger, 2013 BRE80446 USA	BWHS, Prospective Cohort, Age: 21-69 years, W	1 268/ 56 062 12 years	Cancer Registry and National Death Index	FFQ	Incidence, breast cancer	≥200 vs <100 g/week	1.03 (0.89-1.19) Ptrend:0.69	Age at first child birth, age at menarche, age at menopause, alcohol, BMI, educational level, energy Intake, family history of breast cancer, HRT use, menopausal status, oral	Intake converted to g/day, mid-points of exposure categories
		573/			Premenopausal		0.97 (0.80-1.17) Ptrend:0.77		
		520/			Postmenopausal		1.04 (0.83-1.30) Ptrend:0.71		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								contraceptive history, parity, smoking, vigorous physical activity	
Daniel, 2011 BRE80386 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W, Postmenopausal	7 181/ 492 186 9.1 years	Cancer registry	FFQ	Incidence, breast cancer, postmenopausal	21.4 vs 3.6 g/1000 kcal	1.05 (0.97-1.14) Ptrend:0.40	Age, sex, alcohol, BMI, educational level, family history of cancer, HRT use, marital history, poultry, race, red meat, smoking, total energy, vigorous activity, reproductive factors were tested and did not alter the association	Intake in g/1000 kcal converted to g/day using provided total energy intake per quantile
Cade, 2010 BRE80296 UK	UKWCS, Prospective Cohort, Age: 35-69 years, W	786/ 33 725 9 years	NHS central registry	FFQ	Incidence, breast cancer	Per 50 g/day	0.90 (0.75-1.09)	Age, age at menarche, BMI, breastfeeding, educational level, energy Intake, ethanol Intake, fat Intake, HRT use, menopausal status, oral contraceptive use, parity, physical activity, smoking status, socio-economic status	RR rescaled for an increment used
		330/			Premenopausal		0.76 (0.56-1.04)		
		453/			Postmenopause		0.99 (0.78-1.25)		
Engeset, 2006 BRE80109	EPIC, Prospective	4 776/ 366 521	Population cancer registries	FFQ + diary	Incidence, invasive breast	96.77 vs 5.54 g/day	1.07 (0.95-1.20) Ptrend:0.36	Age at first child, age at menarche,	Nothing estimated

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
France, Italy, Spain, UK, Netherlands, Greece, Germany, Sweden, Denmark, Norway	Cohort, Age: 35-70 years, W		and other procedures		cancer			age-underlying cox models, alcohol, body weight, energy from carbohydrates, energy from fat, total energy intake , height, HRT use, length of follow-up, menopausal status, oral contraceptive use, parity/ pregnancies, recruitment center	
		786/			Premenopausal		1.11 (0.84-1.45) Ptrend:0.27		
		2 700/			Postmenopausal		1.10 (0.95-1.28) Ptrend:0.52		
Li, 2005 BRE23123 China	Shanghai BSE, Nested Case Control, W Participants in a trial of breast cancer self-examination	130/ 1200	All histology	Semi-quantitative FFQ, cured fish excluded	Incidence, breast cancer	≥169 vs ≤65 times/year	1.30 (0.70-2.60) Ptrend:0.58		Intake converted to g/day using a standard portion size of 120 g, mid-points of exposure categories
Folsom, 2004 BRE80171 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	1 885/ 41 836 14 years	Cancer registry and death certificates and participant contact	FFQ, total fish and seafood, dark-meat fish canned tuna, otehr fish and shrimp, lobster, scallops	Incidence, breast cancer, postmenopausal	≥2.5 vs ≤0.49 servings/week	0.92 (0.76-1.12) Ptrend:0.49	Age, age at first child birth, alcohol intake, BMI, cholesterol, diabetes, educational level, energy Intake, estrogen use, fruits	Intake in servings/week converted to g/day, mid-points of exposure categories

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								and vegetables Intake, hypertension, pack-years of smoking, physical activity, red meat intake, saturated fat, smoking habits, vitamin use, waist to hip ratio, whole grain intake	
Gago-Dominguez, 2003 BRE17518 China	SCHS, Prospective Cohort, Age: 45-74 years, W	314/ 63 257 5.3 years	Singapore Cancer Registry, Singapore Registry of Births and Deaths	FFQ, fish and shellfish	Incidence, breast cancer	Q4 vs Q1	0.74 (0.54-1.01) Ptrend:0.07	Age, alcohol, educational level, ethnicity, family history, menstrual characteristics, parity/ pregnancies	Person-years per quintile
		93/			Premenopausal		0.89 (0.48-1.66) Ptrend:0.93		Excluded, number of women by menopausal status is not given
		221/			Postmenopausal		0.71 (0.49-1.01) Ptrend:0.03		
Cho, 2003a BRE17370 USA	NHS II, Prospective Cohort, Age: 25-42 years, W, Premenopausal	714/ 90 655 8 years	Medical records, self-reported, death certificate	FFQ-semi-quantitative	Incidence, Invasive breast cancer, premenopausal	0.4 vs 0.07 serving/day	0.92 (0.73-1.15) Ptrend:.52	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, energy Intake , family history, height, menopausal status, oral contraceptive use, parity/pregnancies,	Intake in servings/day converted to g/day using 120g portion size, person years per quantile

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								smoking habits	
Holmes, 2003 BRE15400 USA	NHS I, Prospective Cohort, Age: 30-55 years, W, Registered nurses	88 647 18 years	Medical records	FFQ-semi-quantitative	Incidence, invasive breast cancer	≥0.4 vs ≤0.13 serving/day	1.04 (0.93-1.14) Ptrend:0.55	Age, age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, energy intake, family history, height, HRT use, menopausal status, other anthropometric index, other design issue, other menstrual characteristics, parity/ pregnancies	Superseded by pooled analysis, Missmer 2002, used in stratified analysis by geographic region
		854/			Premenopausal	≥0.4 vs ≤0.13 serving/day	1.17 (0.92-1.50) Ptrend:0.71		Intake in serving/day converted to g/day, mid-points of exposure categories
		2 936/			Postmenopausal	≥0.4 vs ≤0.13 serving/day	1.00 (0.89-1.12) Ptrend:0.79		
Missmer, 2002 Pooled analysis		6994/			Incidence, any breast cancer	Per 100 g/day	1.01 (0.87-1.17)	Age at menarche, parity, age at first birth, oral contraceptive use, history of benign breast disease, family history of breast cancer, menopausal stauts, BMI, HRT use, smoking status, education, height, alcohol intake, total	Nothing estimated
Canada	CNBSS	419/56 837							
USA	IWHS	1 130/34 406							
Netherlands	NLCS	937/62 377							
USA	NYS	367/18 475							
USA	AHS	160/ 15 172							

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
USA	NHS I	1 023/89 046						energy intake	
USA	NHS II	1 638/68 817							
Sweden	SMC	1 320/61 467							
Key, 1999 BRE04758 Japan	LSS, 1969, Prospective Cohort, W	427/ 34 759 24 years	Population-based cancer registries	FFQ	Incidence, breast cancer	≥5 vs ≤1 times/week	1.17 (0.90-1.54) Ptrend:0.209	Age, calendar year, age at atomic bombing and radiation dose received, place of residence	Intake in times/week converted to g/day using 120 g portion size, mid-points of exposure categories

Table 71 Total fish intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Li, 2015 BRE80550 Sweden	WLHS, Prospective Cohort, Age: 29-49 years, W	1 464/ 44 296 20 years	Cancer registry and death registry	FFQ	Incidence, breast cancer	≥20.8 vs 0-20.7 g/day	1.03 (0.92-1.15)	Age, age at first child birth, age at menarche, alcohol, benign breast disease, BMI, breastfeeding, cabbage, cigarettes per day, educational level, energy Intake, family	Superseded by Couto, 2013, only two levels of exposure
		549/			Premenopausal		0.96 (0.81-1.15)		
		915/			Postmenopausal		1.07 (0.93-1.23)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								history of breast cancer, height, number of children, oat, oral contraceptive use, pears, saturated fat Intake, smoking, vegetable, whole grain bread	
Buckland, 2013 BRE80433 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	10 225/ 335 062 11 years	Cancer registries, health Insurance records, pathology records & active follow-up	FFQ in most centres, diet history in two centres	Incidence, breast cancer	Q3 vs Q1	1.00 (0.95-1.05)	Age, age at first child birth, age at menarche, age at menopause, alcohol, BMI, breastfeeding, centre location, cereal, dairy products consumption, educational level, energy, fruits, height, HRT use, legumes, meat, oil, oral contraceptive history, physical activity, saturated fat, smoking, vegetables	Superseded by Engeset, 2006, intake per quantiles is not available

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Trichopoulou, 2010 BRE80320 Greece	EPIC-Greece, Prospective Cohort, Age: 20-68 years	240/ 14 807 9.8 years	Medical records and pathology reports	FFQ	Incidence, breast cancer	Per 16 g/day	1.08 (0.95-1.21)	Age, age at first child birth, age at menarche, age at menopause, BMI, educational level, energy Intake, height, HRT use, menopausal status, metabolic equivalents, parity, smoking	Superseded by Engeset, 2006
					Premenopausal		1.22 (1.05-1.44)		
					Postmenopausal		0.94 (0.78-1.15)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Ferrucci, 2009 BRE80234 USA	PLCO, Prospective Cohort, Age: 55-74 years, W, Postmenopausal	1 205/ 52 158 5.5 years	Self report verified by medical record	FFQ	Incidence, breast cancer, postmenopausal	14.1-229.4 vs ≤3.1 g/1000 kcal/day	1.08 (0.89-1.31) Ptrend:0.76	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, benign breast disease, BMI, educational level, ethnicity, family history of cancer, fat Intake, HRT use, mammography, randomization group, study center, total caloric intake	Excluded, caloric intake per each quantile is not available to convert g/1000 kcal intake
Egeberg, 2008 BRE80153 Denmark	DCH, Nested Case Control, Age: 50-64 years, W, Postmenopausal	378/ 378 controls	Cancer registry	FFQ	Incidence, breast cancer	per 25 g/day	1.14 (0.94-1.39)	Age, age at first child birth, alcohol consumption, BMI, educational level, HRT use, parity	Superseded by Engeset, 2006
						≥35 vs ≤14 g/day	1.58 (1.00-2.49) Ptrend:0.19		
Sonestedt, 2008b BRE80196 Sweden	MDCS, Prospective Cohort, Age: 50- years, W, Postmenopausal	430/ 11 699 10.4 years	Cancer registry	7-day food record & FFQ	Incidence, invasive breast cancer, postmenopausal	Q5 vs Q1	0.84 (0.61-1.13)	Age, energy intake, exposure assessment, season of year	Excluded, only two levels of exposure

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Iso, 2007 BRE80427 Japan	JACC, Prospective Cohort, Age: 40-79 years, W	98/ 15 years	Municipal resident registration records, death certificates	FFQ	Mortality, breast cancer	≥5 vs ≤2.9 /week	0.59 (0.33-1.05)	Age, centre location	Excluded, outcome is mortality
Fung, 2005 BRE22370 USA	NHS I, Prospective Cohort, Age: 30-55 years, W, Registered nurses	71 058 16 years	Medical records + self-reported	FFQ	Incidence, breast cancer ER-, postmenopausal	Per 1 serving	0.92 (0.66-1.30)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, energy intake , family history, height, HRT use, menopausal status, other anthropometric index, parity/pregnancies, physical activity, smoking habits, supplements	Superseded by Missmer, 2002, analysis by hormone receptor status was not conducted
						2-3.9 servings/day vs <1 serving/week	1.37 (0.87-2.15)		
Stripp, 2003 BRE11883 Denmark	DCH, Prospective Cohort, Age: 50-64 years, W, Postmenopausal	424/ 4.8 years	Partially histological - over 80%	FFQ	Incidence, breast cancer, postmenopausal	Per 25 g/day	1.13 (1.03-1.23)	Age at first child, age-underlying cox models, alcohol, benign breast disease, BMI, duration of HRT use, educational level, HRT use, parity/	Superseded by Missmer, 2002, analysis by hormone receptor status was not conducted
						≥59 vs 0-26 g/day	1.47 (1.10-1.98)		
		303/			ER+	Per 25 g/day	1.14 (1.03-1.26)		
		91/			ER-		1.00 (0.81-1.24)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								pregnancies, parous/ nulliparous	
Toniolo, 1994 BRE12398 USA	NYUWHS, Nested Case Control, Age: 35-65 years, W	180 735 7 years	Medical records	Semi-quantitative FFQ	Incidence, invasive breast cancer	73 vs 4 g/day	1.02 (0.61-1.71) Ptrend:0.79	Height, Quetelet index, age at menarche, age at first full-term pregnancy, number of full-term pregnancies, first-degree family history of breast cancer, history of benign breast conditions, race, and religion, energy intake	Superseded by Missmer, 2002 in the main analysis
Vatten, 1990a BRE12832 Norway	NNHSS, Prospective Cohort, Age: 35-51 years, W, Screening Program	152/ 14 500 12 years	Partially histological - over 80%	FFQ, main meal containing fish	Incidence, breast cancer	≥2.1 vs ≤2 times/week	1.20 (0.80-1.70) Ptrend:0.24	Age	Excluded, only two levels of intake
Mills, 1989 BRE17837 USA	AHS, Prospective Cohort, Age: 25-99 years, W,	207/ 20 341 6 years	Medical records	FFQ	Incidence, breast cancer	≥1 vs ≤0 times/week	1.54 (1.00-1.81) Ptrend:0.008	Age, age at first child, age at menarche, benign breast disease, BMI, educational level, family history	Superseded by Missmer, 2002 in the main analysis, excluded

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Adventist								from stratified analysis due very low intakes and resulting wide CIs

Figure 93 RR estimates of breast cancer by levels of total fish intake

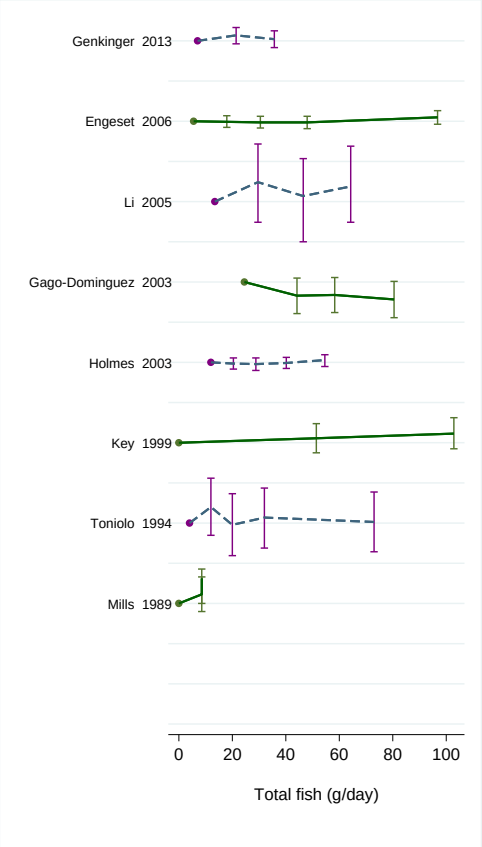


Figure 94 RR estimates of premenopausal breast cancer by levels of total fish intake

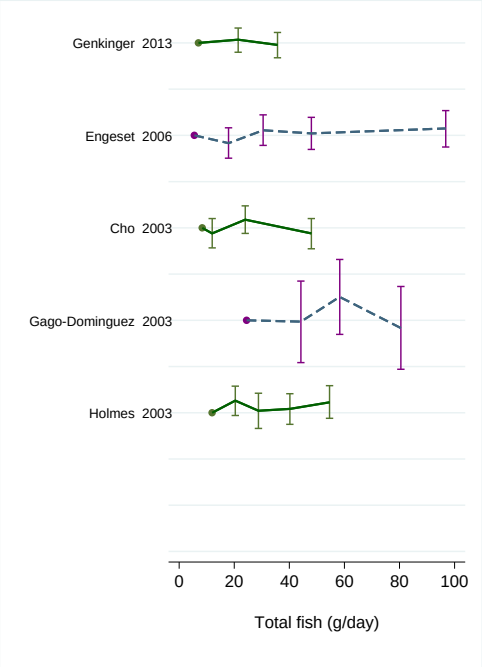


Figure 95 RR estimates of postmenopausal breast cancer by levels of total fish intake

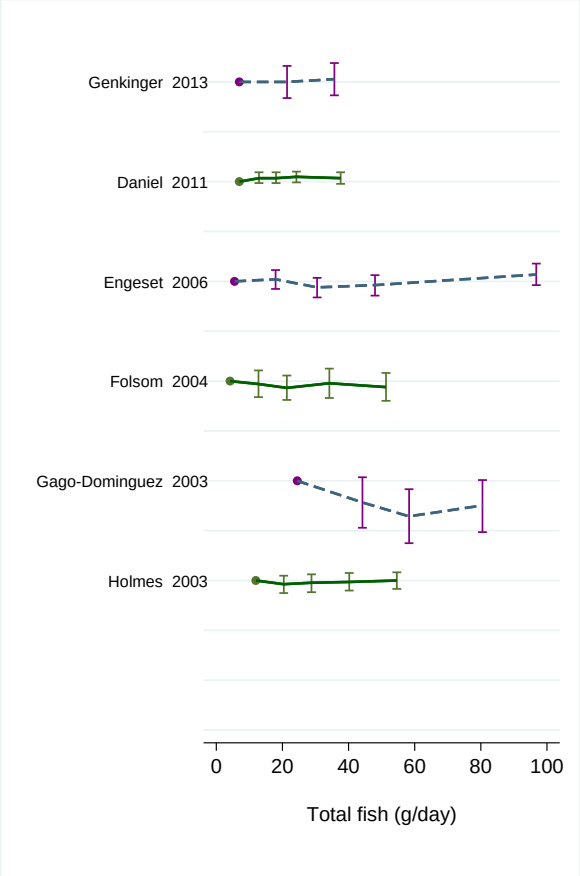
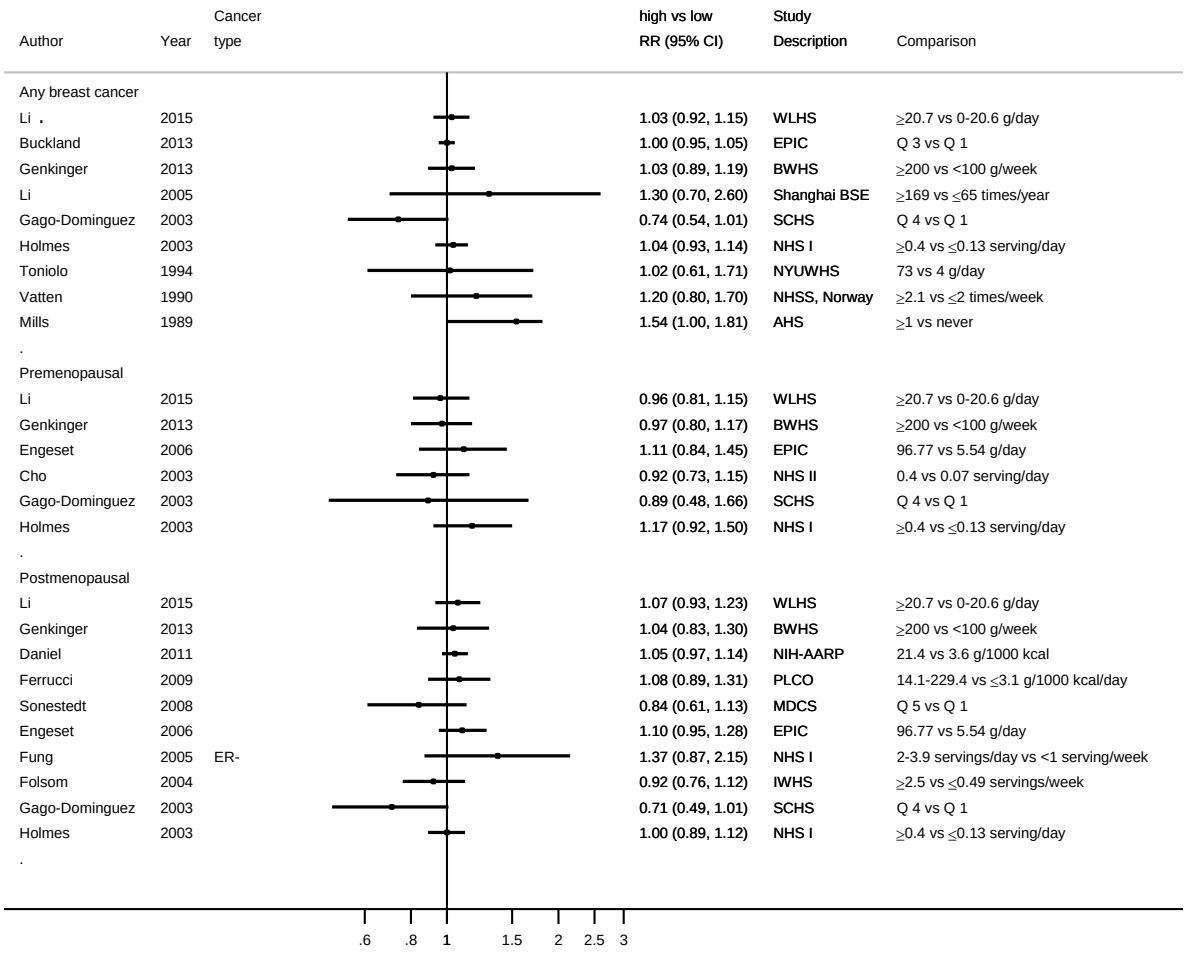


Figure 96 RR (95% CI) of breast cancer for the highest compared with the lowest level of total fish intake



Note: only one study (Fung, 2005) reported results by hormone receptor status for the highest compared to the lowest level of intake.

Figure 97 Relative risk of breast cancer for 100g/day increase of total fish intake

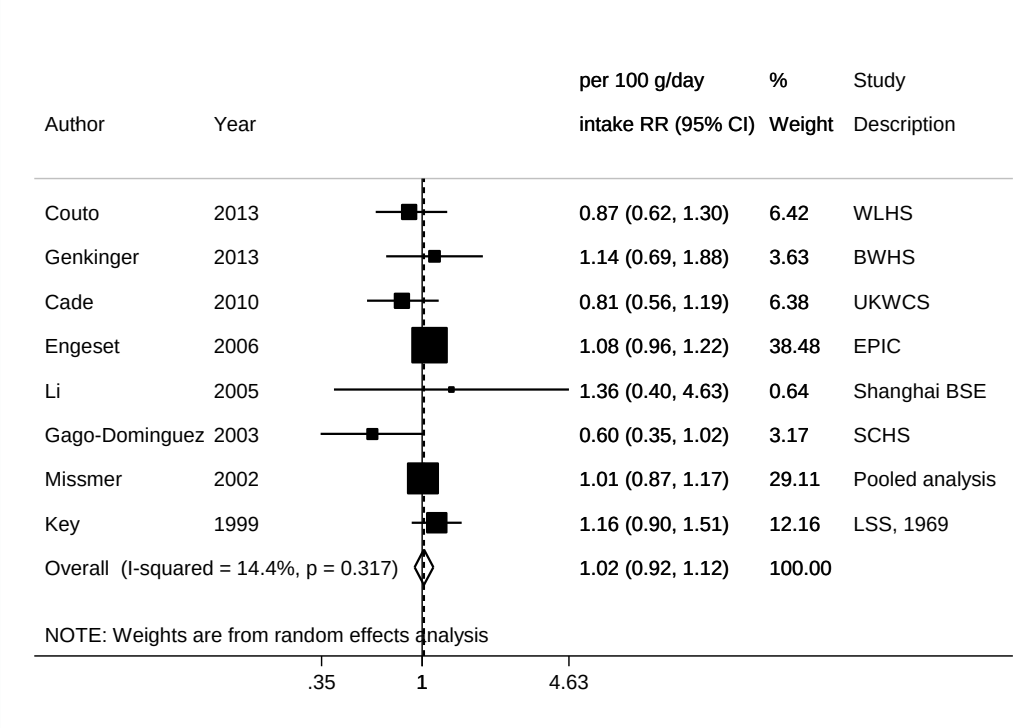


Figure 98 Relative risk of premenopausal breast cancer for 100g/day increase of total fish intake

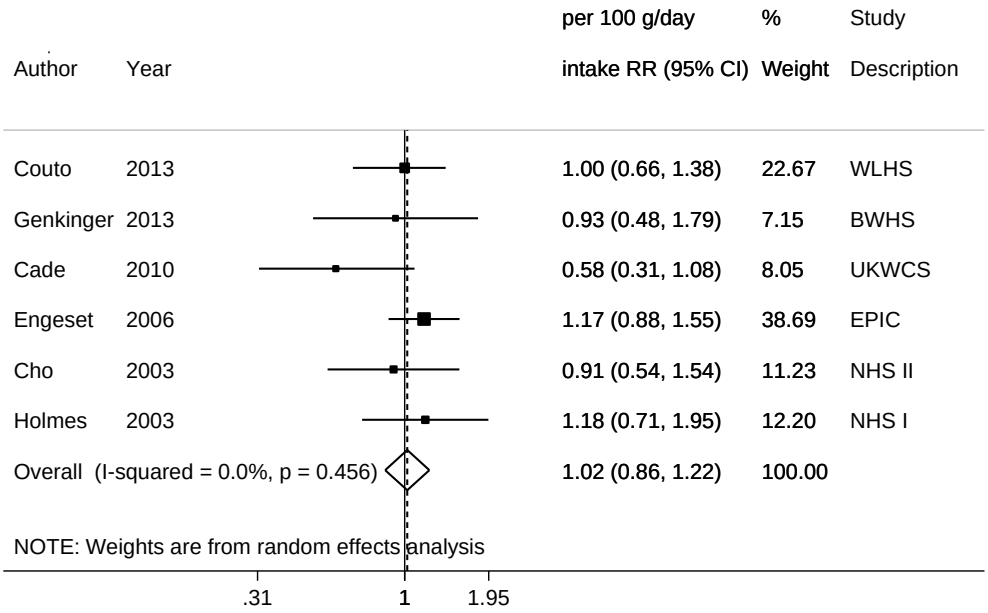


Figure 99 Relative risk of postmenopausal breast cancer for 100g/day increase of total fish intake

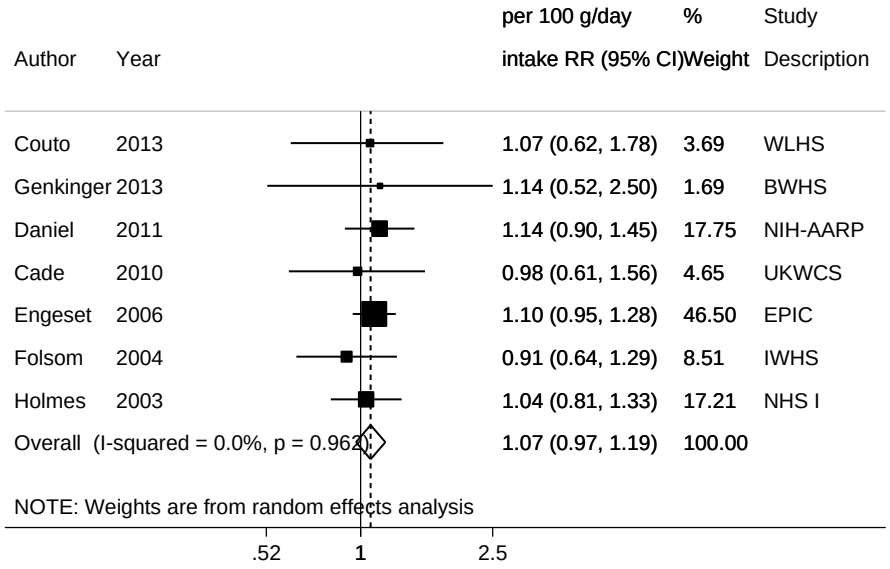


Figure 100 Funnel plot of studies included in the dose response meta-analysis of total fish intake and breast cancer

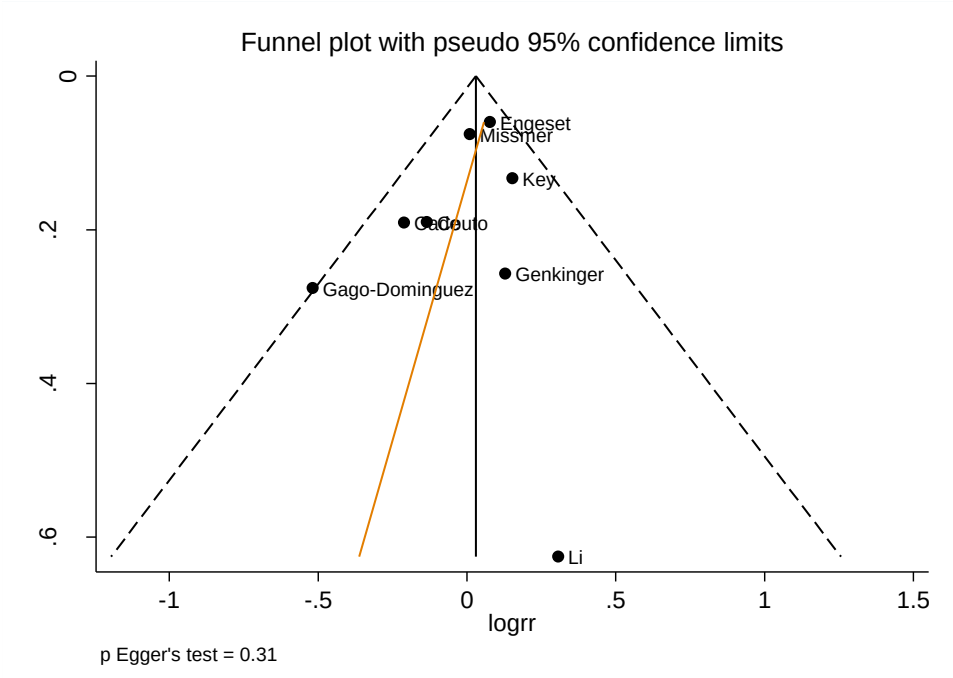


Figure 101 Funnel plot of studies included in the dose response meta-analysis of total fish intake and premenopausal breast cancer

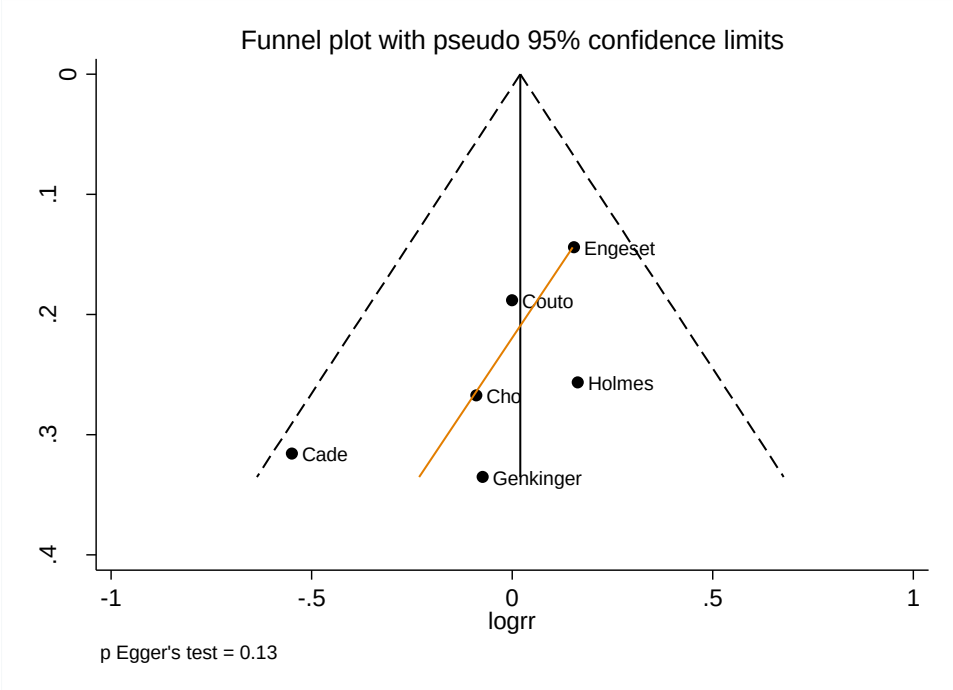


Figure 102 Funnel plot of studies included in the dose response meta-analysis of total fish intake and postmenopausal breast cancer

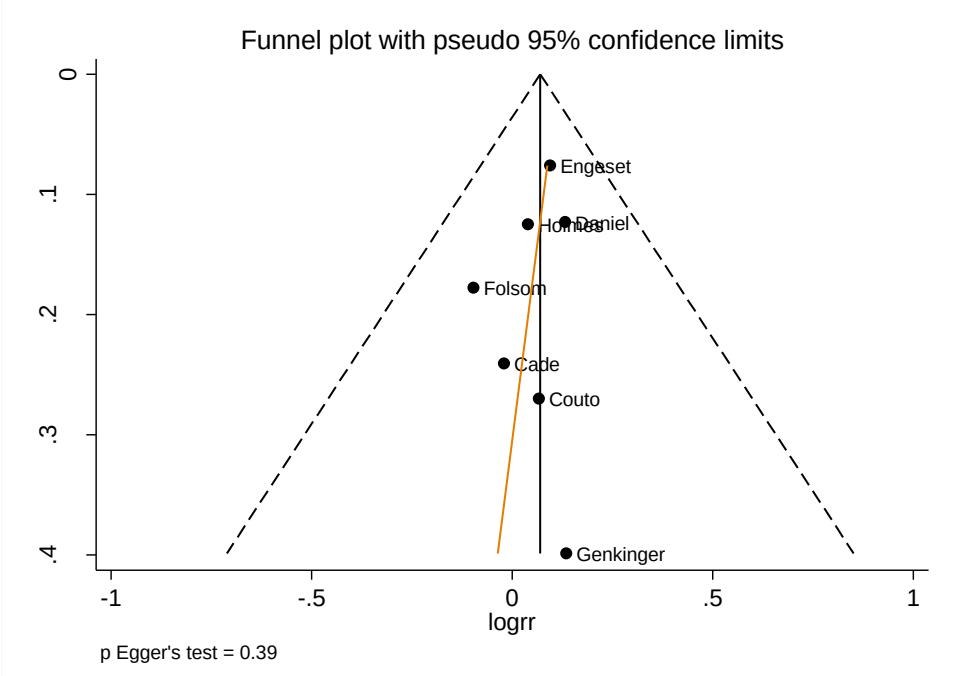


Figure 103 Relative risk of breast cancer for 100g/day increase of total fish intake, by geographic location

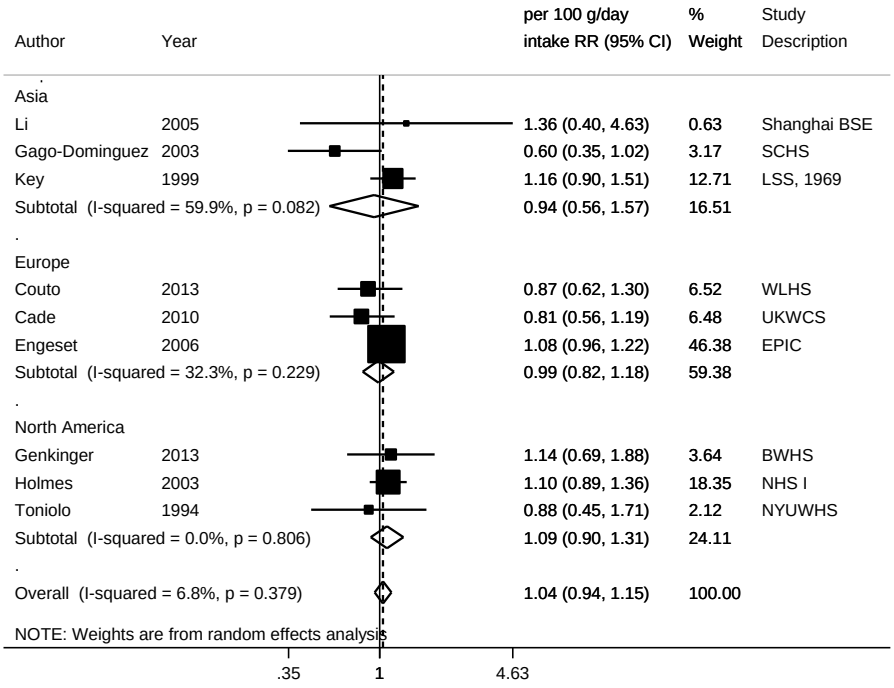


Figure 104 Relative risk of premenopausal breast cancer for 100g/day increase of total fish intake, by geographic location

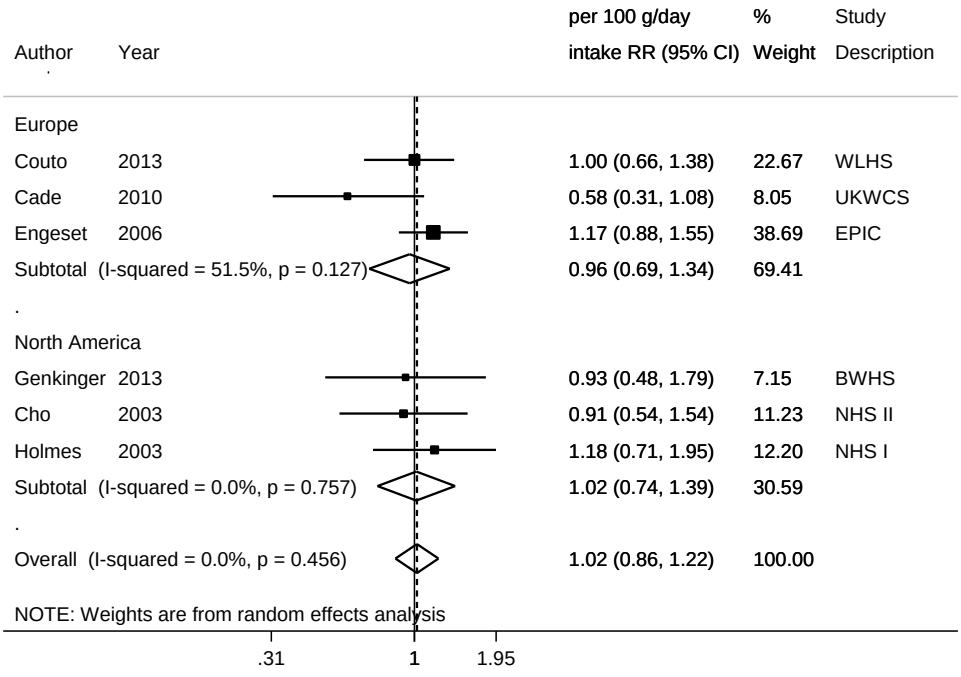
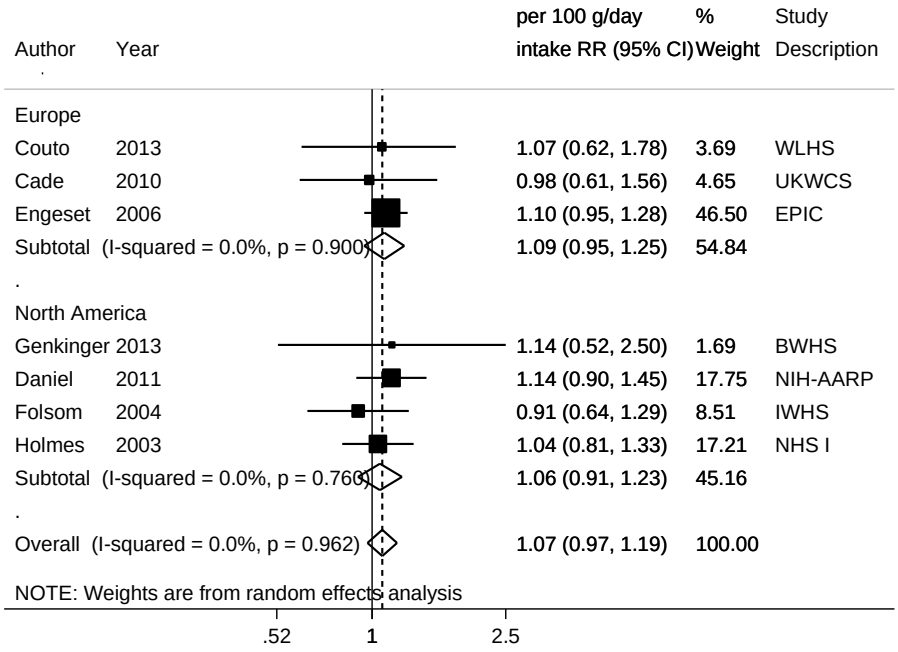


Figure 105 Relative risk of postmenopausal breast cancer for 100g/day increase of total fish intake, by geographic location



2.7 Milk and dairy products

Cohort studies

Overall summary

Fifteen publications (19 studies) on dairy intake and breast cancer risk were identified, including a pooled analysis of eight cohort studies. Study characteristics of all identified studies and results for all cancer types are shown in study inclusion and exclusion tables . For studies that reported dairy intake in servings or times per day, a serving size of 177 g was used to estimate intakes in grams per day for the dose-response meta-analysis.

Study quality:

Total dairy intake was assessed by FFQ in most studies. One study used 24-hour records collected every two months (six records in total) (Kesse-Guyot, 2007) and one used a modified dietary history interview method (Knekt, 1996). In the EPIC study, a combination of FFQ and food records were used (Buckland, 2013).

One nested case-control study was in a follow-up of women with proliferative fibrocystic breast conditions participating in a randomised controlled trial of breast self-examination in Shanghai (Li, 2005).

Loss to follow-up was low for the studies that reported such data, although some studies did not provide data.

Cancer cases were identified by record linkage to cancer registries, mortality registries, or self-reported with verification through pathology reports, medical records, and death certificates.

All studies adjusted for multiple confounders, including age, reproductive factors, BMI, and alcohol consumption. One study did not adjust for alcohol (Trichopoulou, 2010) but alcohol intake was nto lienarly related to breats cancr risk in this study and one did not adjust for alcohol (Li, 2005) and BMI was evaluated as potential confounder but not included in the final model.

Breast cancer (any)

Six studies (7 766 cases) (6 publications) were included in the dose-response meta-analysis. Significant inverse association was observed.

Two studies (Buckland, 2013; Knekt, 1996) and the pooled analysis of eight cohort studies (Missmer, 2002) were excluded from the dose-response meta-analysis. Buckland, 2013 (EPIC) reported non-significant positive association and Knekt, 1996 (FMCHES) study reported significant inverse association with breast cancer risk. In the pooled analysis of eight cohorts, dairy fluids and solids intakes were not associated and non-significantly positively associated with breast cancer risk, respectively (Missmer, 2002).

No heterogeneity was observed in the dose-response meta-analysis. There was no significant evidence of publication or small study bias. However, one study in Sweden (Couto, 2013) and one American study (Park, 2009b) accounted for 41.3% and 52.4% weight in the analysis.

Sensitivity analyses:

The summary RR ranged from 0.95 (95% CI=0.91-0.99) when Park, 2009b (52.4% weight) was omitted to 0.97 (95% CI=0.94-1.01) when Couto, 2013 (41.3% weight) was omitted.

Premenopausal breast cancer

Seven studies (2 862 cases) (7 publications) were included in the dose-response meta-analysis. Significant inverse association was observed.

The pooled analysis of eight cohort studies (Missmer, 2002) was excluded from the dose-response meta-analysis. In this analysis, intakes of dairy fluids and dairy solids were inversely but not significantly associated with premenopausal breast cancer risk.

No heterogeneity was observed. There was no evidence of significant publication or small study bias.

Sensitivity analyses:

The summary RR ranged from 0.94 (95% CI=0.91-0.98) when Cho, 2003a (19.1% weight) was omitted to 0.96 (95% CI=0.92-0.99) when Lin, 2007 (6.8% weight) was omitted.

Postmenopausal breast cancer

Eight studies (8 145 cases) (8 publications) were included in the dose-response meta-analysis. No significant association was observed.

The pooled analysis of eight cohort studies (Missmer, 2002) was excluded from the dose-response meta-analysis. In this analysis, intakes of dairy fluids and dairy solids were not associated and positively but not significantly associated with postmenopausal breast cancer risk, respectively.

Moderate heterogeneity was observed. There was no evidence of a significant publication or small study bias.

Sensitivity analyses:

The summary RR ranged from 0.96 (95% CI=0.93-0.93) when Hjartåker, 2010 (14% weight) was omitted to 0.99 (95% CI=0.96-1.02) when McCullough, 2005 (23.8% weight) was omitted.

Table 72 Dairy product intake and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	19 (15 publications)
Studies included in forest plot of highest compared with lowest exposure	Breast cancer: 6 (6 publications) Premenopausal: 5 (5 publications) Postmenopausal:6 (6 publications)
Studies included in linear dose-response meta-analysis	Breast cancer: 6 (6 publications) Premenopausal: 7 (7 publications) Postmenopausal: 8 (8 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies with available data

Table 73 Dairy product intake and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	1 serving/day	200 g/day
All studies		
Studies (n)	2	6
Cases (total number)	6 027	7 766
RR (95%CI)	0.97 (0.94-0.99)	0.96 (0.94-0.99)
Heterogeneity (I^2, p-value)	78%	0%, 0.75
P value Egger test	-	0.51
	Premenopausal	Postmenopausal
Studies (n)	7	8
Cases	2 862	8 145
RR (95%CI)	0.95 (0.92-0.99)	0.97 (0.93-1.01)
Heterogeneity (I^2, p-value)	0%, 0.59	39%, 0.12

P value Egger test	0.66	0.74

Other stratified analyses

Geographic area	**Asia**	**Europe**	**North-America**
	Breast cancer		
Studies (n)	1	3	2
RR (95%CI)	1.04 (0.58-1.88)_	0.95 (0.91-0.99)	0.95 (0.85-1.05)
Heterogeneity (I^2, p- value)	-	0%, 0.96	51%, 0.15
	Premenopausal		
Studies (n)	-	4	3
RR (95%CI)	-	0.96 (0.91-1.00)	0.94 (0.88-1.00)
Heterogeneity (I^2, p- value)	-	0%, 0.53	12%, 0.32
	Postmenopausal		
Studies (n)	-	5	3
RR (95%CI)	-	0.97 (0.92-1.03)	0.97 (0.92-1.03)
Heterogeneity (I^2, p- value)	-	21%, 0.28	69%, 0.04

Table 74 Dairy product intake and breast cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Dong, 2011	10 prospective cohorts*	14 838	USA, UK, Finland, France	Incidence, breast cancer	Highest vs lowest	0.85 (0.76-0.95)		55%, p=0.01
	5 prospective cohorts	2 317**		Premenopausal breast cancer		0.79 (0.63-0.99)		50%, p=0.09
	4 prospective cohorts			Postmenopausal breast cancer		0.92 (0.83-1.01)		33%, p=0.22
	4 prospective cohorts			Low-fat		0.84 (0.73-0.96)		54%, p=0.07
	4 prospective cohorts			High-fat		0.99 (0.85-1.15)		61%, p=0.04

*All studies are included in the meta-analysis apart from Linos, 2010 and van der Pols, 2007 on dairy intake in adolescence and childhood, respectively.

**The number of cases in the publications was not given and was estimated.

Table 75 Dairy intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Couto, 2013 BRE80454 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	1 278/ 49 258 16 years	Linkage with the national cancer register	Validated, 80-item FFQ	Incidence, breast cancer	Per 290 g/day	0.93 (0.87-0.99)	Age at first child birth, age at menarche, BMI, alcohol, benign breast disease, beverage intake, cereal, educational level, egg, energy intake, fish, fruits intake, height, history of breast cancer, legumes, meat, number of childbirths, potatoes, ratio unsaturated/saturated fat, smoking, sweet products, vegetable	RR rescaled for an increment used
		736/			Premenopausal		0.93 (0.86-0.99)		
		448/			Postmenopausal		0.89 (0.80-0.98)		
Hjartåker, 2010 BRE80327 Norway	NOWAC, Prospective Cohort, W	218/ 64 904 (premenopausal and postmenopausal) 8.6 years	Linkage to the Cancer Registry of Norway and death records	Validated FFQ	Incidence, Invasive breast cancer, premenopausal	≥323.6 vs <107.2 g/day	1.07 (0.69-1.65) Ptrend:0.60	Age, age at first child birth, age at menarche, alcohol, contraception, educational level, energy Intake, family history of breast	
						Per 50 g/day	1.02 (0.97-1.07)		RR rescaled for an increment

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								cancer, height, weight mammography, number of children, physical activity	used
		1 189/			Postmenopausal	≥323.6 vs <107.2 g/day	1.01 (0.83-1.23) Ptrend:0.47		
						Per 50 g/day	1.01 (0.99-1.03)		RR rescaled for an increment used
Trichopoulou, 2010 BRE80320 Greece	EPIC-Greece, Prospective Cohort, Age: 20-68 years	240/ 14 807 9.8 years	Self-reports verified through pathology reports, medical records, discharge diagnoses, death certificates	Validated 150-item semi-quantitative interviewer-administered FFQ	Incidence, breast cancer	Per 144 g/day	0.98 (0.85-1.12)	Age, age at first child birth, age at menarche, age at menopause, BMI, educational level, energy intake, height, HRT use, menopausal status, metabolic equivalents, parity, smoking	RR rescaled for an increment used
		113			Premenopausal		0.95 (0.78-1.15)		
		127			Postmenopausal		0.98 (0.80-1.20)		
Park, 2009b BRE80464 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W, Retired	5 856/ 492 810 7 years	Cancer registry, death records	Validated 124-item self-administered FFQ, excluded butter	Incidence, breast cancer	1.6 vs 0.2 servings 1000 kcal/day	0.96 (0.88-1.04) Ptrend:0.28	Age at first child birth, age at menopause, alcohol consumption, BMI, educational level, family history of cancer, fat intake, marital status,	Person-years per quantile, intake in g/1000kcal/day converted to absolute intakes using average energy intake between Q1 and Q5

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								menopausal oestrogen use, number of children, race/ethnicity, red meat Intake, smoking, total energy, vigorous physical activity	
Kesse-Guyot, 2007 BRE11112 France	SU.VI.MAX, Prospective Cohort, Age: 35-60 years, W, SU.VI.MAX participants	82/ 3 627 7.7 years	Self-reported cases validated by pathological reports	24h recalls, six records per year at most, yogurt, fresh cheese, milk and cheese	Incidence, breast cancer	>400 vs <165 g/day	0.80 (0.34-1.86) Ptrend:0.34	Age, alcohol, BMI, calcium intake, educational level, energy from fat, energy from non-fat sources, family history, group supplementation , HRT use, marital status, menopausal status, parity/pregnancies, physical activity , smoking habits	Mid-points of exposure categories
		48/			Postmenopausal		0.86 (0.27-2.68) Ptrend:0.82		
		45/			Premenopausal		0.67 (0.18-2.47) Ptrend:0.22		
Lin, 2007 BRE80165 USA	WHS, Prospective Cohort, Age: 54-56 years,	743/ 31 487 10 years	Self-reports verified by medical records and pathology reports	Validated 131-item FFQ	Incidence, Invasive breast cancer, postmenopausal	≥3.13 vs ≤0.92 servings/day	1.07 (0.82-1.39) Ptrend:0.83	Age, age at menopause, postmenopausal hormone use, randomized	Intake in servings converted to g/day, mid-points of
		276/			Premenopausal		0.64 (0.42-0.95)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	W						Ptrend:0.09	treatment assignment, BMI, physical activity, family history of breast cancer, history of benign breast disease, age at menarche, parity, age at first birth, multivitamin use, smoking status, alcohol consumption, energy intake	exposure categories, person-years per category
Li, 2005 BRE23123 China Participants in a trial of breast cancer self-examination	Shanghai BSE, Nested Case Control, W	130/ 1 200	All histology	Validated 99-item semi-quantitative FFQ	Incidence, breast cancer	≥376 vs ≤12 times/year	0.90 (0.40-2.10) Ptrend:0.61	Age, energy intake, year, No change after adjustment for education, age at first birth, parity, physical activity, family history of breast cancer	Intake in times/year converted to g/day, mid-points of exposure categories
McCullough, 2005 BRE23368 USA	CPS II, Prospective Cohort, Age: 50-74	2 855/ 68 567 9 years	Self-reports, death records, medical records	Validated 68-item semi-quantitative FFQ,	Incidence, breast cancer, postmenopausal	>3 vs <0.5 serving/day	0.81 (0.69-0.96) Ptrend:0.002	Age, age at first child, age at menopause, alcohol, breast	Intake in servings/day converted to g/day, mid-

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	years, W, Postmenopausal			excluded butter				diseases , educational level, energy intake , ethnicity, family history, height, HRT use, mammography, other anthropometric index, parity/ pregnancies	points of exposure categories
		1 283/			Incidence, breast cancer ER+, postmenopausal		0.73 (0.57-0.93) Ptrend:0.0003		Analysis by tumour hormone receptor status was not conducted
		227/			Incidence, breast cancer ER-, postmenopausal		1.23 (0.70-2.15) Ptrend:0.77		
Cho, 2003a BRE17370 USA	NHS II, Prospective Cohort, Age: 25-42 years, W, Premenopausal	714/ 90 655 8 years	Self-reports, 98% of self-reports were validated through medical records, pathology reports	133-142-item semi-quantitative FFQ	Incidence, invasive breast cancer, premenopausal	4 vs 0.7 serving/day	1.03 (0.79-1.36) Ptrend:.72	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, energy Intake , family history, height, menopausal status, OC use, parity/pregnancies, smoking habits	Intake in servings/day converted to g/day, person-years per quantile
Shin, 2002 BRE16658 USA	NHS I, Prospective Cohort, Age: 47 years, W, Registered nurses	2 345/ 88 691 16 years	Self-reports confirmed by medical records	Validated FFQ, milk, cream, sour cream, sherbet, ice cream, yogurt, cheese, butter	Incidence, Invasive breast cancer, postmenopausal	Per 1 serving/day	1.00 (0.96-1.04)	Age, age at first child, age at menarche, age at menopause, alcohol, BMI, body weight, breast diseases ,	RR rescaled for an increment used
						>3.1 vs ≤1 serving/day	0.97 (0.85-1.12) Ptrend:0.97		
		827/			Premenopausal	Per 1	0.92 (0.84-1.02)		RR rescaled for

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
						serving/day		energy intake , family history, height, HRT use, other design issue, other nutritional factors, parity/ pregnancies, physical activity	an increment used
						>3.1 vs ≤1 serving/day	0.80 (0.63-1.03) Ptrend:0.10		
Voorrips, 2002 BRE13011 Netherlands	NLCS, Case Cohort, Age: 55-69 years, W, Postmenopausal	783/ 62 573 6.3 years	Linkage with cancer registries and national database of pathology reports	Validated 150-item semi-quantitative FFQ	Incidence, breast cancer	532 vs 72 g/day	0.91 (0.67-1.24) Ptrend:.32	Age, age at first child, age at menarche, age at menopause, alcohol, benign breast disease, benign breast disease, BMI, educational level, energy intake , family history, OC use, parity/ pregnancies, smoking habits	Person-years per quantile
Toniolo, 1994 BRE12398 USA	NYUWHS, Nested Case Control, Age: 35-65 years, W	180/ 735 7 years	Medical records	Validated 71-item semi-quantitative FFQ	Incidence, Invasive breast cancer	675 vs 37 g/day	0.59 (0.35-0.99) Ptrend:0.1	Height, Quetelet index, age at menarche, age at first full-term pregnancy, number of full-term pregnancies,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								first-degree family history of breast cancer, history of benign breast conditions, race, and religion, energy intake	

Table 76 Dairy intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Buckland, 2013 BRE80433 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	10 225/ 335 062 11 years	Cancer registries, health Insurance records, pathology records & active follow-up	FFQ in most centres, diet history, food record	Incidence, breast cancer	Q3 vs Q1	1.02 (0.97-1.07)	Age, age at first child birth, age at menarche, age at menopause, alcohol, BMI, breastfeeding, centre location, educational level, energy, fish, fruits, height, HRT use, legumes, meat, oral contraceptive history, physical activity, saturated fat, smoking, vegetables	Excluded, intake in each tertile is not available, used in the highest vs lowest analysis only
Missmer, 2002 Pooled analysis		7 379/351 041			Incidence, breast cancer	Total dairy fluids, per 100 g/day	0.99 (0.97-1.00)	Age at menarche, parity, age at first birth, oral contraceptive use, history of benign breast disease, family history of breast cancer, menopausal status, BMI, HRT use, smoking status, education, height, alcohol intake, total energy intake	Excluded, RRs are reported separately for dairy fluids and dairy solids
					Premenopausal		0.96 (0.90-1.02)		
					Postmenopausal		1.00 (0.98-1.01)		
					Incidence, breast cancer	Total dairy solids, per 100 g/day	1.03 (0.95-1.11)		
					Premenopausal		0.87 (0.68-1.11)		
					Postmenopausal		1.05 (0.94-1.16)		
USA, Canada	AHS	160/15 172							
Canada	CNBSS	419/56 837							
USA	IWHS	1 130/34 406							

Netherlands	NLCS	937/62 377							
USA	NYS	367/18 475							
USA	NYUWHS	385/13 261							
USA	NHS (1980-1986)	1 023/89 046							
USA	NHS (1986-1996)	1 638/68 817							
Sweden	SMC	1 320/61 467							
Knekt, 1996 BRE04900 Finland	FMCHES, Prospective Cohort, Age: 15-90 years, W, Screening Program	88/ 4 697 25 years	Cancer registry + death certificate	Dietary history questionnaire	Incidence, breast cancer	Highest vs lowest	0.42 (0.23-0.78) Ptrend:0.02	Age	Excluded, intake in each tertile is not available

Figure 106 RR estimates of breast cancer (any) by levels of total dairy intake.

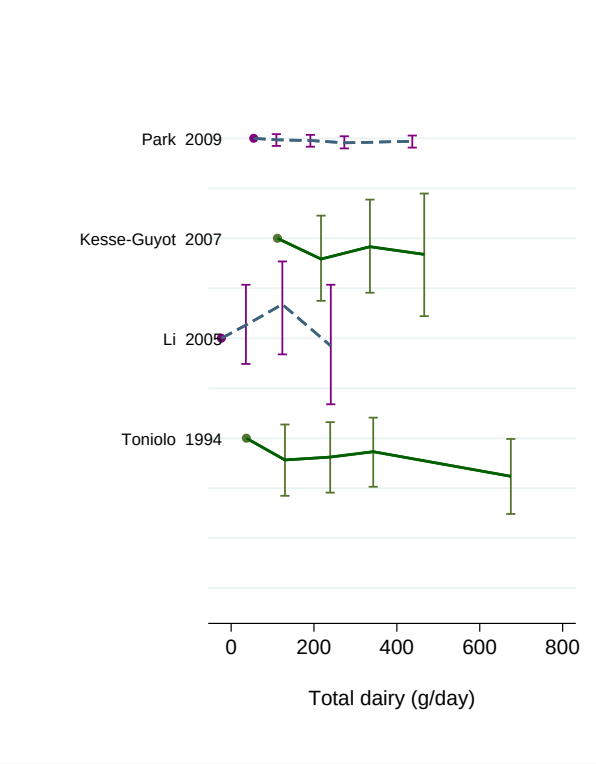


Figure 107 RR estimates of premenopausal breast cancer by levels of total dairy intake.

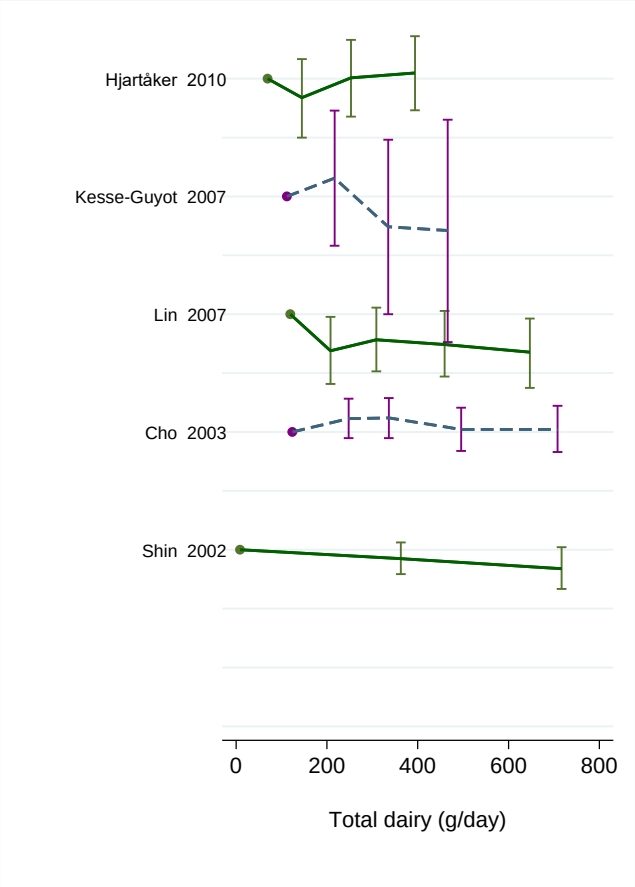


Figure 108 RR estimates of postmenopausal breast cancer by levels of total dairy intake.

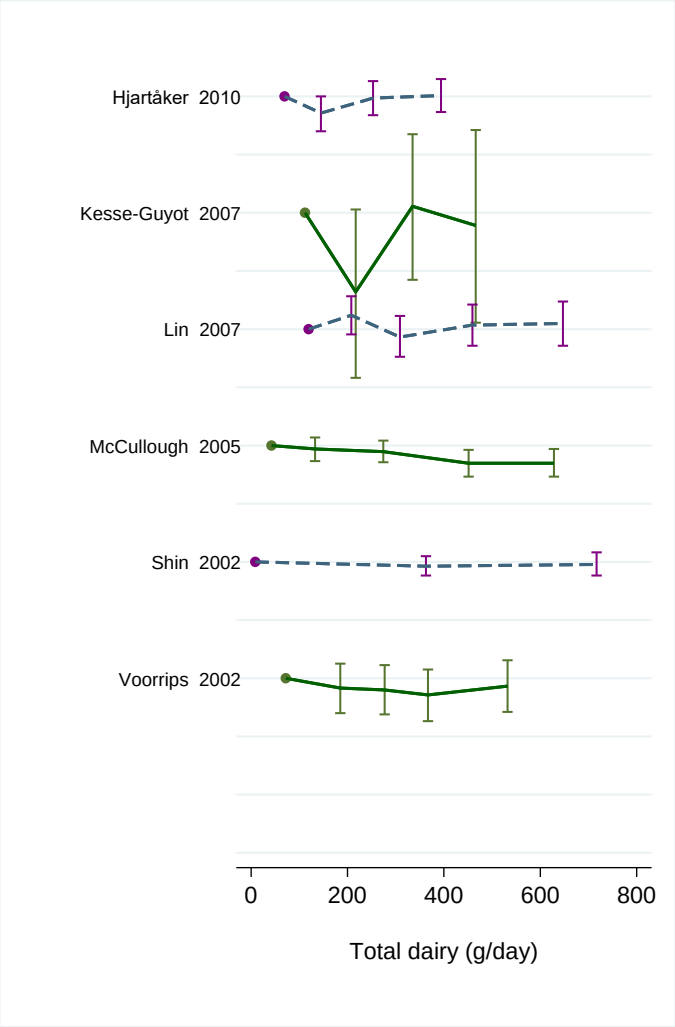
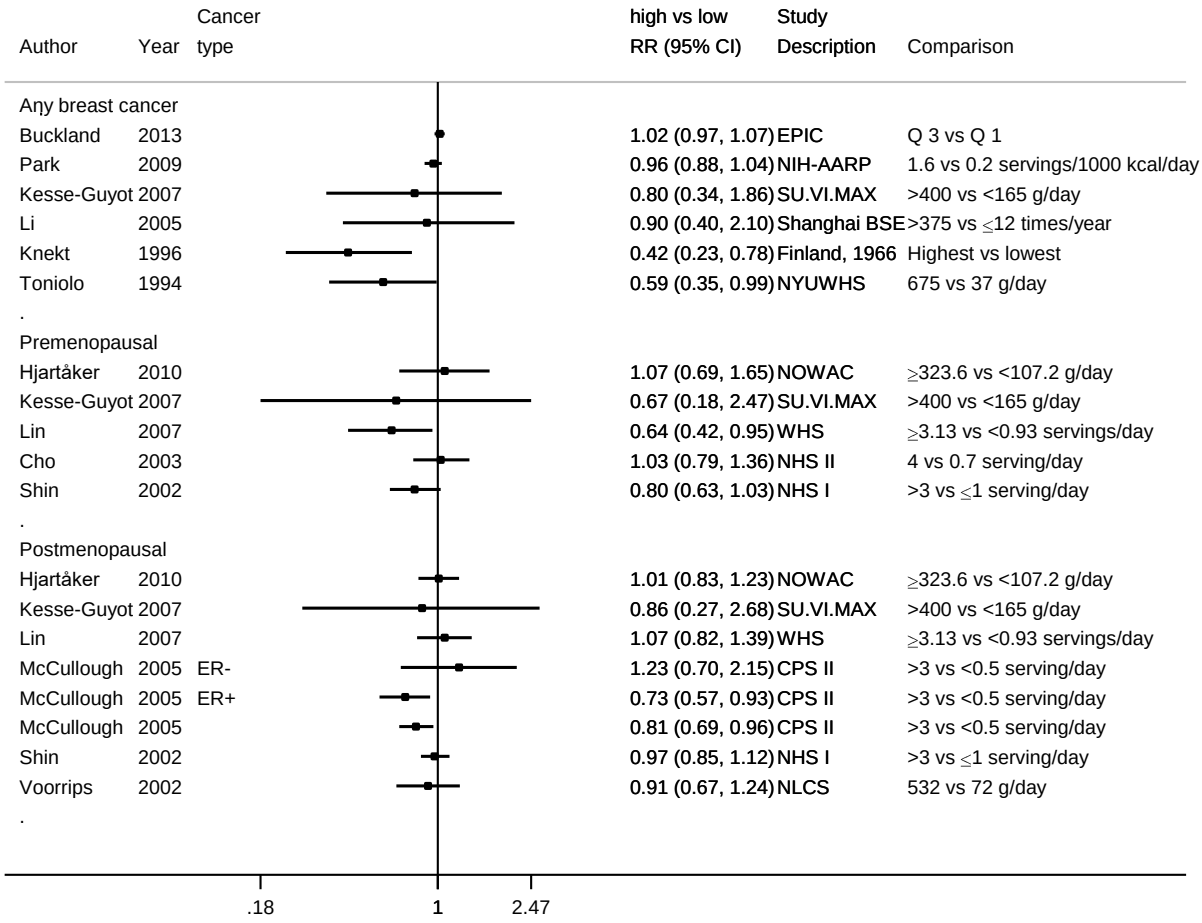


Figure 109 RR (95% CI) of breast cancer for the highest compared with the lowest level of total dairy intake



Note: only one study (McCullough, 2005) reported results by hormone receptor status for the highest compared to the lowest level of intake.

Figure 110 Relative risk of breast cancer (any) for 200 g/day increase of total dairy intake

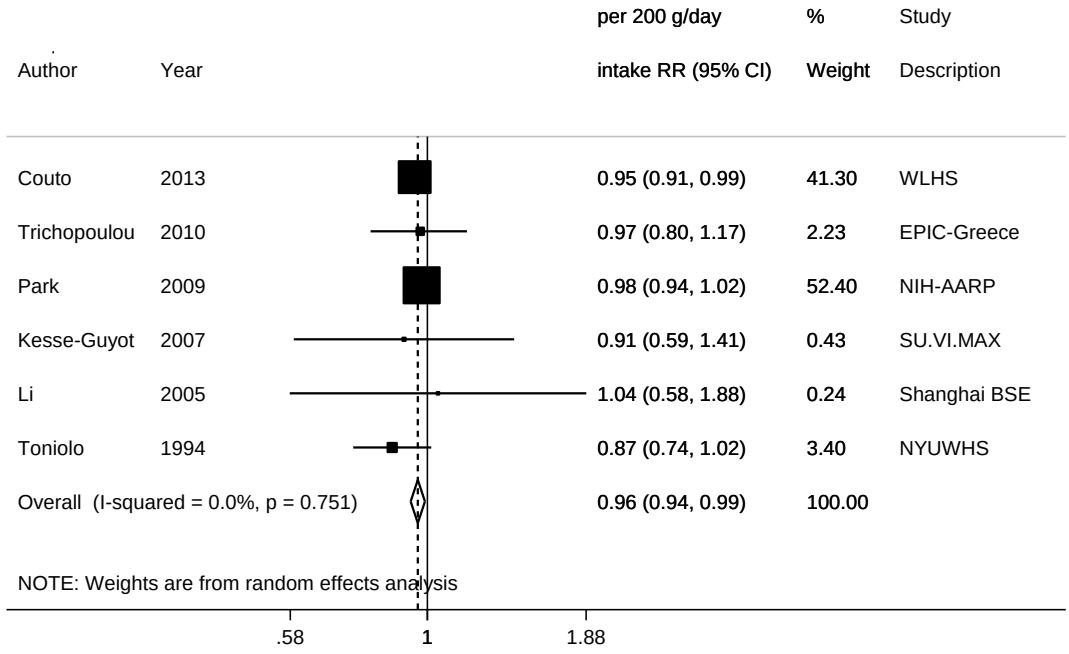


Figure 111 Relative risk of premenopausal breast cancer for 200 g/day increase of total dairy intake

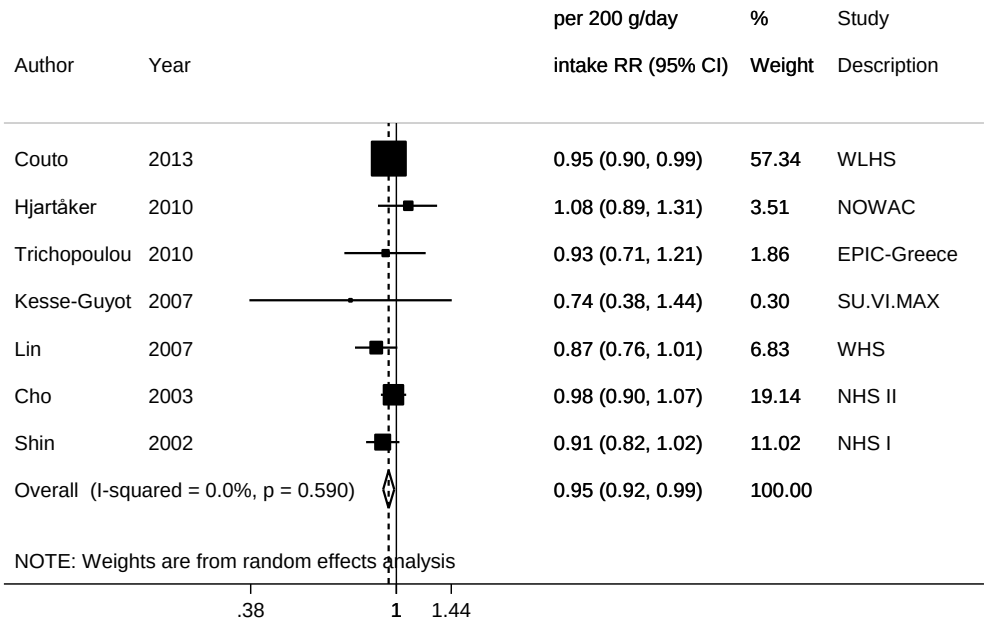


Figure 112 Relative risk of postmenopausal breast cancer for 200 g/day increase of total dairy intake

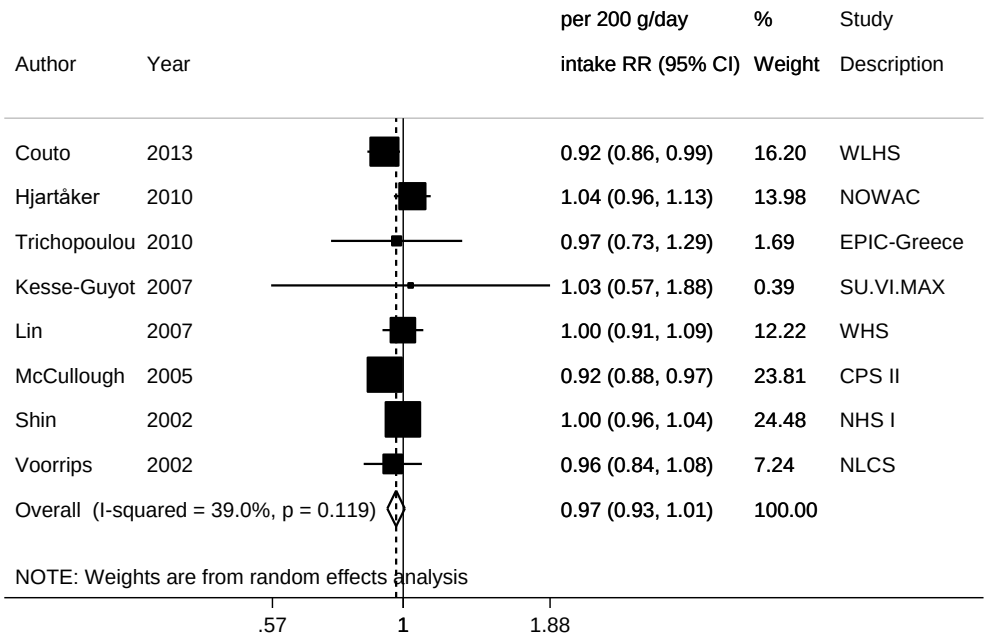


Figure 113 Funnel plot of studies included in the dose response meta-analysis of total dairy intake and breast cancer

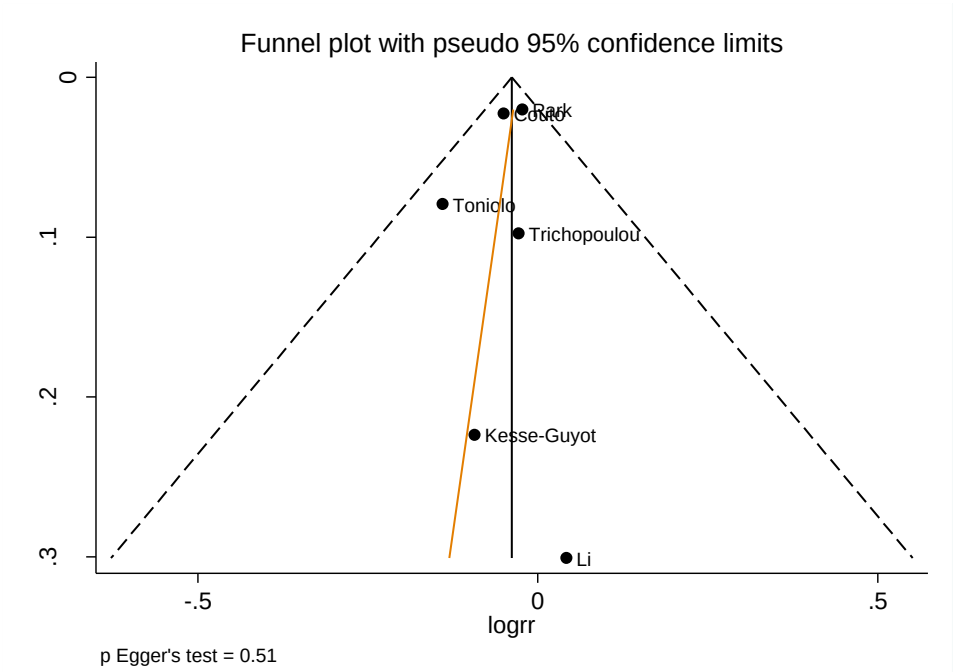


Figure 114 Funnel plot of studies included in the dose response meta-analysis of total dairy intake and premenopausal breast cancer

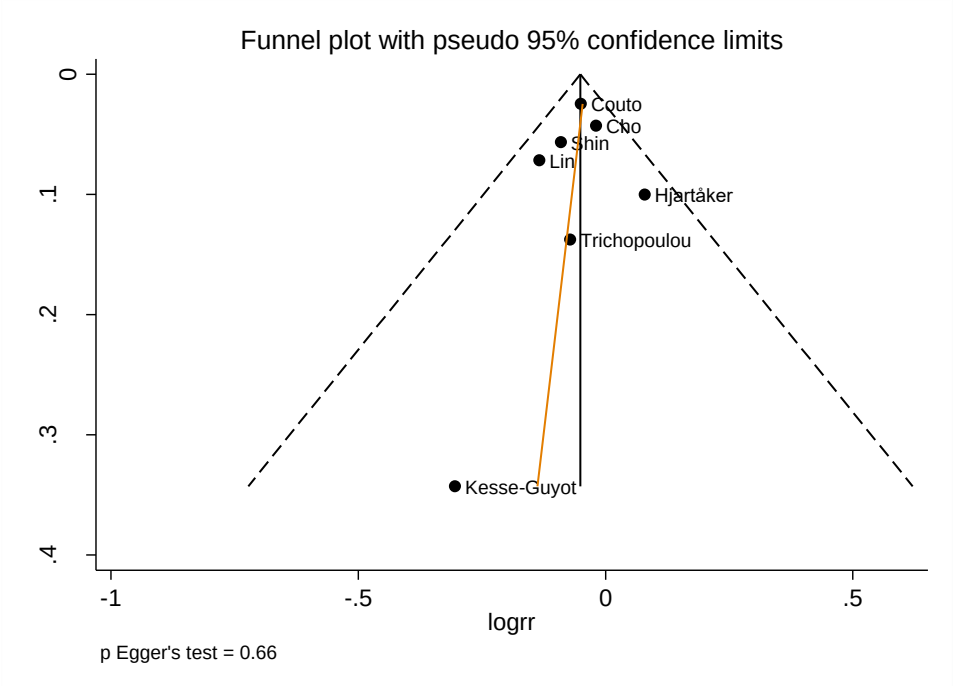


Figure 115 Funnel plot of studies included in the dose response meta-analysis of total dairy intake and postmenopausal breast cancer

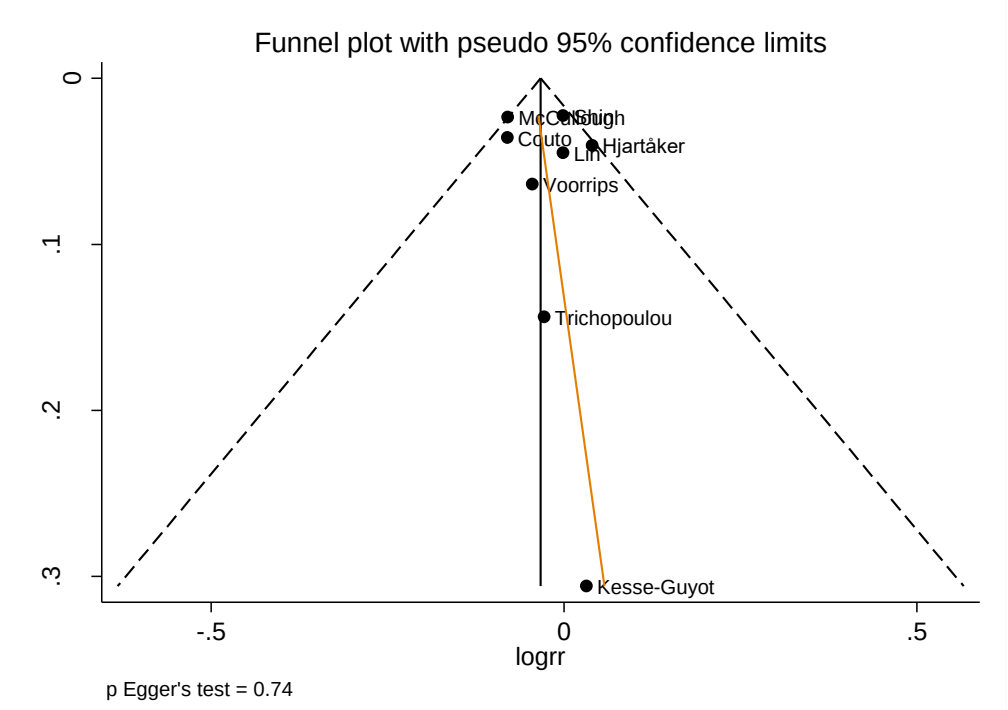
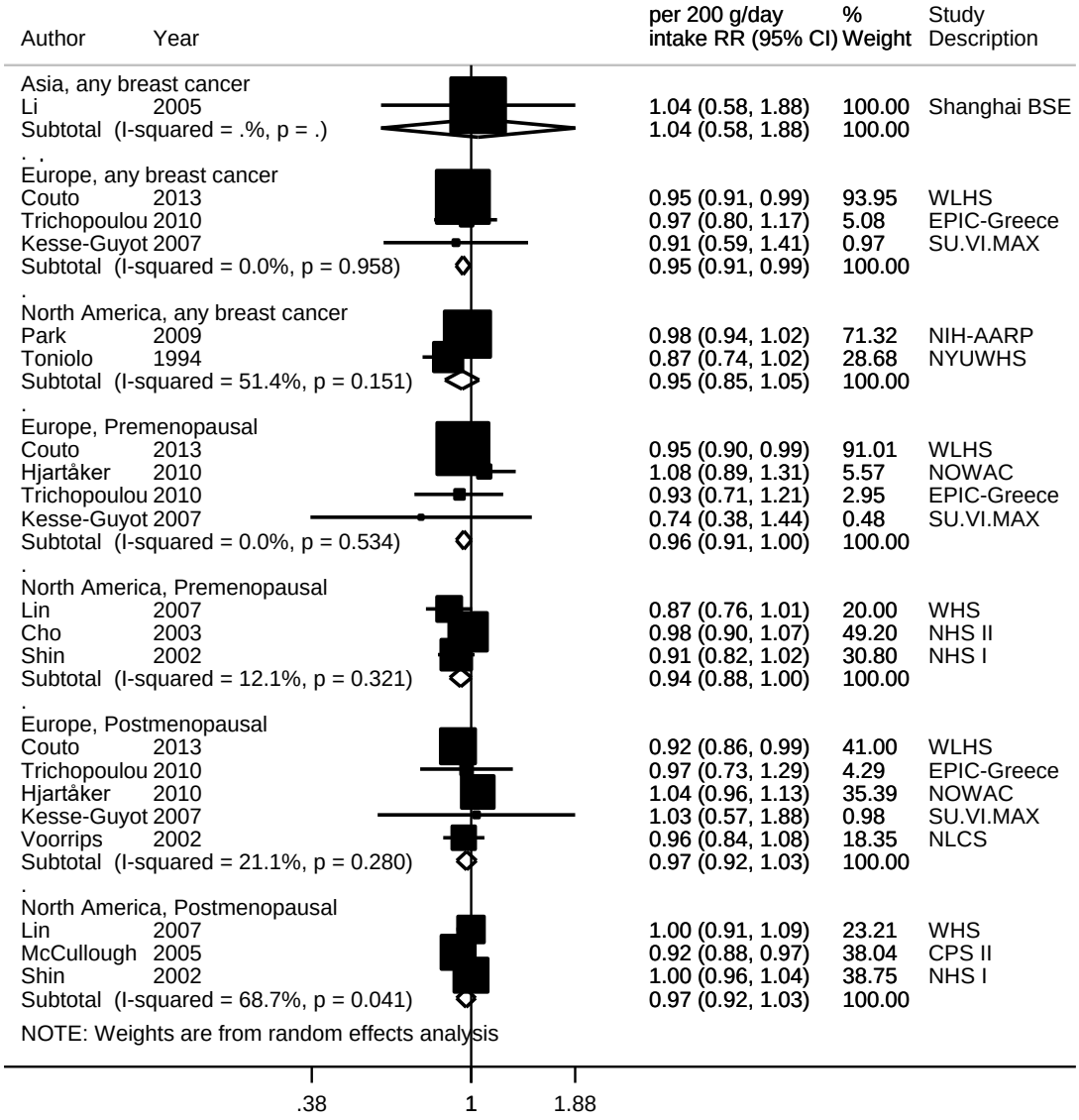


Figure 116 Relative risk of breast cancer for 200 g/day increase of total dairy intake, by geographic location



2.7.1 Total milk

Cohort studies

Overall summary

Sixteen publications (21 studies) on total milk intake and breast cancer risk were identified, including a pooled analysis of eight cohort studies. Study characteristics and results of all identified studies are shown in study inclusion and exclusion tables. For studies that reported milk intake in times or drinks per day and serving size was not available in the article, a serving size of 244 ml (g) was used to estimate intakes in grams per day for the dose-response meta-analysis.

Study quality:

Total dairy intake was assessed by FFQ in most studies. One study used 24-hour records collected every two months (six records in total) (Kesse-Guyot, 2007) and one used a modified dietary history interview method (Knekt, 1996). In the EPIC study, a combination of FFQ and food records were used (Pala, 2009). The NHS (Missmer, 2002; Shin, 2002) had repeated assessment of dietary intake.

Loss to follow-up was low for the studies that reported such data, although some studies did not provide data.

Cancer cases were identified by record linkage to cancer registries, mortality registries, or self-reported with verification through pathology reports, medical records, and death certificates.

Most studies adjusted for multiple confounders, including age, reproductive factors, BMI, and alcohol consumption apart from one study in women from Hiroshima and Nagasaki that did not adjust for reproductive factors, BMI and alcohol intake (Key, 1999).

One study in Norway was only adjusted by age and reported a significant inverse association of milk intake and breast cancer risk (Knekt, 1996). Adjustment for smoking, BMI, number of childbirths, occupation and geographic area did not alter the association between milk intake and breast cancer, and no interactions with these factors were observed.

In one study, the results were not adjusted by reproductive factors (Gaard, 1995).

Breast cancer (any)

Fourteen studies (16 609 cases) (7 publications) were included in the dose-response meta-analysis. No association was observed.

Four studies were excluded from the dose-response meta-analysis. One study in India reported 78% increased risk of breast cancer in women (264 cases) drinking milk regularly compared to non milk drinkers (Jayalekshmi, 2009). A small study (29 cases) reported a positive association (Ursin, 1990, no confidence intervals) with breast cancer incidence. Two studies reported no association of milk intake with breast cancer mortality (Mills, 1988; Iso, 2007). There was evidence of moderate heterogeneity (I^2= 55%, p=0.04). The pooled analysis of cohort studies (Missmer, 2002) and EPIC (Pala, 2009) accounted for 38.9% and 40.4% of weight in the meta-analysis respectively and had similar results (no association). A small study in Finnish women (88 cases) with 25 years of follow-up on average reported an inverse association that was stronger than expected (Knekt, 1996). The results remained similar when this study was excluded from the analysis. There was no significant evidence of publication or small study bias.

Sensitivity analyses:

The summary RR ranged from 0.96 (95% CI=0.86-1.05) when Pala, 2009 (40.4% weight) was omitted to 1.00 (95% CI=0.98-1.02) when Knekt, 1996 (4.6% weight) was omitted.

Premenopausal breast cancer

Five studies (3 293 cases) (5 publications) were included in the dose-response meta-analysis.

No association was observed.

There was some evidence of moderate heterogeneity (I^2=51%, p=0.09). There was no significant evidence of publication or small study bias, but the pooling project of cohort studies could not be included (Missmer, 2002). The authors reported no association of milk intake with breast cancer risk and no effect modification by menopausal status (data not shown in the publication).
Sensitivity analyses:

The summary RR ranged from 0.94 (95% CI=0.88-1.00) when Hjartåker, 2010 (16.5% weight) was omitted to 1.01 (95% CI=0.90-1.13) when Shin, 2002 (36.6% weight) was omitted.

Postmenopausal breast cancer

Six studies (10 238 cases) (6 publications) were included in the dose-response meta-analysis. No association was observed.

One study in Adventist that reported non-significant inverse association with postmenopausal breast cancer mortality was excluded from the dose-response meta-analysis (Mills, 1988). The pooling project of cohort studies could not be included in the dose-response meta-analysis (Missmer, 2002). The authors reported no association of milk intake with breast cancer risk and no effect modification by menopausal status (data not shown in the publication).

Moderate heterogeneity was observed. There was no significant evidence of publication or small study bias (I^2=40%, p=0.14).

Sensitivity analyses:

The summary RR ranged from 1.00 (95% CI=0.96-1.04) when Pala, 2009 (27.5% weight) was omitted to 1.02 (95% CI=0.98-1.06) when McCullough, 2005 (35% weight) was omitted.

Milk intake and breast cancer by hormone receptor status

Only one study was identified (Genginker, 2013). No statistically significant associations were observed between total milk intake and breast cancer risk by hormone receptor status (ER+, PR+, ER-,PR-, ER+/PR+, and ER-/PR- breast cancers). However, significant inverse associations were observed for whole milk and yogurt intakes, and ER- and PR- breast cancers (see corresponding sections).

Table 77 Total milk intake and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	16 (21 publications)
Studies included in forest plot of highest compared with lowest exposure	Breast cancer: 7 (7 publications) Premenopausal: 5 (5 publications) Postmenopausal: 6 (6 publications)

Studies included in linear dose-response meta-analysis	Breast cancer: 14 (7 publications) Premenopausal: 5 (5 publications) Postmenopausal: 6 (6 publications)
Studies included in non-linear dose-response meta-analysis	None, not enough studies

Table 78 Total milk intake and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR*	**CUP**
Increment unit used	1time/week	200 g/day
	All studies	**Any breast cancer**
Studies (n)	2	14
Cases (total number)	663	16 609
RR (95%CI)	1.00 (0.99-1.01)	0.99 (0.94-1.04)
Heterogeneity (I^2, p-value)	0%	55%, 0.04
P value Egger test	-	0.54
	Premenopausal	Postmenopausal
Studies (n)	5	6
Cases	3 293	10 238
RR (95%CI)	0.97 (0.88-1.06)	1.01 (0.97-1.04)
Heterogeneity (I^2, p-value)	51%, 0.09	40%, 0.14
P value Egger test	0.91	0.17

* Under section "Milk as beverage" in 2005SLR

Other stratified analyses

Geographic area	**Asia**	**Europe**	**North-America**
	Breast cancer (any)		
Studies (n)	1	4	1
RR (95%CI)	0.97 (0.77-1.21)	0.96 (0.83-1.12)	0.95 (0.67-1.35)
Heterogeneity (I^2, p- value)	-	73%, 0.01	-
	Premenopausal		
Studies (n)	-	3	2
RR (95%CI)	-	1.02 (0.88-1.19)	0.89 (0.82-0.97)
Heterogeneity (I^2, p- value)	-	48%, 0.15	0%, 0.82
	Postmenopausal		
Studies (n)	-	3	3
RR (95%CI)	-	1.04 (0.98-1.11)	0.98 (0.96-1.01)
Heterogeneity (I^2, p- value)	-	36%, 0.21	0%, 0.91

Table 79 Total milk intake and breast cancer risk. Results of recent meta-analyses and pooled analyses of prospective studies

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Dong, 2011	12 prospective cohorts*	16 150	USA, UK, Japan, Finland, Norway, France	Incidence, breast cancer	Highest vs lowest	0.90 (0.80-1.02)		60%, p=0.003
	5 prospective cohorts			Premenopausal breast cancer		0.79 (0.60-1.02)		67%, p=0.02
	5 prospective cohorts			Postmenopausal breast cancer		1.01 (0.94-1.09)		47%, p=0.11
	5 prospective cohorts			Low-fat		0.93 (0.88-0.99)		42%, p=0.13
	8 prospective cohorts			High-fat		0.98 (0.87-1.12)		42%, p=0.09

*Ten of the 12 studies are included in the CUP meta-analysis. Two studies (Linos, 2010 and van der Pols, 2007) were not included in the CUP meta-analysis because are on dairy intake in adolescence and childhood, respectively.

Table 80 Total milk intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Genkinger, 2013 BRE80446 USA	BWHS, Prospective Cohort, Age: 21-69 years, W	1 268/ 56 062 12 years	Cancer registry and national death index	FFQ, total milk	Incidence, breast cancer	≥1000 vs ≤0 g/week	1.05 (0.74-1.46) Ptrend:0.54	Age at first child birth, age at menarche, age at menopause, alcohol, BMI, educational level, energy intake, family history of breast cancer, HRT use, menopausal status, oral contraceptive history, parity, smoking, vigorous physical activity	Intake in g/week converted to g/day, mid-points of exposure categories
		572/			Premenopausal		1.24 (0.74-2.08) Ptrend:0.55		
		521/			Postmenopausal		1.00 (0.60-1.67) Ptrend:0.92		
		482/			Incidence, breast cancer ER+		0.85 (0.50-1.44) Ptrend:0.45		Analysis by hormone receptor status was not conducted
		279/			Incidence, breast cancer ER-		0.88 (0.39-1.99) Ptrend:0.34		
		379/			Incidence, breast cancer PR+		0.80 (0.44-1.47) Ptrend:0.32		
		367/			Incidence, breast cancer PR-		1.01 (0.50-2.02) Ptrend:0.65		
		366/			Incidence, breast cancer ER+PR+		1.16 (0.83-1.63) Ptrend:0.73		
		264/			Incidence, breast cancer ER-PR-		0.78 (0.52-1.16) Ptrend:0.14		
Hjartåker, 2010 BRE80327 Norway	NOWAC, Prospective Cohort, W	151/ 64 904 8.6 years	Linkage to the Cancer Registry of Norway and death records	Validated FFQ, total milk (whole, low-fat, skimmed)	Incidence, invasive breast cancer, premenopausal	≥269.8 vs <49.1 g/day	1.23 (0.78-1.94) Ptrend:0.27	Age, age at first child birth, age at menarche, alcohol, contraception, educational level, energy intake, family history of breast	
						Per 50 g/day	1.04 (0.99-1.09)		RR rescaled for an increment used
		796/			Postmenopausal	≥269.8 vs <49.1 g/day	1.03 (0.85-1.25) Ptrend:0.76		
						Per 50 g/day	1.01 (0.99-1.03)		RR rescaled for

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								cancer, height, mammography, number of children, physical activity, weight	an increment used
Pala, 2009 BRE80268 Europe	EPIC, Prospective Cohort, Age: 25-70 years, W	7 119/ 319 826 8.8 years	Multiple methods	FFQ, total milk (whole-fat, skim, semiskim, not specified)	Incidence, breast cancer	439 vs 0 g/day	1.05 (0.97-1.14) Ptrend:0.55	Age, centre location, educational level, energy intake, height, menopausal status, smoking habits, weight, alcohol intake, hormone-related factors evaluated as potential confounders	
						per 150 g	1.01 (0.99-1.03)		RR rescaled for an increment used
		3 673/			Postmenopausal	439 vs 0 g/day	1.09 (0.98-1.22) Ptrend:0.13		Nothing estimated
		1 699/			Premenopausal		1.00 (0.85-1.18) Ptrend:0.62		
Kesse-Guyot, 2007 BRE11112 France	SU.VI.MAX, Prospective Cohort, Age: 35-60 years, W, SU.VI.MAX participants	92/ 3 627 7.7 years	Self-reported cases validated by pathological reports	24h recalls (six records in total), total milk	Incidence, breast cancer	>248 vs <25 g/day	1.34 (0.68-2.64) Ptrend:0.44	Age, alcohol, BMI, calcium intake, educational level, energy from fat, energy from nonfat sources, family history, group supplementation , HRT use, marital status, menopausal status, parity/pregnancies, physical activity ,	Mid-points of exposure categories
							0.95 (0.52-1.73) Ptrend:0.09		
		48/			Postmenopausal		2.37 (0.94-5.95) Ptrend:0.80		
		44/			Premenopausal		0.67 (0.23-1.93) Ptrend:0.14		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								smoking habits	
McCullough, 2005 BRE23368 USA	CPS II, Prospective Cohort, Age: 50-74 years, W, Postmenopausal	2 855/ 68 567 9 years	Self-reports, death records, medical records	Validated 68-item semi-quantitative FFQ, total milk	Incidence, breast cancer, postmenopausal	>3 vs 0 serving/day	0.88 (0.76-1.02) Ptrend:0.13	Age , age at first child, age at menopause, alcohol, breast diseases , educational level, energy intake , ethnicity, family history, height, HRT use, mammography, other anthropometric index, parity/ pregnancies	Intake in servings/day converted to g/day using 240g serving, mid-points of exposure categories
Missmer, 2002 Pooled analysis	Cohort studies:	7 379/351 041		Milk products (skim, 0.5%, 1%, 2%, whole, buttermilk, evaporated milk)	Incidence, breast cancer	Milk products, per 100 g/day	0.99 (0.97-1.00)	Age, age at menarche, parity, age at first birth, oral contraceptive use, history of benign breast disease, family history of breast cancer, menopausal status, BMI, HRT use, smoking status, education, height, alcohol intake, total energy intake	RR rescaled for an increment used
USA, Canada	AHS	160/15 172							
Canada	CNBSS	419/56 837							
USA	IWHS	1 130/34 406							
Netherlands	NLCS	937/62 377							
USA	NYS	367/18 475							
USA	NYUWHS	385/13 261							
USA	NHSa (1980-1986)	1 023/89 046							
USA	NHSb (1986-1996)	1 638/68 817							
Sweden	SMC	1 320/61 467							

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Shin, 2002 BRE16658 USA	NHS I, Prospective Cohort, Age: 47 years, W, Registered nurses	2 345/ 88 691 16 years	Self-reports confirmed by medical records	Validated FFQ, total milk (skim, low-fat, whole milk)	Incidence, invasive breast cancer, postmenopausal	Per 1 glass/day	0.99 (0.93-1.05)	Age , age at first child, age at menarche, age at menopause, alcohol, BMI, body weight, breast diseases, energy intake, family history, height, HRT use, other design Issue, other nutritional factors, other nutritional factors, other nutritional factors, other nutritional factors, parity/pregnancies, physical activity	RR estimated and rescaled for an increment used
						>1 glass/day vs ≤3 glasses/month	1.01 (0.87-1.17) Ptrend:0.59		
		827/			Premenopausal	Per 1 glass/day	0.87 (0.79-0.96)		RR estimated and rescaled for an increment used
						>1 glass/day vs ≤3 glasses/month	0.73 (0.56-0.94) Ptrend:0.007		
Key, 1999 BRE04758 Japan	LSS, Prospective Cohort, W	427/ 34 759 24 years	Partially histological - over 80%	FFQ, total milk	Incidence, breast cancer	≥5 vs ≤1 times/week	0.96 (0.76-1.22) Ptrend:0.770	Age, calendar year, city, age at the bombing and radiation dose	Intake in times/week converted to g/day using a standard serving size of 244 g/day, mid-points of exposure categories
Knekt, 1996 BRE04900 Finland	FMCHES, Prospective Cohort,	88/ 4 697 25 years	Cancer registry, death certificate	Dietary history questionnaire, total milk	Incidence, breast cancer	≥620 vs <370 g/day	0.42 (0.24-0.74) Ptrend:0.003	Age	Mid-points of exposure categories, cases

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Age: 15-90 years, W, Screening Program								and persons at risk per quantile
Gaard, 1995 BRE17516 Norway	NHSS, Prospective Cohort, Age: 35-49 years, W, Screening Program	236/ 24 897 10 years	Partially histological - over 80%	FFQ-semi-quantitative, milk (any type)	Incidence, breast cancer	≥5 vs 1 glass/day	1.71 (0.86-3.38) Ptrend:0.30	Age , height, energy intake, BMI, smoking status	Intake in glasses/day converted to g/day using 150ml given in the article, mid-points of exposure categories

Table 81 Total milk intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Jayalekshmi, 2009 BRE80241 India	Kerala, India, Nested Case Control, Age: 20- years, W	264/ 792 controls	Cancer registry	Questionnaire (general)	Incidence, breast cancer	Regular vs occasional	1.78 (1.17-2.69)	Age, age at first child birth, area of residence, educational level, marital status, occupation, parity, poultry, religion, vegetable intake	Excluded, only two levels of exposure, used in highest vs lowest analysis only
Iso, 2007 BRE80427	JACC, Prospective	98/ 15 years	Municipal resident	FFQ	Mortality, breast cancer	≥5 vs ≤2.9 times/week	0.99 (0.60-1.64)	Age, centre location	Excluded, outcome is

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Japan	Cohort, Age: 40-79 years, W		registration records, death certificates						mortality
Hjartåker, 2001 BRE03955 Norway	NOWAC, Prospective Cohort, Age: 34-49 years, W, Young women	266/ 48 844 6.2 years	Partially histological - over 80%	Questionnaire	Incidence, breast cancer, premenopausal	≥3.1 vs ≤0 glasses/day	0.56 (0.31-1.01) Ptrend:0.12	Age , age at first child, age at menarche, alcohol, BMI, educational level, family history, OC use, parity/ pregnancies, physical activity	Superseded by Hjartåker, 2010
Jarvinen, 1997 BRE04383 Finland	FMCHES, Prospective Cohort, Age: 15- years, W	4 697 24 years	Partially histological - over 80%	Dietary history questionnaire	Incidence, breast cancer	Q3 vs Q1	0.42 Ptrend:0.003	Age	Superseded by Knekt, 1996, CIs are not available
Ursin, 1990 BRE80614 Norway	Norwegian prospective study, Prospective Cohort, Age: -75 years, W	29/ 2 679 11.5 years	Cancer registry		Incidence, breast cancer	≥2 vs <1 glass/day	1.48	Age, sex, place of residence	Excluded, CIs are not available
Mills, 1988 BRE17836 USA	AMS, Nested Case Control, Age: 30-85 years, W, Adventist	142/ 16 190 20 years	Death certificate	Questionnaire	Mortality, breast cancer	≥3 drinks/day vs none/occasional	1.03 (0.56-1.90) Ptrend:0.95	Age at first child, age at menarche, age at menopause, body weight, educational level, food	Excluded, outcome is mortality
		76/			Postmenopausal		0.89 (0.34-2.35) Ptrend:0.64		

Figure 117 RR estimates of breast cancer (any) by levels of total milk intake.

Figure 118 RR estimates of premenopausal breast cancer by levels of total milk intake.

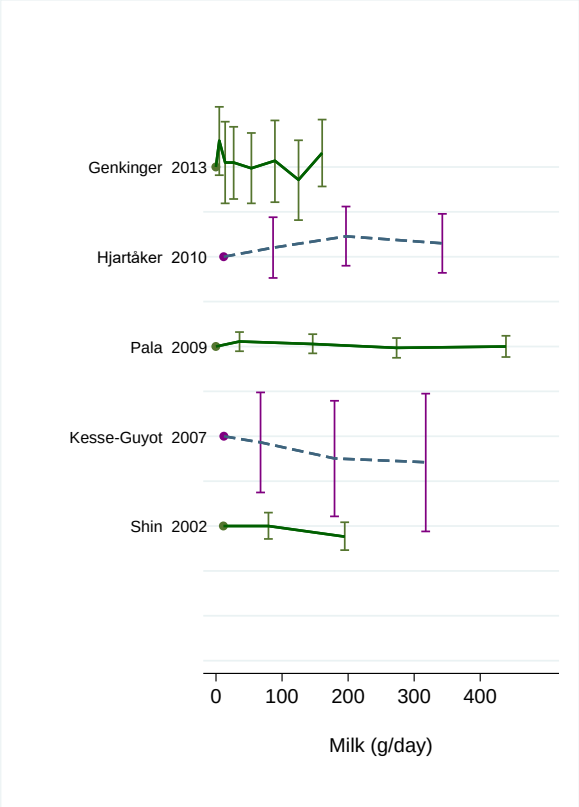


Figure 119 RR estimates of postmenopausal breast cancer by levels of total milk intake.

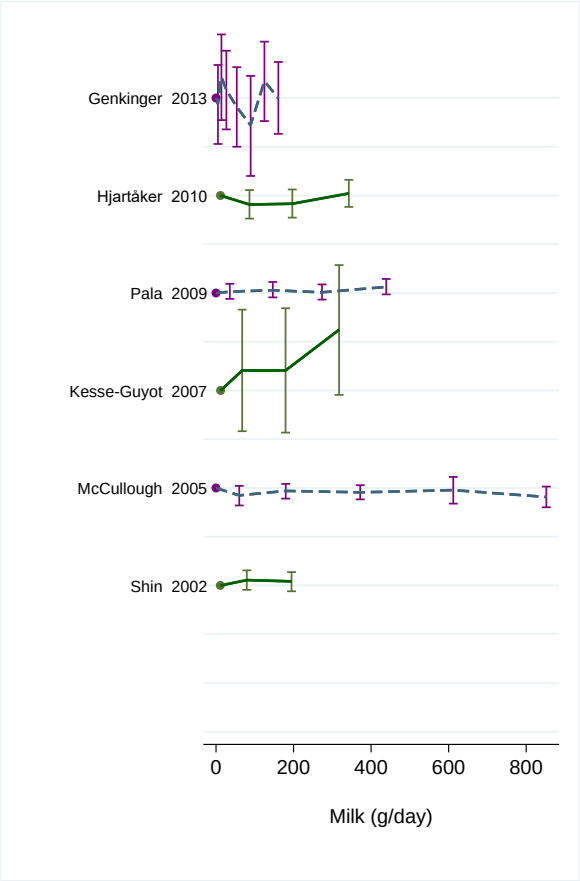
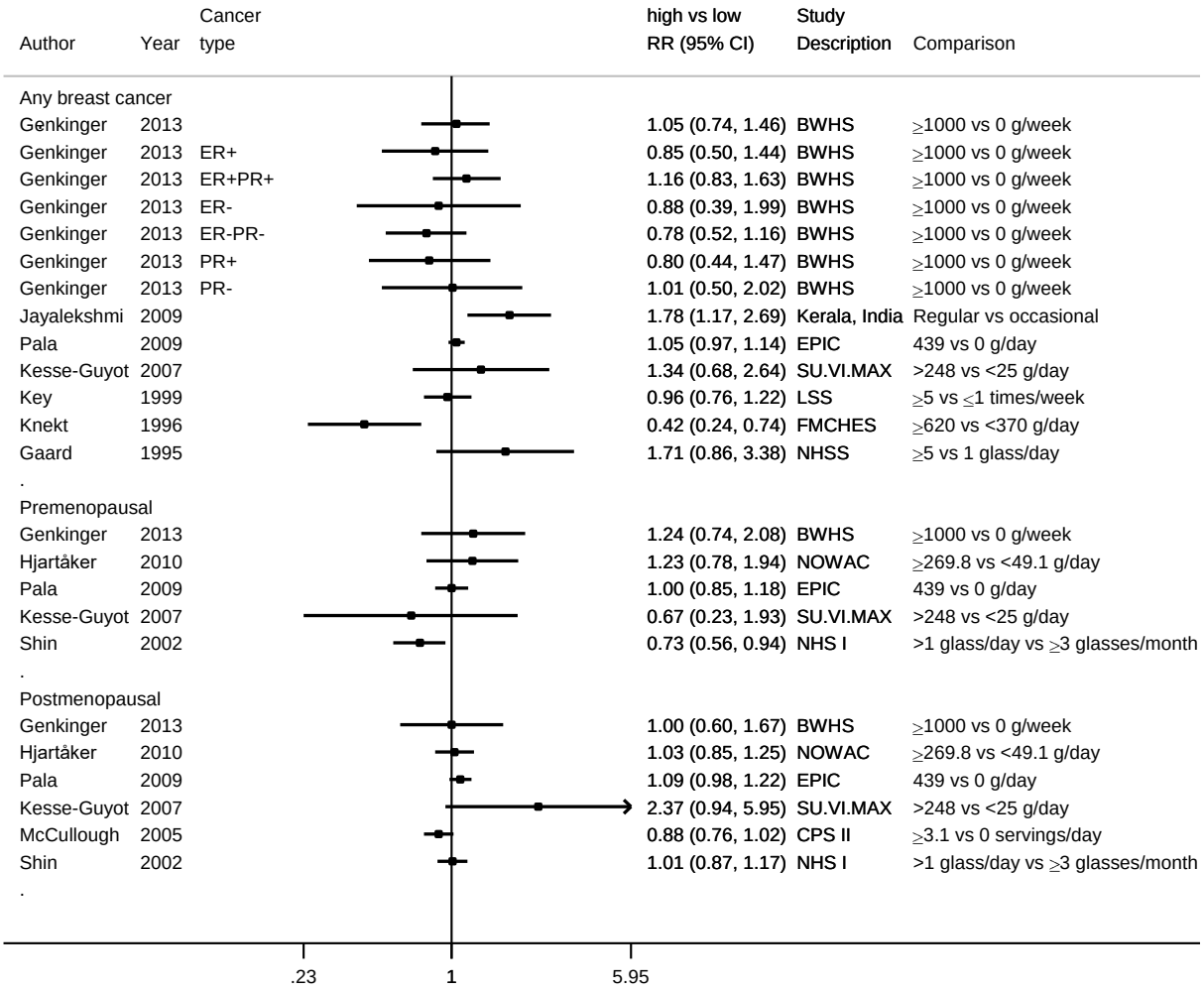


Figure 120 RR (95% CI) of breast cancer for the highest compared with the lowest level of total milk intake



Note: only one study (Genkinger, 2013) reported results by hormone receptor status for the highest compared to the lowest level of intake.

Figure 121 Relative risk of breast cancer (any) for 200 g/day increase of total milk intake

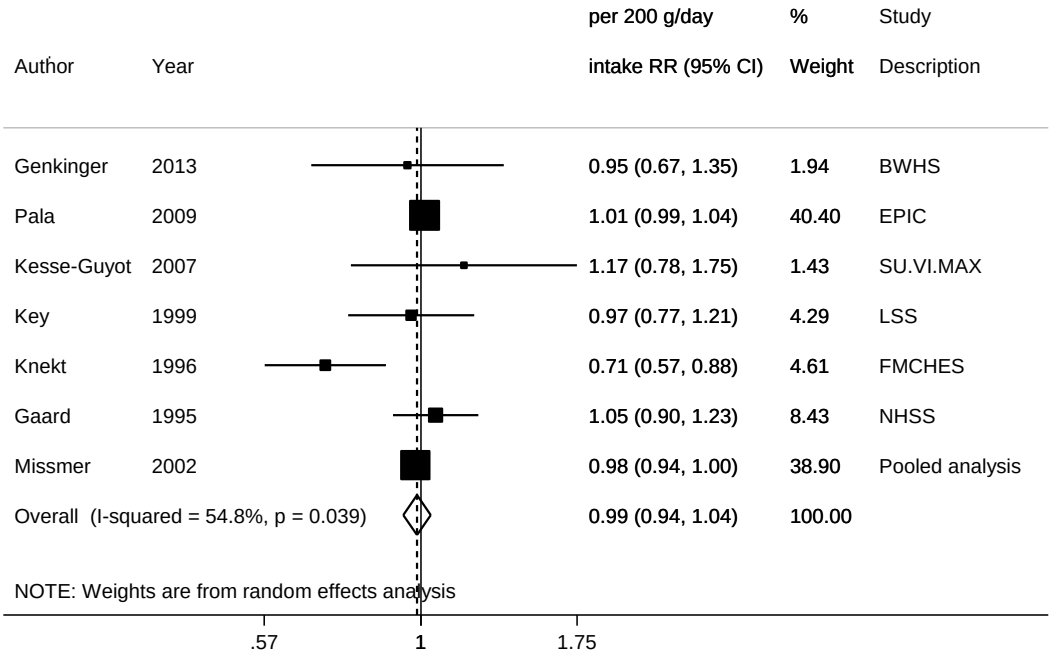


Figure 122 Relative risk of premenopausal breast cancer for 200 g/day increase of total milk intake

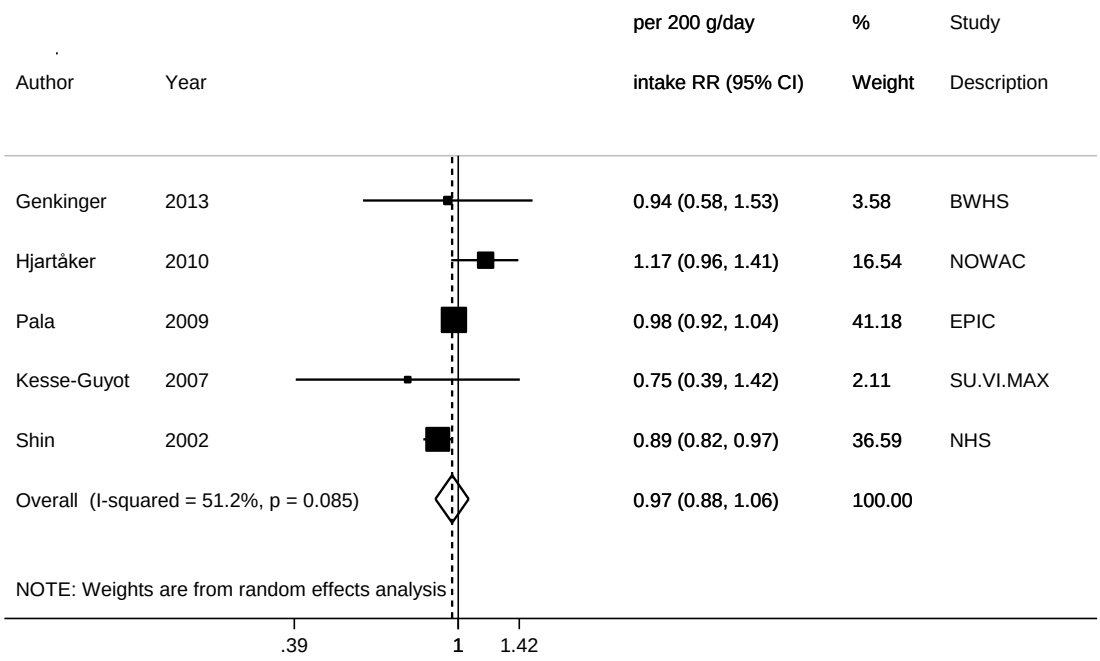


Figure 123 Relative risk of postmenopausal breast cancer for 200 g/day increase of total milk intake

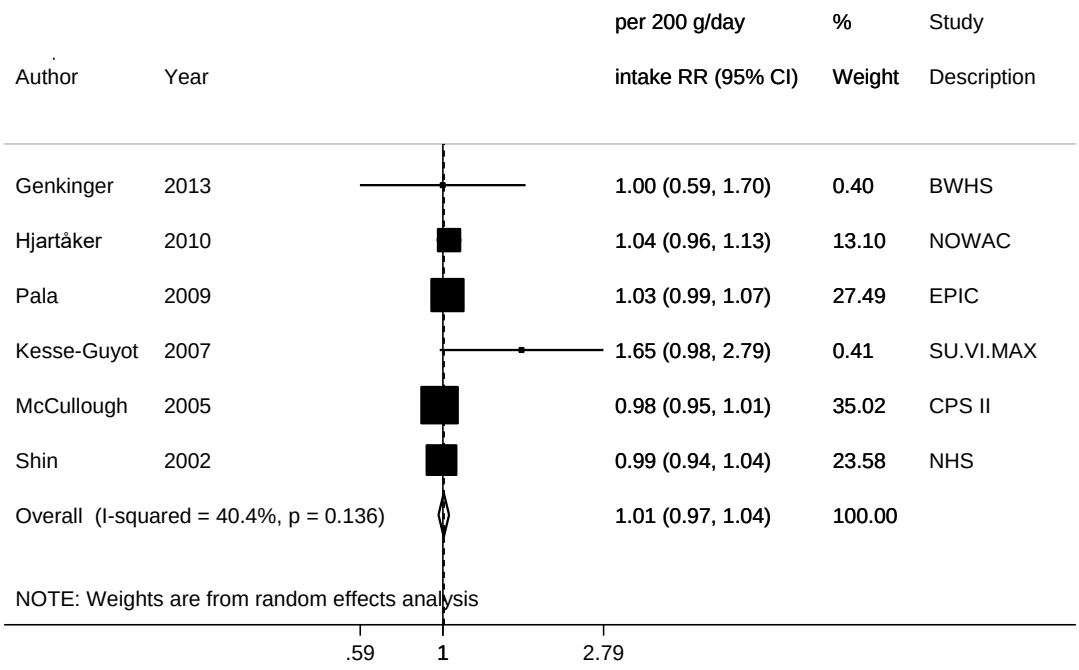


Figure 124 Funnel plot of studies included in the dose response meta-analysis of total milk intake and breast cancer

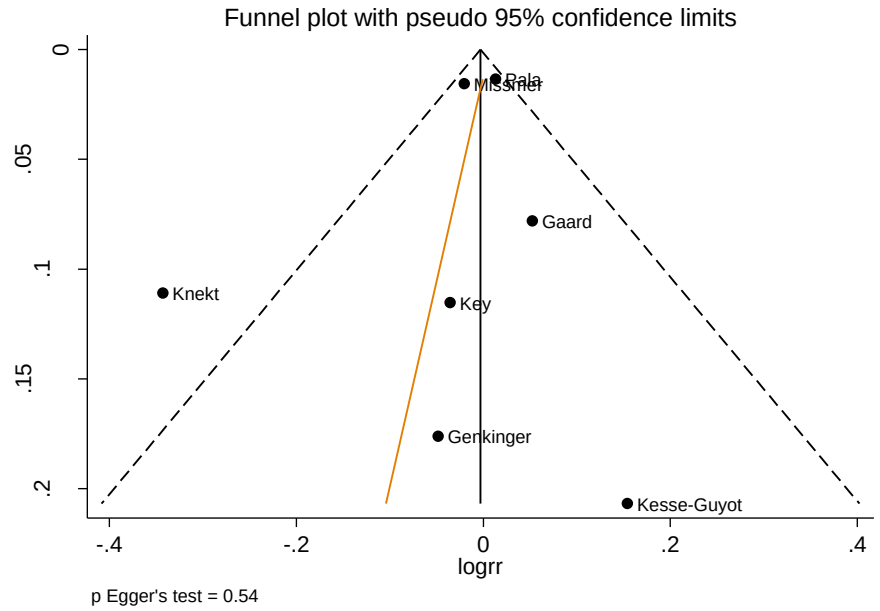


Figure 125 Funnel plot of studies included in the dose response meta-analysis of total milk intake and premenopausal breast cancer

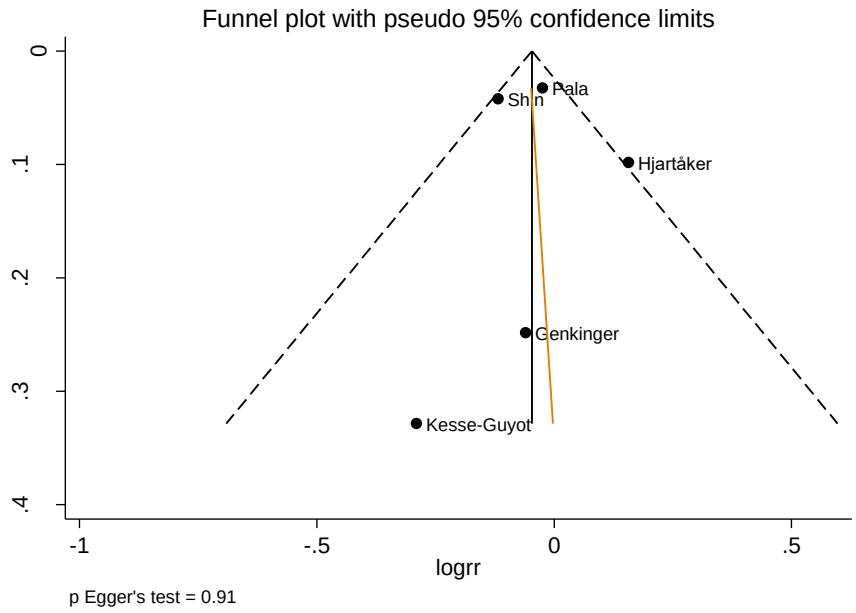


Figure 126 Funnel plot of studies included in the dose response meta-analysis of total milk intake and postmenopausal breast cancer

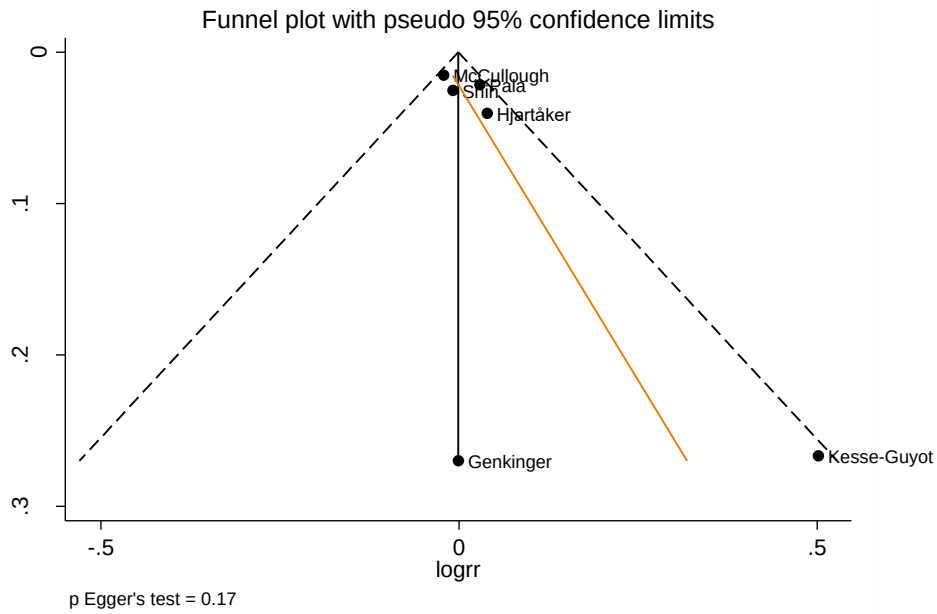
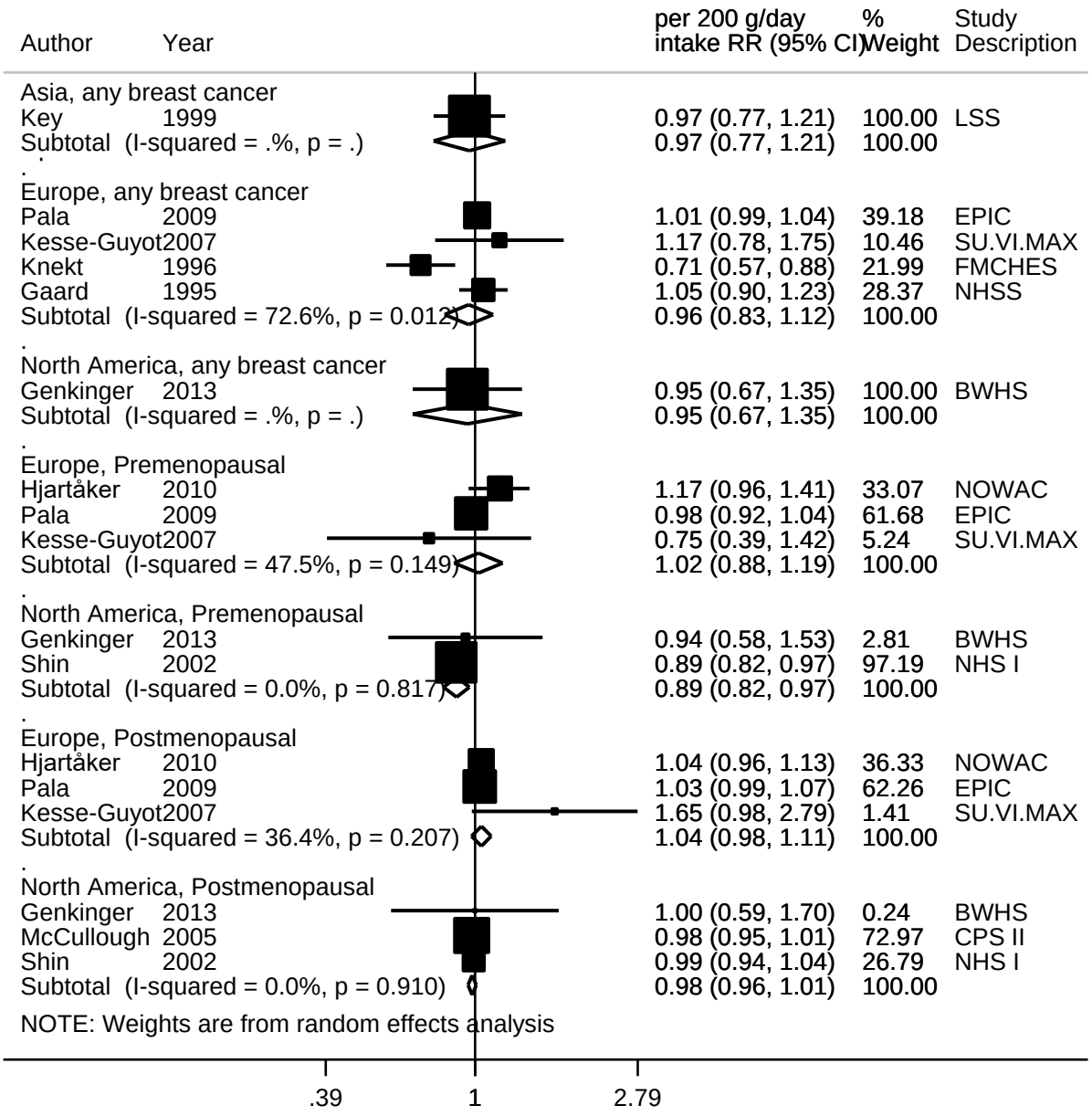


Figure 127 Relative risk of breast cancer for 200 g/day increase of total milk intake, by geographic location



2.7.1.1 Whole milk, full-fat milks

Cohort studies

Overall summary

Eight publications (13 studies) on whole milk intake and breast cancer risk were identified, including a pooled analysis of eight cohort studies. Study characteristics of all identified studies and results for all cancer types are shown in study inclusion and exclusion tables. For studies that reported milk intake in times or cups per day and serving size was not available in the article, a serving size of 244 ml (g) was used to estimate intakes in grams per day for the dose-response meta-analysis.

Study quality:

Total dairy intake was assessed by FFQ in all studies apart from EPIC where a combination of FFQ and food records was (Pala, 2009).

Loss to follow-up was low for the studies that reported such data, although some studies did not provide data.

Cancer cases were identified by record linkage to cancer registries, mortality registries, pathology reports or self-reported with verification through pathology reports, medical records. Multiple methods were used in the EPIC study (Pala, 2009).

All studies adjusted for multiple confounders, including age, reproductive factors, BMI, and alcohol intake apart from one study (Gaard, 1995) that did not adjust for reproductive factors and alcohol intake.

Breast cancer (any)

Twelve studies (16 233 cases) (5 publications) were included in the dose-response meta-analysis. Non-significant inverse association was observed.

No studies were excluded from the dose-response meta-analysis.

Moderate heterogeneity was observed. There was no significant evidence of publication or small study bias.

Sensitivity analyses:

The summary RR ranged from 1.00 (95% CI=0.97-1.03) when Gaard, 1995 (10.9% weight) was omitted to 1.03 (95% CI=0.93-1.14) when Missmer, 2002 (40.9% weight) was omitted.

Premenopausal breast cancer

Three studies (2 985 cases) (3 publications) were included in the dose-response meta-analysis. No association was observed.

No studies were excluded from the dose-response meta-analysis.

Postmenopausal breast cancer

Three studies (6 390 cases) (3 publications) were included in the dose-response meta-analysis. Non association was observed.

One study reported non-significant inverse association and was excluded from the dose-response meta-analysis (Mills, 1989).

Table 82 Whole milk intake and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	13 (8 publications)
Studies included in forest plot of highest compared with lowest exposure	Breast cancer: 5 (5 publications) Premenopausal: 3 (3 publications) Postmenopausal: 3 (3 publications)
Studies included in linear dose-response meta-analysis	Breast cancer: 12 (5 publications) Premenopausal: 3 (3 publications) Postmenopausal: 3 (3 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies with available data

Table 83 Whole milk intake and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	1 cup/day	150 g/day
All studies		
Studies (n)	2	12
Cases (total number)	326	16 233
RR (95%CI)	1.06 (0.97-1.17)	1.01 (0.96-1.06)
Heterogeneity (I^2, p-value)	57%	50%, 0.09
P value Egger test	-	0.84
	Premenopausal	Postmenopausal
Studies (n)	3	3
Cases	2 985	6 390
RR (95%CI)	1.00 (0.93-1.08)	0.99 (0.94-1.03)
Heterogeneity (I^2, p-value)	0%, 0.47	0%, 0.61
P value Egger test	-	-

Other stratified analyses

Geographic area	**Asia**	**Europe**	**North-America**
	Breast cancer		
Studies (n)	-	3	2
RR (95%CI)	-	1.03 (0.92-1.16)	0.97 (0.84-1.13)
Heterogeneity (I^2, p- value)	-	67%, 0.05	0%, 0.97

Table 84 Whole milk intake and breast cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Dong, 2011	5 prospective cohorts		USA, UK, Japan, Finland, Norway, France	Incidence, breast cancer Low-fat milk	Highest vs lowest	0.93 (0.88-0.99)		42%, p=0.13
	8 prospective cohorts			High-fat milk		0.98 (0.87-1.12)		42%, p=0.09

*All studies are included in the meta-analysis apart from Linos, 2010 on dairy intake in adolescence.

Table 85 Whole milk intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Genkinger, 2013 BRE80446 USA	BWHS, Prospective Cohort, Age: 21-69 years, W	1 268/ 56 062 12 years	Cancer registry and national death index	FFQ	Incidence, breast cancer	≥250 vs ≤0 g/week	0.96 (0.73-1.26) Ptrend:0.83	Age at first child birth, age at menarche, age at menopause, alcohol, BMI, educational level, energy Intake, family history of breast cancer, HRT use, menopausal status, oral contraceptive history, parity, smoking, vigorous physical activity	Intake in g/week converted to g/day
		572/			Premenopausal	≥250 vs ≤0 g/week	1.08 (0.75-1.54) Ptrend:0.23		
		521/			Postmenopausal	≥250 vs ≤0 g/week	0.86 (0.54-1.37) Ptrend:0.37		
Pala, 2009 BRE80268 Europe	EPIC, Prospective Cohort, Age: 25-70 years, W	6 678/ 319 826 8.8 years	Multiple methods: cancer and pathology registries, active follow-up, next-of-kin, social security records	FFQ, food records	Incidence, breast cancer	per 150 g	1.02 (0.98-1.06)	Age, centre location, educational level, energy intake, height, menopausal status, smoking habits, weight, alcohol intake; hormone-related risk factors were tested in the multivariate model but resulted in similar risk estimate	Nothing estimated
						150 vs 0 g/day	1.06 (0.97-1.15) Ptrend:0.64		
		3 524/			Postmenopausal		1.03 (0.92-1.16) Ptrend:0.68		
		1 586/			Premenopausal		1.04 (0.89-1.22) Ptrend:0.45		
Missmer, 2002 Pooled analysis		7 379/			Incidence, breast cancer	Whole milk, per 100 g/day	0.99 (0.96-1.01)	Age, age at menarche, parity, age at first birth, oral contraceptive use, history of benign breast disease, family history of breast cancer, menopausal status, BMI, HRT use, smoking status, education,	RR rescaled for an increment used

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								height, alcohol intake, total energy intake	
USA, Canada	AHS	160/15 172							
Canada	CNBSS	419/56 837							
USA	IWHS	1 130/34 406							
Netherlands	NLCS	937/62 377							
USA	NYS	367/18 475							
USA	NYUWHS	385/13 261							
USA	NHS (1980-1986)	1 023/89 046							
USA	NHS (1986-1996)	1 638/68 817							
Sweden	SMC	1 320/61 467							
Shin, 2002 BRE16658 USA	NHS, Prospective Cohort, Age: 47 years, W, Registered nurses	2 345/ 88 691 16 years	Self-report or vital records verified by medical records	FFQ	Incidence, invasive breast cancer, postmenopausal	>1 glass/day vs never	0.87 (0.69-1.10) Ptrend:0.43	Age , age at first child, age at menarche, age at menopause, alcohol, BMI, body weight, breast diseases , energy intake , family history, height, HRT use, other design issue, other nutritional factors, parity/pregnancies, physical activity	
						per 1 glass/day	0.97 (0.90-1.05)		RR rescaled for an increment used
		827/			Premenopausal	≥1.1 vs ≤0 cups/week	0.87 (0.59-1.28) Ptrend:0.56		
						per 1 cups/day	0.96 (0.84-1.10)		RR rescaled for an increment used

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Voorrips, 2002 BRE13011 Netherlands	NLCS, Case Cohort, Age: 55-69 years, W, Postmenopausal	783/ 62 573 6.3 years	Cancer registries, database of pathology reports	FFQ-semi-quantitative	Incidence, breast cancer	232 vs 0 g/day	0.90 (0.66-1.22) Ptrend:.12	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, benign breast disease, BMI, educational level, energy Intake , family history, oral contraceptive use, parity/pregnancies, smoking habits	Person years per quantile
Gaard, 1995 BRE17516 Norway	NNHSS, Prospective Cohort, Age: 35-49 years, W, Screening Program	125/ 24 897 10 years	Cancer registry	FFQ-semi-quantitative	Incidence, breast cancer	≥5 vs 1-1.9 glasses/day	2.91 (1.38-6.14) Ptrend:0.08	Age, attained age, height, BMI, smoking status, energy	Intake in glasses/day converted to g/day using a 150 ml (g)/glass provided in the study

Table 86 Whole milk intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Wirfält, 2011 BRE80383 Sweden	MDCS, Prospective Cohort, Age: 45-73 years, W	544/ 17 000 10.3 years	Cancer registry and medical records	Questionnaire and interview	Incidence, invasive breast cancer	Linear model	0.93 (0.88-0.99)	Age, season, total energy	Superseded by Pala, 2009 (EPIC)
						239 vs 3.6 g	0.65 (0.48-0.88)		
		270/			ER+/PR+	Linear model	0.92 (0.85-1.01)		Dose-response meta-analysis by tumour receptor status was not conducted
		81/			ER+/PR-		0.93 (0.80-1.08)		
		61/			ER-/PR-		1.10 (0.92-1.31)		
Mills, 1989 BRE17837 USA	AHS, Prospective Cohort, Age: 25-99 years, W, Adventist	201/ 20 341 6 years	Medical records	FFQ	Incidence, breast cancer	≥1 vs ≤0 times/day	0.94 (0.66-1.33) Ptrend:0.45	Age , age at first child, age at menarche, benign breast disease, BMI, educational level, family history	Superseded by Missmer, 2002 in the main analysis, used in stratified analysis by geographic location: intake in times/day converted to g/day using a standard serving of 244 g
		171/			Postmenopausal		0.98 (0.66-1.45)		Excluded, no cases or person-years per category

Figure 128 RR estimates of breast cancer by levels of whole milk intake.

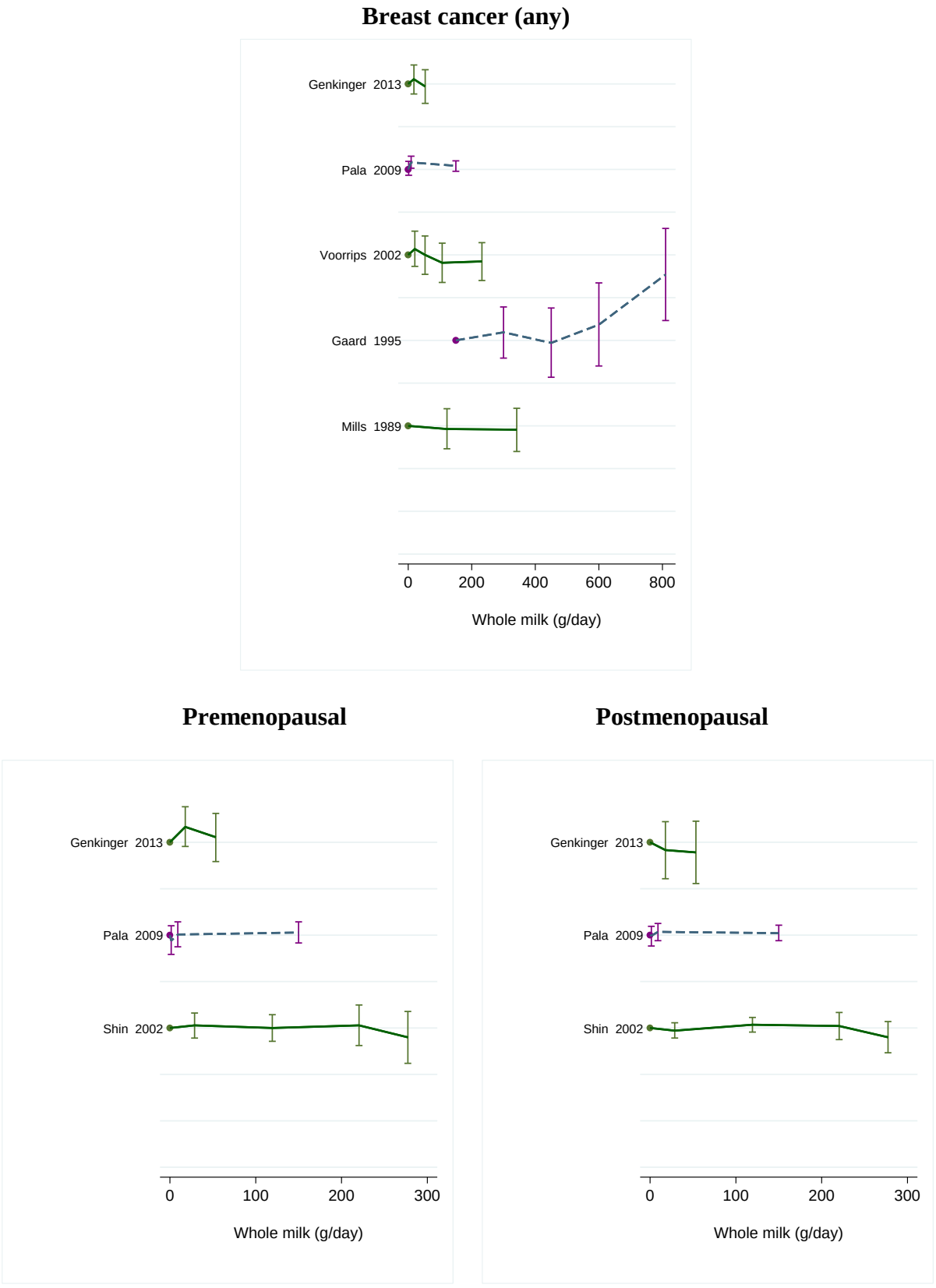


Figure 129 RR (95% CI) of breast cancer for the highest compared with the lowest level of whole milk intake

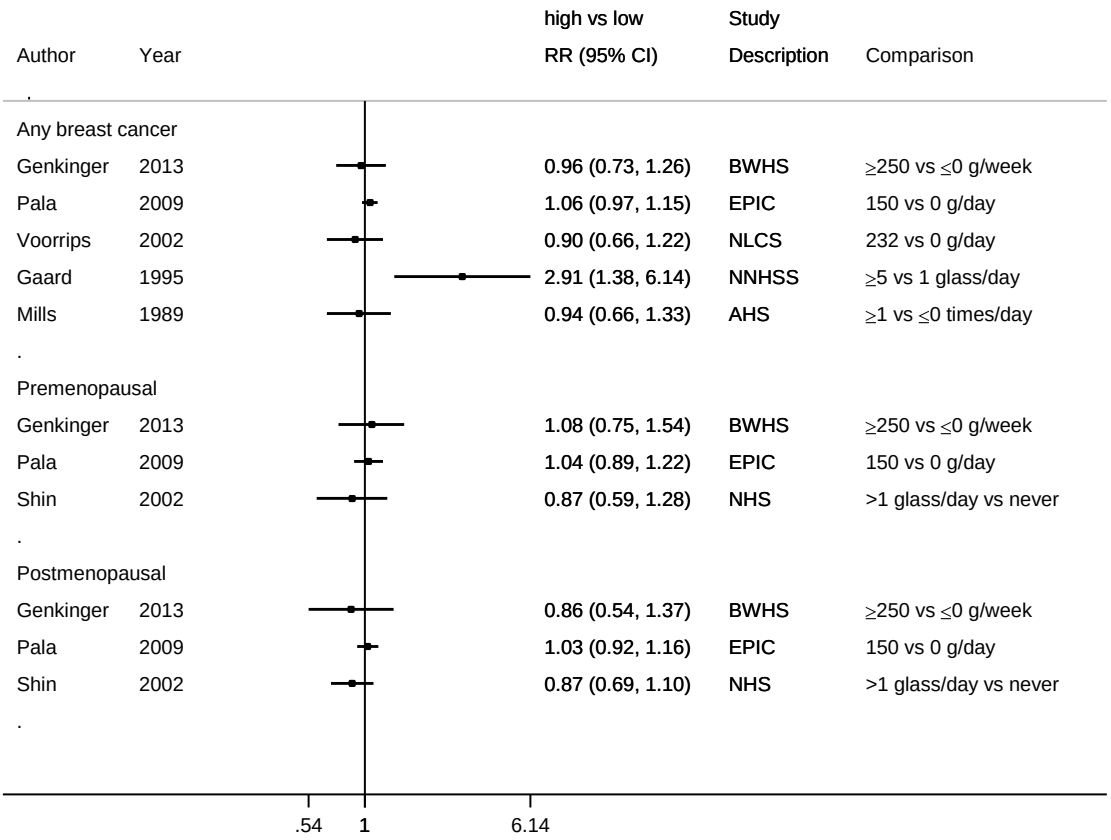


Figure 130 Relative risk of breast cancer (any) for 150 g/day increase of whole milk intake

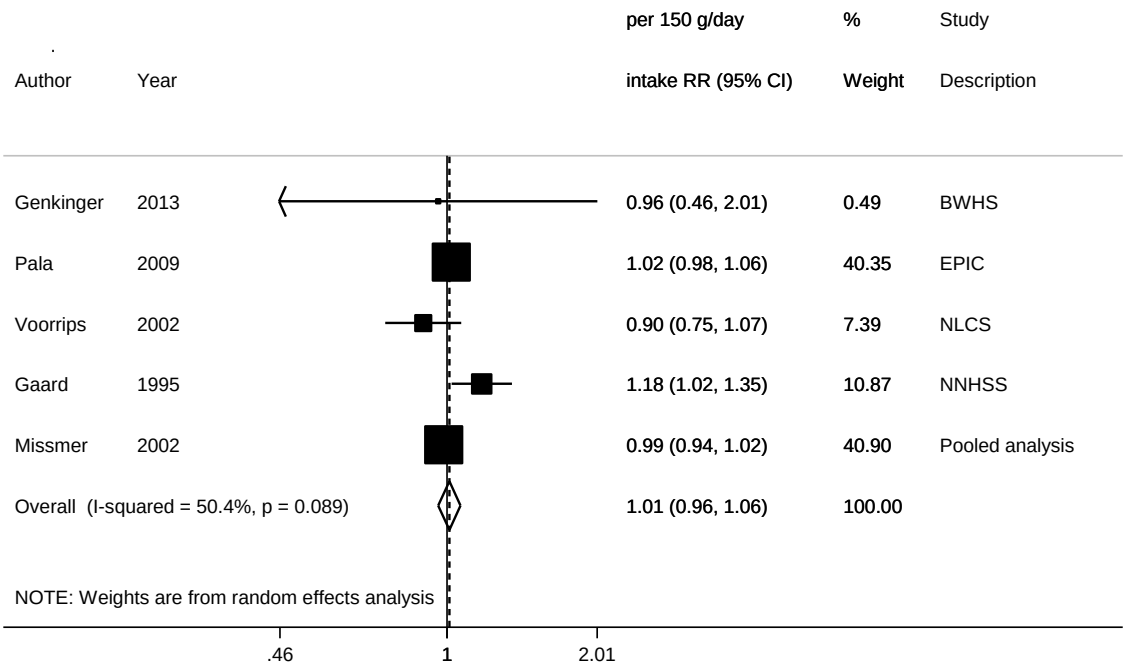


Figure 131 Relative risk of premenopausal breast cancer for 150 g/day increase of whole milk intake

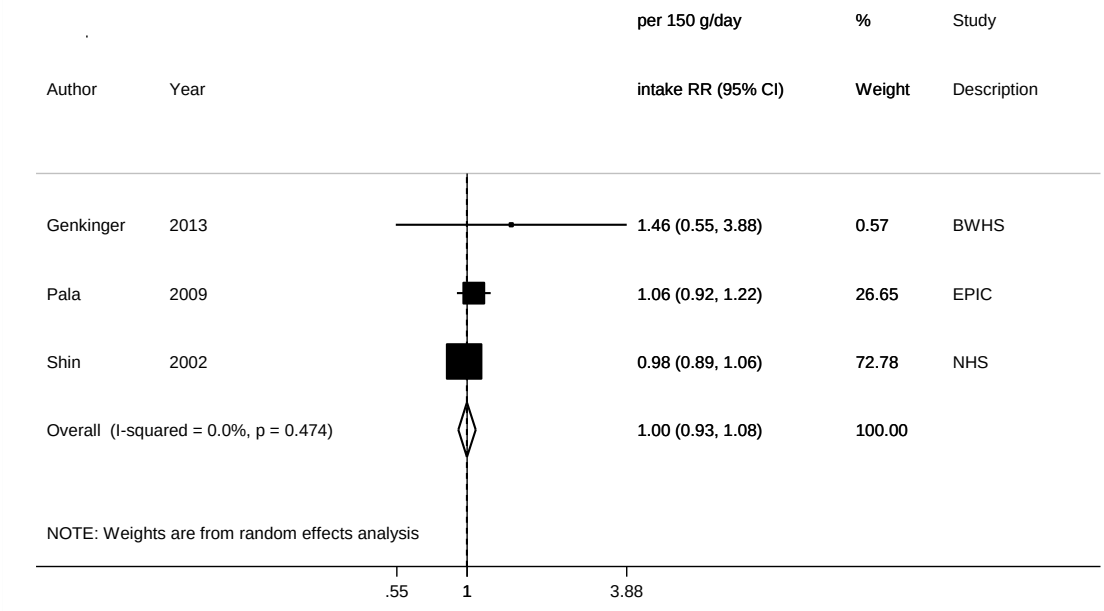


Figure 132 Relative risk of postmenopausal breast cancer for 150 g/day increase of whole milk intake

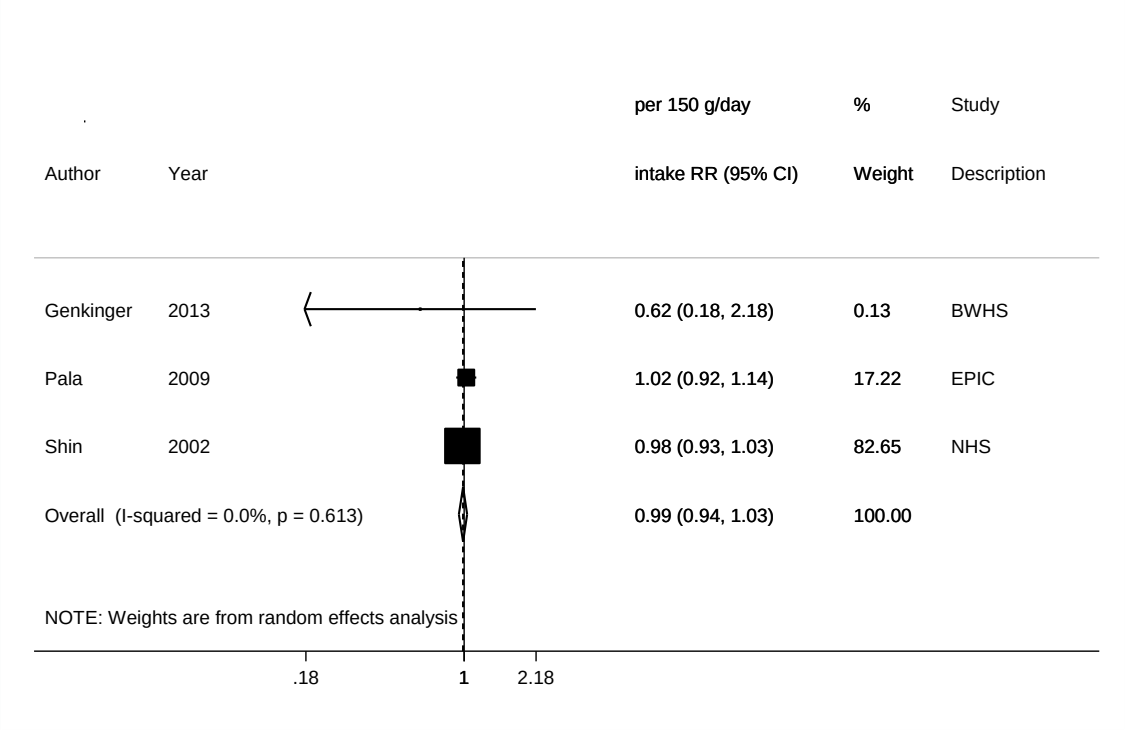


Figure 133 Funnel plot of studies included in the dose response meta-analysis of whole milk intake and breast cancer (any)

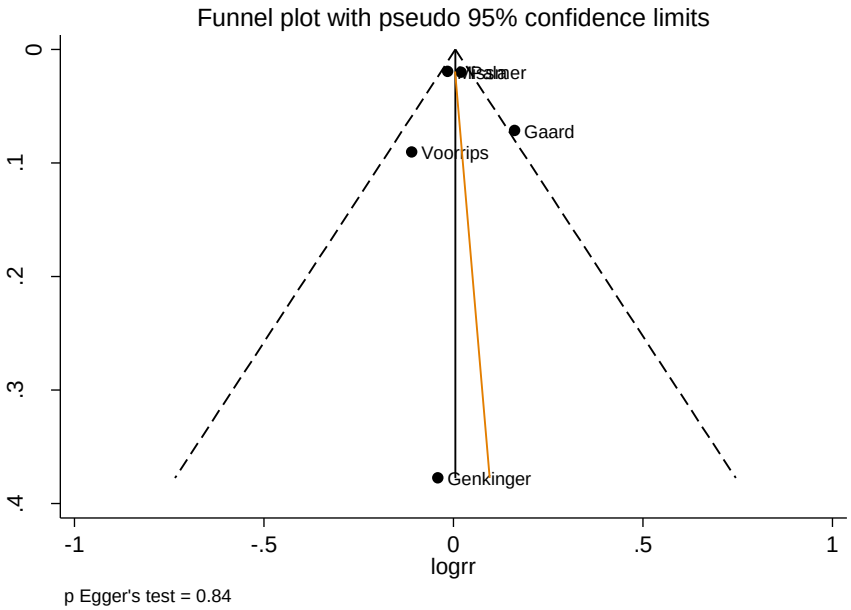
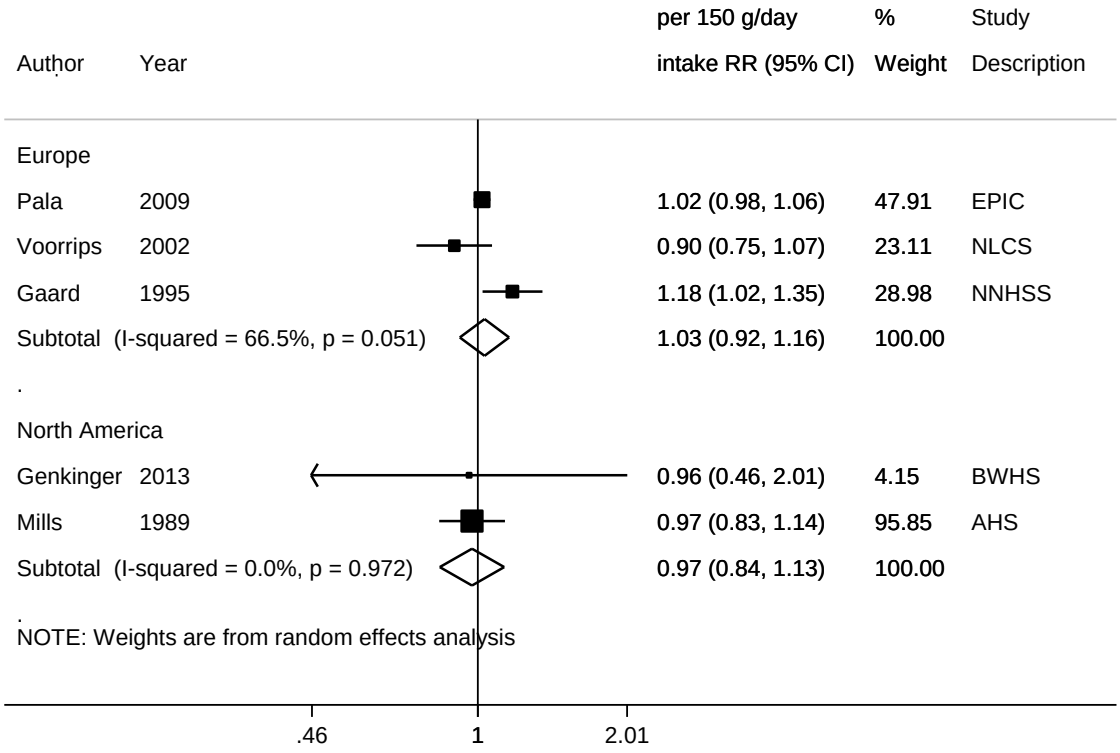


Figure 134 Relative risk of breast cancer (any) for 150 g/day increase of whole milk intake, by geographic location



3 Beverages

3.6.1 Coffee

Cohort studies

Overall summary

Twenty three publications on coffee intake and breast cancer risk were identified. From these, four publications were excluded because were superseded by other publications, one study did not have enough studies, and one publication could be included only in high versus low analysis.

Seven studies investigated postmenopausal breast cancers, seven were on premenopausal breast cancers, and fourteen were on pre- and postmenopausal breast cancers combined.

The study characteristics and results are shown in a Table in this section.

Study quality

Coffee intake was assessed by FFQ in all studies, except two studies which one used solely a 24 h-recall (Hirvonen, 2006) and the other used both FFQ and a 24 h-recall (Vatten, 1990b).

In the studies, cancer outcome was confirmed using medical notes, death records or through cancer registries.

Breast cancer (any)

Summary

Main results:

Fourteen studies (25 335 cases) were included in the dose-response meta-analysis. A borderline significant inverse association was observed.

Low heterogeneity was observed. There was no evidence of a significant publication or small study bias.

No association was found for decaffeinated coffee intake and breast cancer risk.

In stratified analysis by geographic location, no association were found for studies in Asia and Europe and a borderline significant inverse association was observed only in studies in North America (n=4).

Coffee intake and breast cancer risk by BMI status:

Four studies reported results by BMI status. From these, three studies (NHS, WHS, and SMC) were included in stratified analysis by BMI status. No association for 1 cup/day of coffee intake and breast cancer risk was observed in subjects with BMI ≤ 25 kg/m² (RR=1.00 (95%CI: 0.97-1.02, I^2 =0%, p=0.43) and a non-significant inverse association was observed in subjects with BMI ≥25 kg/m² (RR=0.99 (95%CI: 0.97-1.01, I^2 =0%, p=0.40).

Sensitivity analyses:

In influence analysis, the summary RR did not changed materially when excluding studies in turn.

Nonlinear dose-response meta-analysis:

There was no evidence of non-linear relationship (p=0.11).

Premenopausal breast cancer

Summary

Main results:

Seven studies (7 135 cases) were included in the dose-response meta-analysis. No significant association was observed. There was moderate heterogeneity and no significant evidence of publication or small study bias.

In stratified analysis by geographic location, no association was found for studies in Europe and North America.

Sensitivity analyses:

In influence analysis, the summary RR ranged from 0.98 (95% CI=0.96-1.00) when Nilsson, 2010 (7% weight) was omitted to 1.00 (95% CI=0.97-1.04) when Vatten, 1990b (11% weight) was omitted.

Nonlinear dose-response meta-analysis:

There was no evidence of non-linear relationship (p=0.075).

Postmenopausal breast cancer

Summary

Main results:

Seven studies (16 780 cases) were included in the dose-response meta-analysis. A borderline significant inverse association was observed. There was moderate heterogeneity and no significant evidence of publication or small study bias.

In stratified analysis by geographic location, a significant inverse association was observed in studies in Europe, showing a 4% decrease in breast cancer risk. No association was found for studies in North America.

Sensitivity analyses:

The summary RR ranged from 0.97 (95% CI=0.94-0.99) when Ishitani, 2008 (17 % weight) was omitted to 0.98 (95% CI=0.96-1.00) when Nilsson, 2010 (7.5 % weight) was omitted.

Nonlinear dose-response meta-analysis:

Not enough studies to conduct the analysis (n=4).

Coffee intake and breast cancer risk by hormone receptor status:

Three studies investigated the association of coffee intake and breast cancer risk by tumour hormone receptor status. No significant inverse associations were observed when breast cancers were classified simultaneously by ER and PR status.

Table 87 Coffee and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	19 (23 publications)
Studies included in forest plot of highest compared with lowest exposure	Breast cancer: 15 (16 publications) Premenopausal: 7 (8 publications) Postmenopausal: 7 (8 publications)
Studies included in linear dose-response meta-analysis	Breast cancer: 14 (16 publications) Premenopausal: 7 (8 publications) Postmenopausal: 7 (8 publications)
Studies included in non-linear dose-response meta-analysis	Breast cancer:12 (13 publications) Premenopausal: 5 (5 publications) Postmenopausal: not enough studies

Table 88 Coffee intake and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	CUP SLR
Increment unit used	1 cup/day	1 cup/day
All studies		
Studies (n)	3	15
Cases (total number)	1 978	25 335
RR (95%CI)	0.97 (0.93-1.01)	0.99 (0.98-1.00)
Heterogeneity (I^2, p-value)	64.9%	3.1%, 0.41
P value Egger test	-	0.77
CUP SLR		
	Premenopausal	Postmenopausal
Studies (n)	7	7
Cases	7 135	16 580
RR (95%CI)	1.00 (0.97-1.03)	0.98 (0.95-1.00)
Heterogeneity (I^2, p-value)	44.4%, 0.095	45.6%, 0.09
P value Egger test	0.22	0.97

Stratified analyses

Geographic area	**Asia**	**Europe**	**North-America**
	Breast cancer		
Studies (n)	5	6	4
RR (95%CI)	1.05 (0.97-1.14)	0.98 (0.96-1.01)	0.99 (0.98-1.00)
Heterogeneity (I^2, p- value)	0%, 0.64	11.7%, 0.34	18.5%, 0.30
	Premenopausal		
Studies (n)	-	4	3
RR (95%CI)	-	1.00 (0.94-1.06)	0.99 (0.96-1.03)
Heterogeneity (I^2, p- value)	-	65.6%, 0.03	3.1%, 0.36
	Postmenopausal		
Studies (n)	-	4	3
RR (95%CI)	-	0.96 (0.92-0.99)	1.00 (0.97-1.03)
Heterogeneity (I^2, p- value)	-	54.8%, 0.08	12.7%, 0.32
Hormone receptor status			
	ER+/PR-	**ER-/PR+**	**ER-/PR-**	**ER+/PR+**
Studies (n)	3	2	3	3

RR (95%CI)	0.97 (0.91-1.04)	0.90 (0.77-1.06)	0.99 (0.95-1.04)	0.99 (0.97-1.01)
Heterogeneity (I^2, p- value)	46%, 0.16	0%, 0.63	0%, 0.94	0%, 0.56
Coffee type				
	Decaffeinated coffee			
Studies (n)	3			
RR (95%CI)	0.98 (0.96-1.01)			
Heterogeneity (I^2, p- value)	0%, 0.73			

Table 89 Coffee and breast cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Li, 2013	16	-	Worldwide	Incidence, breast cancer	High vs low	0.98 (0.92-1.03)		0%, 0.74
	15				Low to moderate vs lowest	0.98 (0.95-1.01)		22.7%, 0.20
	15				2 cups/day	0.98 (0.97–1.00)		0%, 0.55
Yu, 2011	11	-	Worldwide	Incidence, breast cancer	Low to moderate drinkers vs none/lowest drinkers	0.94 (0.91-0.98)		28.7%, 0.17

Table 90 Coffee intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Bhoo-Pathy, 2015 BRE80551 France, Italy, Spain, UK, Netherlands, Greece, Germany, Sweden, Denmark, Norway	EPIC, Prospective Cohort, Age: 25-70 years, W	9 134/ 335 060 11 years		FFQ, diet history, 7-day food diary	Incidence, postmenopausal breast cancer	Q5 vs Q1	0.95 (0.89-1.01) Ptrend:0.055	Age, age at first child birth, age at menarche, alcohol Intake, breastfeeding, decaffeinated coffee Intake, educational level, energy Intake from fat sources, energy Intake from non-fat sources, fruit and vegetables Intake, height, HRT use, menopausal status, oral contraceptive use, physical activity level, saturated fat Intake, smoking status, study centre, tea Intake, weight	Mid-point exposure Increment converted to 200 mL Hamling method used to recalculate RR's
						per 100 ml	0.99 (0.98-0.99)		
		6 070			Incidence, postmenopausal breast cancer (Caffeinated coffee)	Q5 vs Q1	0.90 (0.82-0.98) Ptrend:0.029		
						per 100 ml	0.98 (0.97-1.00)		
		3 206/			Incidence, breast cancer ER+ & PR+, postmenopausal	per 100 ml	0.99 (0.97-1.00)		
		1 052			Incidence, breast cancer ER- & PR-, postmenopausal	per 100 ml	0.99 (0.97-1.01)		
		1 064			Incidence, premenopausal breast cancer	Q5 vs Q 2	1.15 (0.96-1.39) Ptrend:0.27		
		724/			Incidence, premenopausal breast cancer (Caffeinated coffee)	high vs low	1.19 (0.93-1.53) Ptrend:0.547		
		1 064/			Incidence, premenopausal breast cancer	per 100 ml	1.00 (0.98-1.03)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		724/			Incidence, premenopausal breast cancer (Caffeinated coffee)	per 100 ml	1.00 (0.97-1.03)		
		2 142			Incidence, breast cancer ER+ & PR+, postmenopausal (Caffeinated coffee)	per 100 ml	0.98 (0.96-0.99)		
		605/			Incidence, breast cancer ER- & PR-, postmenopausal (Caffeinated coffee)	per 100 ml	0.96 (0.93-1.00)		
Oh, 2015 BRE80594 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	1 395/ 42 099 856 529 person-years	Cancer and mortality registries	FFQ	Incidence, Invasive breast cancer	per 1 cup/day	0.97 (0.94-0.99)	Age, alcohol consumption, BMI, breastfeeding	Mid-point exposure Increment converted to 200 mL Hamling method used to recalculate RR's
					Incidence, Invasive breast cancer	≥5 vs 1-2 cups/day	0.81 (0.70-0.94)		
		866/			Incidence, Invasive breast cancer, postmenopausal	≥5 vs 1-2 cups/day	0.81 (0.67-0.97)		
		863/			Incidence,	per 1 cup/day	0.96 (0.93-1.00)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					Invasive breast cancer, postmenopausal				
		847/			Incidence, breast cancer, ER+/PR+	per 1 cup/day	0.98 (0.94-1.01)		
						≥5 vs 1-2 cups/day (Caffeine)	0.91 (0.75–1.10)		
		532/			Incidence, Invasive breast cancer, premenopausal	per 1 cup/day	0.97 (0.93-1.01)		
		532/			Incidence, Invasive breast cancer, premenopausal	≥5 vs 1-2 cups/day	0.82 (0.65-1.03)		
		194/			Incidence, breast cancer, caffeine intake in ER+/PR-	per 1 cup/day	0.92 (0.85-0.99)		
						≥5 vs 1-2 cups/day (Caffeine)	0.52 (0.36-0.76)		
		170/			Incidence, breast cancer, caffeine intake in ER-/PR-	per 1 cup/day	1.00 (0.92-1.08)		
						≥5 vs 1-2 cups/day (Caffeine)	1.14 (0.74-1.75)		
		26/			Incidence, breast cancer, caffeine intake in ER-/PR+	per 1 cup/day	0.89 (0.73-1.09)		
						≥5 vs 1-2 cups/day	0.61 (0.21-1.84)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
						(Caffeine)			
Gierach, 2012 BRE80395 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W	9 915/ 198 404 1 906 185 person-years	Cancer registry and national death Index	FFQ	Incidence, breast cancer	≥4 vs never cups	0.98 (0.91-1.07) Ptrend:0.38	Age, age at first child birth, alcohol, BMI, breast biopsies, educational level, family history of breast cancer, HRT use, race, smoking, total energy fat	Mid-point exposure Person years of follow up
		7 959/			Incidence, Invasive breast cancer		0.98 (0.89-1.07) Ptrend:0.37		
		1 892/			Incidence, In Situ breast cancer		1.02 (0.85-1.24) Ptrend:0.99		
		2 051/			Incidence, breast cancer ER+/PR+		1.11 (0.91-1.34) Ptrend:0.93		
		453/			Incidence, breast cancer ER-/PR-		1.08 (0.74-1.58) Ptrend:0.95		
		425/			Incidence, breast cancer ER+/PR-		0.97 (0.64-1.48) Ptrend:0.97		
		55/			Incidence, breast cancer ER-/PR+		1.02 (0.29-3.61) Ptrend:0.63		
		33/			Incidence, breast cancer ER-/PR+		1.38 (0.39-4.88) Ptrend:0.96		
Boggs, 2010b BRE80326 USA	BWHS, Prospective Cohort, Age: 21-69 years, W	1 268/ 52 062 12 years	Self-report verified by medical record		Incidence, breast cancer	≥4 cups/day vs never/<1 cups/month (Caffeinated coffee)	1.03 (0.77-1.39) Ptrend:0.90	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, BMI,	Mid-point exposure
		562/			Incidence, breast cancer, premenopausal		1.33 (0.83–2.11) Ptrend:0.31		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		570/			Incidence, breast cancer, postmenopausal		0.85 (0.55–1.32) Ptrend:0.28	contraception, educational level, energy Intake, family history of breast cancer, geographic region, HRT use, menopausal status, parity, smoking, vigorous activity	
		1 268/			Incidence, breast cancer	≥4 cups/day vs never/<1 cups/month (Decaffeinated coffee)	0.82 (0.61–1.11) Ptrend:0.33		
		562/			Incidence, breast cancer, premenopausal		0.99 (0.56–1.72) Ptrend:0.41		
		570/			Incidence, breast cancer, postmenopausal		0.93 (0.65–1.33) Ptrend:0.42		
Iwasaki, 2010 BRE80329 Japan	JPHC I and II, Prospective Cohort, Age: 40-69 years	577/ 97 432	Hospital records/cancer registries	FFQ	Incidence, breast cancer	≥3 vs <1 cups/week	1.22 (0.87-1.71) Ptrend:0.26	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, area, BMI, family history of breast cancer, height, HRT use, leisure time physical activity, menopausal status, number of childbirths, smoking, tea Intake, tea Intake	Mid-point exposure Unit converted to cups/day
Nilsson, 2010	VIP,	588/	Cancer registry	FFQ	Incidence, breast	≥4 vs <1	0.92 (0.68-1.25)	Age, sex, BMI,	Mid-point

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
BRE80310 Sweden	Prospective Cohort, Age: 50 years, M/W				cancer	times/day		educational level, recreational activity, smoking	exposure Person years of follow up
		320/			Incidence, breast cancer, >55y	≥4 vs <1 times/day	0.60 (0.39-0.93)		
		109/			Incidence, breast cancer, <49y	≥4 vs <1 times/day	1.69 (0.96-2.98)		
Sugiyama, 2010 BRE80451 Japan	MCS, Prospective Cohort, Age: 40-64 years, W	19/ 37 742 10.3 years	Death certificate	Questionnaire	Mortality, breast cancer	1 cup/day vs never	1.54 (0.34-6.93) Ptrend:0.65	Age, alcohol consumption, cigarette smoking, dairy products consumption, educational level, energy Intake, fish Intake, fruit Intake, green tea, history of diabetes, history of hypertension, miso soup, rice Intake, tea Intake, total meat, vegetable Intake, walking time	Mid-point exposure Person years of follow up Unit converted to the 200 mL
Larsson, 2009b BRE80251 Sweden	SMC, Prospective Cohort, Age: 40-76 years,	2 952/ 61 433 17.4 years	Cancer registry	FFQ	Incidence, Invasive breast cancer	≥4 vs <1 cups/day	1.02 (0.87-1.20) Ptrend:0.74	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake,	Mid-point exposure
		1 286/			Incidence, breast cancer ER+/PR+		1.12 (0.87-1.44) Ptrend:0.49		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	W	417/			Incidence, breast cancer ER+/PR-		0.98 (0.63-1.53) Ptrend:0.99	BMI, educational level, family history of cancer, height, HRT use, OC use, parity, tea Intake, total caloric Intake	
		266/			Incidence, breast cancer ER-/PR-		0.91 (0.59-1.38) Ptrend:0.64		
Wilson, 2009 BRE80279 USA	NHS II, Prospective Cohort, Age: 26-46 years, W, Premenopausal	1 179/ 90 628 14 years	Self-report verified by medical record	Semi-quantitative FFQ	Incidence, breast cancer, premenopausal	3.5 vs 0 servings/day	0.92 (0.77-1.11) Ptrend:0.28	Age, age at first child birth, age at menarche, alcohol Intake, animal fat Intake, benign breast disease, BMI, calendar year, energy Intake, family history of cancer, glycemic load, height, OC use, parity, physical activity, smoking habits	Person years of follow up
Ganmaa, 2008 BRE80158 USA	NHS, Prospective Cohort, Age: 30-55 years	5 272/ 85 987 22 years	Questionnaire/medical records/death record	FFQ	Incidence, breast cancer	≥4 vs ≤0.9 cup/month	0.92 (0.82-1.03) Ptrend:0.14	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, benign breast	Mid-point exposure
		3 784/			Incidence, breast cancer (Decaffeinated		1.03 (0.81–1.31) Ptrend:0.26		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					coffee)			disease, BMI, duration of HRT use, family history of cancer, height, HRT use, menopausal status, parity, physical activity, smoking status, tea Intake, weight	
		2 685/			BMI < 25 kg/m²		0.93 (0.80-1.08)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, benign breast disease, duration of HRT use, family history of cancer, height, HRT use, menopausal status, parity, physical activity, smoking status, tea Intake, weight	
		1 666/			BMI ≥ 25-29.9 kg/m²		0.87 (0.71-1.07)		
		913/			BMI ≥ 30 kg/m²		1.02 (0.78-1.33)		
Ishitani, 2008	WHS,	1 181/	Self-	FFQ	Incidence,	≥4 cups/day vs	1.08 (0.89-1.30)	Age, age at first	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
BRE80189 USA	Prospective Cohort, Age: 45- years, W	38 432 10 years	reported/death certificate/ medical records		Invasive breast cancer	almost never	Ptrend:0.27	child birth, age at menarche, age at menopause, alcohol consumption, benign breast disease, BMI, energy Intake, family history of cancer, hysterectomy, menopausal status, multivitamin supplement Intake, number of full-term pregnancies, oophorectomy/hysterectomy, physical activity, postmenopausal hormone use, randomized treatment assignment, smoking status	
		1 167			Incidence, Invasive breast cancer (Decaffeinated coffee)		0.93 (0.78-1.10) Ptrend:0.23		
		735/			Incidence, Invasive breast cancer, postmenopausal		1.08 (0.85-1.38) Ptrend:0.50		
		275/ 38 432 10 years			Incidence, Invasive breast cancer, premenopausal		0.97 (0.64-1.46) Ptrend:0.85		
		654/			BMI < 25 kg/m²		1.13 (0.88-1.46)		
		527/			BMI ≥ 25 kg/m²		0.99 (0.74-1.32)		
Iso, 2007 BRE80427 Japan	JACC, Prospective Cohort, Age: 40-79 years,	98/ 15 years	Municipal resident registration records, death certificates	FFQ	Mortality, breast cancer	≥2 vs ≤1-2 times/month	0.72 (0.38-1.35)	Age, centre location	Unit converted to cup/day

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	W								
Hirvonen, 2006 BRE80105 France	SU.VI.MAX, Prospective Cohort, Age: 35-60 years, W, participants of a RCT	95/ 4 396 6.6 years	Medical records	24h recall	Incidence, breast cancer	≥253 vs 0-111 ml/day	1.10 (0.66-1.84) Ptrend:0.71	Age , family history, menopausal status, OC use, parity/pregnancies, smoking habits	Mid-point exposure Person years of follow up
Key, 1999 BRE04758 Japan	LSS, 1969, Prospective Cohort, W	427/ 34 759 24 years	Partially histological - over 80%	Questionnaire	Incidence, breast cancer	≥5 vs ≤1 times/week	1.19 (0.93-1.52) Ptrend:0.258	Age , calendar year, other factors , other factors , place of residence	Mid-point exposure Unit converted to cup/day
Stensvold, 1994 BRE80618 Norway	Norway cardiovascular screening (1977-1982), Prospective Cohort, Age: 35-54 years, W	211/ 21 238 10.1 years	Cancer registry	FFQ	Incidence, breast cancer		1.2	Age, cigarettes per day, county of residence	Mid-point exposure Confidence Intervals were calculated
Folsom, 1993 USA	IWHS, Prospective cohort study, W	580/ 34 388 5 years	SEER	FFQ	Incidence, breast cancer, postmenopausal	≥ 4 cups/day vs never/ <1 cup/month	1.02 (0.79-1.3)	Age, waist/hip ratio, number of live births, age at first live birth, age at menarche, family history of breast cancer, family history x	Mid-point exposure Person years of follow up

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								waist/hip ratio, and family history x number of live birth	
Vatten, 1990b BRE12833 Norway	Norway National Health Screening Service, 1974, Prospective Cohort, W	152/ 14 593 12 years	Partially histological - over 80%	FFQ + recall	Incidence, breast cancer	≥7 vs ≤2 cups/day	0.80 (0.50-1.40) Ptrend:0.81	Age	Mid-point exposure
		90/			BMI <24 kg/m²		0.60 (0.30-1.20)		
		62/			BMI ≥24 kg/m²		1.80 (0.60-5.40)		

Table 91 Coffee intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Fagherazzi, 2011 BRE80371 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W, Premenopausal+ postmenopausal	2 868/ 67 703 11 years	Pathology reports	Dietary history questionnaire	Incidence, Invasive breast cancer	>3 vs non consumers cups	0 (0.90-1.16) Ptrend:0.79	Age, age at first child birth, age at menarche, age at menopause, benign breast disease, BMI, family history of breast cancer, HRT use, menopausal status, number of children, oral	Superseded by Bhoo-Pathy, 2015 BRE80551

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								contraceptive history, school education, total energy Intake	
Bhoo Pathy N, 2010 BRE80230 Netherlands	EPIC, NL Prospective Cohort, Age: 20-70 years, W	681/ 27 323 9.6 years	Cancer registry	FFQ	Incidence, breast cancer	≥5.1 vs 0.1-1 cup/day	0.94 (0.72-1.24)	Propensity score	Superseded by Bhoo-Pathy, 2015 BRE80551
Suzuki, 2004 BRE80557 Japan	MCS, Prospective Cohort, Age: ≥40 years	222/ 35 004 9 years	Population register			≥3 cups/day vs never	0.88 (0.51-1.18) Ptrend:0.44		Superseded by Sugiyama, 2010 BRE80451
Michels, 2002 BRE20406 Sweden	SMC, Prospective Cohort, Age: 40-76 years, W	1 271/ 59 036 9.5 years	All histology	FFQ-semi-quantitative	Incidence, Invasive breast cancer	≥4 cups/day vs ≤1 cups/week	0.94 (0.75-1.28) Ptrend:0.91	Age , age at first child, alcohol, BMI, educational level, energy Intake , family history, height, parous/nulliparous	Superseded by Larsson, 2009b BRE80251 Data by BMI status were used in stratified analysis
		864/ 59 036 9.5 years			Incidence, Invasive breast cancer, postmenopausal		0.85 (0.61-1.19) Ptrend:0.51		
		717/ 59 036 9.5 years			Incidence, Invasive breast cancer, lean		1.01 (0.71-1.45) Ptrend:0.74		
		554/ 59 036 9.5 years			Incidence, Invasive breast cancer, overweight		0.95 (0.64-1.41) Ptrend:0.78		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		407/ 59 036 9.5 years			Incidence, Invasive breast cancer, premenopausal		1.24 (0.79-1.94) Ptrend:0.24		
		717/			BMI ≤25 kg/m²		1.01 (0.71-1.45)		
		554/			BMI > 25 kg/m		0.95 (0.64-1.41)		
Hoyer, 1992 BRE04086 Denmark	Glostrup Population Studies, 1982, Prospective Cohort, Age: 30-80 years, W	5 207 26 years	Partially histological - over 80%	Questionnaire	Incidence, breast cancer	≥7 vs 0-2 cups/day	1.70 (0.70-4.30) Ptrend:>0.20		Not enough data
Snowdon, 1984 BRE11552 USA	SDA, Prospective Cohort, Age: 30- years, W, Adventist	175/ 21 years	Death certificate	Questionnaire	Mortality, breast cancer	≥2 vs ≤0.9 cups/day	0.90 (0.60-1.30) Ptrend:0.62	Age	Used only in high vs low analysis

Figure 135 RR estimates of breast cancer by levels of Coffee intake

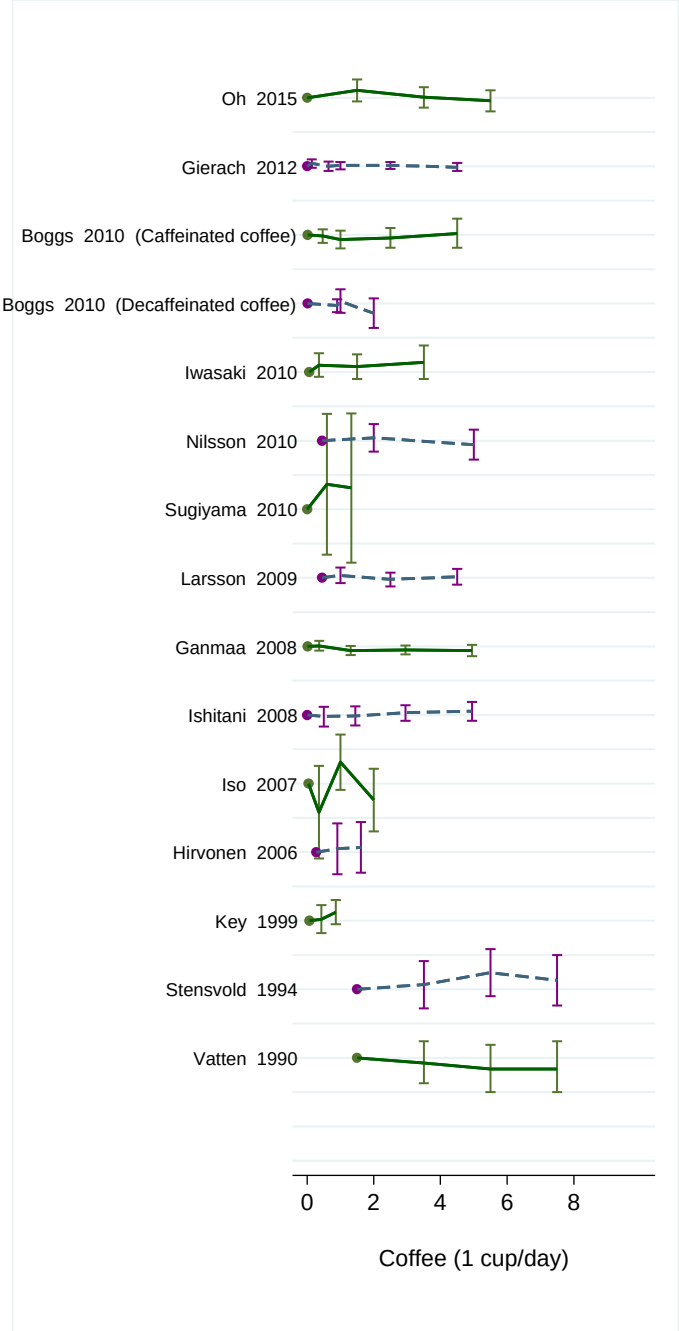


Figure 136 RR estimates of premenopausal breast cancer by levels of Coffee intake

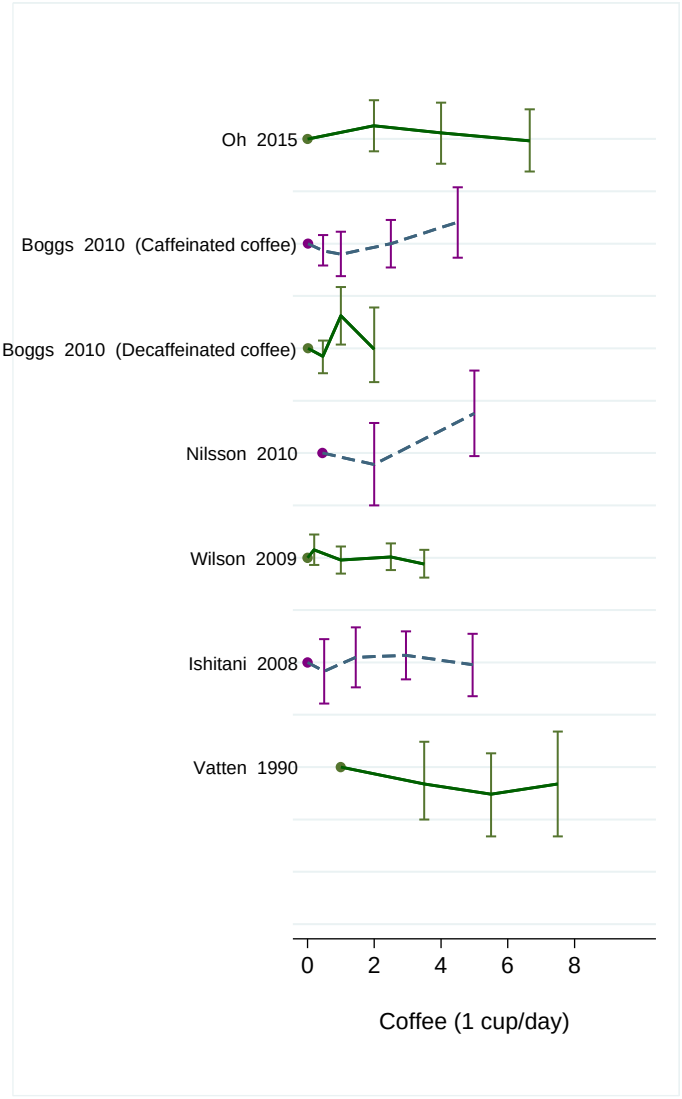


Figure 137 RR estimates of postmenopausal breast cancer by levels of Coffee intake

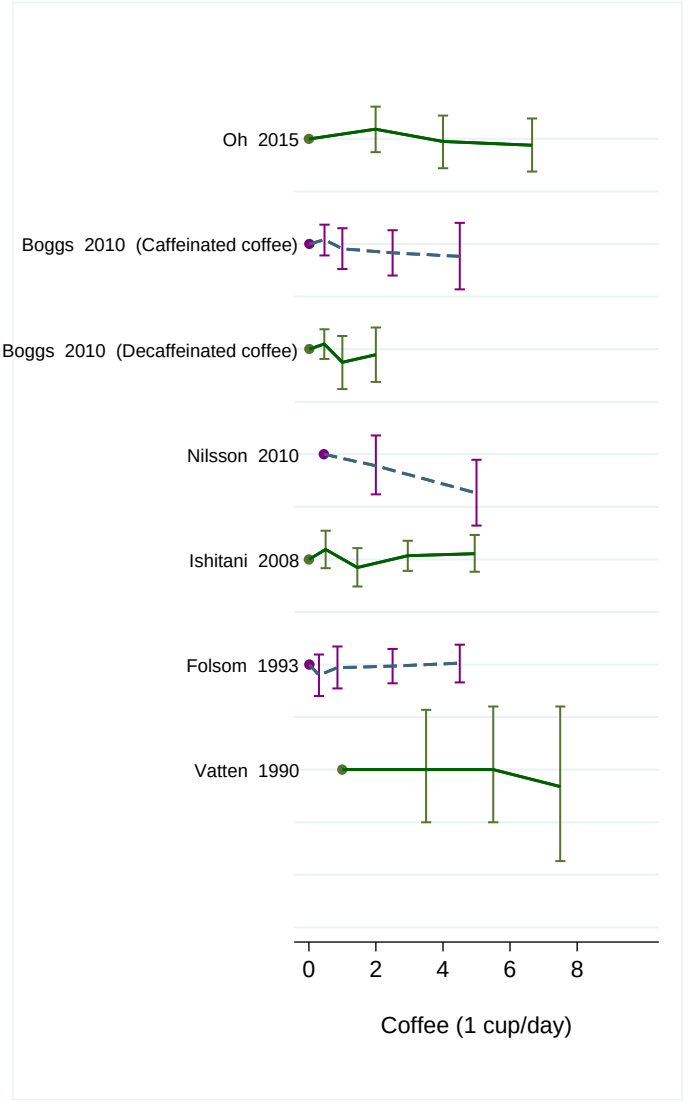
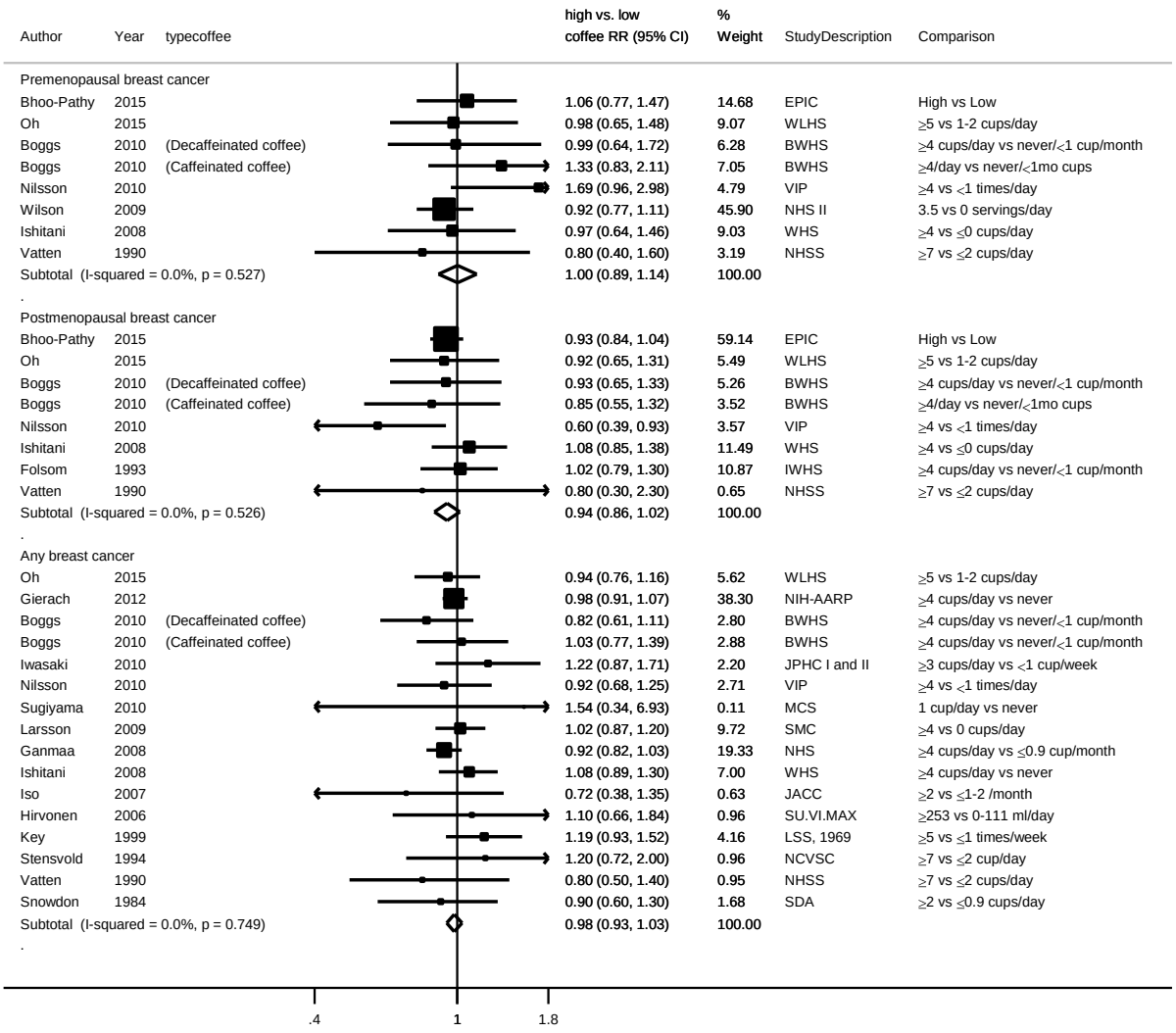


Figure 138 RR (95% CI) of breast cancer for the highest compared with the lowest level of Coffee intake



* Hamling method was used to recalculate the RR's in two studies (Bhoo-Pathy, 2015; Oh, 2015).

Figure 139 Relative risk of breast cancer for 1 cup/day increase of Coffee intake

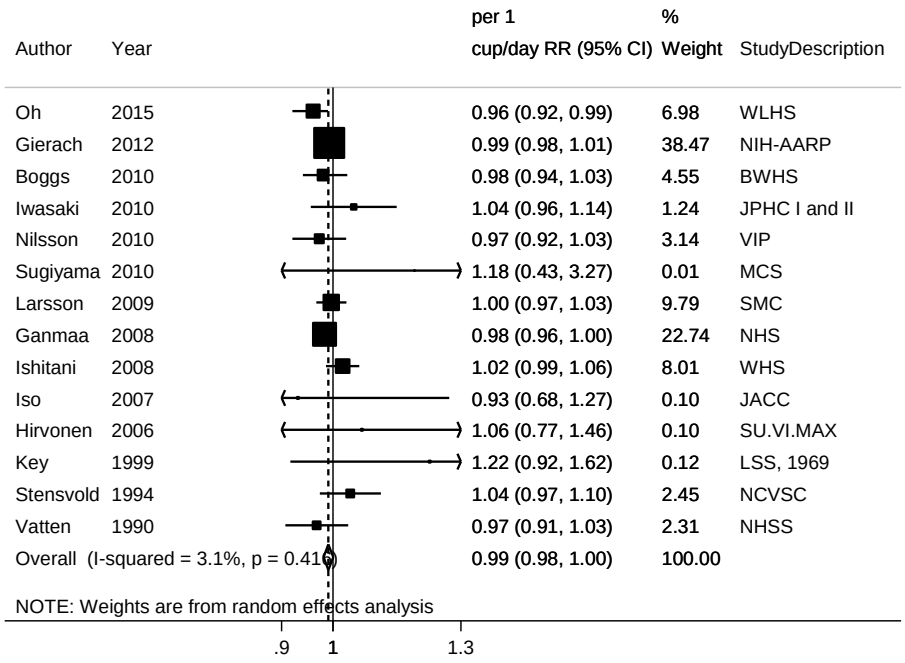


Figure 140 Relative risk of breast cancer for 1 cup/day increase of Coffee intake by geographical area

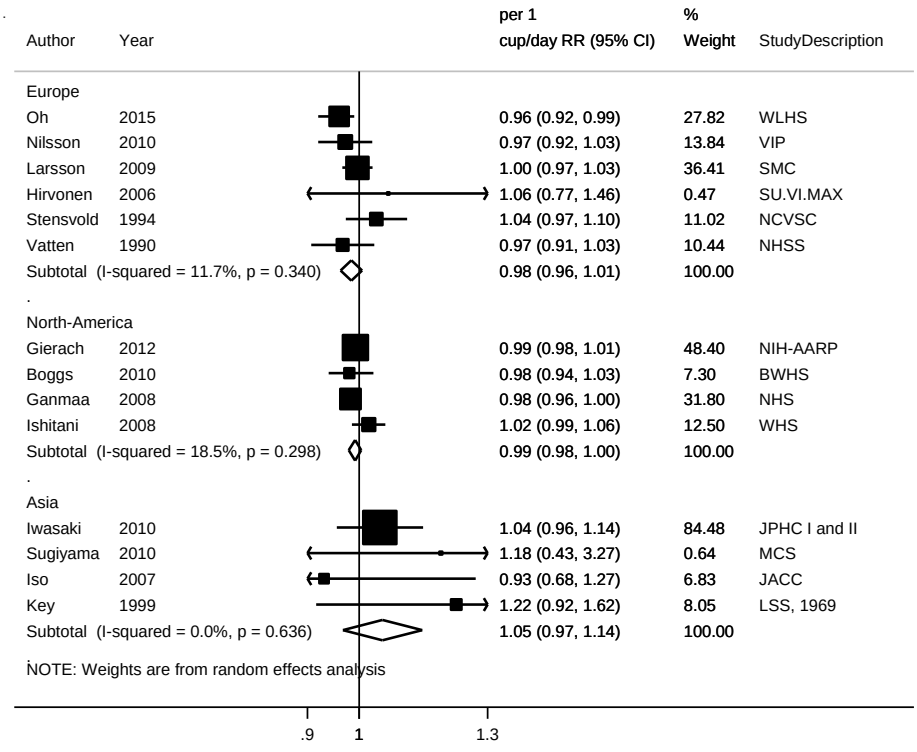


Figure 141 Relative risk of breast cancer for 1 cup/day increase of Coffee intake by hormone status

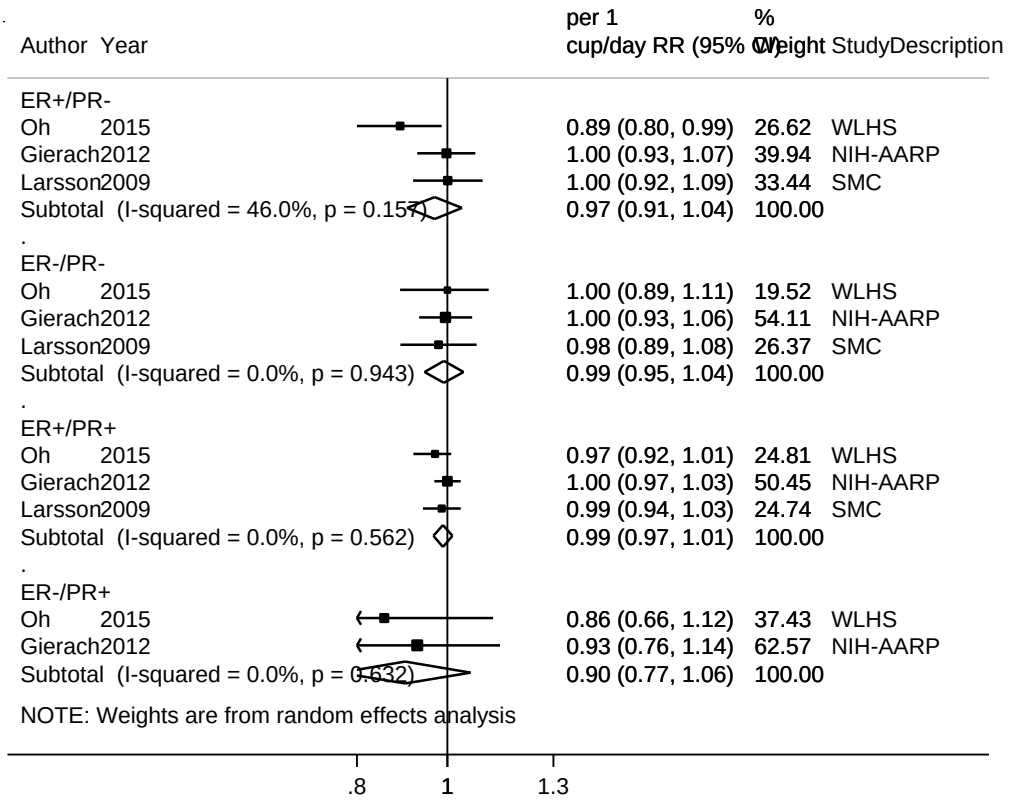


Figure 142 Relative risk of premenopausal breast cancer for 1 cup/day increase of Coffee intake

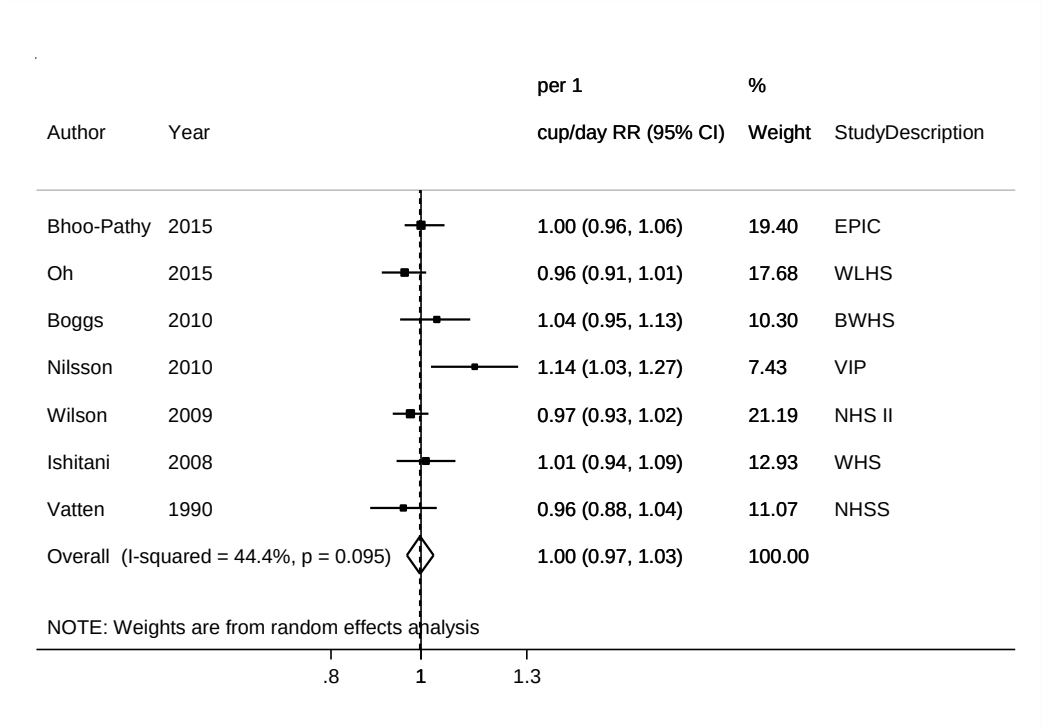


Figure 143 Relative risk of premenopausal breast cancer for 1 cup/day increase of Coffee intake by geographic area

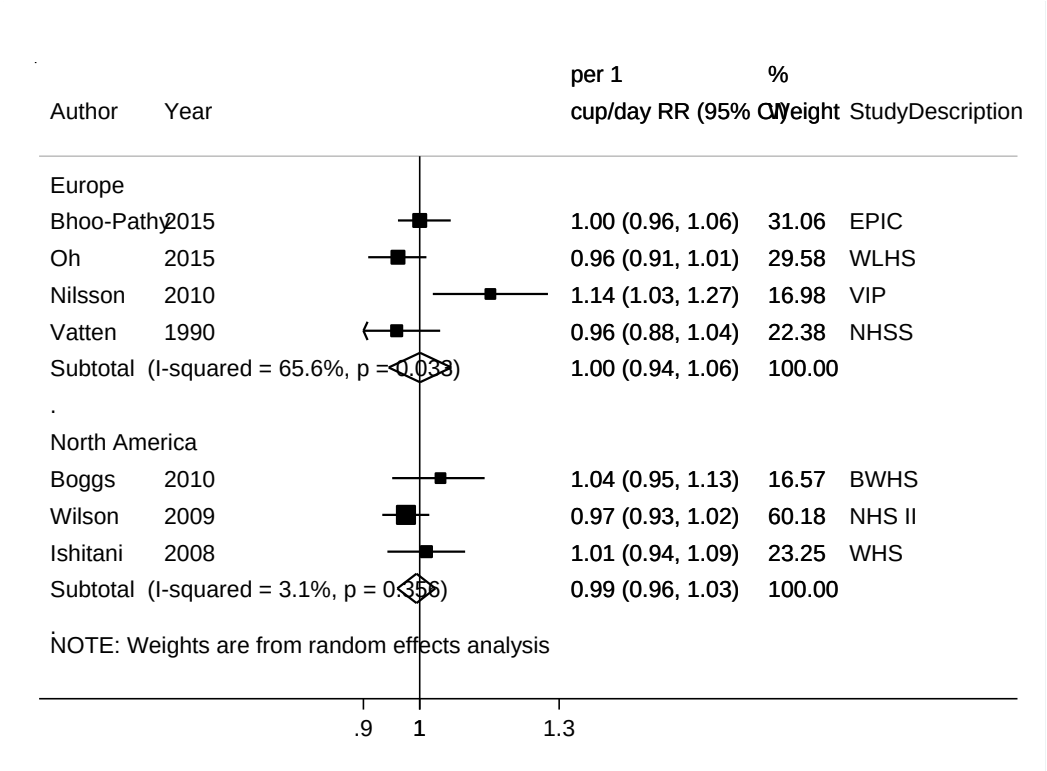


Figure 144 Relative risk of postmenopausal breast cancer for 1 cup/day increase of Coffee intake

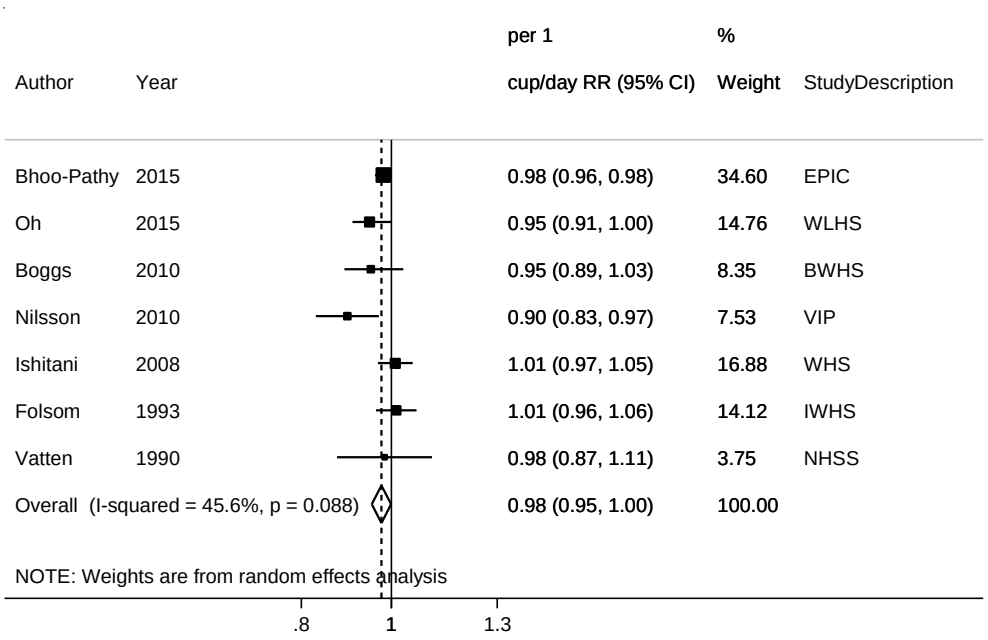


Figure 145 Relative risk of postmenopausal breast cancer for 1 cup/day increase of Coffee intake by geographic area

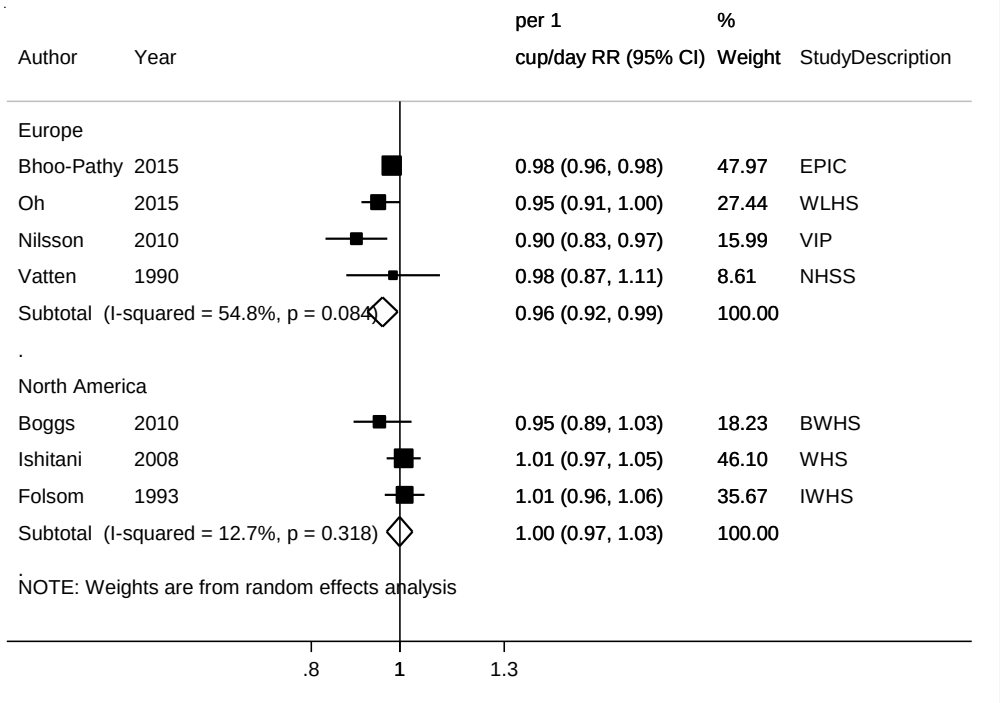


Figure 146 Funnel plot of studies included in the dose response meta-analysis of coffee and breast cancer

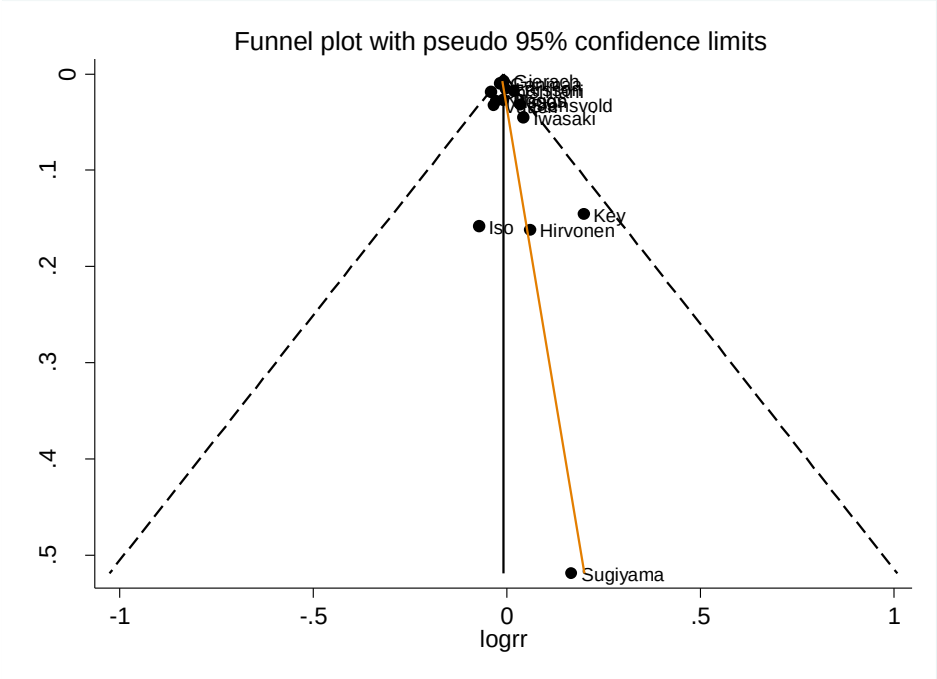


Figure 147 Funnel plot of studies included in the dose response meta-analysis of coffee and premenopausal breast cancer

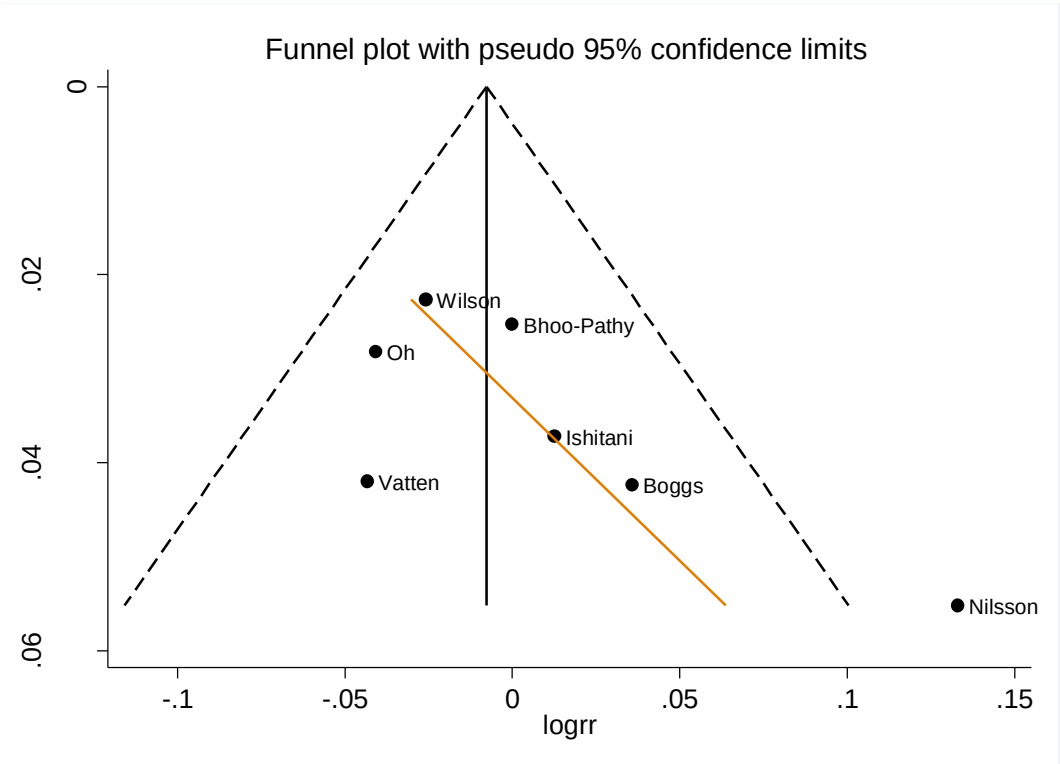
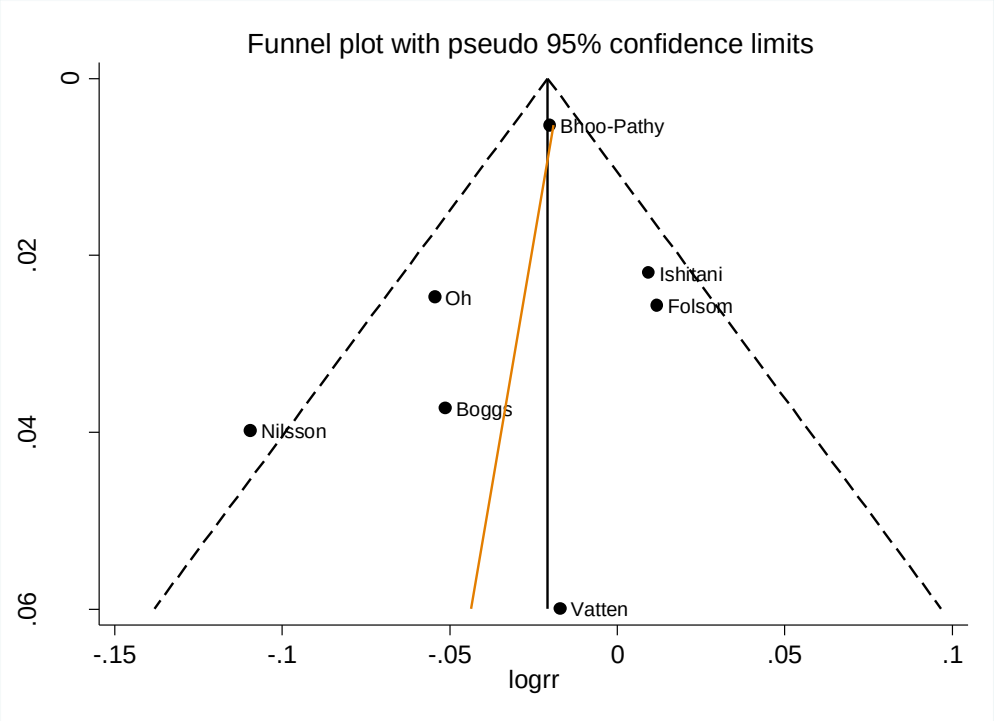


Figure 148 Funnel plot of studies included in the dose response meta-analysis of coffee and postmenopausal breast cancer



3.6.2 Tea

Cohort studies

Overall summary

Fourteen publications on tea intake and breast cancer risk were identified. From these, four publications were excluded because were superseded by other publications, two studies could be included only in highest vs lowest analysis, and one study could be included only in pre and postmenopausal breast cancer analysis.

Five studies investigated postmenopausal breast cancers, four were on premenopausal breast cancers, and fourteen were on pre- and postmenopausal breast cancers combined.

The study characteristics and results are shown in a Table in this section.

Study quality

Tea intake was assessed by FFQ in all studies, except one study which used solely a 24 h-recall (Hirvonen, 2006).

In the studies, cancer outcome was confirmed using medical notes, death records or through cancer registries.

Breast cancer (any)

Summary

Main results:

Six studies (16 808 cases) were included in the dose-response meta-analysis. No significant association was observed.

High heterogeneity was observed. There was no evidence of a significant publication or small study bias (p=0.10), although the visual inspection of funnel plot shows that the studies of Oh, 2015 and Larsson, 2009b were outliers.

In stratified analysis by geographic location, no associations were found for studies in Europe and North America.

Sensitivity analyses:

In influence analysis, the summary RR ranged from 1.01 (95% CI=0.97-1.06) when Larsson, 2009b was omitted to 1.05 (95% CI=0.98-1.11) when Ganmaa, 2008 was omitted.

Nonlinear dose-response meta-analysis:

Not enough studies to conduct the analysis (n=4).

Premenopausal breast cancer

Summary

Main results:

Four studies (14 149 cases) were included in the dose-response meta-analysis, as three new studies were identified and no meta-analysis was performed in the previous SLR.

No significant association was observed. No heterogeneity was observed. There was no evidence of a significant publication or small study bias (p=0.83).

Sensitivity analyses:

In influence analysis, the summary RR ranged from 0.99 (95% CI=0.95-1.04) when Oh, 2015 was omitted to 1.01 (95% CI=0.91-1.10) when Bhoo-Pathy, 2015 was omitted.

Nonlinear dose-response meta-analysis:

Not enough studies to conduct the analysis (n=2).

Postmenopausal breast cancer

Summary

Main results:

Five studies (24 559 cases) were included in the dose-response meta-analysis, as three new studies were identified and no meta-analysis was performed in the previous SLR. No significant association was observed.

High heterogeneity was observed. There was no evidence of a significant publication or small study bias (p=0.15), although the visual inspection of funnel plot shows that the study of Oh, 2015 was an outlier.

Sensitivity analyses:

In influence analysis, the summary RR ranged from 1.01 (95% CI=0.98-1.04) when Oh, 2015 was omitted to 1.07 (95% CI=1.00-1.14) when Bhoo-Pathy, 2015 was omitted.

Nonlinear dose-response meta-analysis:

Not enough studies to conduct the analysis (n=3).

Table 92 Tea and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	10 (14 publications)
Studies included in forest plot of highest compared with lowest exposure	Breast cancer: 8 (10 publications) Premenopausal: 4 (4 publications) Postmenopausal: 5 (5 publications)
Studies included in linear dose-response meta-analysis	Breast cancer: 6 (8 publications) Premenopausal: 4 (4 publications) Postmenopausal: 5 (5 publications)
Studies included in non-linear dose-response meta-analysis	Breast cancer: not enough studies. Premenopausal: not enough studies. Postmenopausal: not enough studies.

Table 93 Tea intake and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP SLR**
Increment unit used	1 cup/day	1 cup/day
All studies		
Studies (n)	2	6
Cases (total number)	1 981	16 808
RR (95%CI)	1.00 (1.00-1.01)	1.03 (0.98-1.09)
Heterogeneity (I^2, p-value)	33.6%	71.6%, 0.003
P value Egger test	-	0.10
CUP SLR		
	Premenopausal	Postmenopausal
Studies (n)	4	5
Cases	14 149	24 559
RR (95%CI)	1.00 (0.96-1.05)	1.05 (0.99-1.11)
Heterogeneity (I^2, p-value)	0%, 0.46	68.2%, 0.01

P value Egger test	0.83	0.15

Stratified analyses

Geographic area	**Asia**	**Europe**	**North-America**
	Breast cancer		
Studies (n)	-	3	3
RR (95%CI)	-	1.08 (0.99-1.18)	1.00 (0.97-1.02)
Heterogeneity (I^2, p- value)	-	57.5%, 0.09	0%, 0.78

Table 94 Tea and breast cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Zhang YF, 2015	6	16 741	USA, Europe and Asia	Incidence, breast cancer	High vs low	1.00 (0.91-1.11)		
					Per 1 cup/day increase	0.99 (0.97-1.01)		5.8%, 0.38
Yu, 2014	15	20 500	USA, Europe and Asia	Incidence, breast cancer	Per 3 cups/day increase	1.02 (0.98-1.05)		21.2%, 0.22

Table 95 Tea intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Bhoo-Pathy, 2015 BRE80551 France, Italy, Spain, UK, Netherlands, Greece, Germany, Sweden, Denmark, Norway	EPIC, Prospective Cohort, Age: 25-70 years, W	6 070/ 335 060 11 years		FFQ, diet history, 7-day food diary	Incidence, postmenopausal breast cancer	Q5 vs Q1	0.95 (0.88-1.03) Ptrend:0.37	Age, age at first child birth, age at menarche, alcohol Intake, breastfeeding, decaffeinated coffee Intake, educational level, energy Intake from fat sources, energy Intake from non-fat sources, fruit and vegetables Intake, height, HRT use, menopausal status, oral contraceptive use, physical activity level, saturated fat Intake, smoking status, study centre, tea Intake, weight	Mid-point exposure Increment converted to 200 mL Hamling method used to recalculate RR's
						per 100 ml	1.00 (0.99-1.00)		
		2 142/			Incidence, breast cancer ER+ & PR+, postmenopausal	per 100 ml	1.00 (0.99-1.02)		
		605/			Incidence, breast cancer ER- & PR-, postmenopausal	per 100 ml	1.00 (0.98-1.02)		
		724/			Incidence, premenopausal breast cancer	Q5 vs Q 2	0.98 (0.77-1.26) Ptrend:0.62		
		724/			Incidence, premenopausal breast cancer	per 100 ml	1.00 (0.98-1.03)		
Oh, 2015 BRE80594 Sweden	WLHS, Prospective Cohort, Age: 30-49 years,	1 395/ 42 099 856 529 person-years	Cancer and mortality registries	FFQ	Incidence, Invasive breast cancer	per 1 cup/day	1.14 (1.05–1.24)	Age, alcohol consumption, BMI, breastfeeding	Mid-point exposure
					Incidence, Invasive breast	>1 vs 0 cups/day	1.19 (1.00–1.42)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	W				cancer				
		954/			Incidence, Invasive breast cancer, postmenopausal	>1 vs 0 cups/day	1.22 (0.97–1.53)		
		954/			Incidence, Invasive breast cancer, postmenopausal	per 1 cup/day	1.17 (1.06–1.30)		
		532/			Incidence, Invasive breast cancer, premenopausal	per 1 cup/day	1.10 (0.96–1.25)		
		532/			Incidence, Invasive breast cancer, premenopausal	>1 vs 0 cups/day	1.13 (0.87–1.47)		
		847/			Incidence, breast cancer ER+ & PR+, postmenopausal	per 1 cup/day	1.21 (1.09–1.34)		
		194/			Incidence, breast cancer ER+ & PR-, postmenopausal		1.17 (0.94–1.45)		
		26/			Incidence, breast cancer ER- & PR+, postmenopausal		0.88 (0.46–1.69)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		170/			Incidence, breast cancer ER- & PR-, postmenopausal		0.98 (0.77–1.26)		
Boggs, 2010b BRE80326 USA	BWHS, Prospective Cohort, Age: 21-69 years, W	1 268/ 52 062 12 years	Self-report verified by medical record		Incidence, breast cancer	≥4 cups/day vs never/<1 cups/month	1.13 (0.78–1.63) Ptrend:0.67	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, BMI, contraception, educational level, energy Intake, family history of breast cancer, geographic region, HRT use, menopausal status, parity, smoking, vigorous activity	Mid-point exposure
		562/			Incidence, breast cancer, premenopausal		0.90 (0.48–1.69) Ptrend:0.43		
		570/			Incidence, breast cancer, postmenopausal		1.44 (0.89–2.34) Ptrend:0.12		
Larsson, 2009b BRE80251 Sweden	SMC, Prospective Cohort, Age: 40-76 years, W	2 952/ 61 433 17.4 years	Cancer registry	FFQ	Incidence, Invasive breast cancer	≥2 vs 0 cups/day	1.22 (1.05–1.42) Ptrend:0.007	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, BMI, educational level, family history of cancer, height,	Mid-point exposure
		1 286/			Incidence, breast cancer ER+/PR+		1.36 (1.09–1.69) Ptrend:0.007		
		417/			Incidence, breast cancer ER+/PR-		0.97 (0.64–1.48) Ptrend:0.69		
		266/			Incidence, breast		1.03 (0.61–1.76)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					cancer ER-/PR-		Ptrend:0.85	HRT use, OC use, parity, tea Intake, total caloric Intake	
Ganmaa, 2008 BRE80158 USA	NHS, Prospective Cohort, Age: 30-55 years	5 272/ 85 987 22 years	Questionnaire/medical records/death record	FFQ	Incidence, breast cancer	≥4 vs ≤0.9 cup/month	0.94 (0.77–1.14) Ptrend:0.25	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, benign breast disease, BMI, duration of HRT use, family history of cancer, height, HRT use, menopausal status, parity, physical activity, smoking status, tea Intake, weight	Mid-point exposure

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Ishitani, 2008 BRE80189 USA	WHS, Prospective Cohort, Age: 45- years, W	1 181/ 38 432 10 years	Self-reported/death certificate/ medical records	FFQ	Incidence, Invasive breast cancer	≥2 cups/day vs almost never	1.03 (0.85-1.25) Ptrend:0.99	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, benign breast disease, BMI, energy Intake, family history of cancer, hysterectomy, menopausal status, multivitamin supplement Intake, number of full-term pregnancies, oophorectomy/hysterectomy, physical activity, postmenopausal hormone use, randomized treatment assignment, smoking status	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Hirvonen, 2006 BRE80105 France	SU.VI.MAX, Prospective Cohort, Age: 35-60 years, W, participants of a RCT	95/ 4 396 6.6 years	Medical records	24h recall	Incidence, breast cancer	≥350 vs 0 ml/day	0.75 (0.45–1.28) Ptrend:0.37	Age , family history, menopausal status, OC use, parity/pregnancies, smoking habits	Mid-point exposure Person years of follow up
Zheng, 1996 BRE13990 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	1 015/ 35 369 8 years	Not specified	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	≥30 vs 0-3.9 cups/month	1.14 (0.92-1.41) Ptrend:0.28	Age , age at first child, age at menarche, age at menopause, educational level, family history, food, physical activity , smoking habits, W/HR	Mid-point exposure Person years of follow up

Table 96 Tea intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Fagherazzi, 2011 BRE80371 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years,	2 868/ 67 703 11 years	Pathology reports	Dietary history questionnaire	Incidence, Invasive breast cancer	>3 vs ≤1 cup/day	0.79 (0.62-1.01) Ptrend:0.22	Age, age at first child birth, age at menarche, age at menopause, benign breast disease, BMI,	Superseded by Bhoo-Pathy, 2015 BRE80551

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	W, Premenopausal+ postmenopausal							family history of breast cancer, HRT use, menopausal status, number of children, oral contraceptive history, school education, total energy Intake	
Bhoo Pathy N, 2010 BRE80230 Netherlands	EPIC, NL Prospective Cohort, Age: 20-70 years, W	681/ 27 323 9.6 years	Cancer registry	FFQ	Incidence, breast cancer	>5 vs 0 cup/day	0.83 (0.62-1.11)	Propensity score	Superseded by Bhoo-Pathy, 2015 BRE80551
Lee, 2010 BRE80556 China	SWHS, Nested Case Control, Age: 52 years, W	354/ 712 controls 7 years	Active follow up and cancer registry	Questionnaire	Incidence, breast cancer	yes vs no	1.05 (0.80-1.38)	Age, antibiotics use, date of urine collection, history of cancer, menopausal status	Used only in HvsL analysis
Adebamowo, 2005 BRE21537 USA	NHS, Prospective Cohort, Age: 25-46 years, W, Registered nurses	710/ 90 638 8 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, Invasive breast cancer	60 vs ≥0.99 serving/month	1.02 (0.81-1.28) Ptrend:0.83	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, energy Intake , family history, height, menopausal status, OC use, parity/pregnancies	Superseded by Ganmaa, 2008 BRE80158

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								, physical activity, smoking habits	
Li, 2005 BRE23123 China	Shanghai BSE, Nested Case Control, W	130/ 1070 controls	All histology	FFQ-semi-quantitative	Incidence, breast cancer	ever vs never times/year	0.80 (0.50-1.30)	Age	Used only in HvsL analysis
Michels, 2002 BRE20406 Sweden	SMC, Prospective Cohort, Age: 40-76 years, W	1 271/ 59 036 9.5 years	All histology	FFQ-semi-quantitative	Incidence, Invasive breast cancer	≥4 cups/day vs <1 cups/week or less	1.13 (0.91-1.40) Ptrend:0.11	Age , age at first child, alcohol, BMI, educational level, energy Intake , family history, height, parous/nulliparous	Superseded by Larsson, 2009b BRE80251

Figure 149 RR estimates of breast cancer by levels of tea intake

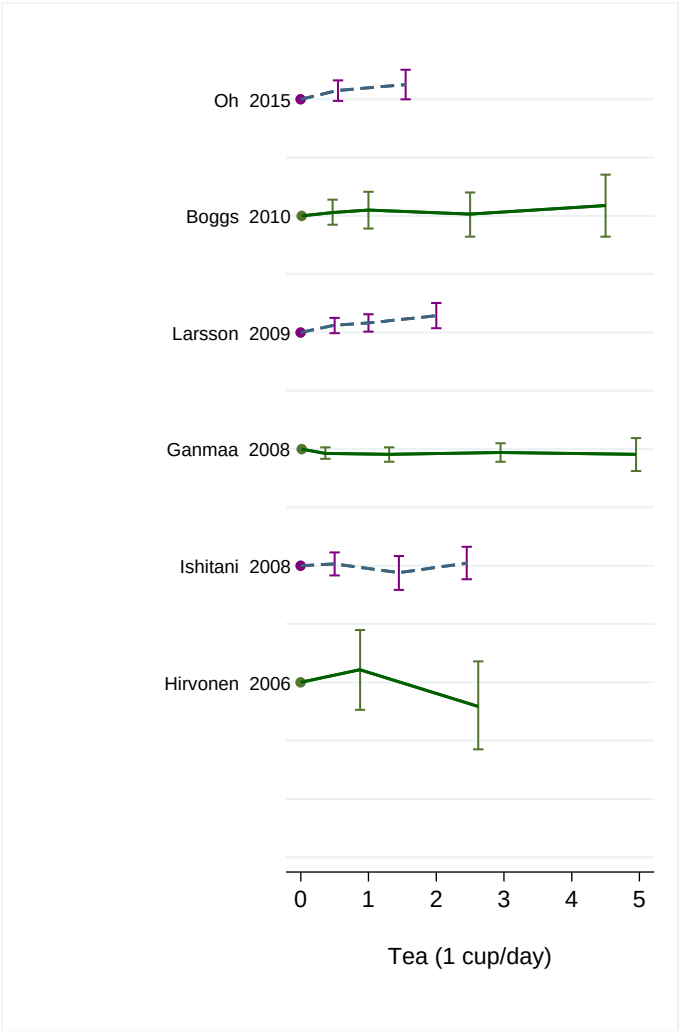


Figure 150 RR estimates of premenopausal breast cancer by levels of tea intake

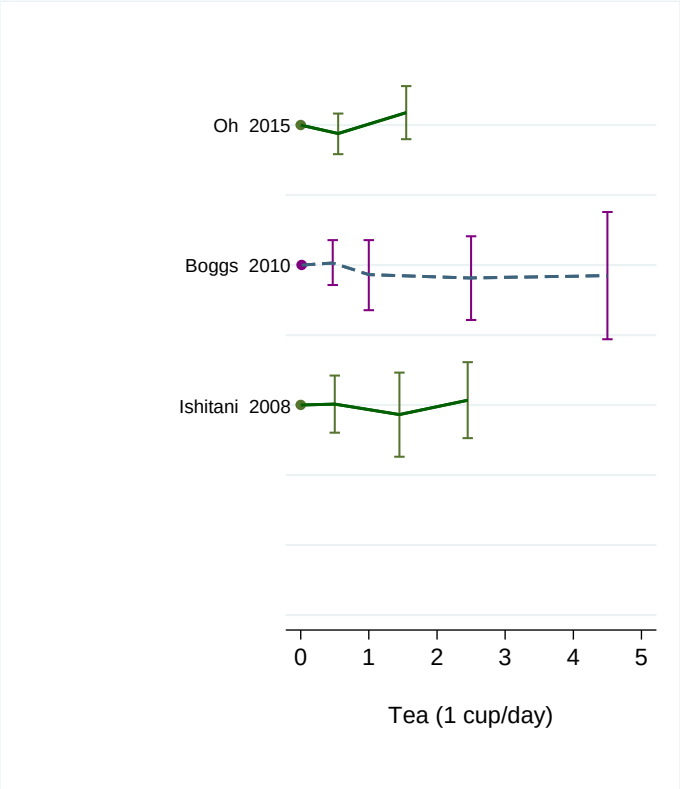


Figure 151 RR estimates of postmenopausal breast cancer by levels of tea intake

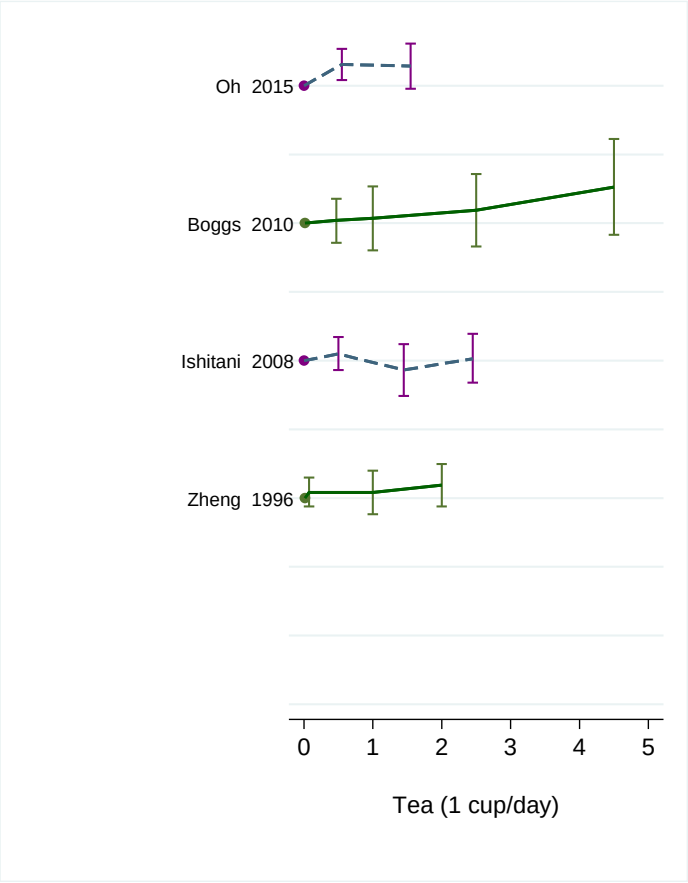
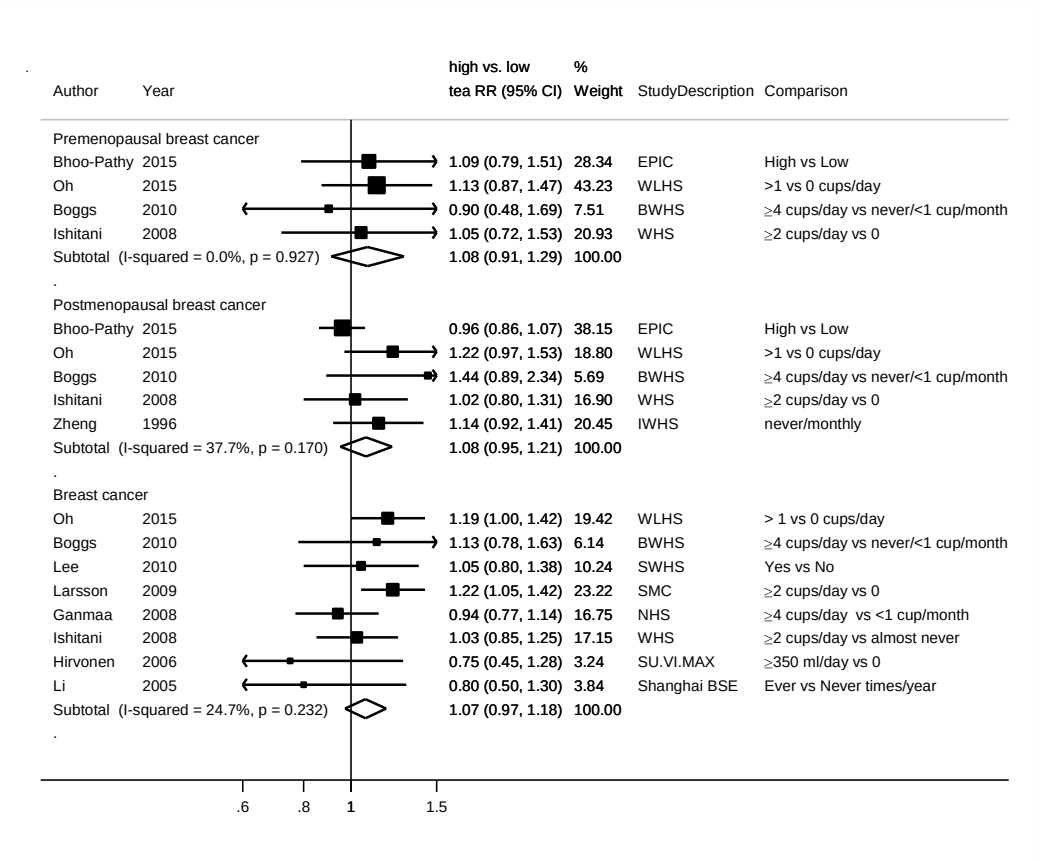


Figure 152 RR (95% CI) of breast cancer for the highest compared with the lowest level of tea intake



* Hamling method was used to recalculate the RR's in the study of Bhoo-Pathy, 2015.

Figure 153 Relative risk of breast cancer for 1 cup/day increase of tea intake

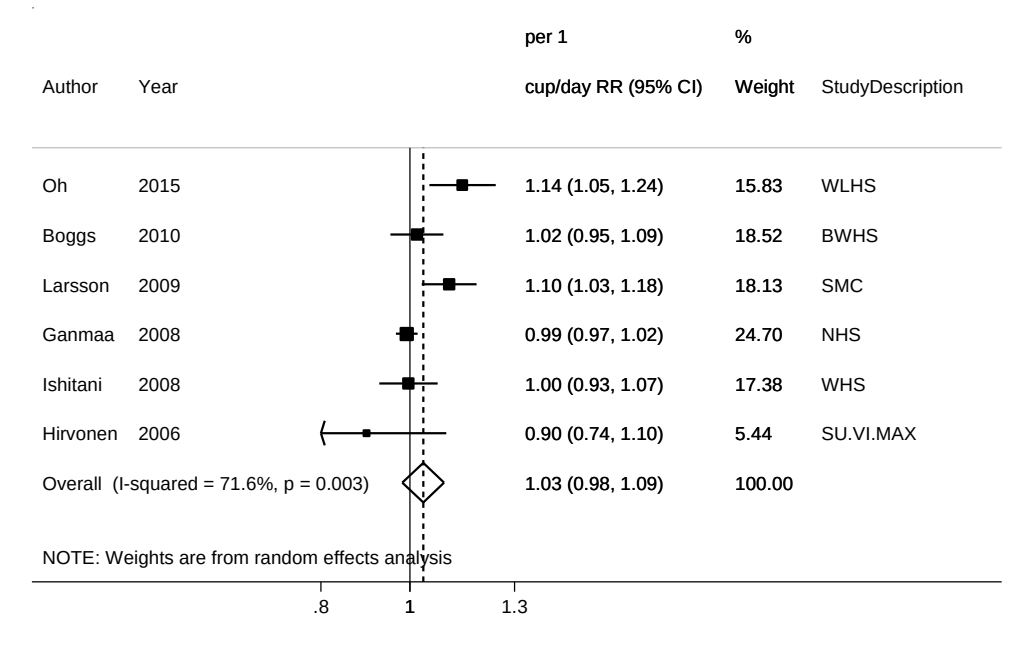


Figure 154 Relative risk of premenopausal breast cancer for 1 cup/day increase of tea intake

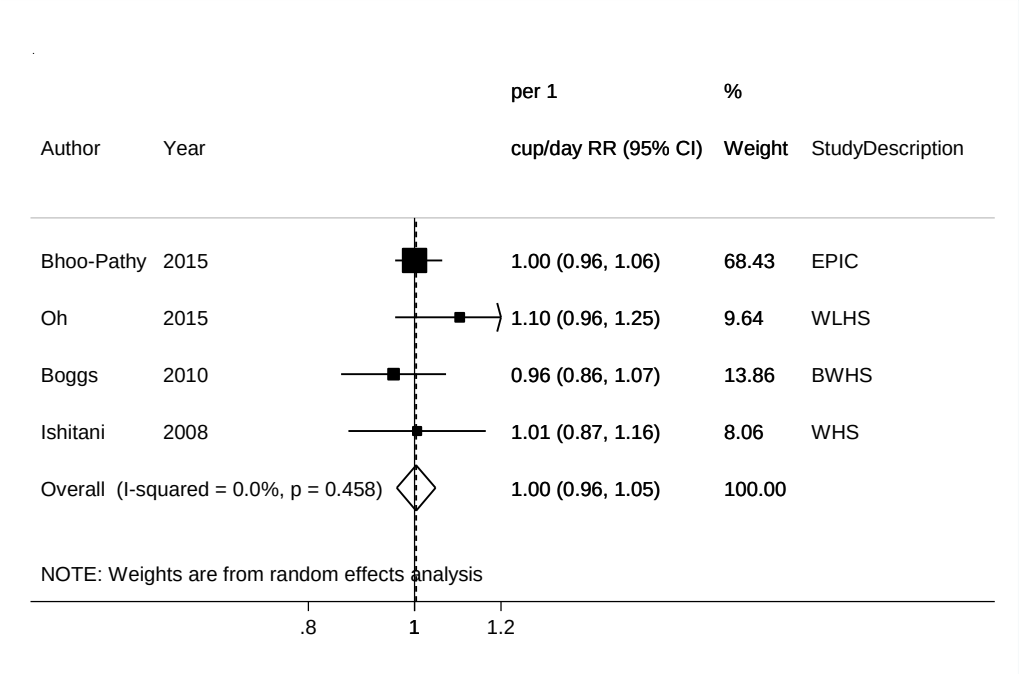


Figure 155 Relative risk of postmenopausal breast cancer for 1 cup/day increase of tea intake

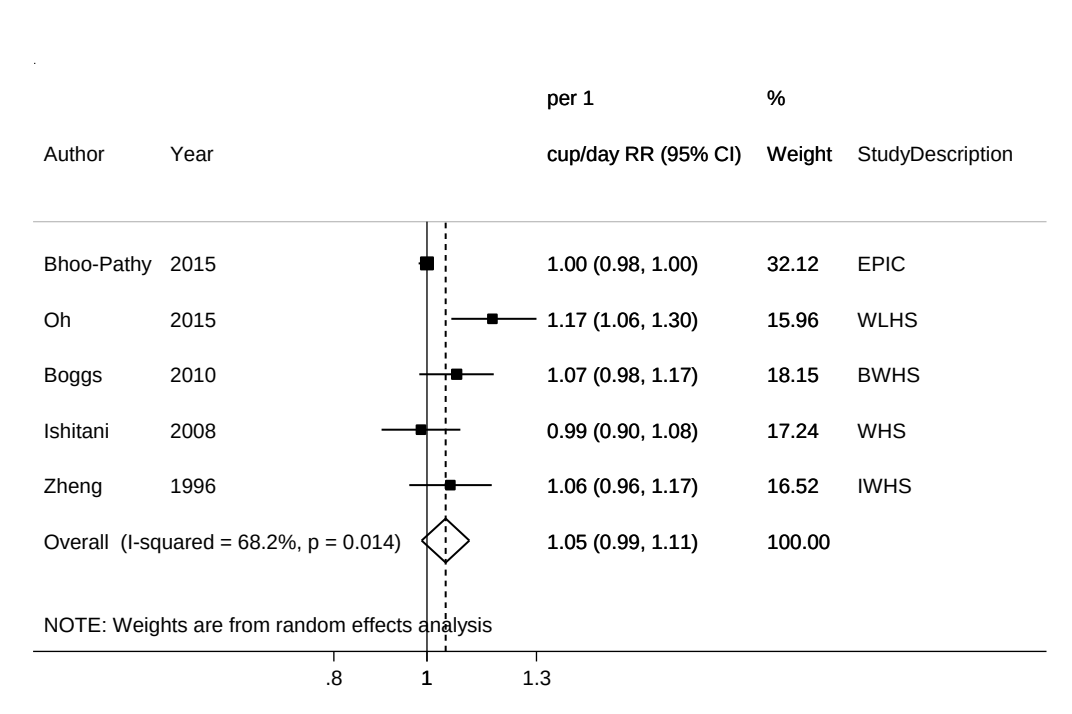


Figure 156 Funnel plot of studies included in the dose response meta-analysis of tea and breast cancer

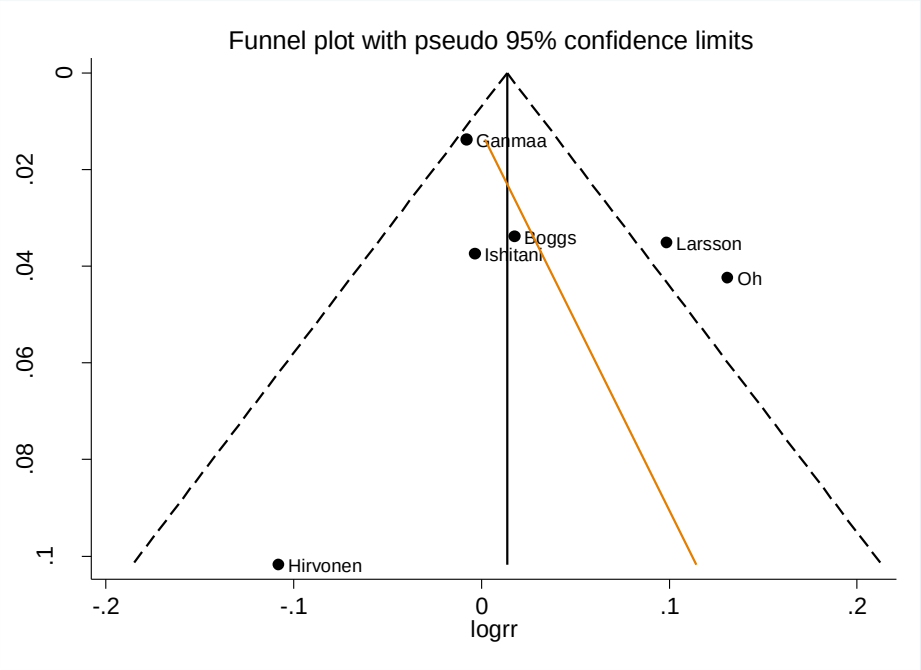


Figure 157 Funnel plot of studies included in the dose response meta-analysis of tea and premenopausal breast cancer

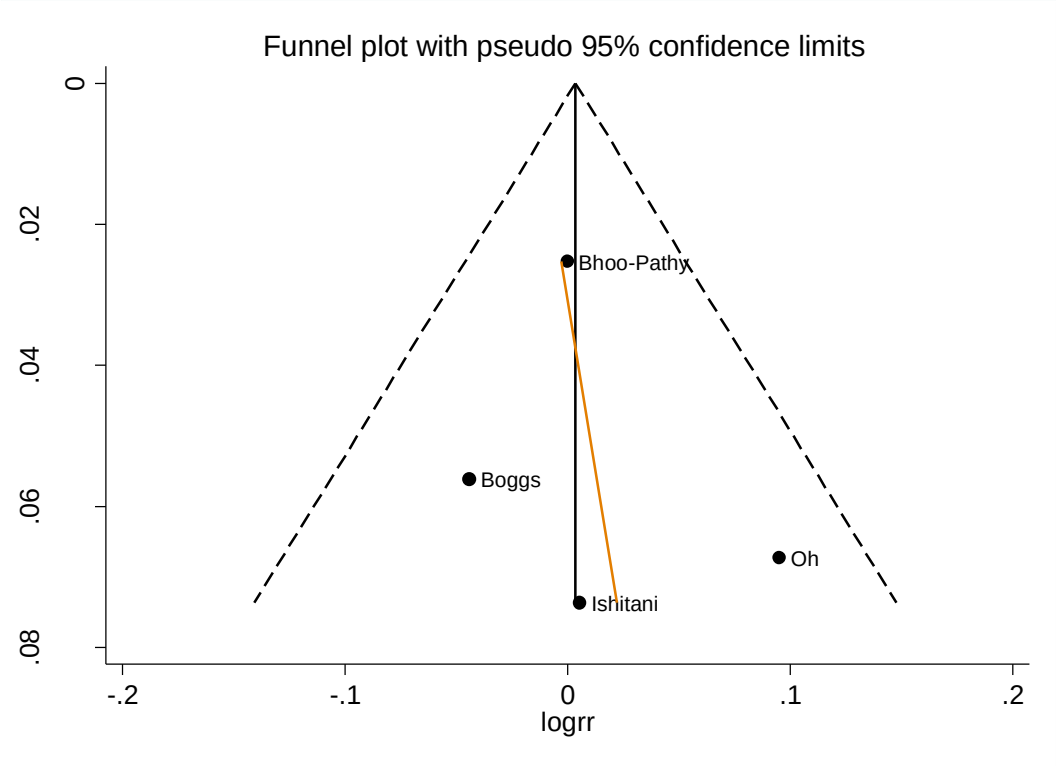
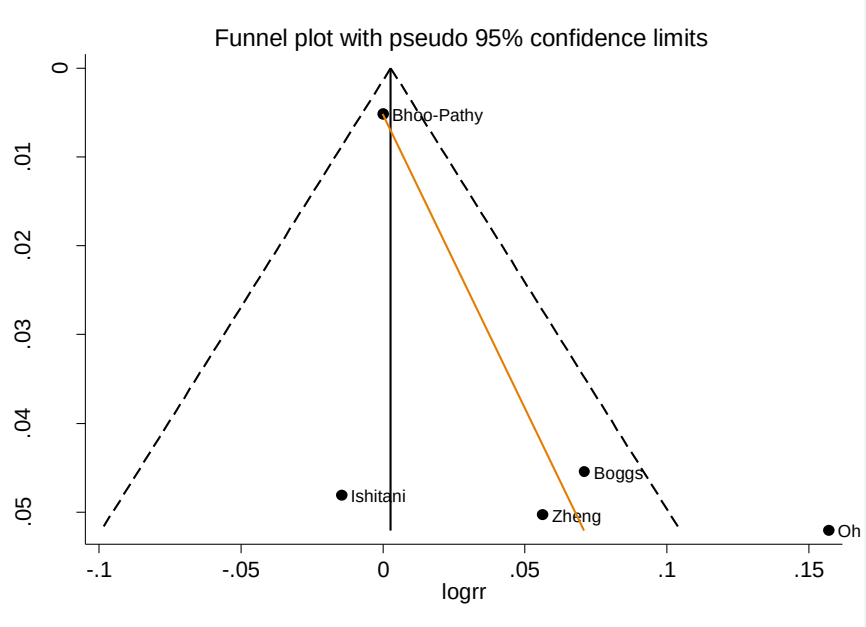


Figure 158 Funnel plot of studies included in the dose response meta-analysis of tea and postmenopausal breast cancer



3.6.2 Black tea

Cohort studies

Five publications, including one new study on black tea intake and breast cancer risk were identified. No meta-analysis was conducted. In the SLR 2005, three studies (Goldbohm, 1996; Key, 1999; Yuan, 2005) were included in the meta-analysis and black tea was not shown to be related to breast cancer.

The study characteristics and results are shown in a Table in this section.

Table 97 Black tea intake and breast cancer risk. Main characteristics of studies.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Iwasaki, 2010 BRE80329 Japan	JPHC I and II, Prospective Cohort, Age: 40-69 years	576/ 97 432	Hospital records/cancer registries	FFQ	Incidence, breast cancer	≥1 cup/day vs <1 cups/week	1.30 (0.84-2.02) Ptrend:0.80	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, area, BMI, coffee Intake, family history of breast cancer, height, HRT use, leisure time physical activity, menopausal status, number of childbirths, smoking, tea Intake	
Iso, 2007 BRE80427 Japan	JACC, Prospective Cohort, Age: 40-79 years, W	73/ 15 years	Municipal resident registration records, death certificates	FFQ	Mortality, breast cancer	≥ 1-2 per/week vs rare	0.65 (0.29-1.44)	Age, centre location	
Yuan, 2005 BRE24717 Singapore	SCHS, Nested Case Control, Age: 45-74 years, W	367/ 799 controls 9 years	Partially histological - over 80%	FFQ	Incidence, breast cancer	Weekly or more frequently vs non-drinkers	1.21 (0.86-1.71)	Age , educational level, food, other menstrual characteristics, parity/pregnancies, time of	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								recruitment	
Key, 1999 BRE04758 Japan	LSS, 1969, Prospective Cohort, W	427/ 34 759 24 years	Partially histological - over 80%	Questionnaire	Incidence, breast cancer	≥5 vs ≤1 times/week	1.10 (0.82-1.48) Ptrend:0.981	Age , calendar year, other factors , other factors , place of residence	
Goldbohm, 1996 BRE03308 Netherlands	NLCS, Case Cohort, Age: 55-69 years, W	507/ 62 573 4.3 years	All histology	FFQ-semi-quantitative	Incidence, Invasive breast cancer	≥5 vs ≤0 cups/day	1.31 (0.86-1.99) Ptrend:0.185	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, educational level, energy Intake , family history, OC use, other factors , parity/pregnancies, smoking habits	

3.6.2.2 Green tea

Cohort studies

Seven publications on green tea intake and breast cancer risk were identified. From these, one study could be included only in highest vs lowest analysis.

Two studies investigated postmenopausal breast cancers, two were on premenopausal breast cancers, and seven were on pre- and postmenopausal breast cancers combined.

The study characteristics and results are shown in a Table in this section.

Study quality

Tea intake was assessed by FFQ and questionnaires in all studies.

In the studies, cancer outcome was confirmed using medical notes, death records or through cancer registries.

Breast cancer (any)

Summary

Main results:

Six studies (3 113 cases), all from Asia, were included in the dose-response meta-analysis. No significant inverse association was observed.

No heterogeneity was observed. There was no evidence of a significant publication or small study bias (p=0.91).

Sensitivity analyses:

In influence analysis, the summary RR ranged from 0.98 (95% CI=0.95-1.02) when Iwasaki, 2010 was omitted to 1.00 (95% CI=0.97-1.04) when Key, 1999 was omitted.

Nonlinear dose-response meta-analysis:

Not enough studies to conduct the analysis (n=2).

Premenopausal breast cancer

Not enough studies were identified (n=2).

Postmenopausal breast cancer

Not enough studies were identified (n=2).

Table 98 Green tea and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	7 (7 publications)
Studies included in forest plot of highest compared with lowest exposure	Breast cancer: 7 (7 publications) Premenopausal: not enough studies (n=2). Postmenopausal: not enough studies (n=2).
Studies included in linear dose-response meta-analysis	Breast cancer: 6 (6 publications) Premenopausal: not enough studies (n=2). Postmenopausal: not enough studies (n=2).
Studies included in non-linear dose-response meta-analysis	Breast cancer: not enough studies Premenopausal: not enough studies Postmenopausal: not enough studies

Table 99 Green tea intake and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005SLR	**CUP SLR**
Increment unit used	1 cup/day	1 cup/day
All studies		
Studies (n)	2	6
Cases (total number)	794	3 113
RR (95%CI)	0.96 (0.90-1.03)	0.99 (0.97-1.02)
Heterogeneity (I^2, p-value)	0%	0%, 0.56
P value Egger test	-	0.91

Table 100 Green tea and breast cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Zhang YF, 2015	4	16 741	Asia	Incidence, breast cancer	Per 1 cup/day increase	0.99 (0.96-1.02)		0%, 0.72
Ogunleye, 2010	2	649	Japan	Incidence, breast cancer	≥3 cups/day	0.85 (0.65-1.21)		0%, 0.93

Table 101 Green tea intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Iwasaki, 2010 BRE80329 Japan	JPHC I and II, Prospective Cohort, Age: 40-69 years	577/ 97 432	Hospital records/cancer registries	FFQ	Incidence, breast cancer	≥5 cups/day vs <1 cups/week	1.12 (0.81-1.56) Ptrend:0.60	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, area, BMI, family history of breast cancer, height, HRT use, leisure time physical activity, menopausal status, number of childbirths, smoking, tea Intake, tea Intake	Mid-point exposure Unit converted to cups/day
Inoue, 2008a BRE80222 Singapore	SCHS, Nested Case Control, Age: 45-74 years, W	380/ 662 controls	Cancer registry	FFQ	Incidence, breast cancer	daily vs none or <weekly	1.00 (0.82-1.22) Ptrend:0.41	Age, age at menarche, black tea consumption, BMI, educational level, ethnicity, number of full-term pregnancies, year of recruitment	Mid-point exposure Unit converted to cups/day

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Iso, 2007 BRE80427 Japan	JACC, Prospective Cohort, Age: 40-79 years, W	93/ 15 years	Municipal resident registration records, death certificates	FFQ	Mortality, breast cancer	≥4 /day vs ≤3-4 /week	1.24 (0.70-2.19)	Age, centre location	Mid-point exposure Unit converted to cup/day
Yuan, 2005 BRE24717 Singapore	SCHS, Nested Case Control, Age: 45-74 years, W	367/ 799 controls 9 years	Partially histological - over 80%	FFQ	Incidence, breast cancer	Weekly or frequent drinkers vs non drinkers	0.91 (0.66--1.26)	Age , educational level, food, other SES Index, other menstrual characteristics, parity/pregnancies, time of recruitment	Mid-point exposure Unit converted to cup/day
Suzuki, 2004 BRE80557 Japan	MCS I, Prospective Cohort, Age: 40- years, W	222/ 35 004 9 years	Population registers	FFQ	Incidence, breast cancer, pooled (cohort I & II)	≥5 vs 0-0.9 cup/day	0.84 (0.57-1.24) Ptrend:0.69	Age, age at first child birth, age at menarche, alcohol drinking, black tea consumption, BMI, coffee, family history of breast cancer, health Insurance, menopausal status, parity, smoking status	Mid-point exposure
		103/			Cohort I		1.17 (0.67 – 2.05) Ptrend:0.26		
		119/			Cohort II		0.61 (0.36 – 1.06) Ptrend:0.12		
Key, 1999 BRE04758	LSS, 1969, Prospective	427/ 34 759	Partially histological -	Questionnaire	Incidence, breast cancer	≥5 vs ≤1 times/day	0.86 (0.62–1.21) Ptrend:0.28	Age , calendar year, other	Mid-point exposure

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Japan	Cohort, W	24 years	over 80%					factors , other factors , place of residence	

Table 102 Green tea intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Dai, 2010 BRE80235 China	SWHS, Prospective Cohort, Age: 40-70 years, W	614/ 72 861 7.3 years	Self-report, cancer registry, death report		Incidence, breast cancer	yes vs no	1.04 (0.88-1.26)	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, benign breast disease, BMI, educational level, family history of cancer, fish, fruits Intake, HRT use, Income, Isoflavone, menopausal status, nutritional factors , physical activity, red meat Intake, smoking habits, smoking status, total caloric Intake, vegetable Intake, waist to hip ratio	Used only in HvsL analysis

Figure 159 RR estimates of breast cancer by levels of green tea intake

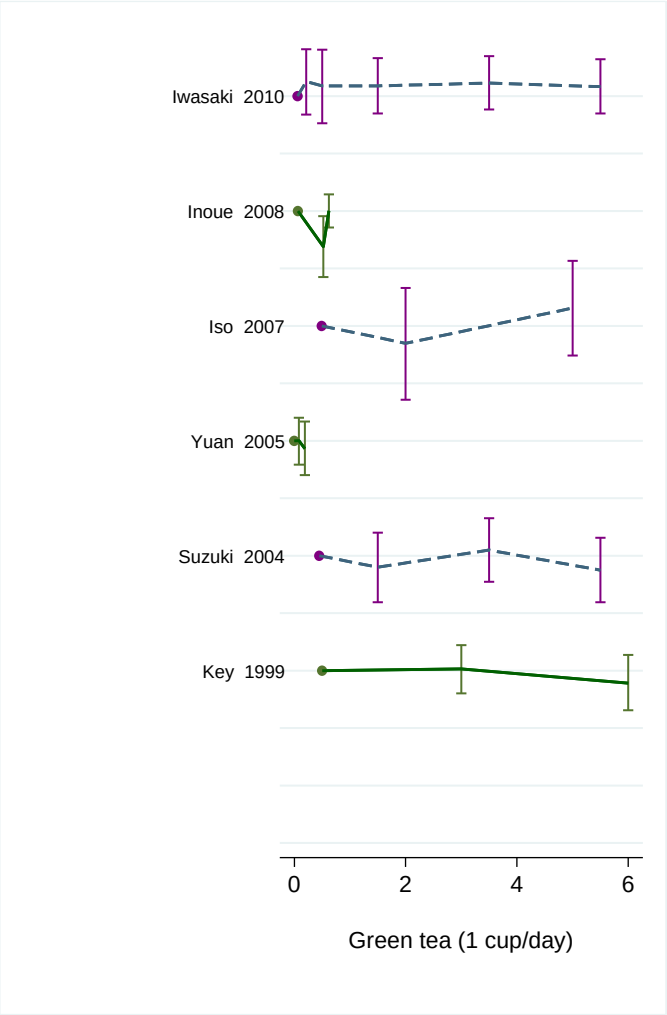


Figure 160 RR (95% CI) of breast cancer for the highest compared with the lowest level of green tea intake

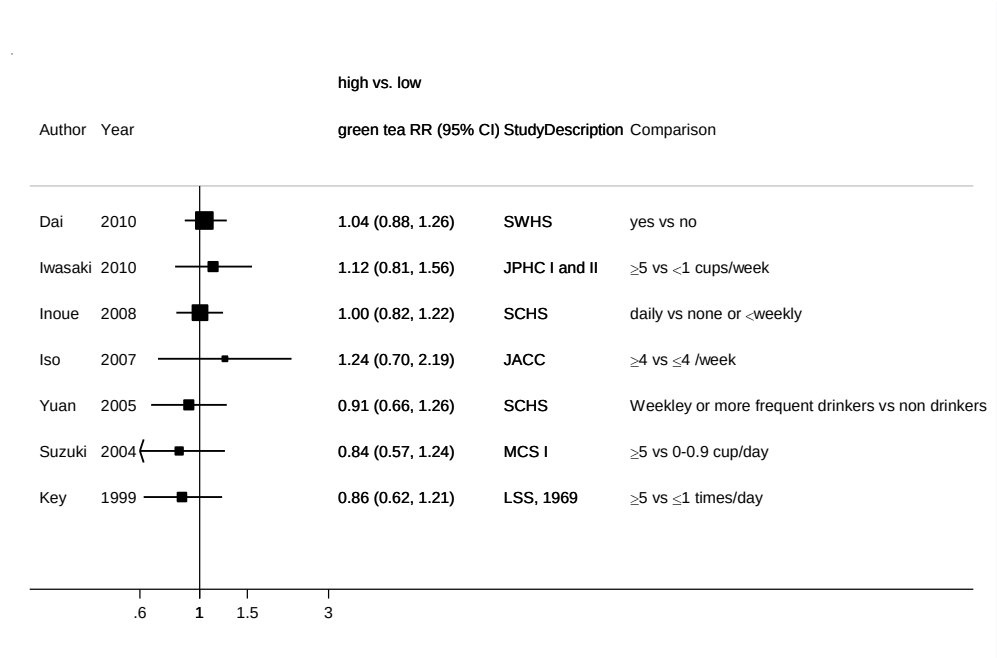


Figure 161 Relative risk of breast cancer for 1 cup/day increase of green tea intake

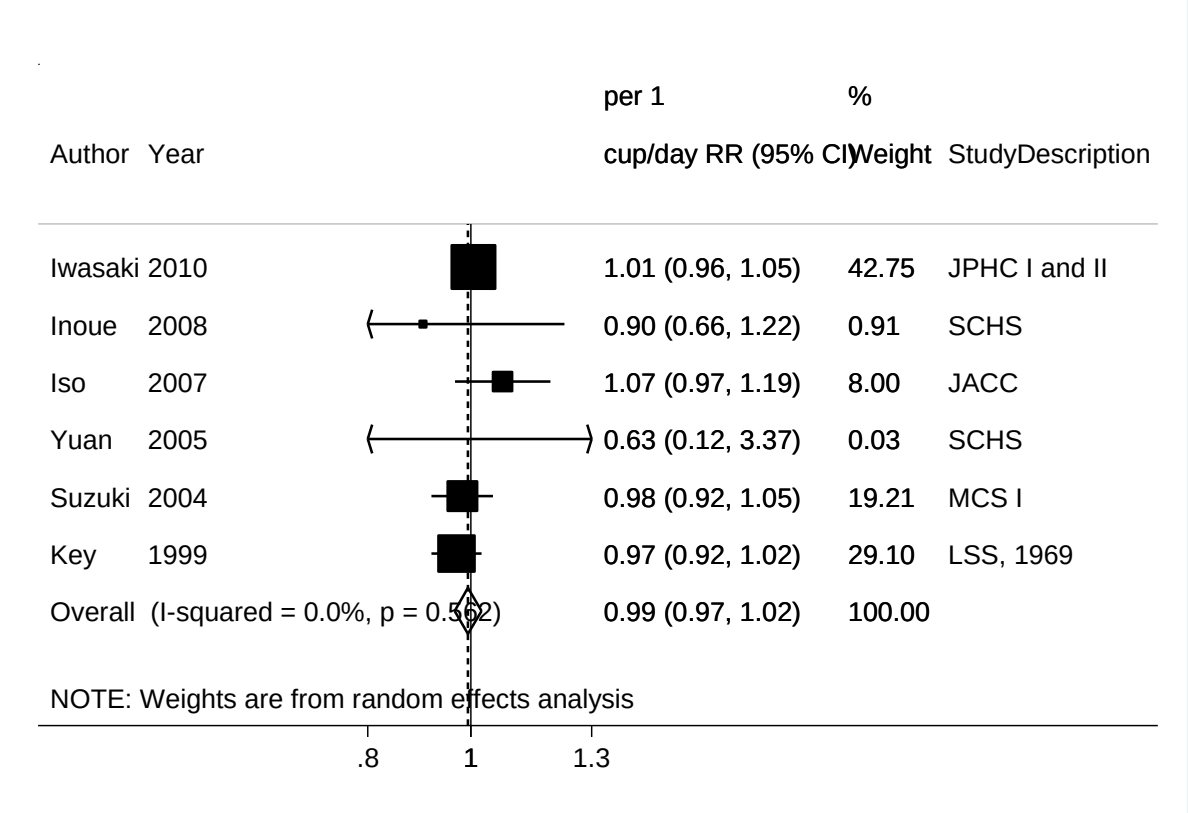
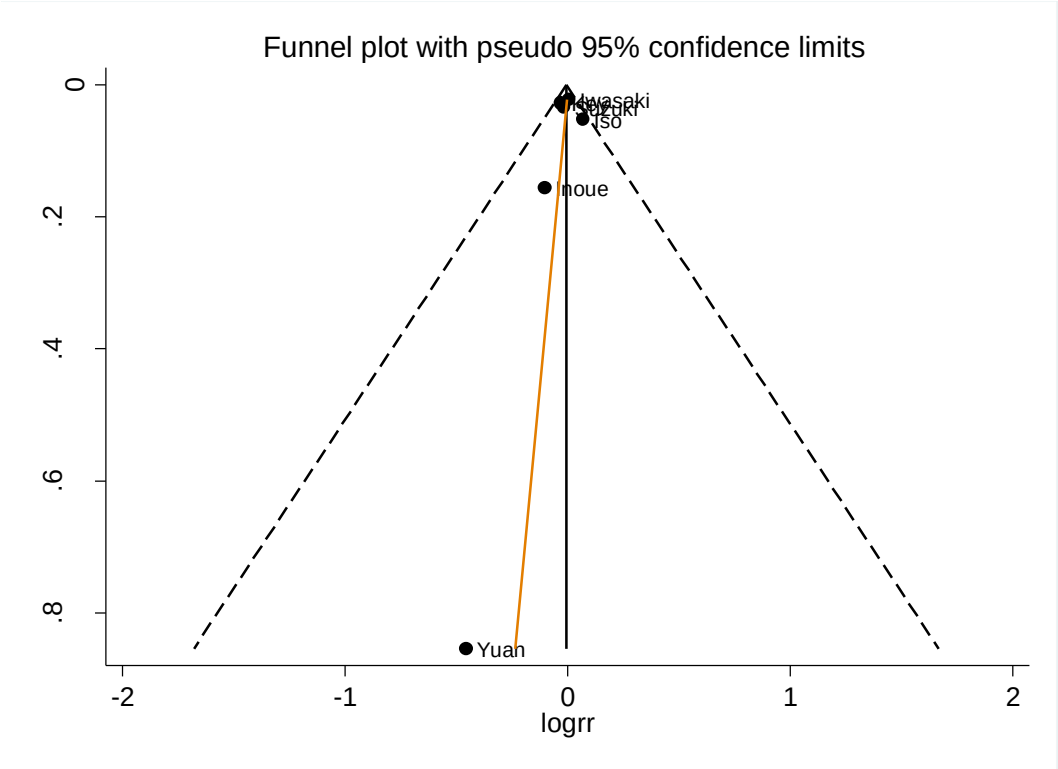


Figure 162 Funnel plot of studies included in the dose response meta-analysis of green tea and breast cancer



4 Food production, preservation, processing and preparation

4.4.2 Acrylamide

Cohort studies

Summary

Eight publications from seven cohorts that examined dietary acrylamide intake were identified. One meta-analysis was identified and no pooled analysis was identified.

Dose response meta-analyses were not conducted due to insufficient data.

Breast cancer (any)

Four publications (four cohorts) were identified (Burley, 2010; Wilson, 2010; Larsson, 2009a; Mucci, 2006). None of those studies found significant associations between acrylamide intake and breast cancer, however there results are conflicting.

More specifically, the cohorts UKWCS (Burley, 2010) and WLHS (Mucci, 2006) showed that there was a non-significant positive association between breast cancer and acrylamide consumption. In addition, Burley et al (2010) reported that among non-smokers participants, per 10μg/day increase of acrylamide intake there was a non-significant positive association with breast cancer, while results on highest versus lowest acrylamide intake showed a non-significant slightly decreased risk of breast cancer.

The NHS (Wilson, 2010) and SMC (Larsson, 2009a) cohorts reported that higher intake of acrylamide had a non-significant inverse association with breast cancer, compared to lower intake. Among never smokers there was a deeper decrease on breast cancer risk with higher consumption of acrylamide, yet not significant (Wilson, 2010). The association remained inversely non-significant for ER+PR+ and ER+PR- breast cancer, while positively non-significant association was found for ER-PR- breast cancer. Furthermore, Wilson et al. (2010) did not find a significant association between acrylamide intake and breast cancer in stratified analyses by BMI.

Table 103 Acrylamide intake and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Pelucchi, 2015	8 studies* (5 cohorts, 2 case-cohorts, 1 case-control study)	16 773	UK, Netherlands, USA, Sweden , Denmark	Total Premenopausal Postmenopausal ER+PR+ cancer ER+PR- cancer ER-PR+ cancer ER-PR- cancer Never smokers Ever smokers	Highest vs lowest acrylamide intake	0.96 (0.91-1.02) 1.02 (0.89-1.17) 0.93 (0.85-1.02) 0.98 (0.89-1.08) 1.09 (0.89-1.33) 1.09 (0.63-1.87) 0.89 (0.75-1.06) 0.91 (0.83-1.01) 0.98 (0.78-1.24)		0.37
				Total	10µg/day increment in acrylamide intake	1.00 (0.98-1.01)		0.33

*Seven out of the eight identified studies were included since two studies used data from the same cohort.

Premenopausal breast cancer

Three studies were identified reporting results on premenopausal breast cancer and acrylamide intake (Burley, 2010; Wilson, 2010; Wilson, 2009). The UKWCS study showed that per 10µg per day increment of acrylamide intake had a significant positive association with premenopausal breast cancer (Burley, 2010). However, a significant association was not found for the highest versus lowest analysis neither among only non-smokers women.

The NHS presented that there was a non-significant positive association with higher consumption of acrylamide and premenopausal breast cancer (Wilson, 2010).

The NHS II revealed a non-significant inverse association of premenopausal breast cancer and higher acrylamide intake (Wilson, 2009). Stratified analyses by smoking status showed a non-significant positive association between higher acrylamide intake and premenopausal breast cancer among former smokers and current smokers, while a non-significant inverse association was found among never smokers. Analyses by ER and PR status showed a non-significant positive association for ER+PR+ breast cancer and a non-significant inverse association for ER-PR- breast cancer.

Postmenopausal breast cancer

Five publications from four cohorts were identified on postmenopausal breast cancer and acrylamide intake (Olesen, 2008; Wilson, 2010; Pedersen, 2010; Hogervost, 2007; Burley, 2010). The DCH study examined the association between breast cancer and exposure to acrylamide using the biomarkers (AA-Hb and GA-Hb) (Olesen, 2008). The study showed that per 10-fold increase in concentrations of AA-Hb and GA-Hb there was a non-significant positive association and a non-significant inverse association with postmenopausal breast cancer, respectively. Similar trends were observed for 10-fold increment of AA-Hb and GA-Hb among ER+ postmenopausal breast cancer. Among ER- breast cancer a 10-fold increment of AA-Hb and GA-Hb showed a non-significant inverse association. In addition, stratified analyses by smoking status did not show a significant association with total postmenopausal breast cancer as well as among ER+ postmenopausal breast cancer.

The NHS study showed a non-significant positive association between higher dietary acrylamide intake and postmenopausal breast cancer (Wilson, 2010).

Two publications reporting results from NLCS cohort, examined the association between dietary acrylamide intake and postmenopausal breast cancer (Pedersen, 2010; Hogervost, 2007). Both of the studies showed a non-significant inverse association with higher acrylamide consumption and total breast cancer, while a non-significant positive association was detected among never smokers. In addition, Pederson et al. (2010) presented that stratified analyses by oestrogen and progesterone receptor status, did not show a significant association between higher acrylamide intake and postmenopausal ER+, ER-, PR+, PR-, ER+PR+, ER+PR-, ER-PR+, ER-PR- breast cancer among smokers and non-smokers combined as well as among only non-smokers (Pederson, 2010).

The UKWCS cohort (Burley, 2010) revealed a non-significant slight decreased risk for postmenopausal breast cancer with higher acrylamide intake among smokers and never-smokers combined as well as among only never-smokers. In addition, per 10µg/day increment of acrylamide intake did not show an association among smokers and never-smokers combined as well as among only never-smokers.

5 Dietary constituents

5.1.1 Total carbohydrate

Cohort studies

Overall summary

Twenty publications from 13 studies on total carbohydrate intake and one study on percentage of energy from carbohydrates and breast cancer risk were identified. From the 20 publications, three are from cohort studies that participated in EPIC and were not counted as separated studies from EPIC. Dose-response meta-analyses were conducted for studies that reported associations with pre- and postmenopausal breast cancers combined (Any breast cancer), premenopausal breast cancers (Pre), postmenopausal breast cancers (Post), and by hormone receptor status.

Another study in the NHSII investigated percentage of energy from carbohydrates in early adulthood and breast cancer risk. These results are not included in the meta-analyses.

Table 104 Carbohydrate intake and breast cancer. Number of studies in the CUP SLR by analysis

Analysis		Number
Studies identified	Total	13 (20 publications)
Studies included in forest plot of highest compared with lowest CHO intake		
	Any breast cancer	7
	Premenopausal	3
	Postmenopausal	7
Studies included in linear dose-response meta-analysis		
	Any breast cancer	4
	Premenopausal	3
	Postmenopausal	8

Table 105 Summary of results of the dose-response meta-analyses on CHO intake and breast cancer risk in the CUP SLR and the 2005 SLR

	2005 SLR	**CUP SLR**		
	Post-menopausal breast cancer	**Any breast cancer**	**Pre-menopausal breast cancer**	**Post-menopausal breast cancer**
Increment unit	Per 50 g/day	Per 50 g/day		
Studies (n)	3	4	3	8
Cases		13 696	3 679	18 785
RR (95%CI)	1.09 (1.00-1.18)	1.00 (0.93-1.07)	1.09 (0.90-1.33)	1.02 (0.97-1.08)
Heterogeneity (I^2, p-value)	60.9%	50.4%, 0.11	81.4%, 0.005	53.0%, 0.04
P value Egger test	NA	0.41	0.33	0.60
	-	**ER+/PR+**	**ER-/PR-**	**ER-/PR-**
Studies (n)	-	3	3	4

Cases	-	4564	1156	1877
RR (95%CI)	-	0.93 (0.81-1.06)	1.05 (0.78-1.40)	1.09 (0.96-1.24)
Heterogeneity (I2, p-value)	-	73.2%, 0.02	62.2%, 0.07	32.5%, 0.21
P value Egger test	-	0.79	0.77	0.40

Breast cancer (any)

Seven studies on carbohydrate intake and risk of any breast cancer were identified. Four studies reported the data needed for dose-response meta-analysis; no significant association was observed. No heterogeneity was observed.

Amongst excluded studies (see tabulated reasons for exclusion), dietary carbohydrates intake was inversely but not statistically significantly related to breast cancer risk in two studies (Giovannucci, 1993a, Horn-Ross, 2002). A positive not significant association was observed in the fourth excluded study (Martin, 2011)

A study (EPIC Italy, Sieri, 2013) participating in EPIC was not included in the counts as a separate study.

There is no statistical evidence of publication bias but only three studies were included in the analysis.

The study on percentage of energy from carbohydrates in early adulthood

Premenopausal breast cancer

Three studies on premenopausal breast cancer were identified. All were included in the dose-response meta-analysis. Positive but not significant association was observed. There was high heterogeneity driven by a study in Chinese women (Wen, 2009) that reported a strong increase in breast cancer risk in premenopausal women with increasing levels of dietary carbohydrate. Publication bias was not tested due to low number of studies.

There is no statistical evidence of publication bias but only three studies were included in the analysis.

Postmenopausal

Nine studies were identified and eight could be included in the dose-response meta-analysis. Overall, no association was observed. There was moderate heterogeneity. A small study (Barrett-Connor, 1993) was the only study to report a significant positive association and a not statistically significant positive association was also observed in the study in Chinese women (Wen, 2009). A significant inverse association when comparing the highest with the lowest intake was observed in the Italian ORDET study (Sieri, 2002).

In one of the excluded studies a positive dose-response association was observed (Giles, 2006) that was statistically significant in localized but not in non localized breast cancer.

There is no statistical evidence of publication bias (p=0.60) but the funnel plot including the limited number of studies available shows a small study reporting a strong positive

association (Barrett-Connor, 1993) and suggests that small studies showing weaker association than the summary may be missing.

Breast cancer by hormone receptor status

Six studies reported on the association of carbohydrate intake and breast cancer by hormone receptor status. Three to four studies could be included in dose-response meta-analyses. In general, results were discordant and no clear pattern of association emerged.

Sensitivity analyses:

Subgroup and sensitivity analyses were not conducted due to low number of studies.

Non-linear dose-response meta-analysis:

Not conducted due to low number of studies

Study quality:

Most publications (twelve) are from 2005 or before. All studies are in North America or Europe except a study in urban Chinese women (Wen, 2009).

No issues relevant to study quality were identified in the studies included in the dose-response meta-analysis.

All studies investigated invasive breast cancer as outcome, except the Chinese study in which less than 30 cases were in situ breast cancers (Wen, 2009) and the WHI trial and OS (Shikany, 2011). In the WHI study, the RR for the highest compared to the lowest CHO intake were 0.89 (0.74–1.08) p trend 0.36 for invasive breast cancer and 1.24 (0.81–1.88) ptrend 0.09 for in situ. The RRs for all cancers identified in this study were included in the dose-response meta-analysis.

All studies investigated dietary carbohydrates in g/day. The WHI investigated available carbohydrate, defined as grams of carbohydrate/ serving minus grams of fibre/ serving.

Follow-up was through cancer registries or active follow-up with medical confirmation and there was no report of important losses to follow-up. A Canadian study not included in the dose-response meta-analysis was a randomized controlled trail of low fat diet (Martin, 2011). Minimum follow-up was 7 years and there was 12% drop out of the trial but the analysis was intention-to-treat using diet at baseline assessment.

All studies adjusted for main confounders.

Dietary carbohydrate during adolescence and breast cancer risk during adulthood

Carbohydrate intake during adolescence was not significantly related to breast cancer incidence in the Nurses' Health Study II (Farvid, 2015b; Linos, 2010; Frazier, 2004). A number of 39,268 premenopausal women aged 34 to 53 years completed a 124-item food frequency questionnaire on their diet during high school in 1998; 455 incident cases of invasive breast cancer were diagnosed up to 2005. The multivariable-adjusted RR for the highest compared to the lowest quintile of carbohydrate intake was 0.85 (95% CI 0.63-1.14) p trend 0.10 (Linos, 2010). When comparing highest to lowest quintile of percentage of

energy from carbohydrates, the RR was 1.00 (95% CI 0.83–1.21) p trend 0.47 (Farvid, 2015b).

Table 106 Dietary carbohydrate and breast cancer risk. Main characteristics of studies included in linear dose-response meta-analyses.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Romieu, 2012 BRE80418 Denmark, France,Germany Greece, Italy, Netherlands, Norway, Spain,Sweden, UK	EPIC, Prospective Cohort Age: 35-70 years	11 576/334 849 11.5 years	Cancer and pathology registry, mortality registry, combination of methods active follow up (health insurance record, contact of participants or next-of-kin and confirmation with medical records)	FFQ in most countries, diet history	Incidence, invasive breast cancer	≥244.2 vs ≤185.2 g/day	1.04 (0.96-1.12) Ptrend:0.439	Age, baseline menopausal status, weight, height, smoking status, educational level, physical activity , age at menarche, age at first full-term birth, age at menopause, ever used contraceptive pills, ever used hormones, energy intake, alcohol intake, fibre intake	Midpoints of CHO intake per quintile
		2 827/			Premenopausal		(0.87-1.17) Ptrend:0.709		
		5 872/			Postmenopause		1.01 (0.87-1.17) Ptrend:0.206		
		5 823/			ER+		0.95 (0.86-1.06) Ptrend:0.292		
		176/			ER-/PR-/HER2+		1.67 (0.93-2.89) Ptrend:0.044		
		224/			ER-/PR-/HER2-		1.26 (0.75-2.11) Ptrend:0.230		
		1 053/			ER-/PR-		1.33 (1.05-1.67) Ptrend:0.013		
		1 443/			ER-		1.24 (1.02-1.52) Ptrend:0.013		
Shikany, 2011 BRE80382 USA	Women's Health Initiative, Prospective Trial and Observational study Age: 50-79 years, Postmenopausal	6 098/ 148 767 8 years	Self-report verified by medical record	FFQ Available carbohydrate (excluding fibre)	Incidence, in situ and invasive postmenopausal breast cancer	Median intake 305.7 vs 112.3 g/day	0.95 (0.80–1.14) Ptrend:0.98	Age, age at first child birth, age at menarche, age at menopause, alcohol, BMI, educational level, energy intake, ethnicity, family history of	Person years per quintile
		3 016/			ER+/PR+		0.99 (0.77-1.27) Ptrend:0.20		
		664/			ER+/PR-		0.75 (0.42-1.34) Ptrend:0.56		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		616/			ER-/PR-		1.33 (0.75-2.38) Ptrend:0.29	breast cancer, hormone use, HRT use, mammogram in past 2 years, oral contraceptive history, parity, physical activity, smoking, trial assignment	
Larsson, 2009c BRE80248 Sweden	SMC, Prospective Cohort, Mean age: 54 years, Postmenopausal	2 952/ 61 433 17.4 years	Cancer registry	Two FFQ questionnaires (67 and 96 items)	Incidence, postmenopausal invasive breast cancer	≥246 vs ≤210 g/day	1.09 (0.95-1.25) Ptrend:0.15	Age, age at first child birth, age at menarche, age at menopause, alcohol intake, BMI, dietary fibre, educational level, family history of cancer, height, HRT use, OC use, parity, total energy intake	Midpoints and person years per quintile
		1 286/			ER+/PR+		1.08 (0.88-1.33) Ptrend:0.63		
		417/			ER+/PR-		1.34 (0.93-1.94) Ptrend:0.04		
		266/			ER-/PR-		1.14 (0.73-1.79) Ptrend:0.50		
Wen, 2009 BRE80209 China	SWHS, Prospective Cohort, Age: 40-70 years, W	616/ 73 328 7.35 years	In-person surveys and periodic linkage with the Shanghai Tumour Registry and death certificate registry	FFQ	Incidence, Invasive and in situ breast cancer	343.5 vs 257.5 g /day	1.22 (0.94, 1.58) Ptrend=0.204	Age, age at first child birth, benign breast disease, BMI, educational level, energy Intake, family history of cancer, physical	Cases and person-years per quintile
		426			Postmenopausal		0.98 (0.72-1.34) Ptrend:0.549		
		190/			Premenopausal		2.01 (1.26-3.19) Ptrend:0.001		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								activity	
Silvera, 2005 BRE24119 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W, Screening Program	1 450/ 49 111 16.6 years	Cancer registry and mortality registry	Self-administered FFQ (86 items)	Incidence, breast cancer	≥249.1 vs ≤143 g/day	0.93 (0.70-1.22) Ptrend:0.86	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, energy intake , family history, mammography, menopausal status, HRT use, OC use, other nutritional factors, parity/ pregnancies, recruitment centre	Midpoints of intake
Holmes, 2004 BRE04010 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	2 924/ 88 678 18 years	Self-reported confirmed with medical records	FFQ-semi-quantitative	Incidence, invasive breast cancer, Postmenopausal	240 vs 159 g/day	0.96 (0.84-1.09) Ptrend:0.82	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, energy intake , family history, height, HRT use, menopausal status, parity/ pregnancies	Cases and person-years per quintile
		852/			Premenopausal		0.98 (0.78-1.23) Ptrend:0.61		
Sieri, 2002 BRE20941 Italy	ORDET, Nested Case Control,	56/ 214 controls 5.5 years	Cancer registry + death certificate	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	217.6-303.4 vs ≤190.2 g/day	0.42 (0.18-0.95) Ptrend:0.040	Birth cohort, educational level, parity/	Cases and person-years per tertile

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Age: 41-70 years, Postmenopausal							pregnancies, energy intake	
Kushi, 1995 BRE05142 USA	IWHS, Prospective Cohort, Age: 55-69 years, Postmenopausal	262/ 34 388 6 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, invasive postmenopausal breast cancer ER+/PR+	≥225 vs ≤197 g/day	0.79 (0.60-0.79) Ptrend:0.07	Age , energy Intake	Midpoints of intake and person-years per tertile
		75/			ER+/PR-		0.78 (0.44-1.39) Ptrend:0.42		
		14/			ER-/PR+		3.82 (0.76-19.19) Ptrend:0.10		
		61/			ER-/PR-		0.60 (0.31-1.14) Ptrend:0.12		
Barrett-Connor, 1993 BRE00581 USA	Rancho Bernardo, 1972, Prospective Cohort, Age: 40-79 years	15/ 590 15 years	Medical records and death certificate	24h recall	Incidence, breast cancer, postmenopausal	per 66 g/day	1.93 (1.18-3.16)	Age , age at menopause, alcohol, BMI, parity/ pregnancies	Increment rescaled to 50 g/day
Kushi L H, 1992 BRE05141 USA	IWHS, Prospective Cohort, Age: 55-69 years, Postmenopausal	459/ 34 388 4 years	Linkage with State Health Registry	FFQ-semi-quantitative (same used in 1984 in NHS)	Incidence, breast cancer, postmenopausal	252.7 vs 181 g/day	1.16 (0.72-1.86) Ptrend:0.51	Age , age at first child, age at menarche, age at menopause, age-underlying cox models, alcohol, benign breast disease, BMI, BMI, energy Intake , family	All data available

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								history, WHR	
Knekt, 1990 BRE04898 Finland	Mobile Clinic Health Examination Survey, 1973, Prospective Cohort, Age: 20-69 years	54/ 3 988 20 years	Record linkage to Finnish Cancer Registry	Dietary history method	Incidence, breast cancer	≥278 vs ≤207 g/day	0.40 (0.16-1.00) Ptrend:0.04	Age , energy	Cases and person-years per tertile

Table 107 Dietary carbohydrate and breast cancer risk. Main characteristics of studies excluded from linear dose-response meta-analyses.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Farvid, 2015b BRE80569 USA	NHS II, Prospective Cohort, Age: 27-44 years, W		Self-reported/death certificate/ medical records	FFQ (Diet at early adulthood-baseline)	Incidence, Invasive breast cancer	59.2% vs 40.6%	0.88 (0.78–0.99) Ptrend:0.05	Age, age at menarche, age at menopause, alcohol intake, benign breast disease, BMI at age 18 years, weight gain since 18, height, energy intake, family history of breast cancer, HRT use, oral contraceptive use, menopause status, parity and age at first birth, race, smoking	Percentage of energy from carbohydrates (not g/day)
		1 547/			Premenopausal		0.88 (0.75–1.03) Ptrend: 0.16		
		919/			Postmenopausal		0.87 (0.70–1.08) Ptrend: 0.46		
Sieri, 2013 BRE80408 Italy	EPIC-Italy, Prospective Cohort, Age: 50 years, W	879/ 26 066 11 years	Cancer registry	FFQ	Incidence, breast cancer	346 vs 227 g/day	1.19 (0.95-1.50) Ptrend:0.085	Age at menarche, alcohol, BMI, educational level, fibre, menopausal status, non-alcohol energy, parity, recreational activity, smoking, sport,	Included in EPIC
		391/			Premenopausal	359 vs 237 g/day	1.03 (0.40-1.44) Ptrend:0.371		
		419/			Post menopause	333 vs 218 g/day	1.38 (0.97-1.95) Ptrend:0.051		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								occupational physical activity	
Martin, 2011 BRE80323 Canada	CDBCPT, Nested Case Control, Age: 47 years	220/ 440 controls 10	Mammographic periodic screening and pathology confirmation	Food records	Incidence, Invasive breast cancer	252 vs 210 g/day	0.81 (0.61-1.07)	Age, age at first child birth, age at menarche, family history of breast cancer, HRT use, menopausal status, number of childbirths, randomisation, smoking	Only RR for highest vs lowest comparison
		42/ 84 controls			ER-	232 vs 187 g/day	1.27 (0.69-2.37)		
		167/ 334 controls			ER+	232 vs 187 g/day	0.74 (0.56-0.97)		
Lajous, 2008 BRE80218 France	E3N EPIC-France, Prospective Cohort, Age: 42-72 years, Postmenopausal	1 812/ 62 739 9 years	Cancer registry	Dietary history	Incidence, breast cancer, postmenopausal	267 vs 177 g/day	1.05 (0.90, 1.22) Ptrend:0.64	Age, 2-y follow-up period, residence, education , family breast cancer, history of benign breast disease ,age at menarche and menoapause, parity, breastfeeding , oral contraceptives use, HRT, BMI vitamin supplement , total energy intake , intakes of folate, fibre, alcohol,	Included in EPIC

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								physical activity	
Giles, 2006 BRE22430 Australia	MCCS, Prospective Cohort, Age: 40-69 years, W, Postmenopausal	12 273 9.1 years	Pathology report + cancer registry	Self administered FFQ 131 items	Incidence, invasive breast cancer, postmenopausal	per 1 SD/day	1.31 (0.98-1.75)	Age , energy intake , HRT use, place of residence (not included for less than 5% change of RR: parity/reproductive factors, HRT, OC use, age at menarche and menopause, maternal family history of cancer, physical activity, alcohol intake, education level, height, BMI, WHR, multi-vitamin supplement use and total fat intake	g/day of SD (increment unit) not reported
					ER+/PR+, postmenopausal	per 1 SD/day	1.38 (0.91-2.09)		
					ER+/PR-, postmenopausal	per 1 SD/day	1.91 (0.75-4.86)		
					ER-/PR-, postmenopausal	per 1 SD/day	0.88 (0.45-1.71)		
Nielsen, 2005 BRE23581 Denmark	DCH, Prospective Cohort, Age: 50-65	23 870 6.6 years	Cancer registry	FFQ	Incidence, breast cancer, postmenopausal	per 50 g/day	1.06 (0.97-1.16)	Alcohol, BMI, educational level, HRT use, parity/pregnanci	Partially overlapping with EPIC
					ER+,		1.02 (0.92-1.14)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	years, Postmenopausal				postmenopausal			es	
					ER-, postmenopausal		1.09 (0.89-1.34)		
Byrne, 2002 BRE01315 USA	NHS, Prospective Cohort, Age: 57 years, Postmenopausal	1 071/ 44 697 14 years	Self reported, medical confirmation	Block FFQ-103 items	Incidence, Invasive breast cancer, postmenopausal	Q5 vs Q1	0.88 (0.72-1.09) Ptrend:0.53	Age , age at first child, age at menopause, age at menopause, alcohol, BMI, density, family history, height, nutrients, parity /pregnancies	Superseded by Holmes, 2004
Horn-Ross, 2002 BRE15412 USA	CTS, Prospective Cohort, Age: 21-103 years, Registered teachers	111 383 2 years	Annual linkage with California Cancer Registry (~97% completeness)	FFQ	Incidence, Invasive breast cancer	≤240 vs ≤128 g/day	0.80 (0.50-1.20) Ptrend:0.8	Age , age at first child, age at menarche, BMI, energy intake , ethnicity, family history, menopausal status, physical activity	g/day reported only for extreme quintiles
Giovannucci, 1993a BRE03262 USA	NHS, Nested Case Control, Age: 30-55 years, Registered nurses	392/ 786 controls 2 years	Medical records and death certificate	FFQ-semi-quantitative	Incidence, breast cancer	Q5 vs Q1	0.89 (0.53-1.50) Ptrend:0.62	Age	Superseded by Holmes, 2004
Howe, 1991 BRE17622 Canada	CNBSS, Nested Case Control, Age: 40-59 years,	519/ 1182 controls 5 years	All histology	Dietary history questionnaire	Incidence, breast cancer	Q4 vs Q1	0.73 (0.51-1.03) Ptrend:.042	Age , energy Intake , recruitment centre, time of recruitment	Superseded by Silvera, 2005
						per 693 kcal/day	0.72 (0.52-0.99)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Screening Program								

Figure 163 RR estimates of breast cancer by levels of carbohydrate intake

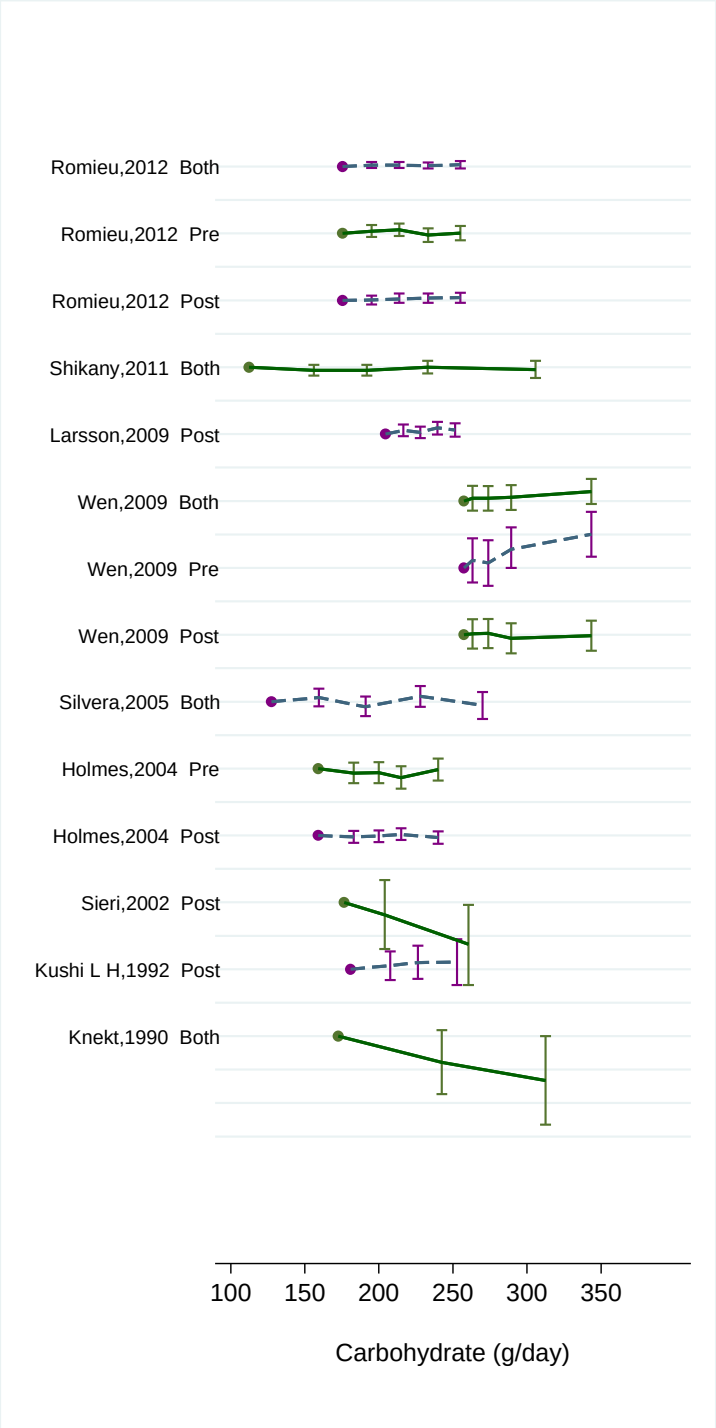


Figure 164 RR (95% CI) of breast cancer for the highest compared with the lowest carbohydrate intake by menopausal status

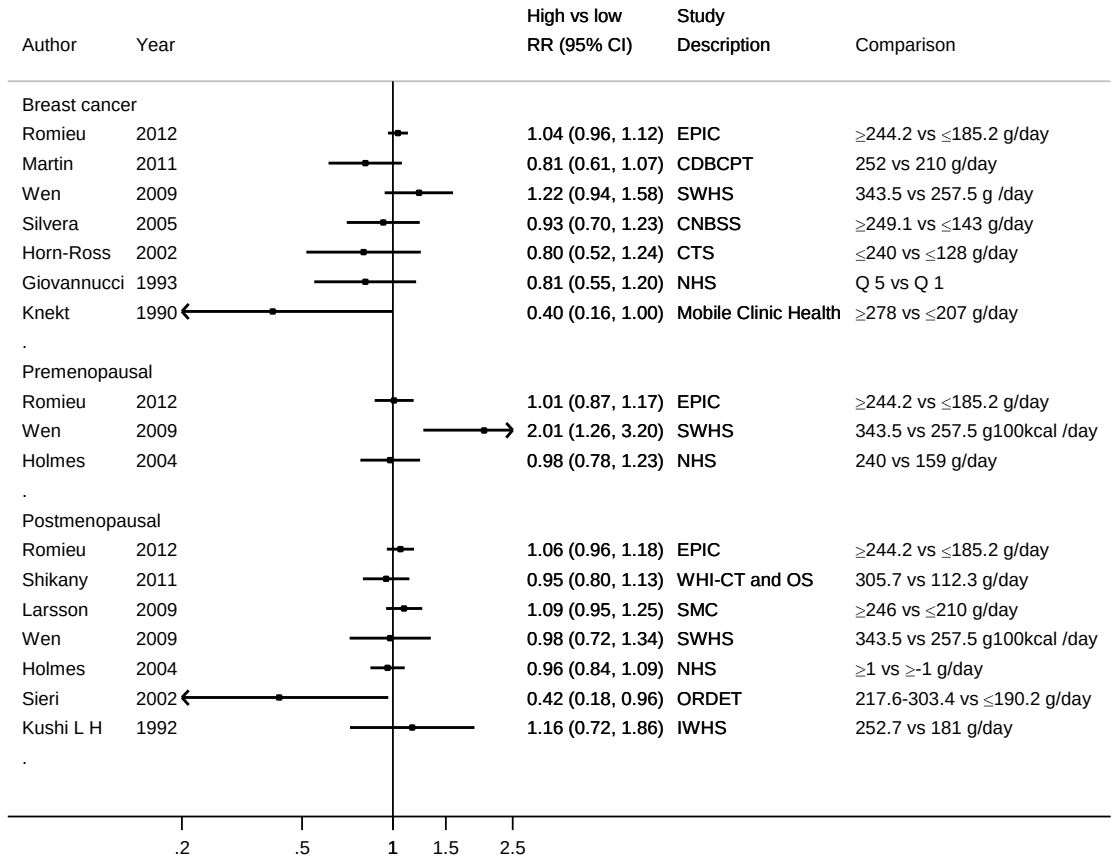


Figure 165 RR (95% CI) of breast cancer for 50 g/day increment by menopausal status

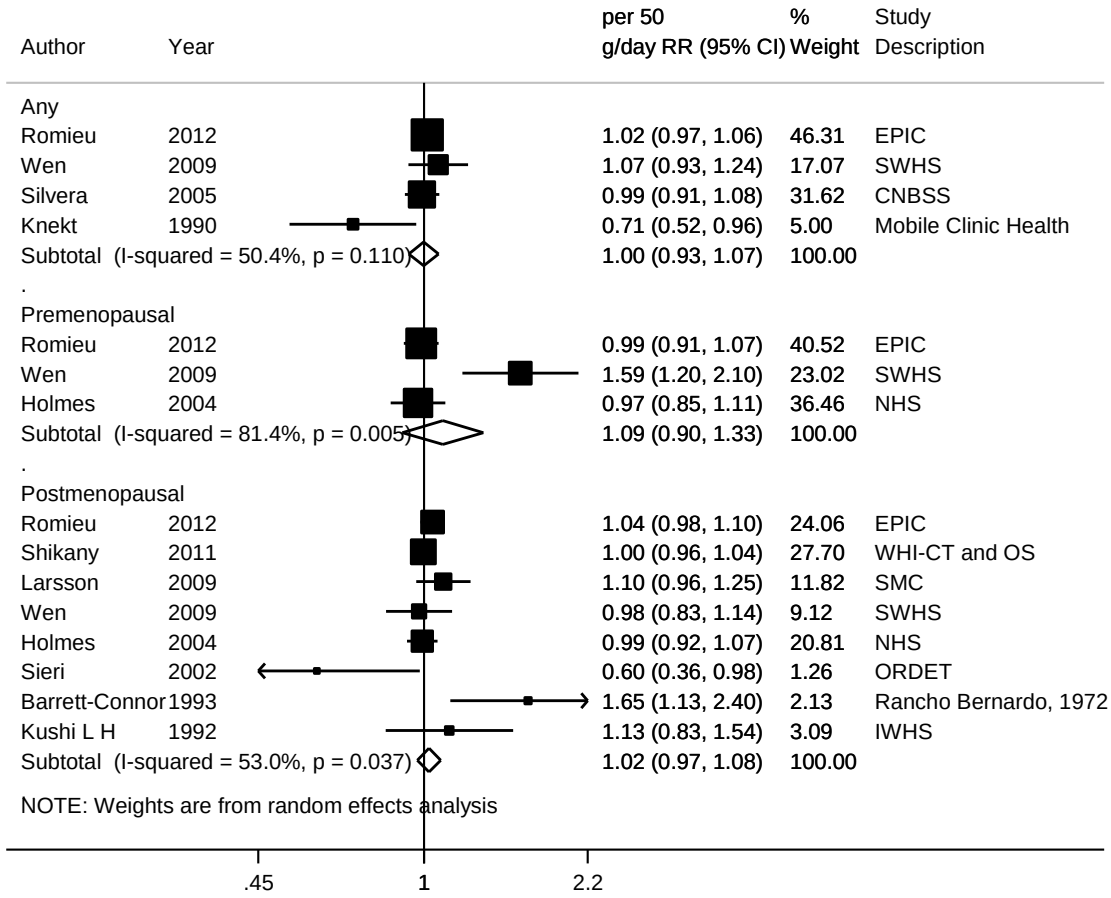


Figure 166 Funnel plot of studies included in the dose response meta-analysis of carbohydrate intake and postmenopausal breast cancer

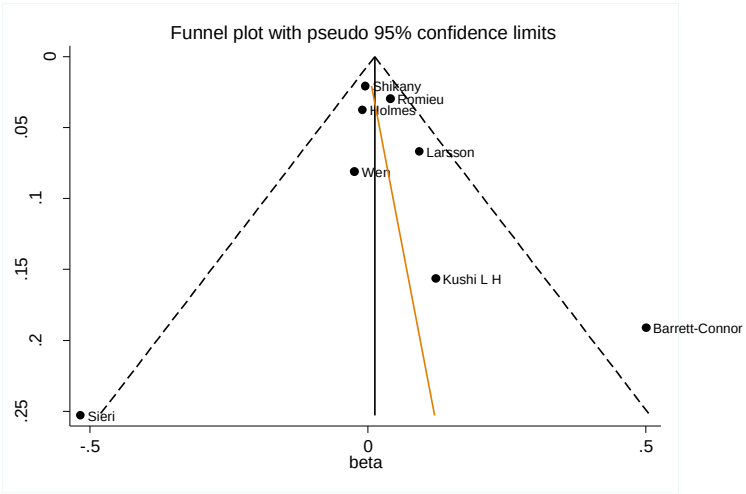


Figure 167 RR (95% CI) of breast cancer for the highest compared with the lowest carbohydrate intake by hormone receptor status

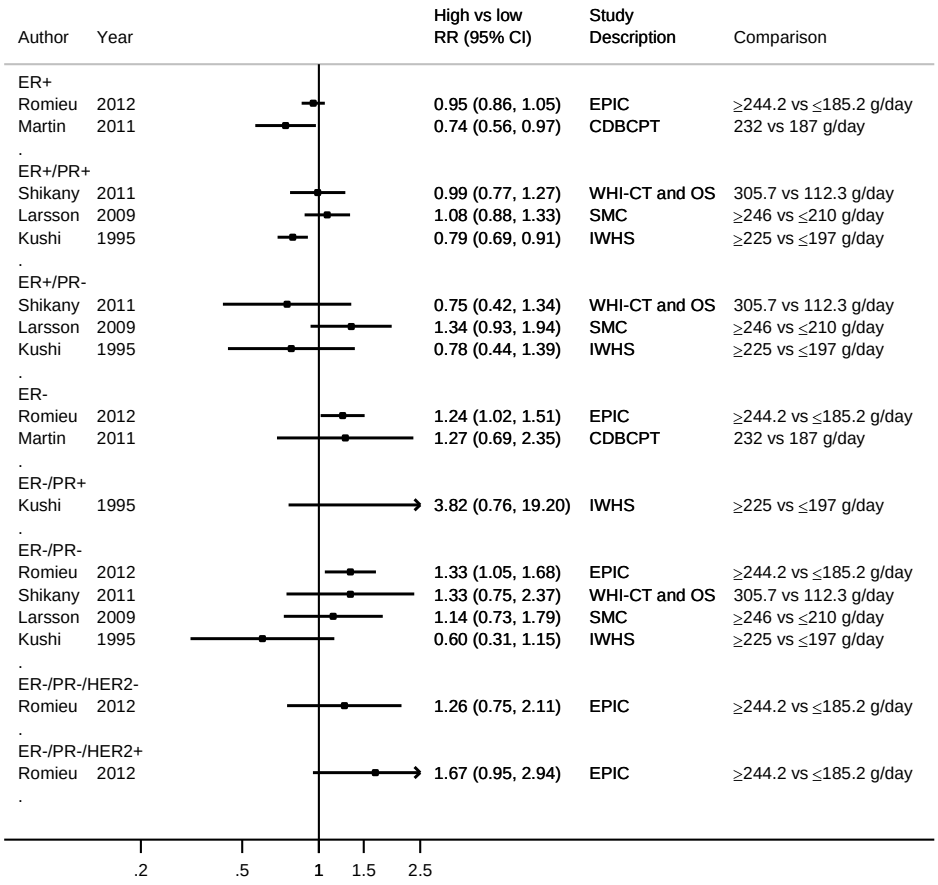
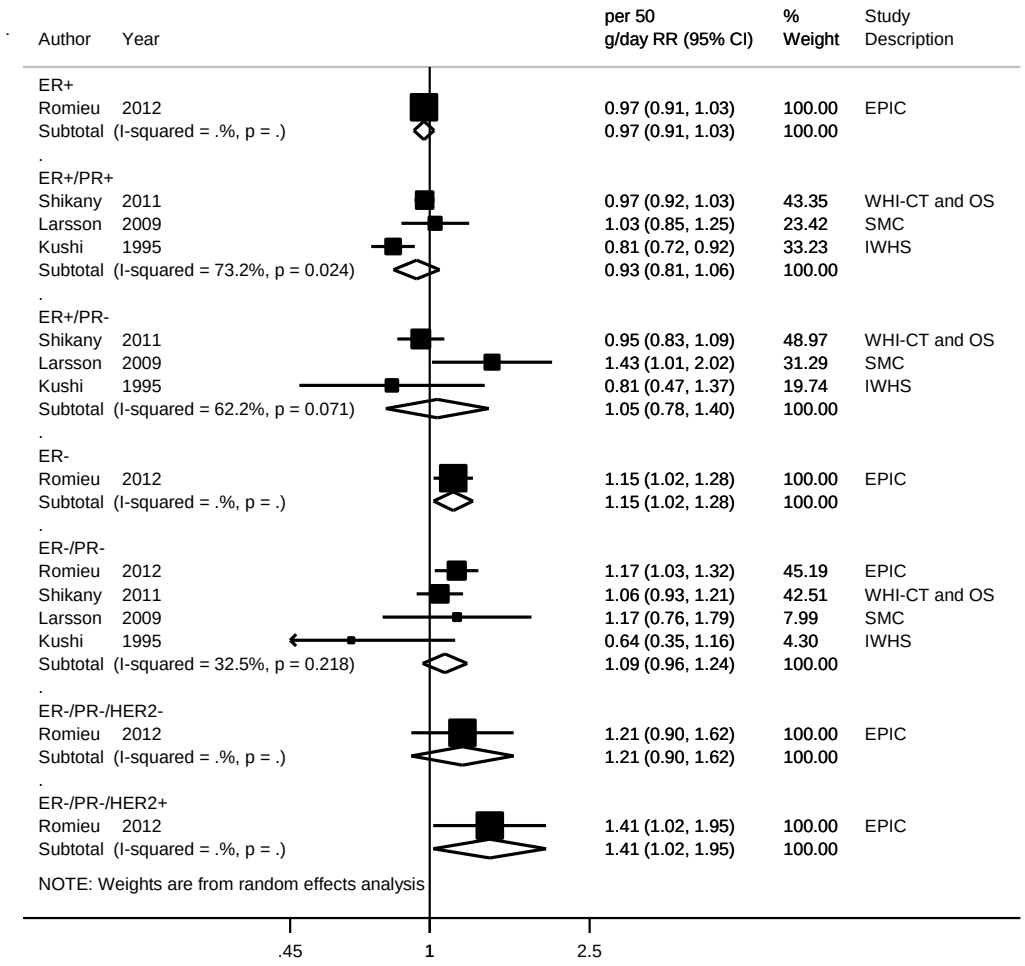


Figure 168 RR (95% CI) of breast cancer for 50 g/day increment by hormone receptor status



5.1.2 Dietary fibre

Overall summary

Sixteen studies on fibre intake and breast cancer risk were identified. Nine studies investigated breast cancers (any), one was on premenopausal breast cancers only, and six were on pre- and postmenopausal breast cancers. Three studies contained results stratified by estrogen receptor status. Study characteristics and results for all cancer types are shown in the Table.

Study quality:

Fibre intake was estimated from food intake assessed by FFQ in all, but one study (Deschasaux, 2014), which used repeated 24-hour recalls. One study used a combination of

dietary assessment methods including FFQ, dietary records, and dietary interviews (Ferrari, 2013).

Loss to follow-up was low for the studies that reported such data, although some studies did not provide data.

Cancers were identified by record linkages to health registries, cancer registries, mortality registries, or death indexes.

All studies adjusted for at least age, and most of the studies adjusted for most of the established breast cancer risk factors, including: age, parity, age at menarche, age at menopause, physical activity, BMI, and alcohol consumption.

One study had only 56 cases and therefore limited statistical power (Sieri, 2002), however, all the remaining studies had more than 350 cases.

Breast cancer (any)

Sixteen studies (35 910 cases) were included in the dose-response meta-analysis. The summary RR for a 10 g/d increase in fibre intake was 0.95 (95% CI: 0.93-0.98) and there was no evidence of heterogeneity, I^2=0%, $p_{heterogeneity}$=0.81. There was no evidence of small study bias or publication bias with Egger's test, p=0.74. One large European study, the EPIC study (Ferrari, 2013), contributed to 46% of the weight in the meta-analysis, however, in influence analyses the findings were robust; the summary RR ranged from 0.95 (95% CI: 0.92-0.98) when the EPIC study (Ferrari, 2013) was excluded to 0.96 (95% CI: 0.93-0.98) when the Canadian National Breast Screening Study was excluded (Terry, 2002).

Nonlinear dose-response analysis

There was indication of a nonlinear association, $p_{nonlinearity}$=0.05, with a suggestion of a threshold effect, with significantly reduced risk at intakes of 35 g/d.

Premenopausal breast cancer

Four studies (2013 cases) were included in the dose-response meta-analysis of fibre intake and premenopausal breast cancer. The summary RR per 10 g/d increase in fibre intake was 0.91 (95% CI: 0.75-1.10) and there was moderate heterogeneity, I^2=43.0%, $p_{heterogeneity}$=0.15.

Postmenopausal breast cancer

Eleven studies (18591 cases) were included in the dose-response meta-analysis of fibre intake and postmenopausal breast cancer. The summary RR per 10 g/d increase in fibre intake was 0.95 (95% CI: 0.92-0.99), with no evidence of heterogeneity, I^2=0%, $p_{heterogeneity}$=0.73. There was no evidence of publication bias, p=0.69.

Nonlinear dose-response analysis

There was indication of a nonlinear association, $p_{nonlinearity}$=0.001, with a suggestion of a threshold effect, with significantly reduced risk at intakes of 35 g/d.

Table 108 Fibre intake and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	16
Studies included in forest plot of highest compared with lowest intake	Breast cancer: 16 Premenopausal: 4 Postmenopausal: 11
Studies included in linear dose-response meta-analysis	Breast cancer: 16 Premenopausal: 4 Postmenopausal: 11
Studies included in non-linear dose-response meta-analysis	Breast cancer: 16 Premenopausal: not enough studies Postmenopausal: 11

Table 109 Fibre intake and breast cancer risk. Summary of the linear dose-response meta-analysis in the CUP (no dose-response meta-analysis was conducted in the 2005 SLR)

	Breast cancers (any)	**Premenopausal**	**Postmenopausal**
Increment unit used	10 g/day		
Studies (n)	16	4	11
Cases (total number)	35910	2013	18591
RR (95%CI)	0.95 (0.93-0.98)	0.91 (0.75-1.10)	0.95 (0.92-0.99)
Heterogeneity (I^2, p-	0%, p=0.81	43.0%, p=0.15	0%, p=0.73
P value Egger test	0.74	0.38	0.69

Stratified analyses

Geographic area	**Asia**	**Europe**	**North-America**
Studies (n)	1	6	9
RR (95%CI)	1.08 (0.83-1.40)	0.93 (0.87-0.99)	0.95 (0.92-0.99)
Heterogeneity (I^2, p- value)	-	11.4%, p=0.34	0%, p=0.89

Table 110 Fibre and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Dong et al, 2011	10	16848	North America, Europe, Asia	Incidence	High vs. low Per 10 g/d	0.89 (0.83-0.96) 0.93 (0.88-0.98)	- -	0%,p=0.44 NA, p=0.16
Aune et al, 2012	16	26523	North America, Europe, Asia	Incidence	High vs. low Per 10 g/d	0.93 (0.89-0.98) 0.95 (0.91-0.98)	- -	0%, p=0.89 0%, p=0.82

Table 111 Fibre intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Deschasaux, 2013 BRE80487 France	SU.VI.MAX, Prospective Cohort, Age: 47 years, W	167/ 4 684 12.6 years	Self-report/ medical records/histology	24 hour diet recall	Incidence, breast cancer	≥20.3 vs ≤13.2 g/day	1.29 (0.66-2.50)	Age-underlying cox models, alcohol, BMI, dietary pattern score, dietary records, educational level, family history of breast cancer, fat Intake, height, HRT use, Intervention group, menopausal status, non-alcohol energy Intake, number of children, physical activity, smoking status
Ferrari, 2013 BRE80436 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	11 576/ 334 849 11.5 years	Cancer and pathology registry, active follow up, health Insurance record, mortality registry and contact of participants or next-of-kin	Questionnaire	Incidence, breast cancer	≥26.3 vs ≤17.6 g/day	0.95 (0.89-1.01)	Age, age at first child birth, age at menarche, alcohol, contraception, educational level, energy Intake, height, menopausal status, physical activity, smoking, study center, weight
					Observed	per 10 g/day	0.96 (0.93-1.00)	
					Calibrated	per 10 g/day	0.93 (0.87-0.99)	
					ER+/PR+	≥26.3 vs ≤17.6 g/day	0.89 (0.80-1.00)	
					ER-/PR-	≥26.3 vs ≤17.6 g/day	0.96 (0.78-1.18)	
Shikany, 2011 BRE80382 USA	Women's Health Initiative, Prospective Cohort, Age: 50-79	6 098/ 148 767 8 years	Self report verified by medical record	FFQ	Incidence, breast cancer	25.1 vs 8.2 g/day	0.93 (0.82-1.07)	Age, age at first child birth, age at menarche, age at menopause, alcohol, BMI, educational

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	years, W, Postmenopausal							level, energy Intake, ethnicity, family history of breast cancer, hormone use, HRT use, mammogram In the past 2 years, oral contraceptive history, parity, physical activity, smoking, trial assignment, trial assignment
Park, 2009a BRE80264 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W, Postmenopausal	5 461/ 185 598 7 years	Cancer registry	FFQ	Incidence, breast cancer	26 vs 11 g/day per 10 g/day	0.87 (0.77-0.98) 0.95 (0.89-1.01)	Age, age at first child birth, age at menopause, alcohol Intake, BMI, breast biopsies, educational attainment, energy Intake, family history of cancer, fat Intake, fruits and vegetables Intake, menopausal hormone use, oophorectomy/hysterectomy, parity, physical activity, race, smoking status
					Incidence, ductal carcinomas	26 vs 11 g/day per 10 g/day	0.90 (0.77-1.04) 0.94 (0.87-1.02)	
					Incidence, breast cancer ER+	26 vs 11 g/day	0.91 (0.74-1.12)	
					Incidence, breast cancer PR+	26 vs 11 g/day	0.95 (0.76-1.19)	
					Incidence, breast cancer ER+/PR+	26 vs 11 g/day	0.95 (0.76-1.20)	
					Incidence, other non-ductal/lobular breast cancer	26 vs 11 g/day per 10 g/day	0.92 (0.69-1.23) 1.05 (0.90-1.23)	
					Incidence, breast cancer PR-	26 vs 11 g/day	0.64 (0.46-0.89)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					Incidence, lobular carcinoma	26 vs 11 g/day per 10 g/day	0.66 (0.44-0.97) 0.81 (0.65-1.01)	
					Incidence, ductal-lobular breast cancer	26 vs 11 g/day per 10 g/day	0.83 (0.53-1.29) 0.96 (0.76-1.21)	
					Incidence, breast cancer ER-	26 vs 11 g/day	0.59 (0.38-0.92)	
					Incidence, breast cancer ER-/PR-	26 vs 11 g/day per 10 g/day	0.56 (0.35-0.90) 0.77 (0.60-1.00)	
					Incidence, breast cancer ER+/PR-	26 vs 11 g/day	0.74 (0.45-1.21)	
Wen, 2009 BRE80209 China	SWHS, Prospective Cohort, Age: 40-70 years, W	616/ 73 328 7.35 years	Cancer registry	Quantitative FFQ	Incidence, Invasive & In situ breast cancer	16.3 vs 7.7 g100kcal /day	1.09 (0.84-1.40)	Age, age at first child birth, benign breast disease, BMI, educational level, energy Intake, family history of cancer, physical activity
					Premenopausal	16.3 vs 7.7 g100kcal /day	1.01 (0.64-1.57)	
					Postmenopausal	16.3 vs 7.7 g100kcal /day	1.12 (0.83-1.53)	
Maruti, 2008a BRE80197 USA	VITAL, Prospective Cohort, Age: 50-76 years, W, Postmenopausal	455/ 28 586 5 years	Cancer registry	FFQ	Incidence, Invasive breast cancer, postmenopausal	19.8-58.3 vs ≤10.4 g/day	1.14 (0.82-1.60)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, BMI, breast biopsies, family history of cancer, height, mammography,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								menopausal hormone use, physical activity, race, total energy Intake
Suzuki, 2008a BRE80148 Sweden	SMC, Prospective Cohort, Age: 60 years, W, Postmenopausal	1 248/ 51 823 8.3 years	Cancer registry	FFQ	Incidence, Invasive breast cancer	≥26.7 vs ≤18.4 g/day	0.85 (0.69-1.05)	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, benign breast disease, BMI, educational level, family history of cancer, fruit and vegetables Intake, height, menopausal status, parity, postmenopausal hormone use, total energy Intake, total fat, use of oral contraception
					Incidence, breast cancer ER+/PR+	≥26.7 vs ≤18.4 g/day	0.85 (0.64-1.13)	
					Incidence, breast cancer ER+/PR-	≥26.7 vs ≤18.4 g/day	0.83 (0.52-1.31)	
					Incidence, breast cancer ER-/PR-	≥26.7 vs ≤18.4 g/day	0.94 (0.49-1.80)	
Cade, 2007 BRE20021 UK	UKWCS, Prospective Cohort, Age: 35-69 years, W	286/ 35 792 7.5 years	NHS central registry	FFQ	Incidence, breast cancer, postmenopause	≥30 vs ≤20.9 g/day	1.18 (0.70-1.99)	Age , alcohol, BMI, energy Intake , HRT use, oc use, parity/pregnancies, physical activity , smoking habits
					Incidence, breast cancer, premenopause	≥30 vs ≤19.9 g/day	0.48 (0.24-0.96)	
Holmes, 2004 BRE04010 USA	NHS, Prospective Cohort,	2 924/ 88 678 18 years	Medical records + self-reported	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	24.8 vs 12.1 g/day	0.96 (0.83-1.10)	Age , age at first child, age at menarche, age at

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Age: 30-55 years, W, Registered nurses				Incidence, breast cancer, premenopausal	24.8 vs 12.1 g/day	0.99 (0.75-1.29)	menopause, alcohol, benign breast disease, BMI, energy Intake , family history, height, HRT use, menopausal status, other design Issue, parity/pregnancies
Cho, 2003b BRE01651 USA	NHS II, Prospective Cohort, Age: 26-46 years, W, Registered nurses	714/ 90 655 8 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, breast cancer, premenopausal	24.8 vs 12.5 g/day	0.88 (0.67-1.14)	Age at first child, age at menarche, alcohol, benign breast disease, BMI, family history, height, menopausal status, nutrients, oc use, parity/pregnancies, residual (willet), smoking habits
Horn-Ross, 2002 BRE15412 USA	CTS, Prospective Cohort, Age: 21-103 years, W, Registered teachers	111 383 2 years	Partially histological - over 80%	FFQ	Incidence, Invasive breast cancer,	≤19 vs ≤9 g/day	0.90 (0.70-1.20)	Age , age at first child, age at menarche, BMI, energy Intake , ethnicity, family history, menopausal status, physical activity
Sieri, 2002 BRE20941 Italy	ORDET, Nested Case Control, Age: 41-70 years, W,	56/ 214 controls 5.5 years	Cancer registry + death certificate	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	20.1-37.4 vs ≤16.6 g/day	0.73 (0.33-1.59)	Birth cohort, educational level, parity/pregnancies, residual (willet)

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Postmenopausal							
Terry, 2002 BRE12199 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	89 835 16.2 years	Partially histological - over 80%	FFQ	Incidence, Invasive & In situ breast cancer,	≥25.8 vs ≤15.1 g/day	0.92 (0.78-1.09)	Age , alcohol, benign breast disease, BMI, educational level, energy Intake , family history, HRT use, menopausal status, nutrients, oc use, other specified factor, other specified factor, parity/pregnancies, physical activity , recruitment center, smoking habits
Verhoeven, 1997 BRE12868 Netherlands	NLCS, Case Cohort, Age: 55-69 years, W	519/ 62 573 4.3 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, Invasive breast cancer,	34.5 vs 16.9 g/day	0.83 (0.56-1.24)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, energy Intake , family history, parity/pregnancies
Graham, 1992 BRE03424 USA	New York State Cohort, 1980, Prospective Cohort, Age: 50-107 years, W, Postmenopausal	344/ 18 586 8 years	Partially histological - over 80%	FFQ	Incidence, breast cancer, postmenopausal	982-5184 vs 88-478 g/month	1.07 (0.76-1.51)	Age , educational level

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Kushi L H, 1992 BRE05141 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	459/ 34 388 4 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	27 vs 14.1 g/day	0.99 (0.69-1.41)	Age , age at first child, age at menarche, age at menopause, age-underlying cox models, alcohol, benign breast disease, BMI, BMI, energy Intake , family history, WHR

Table 112 Fibre intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Inclusion /exclusion
Sieri, 2013 BRE80408 Italy	EPIC-Italy, Prospective Cohort, Age: 50 years, W	879/ 26 066 11 years	Cancer registry	FFQ	Incidence, breast cancer	33.1 vs 16.6 g/day	0.88 (0.68-1.15)	Age at menarche, alcohol, BMI, educational level, energy, fibre, menopausal status, non-alcohol energy, parity, recreational activity, smoking, sport, work - physical activity	Overlap with Ferrari, 2013 BRE80436
Linos, 2010 BRE80298 USA	NHS II, Prospective Cohort, Age: 34-53	517/ 39 268 7.8 years	Follow up questionnaires, medical records	Semi-quantitative FFQ	Incidence, Invasive breast cancer	27.5 vs 15.1 g/day	0.90 (0.67-1.20)	Age, age at first child birth, age at menarche, alcohol consumption, benign	Overlap with Cho, 2003b BRE01651

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Inclusion /exclusion
	years, W, Premenopausal							breast disease, BMI, energy Intake, family history of cancer, menopausal status, oc use, parity, weight gain	
Sonestedt, 2008a BRE80192 Sweden	MDCS, Prospective Cohort, Age: 46-75 years, W	544/ 15 773 10.3 years	Cancer registry	7-day food record & FFQ	Incidence, Invasive breast cancer	26 vs 12 g/day	0.82 (0.61-1.09)	Age, age at menopause, alcohol Intake, educational level, exposure assessment, height, household physical activity, Interviewer, menopausal hormone use, parity, physical activity, residual (willet), season of Interview, smoking status, total energy Intake, weight	Overlap with Ferrari, 2013 BRE80436
					Incidence, breast cancer ERα+	per 1 quantile	0.98 (0.91-1.05)		
					Incidence, breast cancer ERβ-	per 1 quantile	1.01 (0.91-1.12)		
					Incidence, breast cancer ERβ+	per 1 quantile	1.00 (0.90-1.11)		
					Incidence, breast cancer ERα+/ERβ+	per 1 quantile	0.98 (0.88-1.09)		
					Incidence, breast cancer ERα+/ERβ-	per 1 quantile	0.99 (0.89-1.11)		
					Incidence, breast cancer ERα-	per 1 quantile	1.09 (0.90-1.31)		
Lajous, 2008 BRE80218 France	E3N EPIC-France, Prospective Cohort,	62 739 9 years	Cancer registry	Dietary history	Incidence, breast cancer, postmenopausal	Q 4 vs Q 1	0.99 (0.85-1.16)	Age, age at menarche, age at menopause, alcohol consumption, benign	Overlap with Ferrari, 2013

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Inclusion /exclusion
	Age: 42-72 years, W, Postmenopausal				Incidence, breast cancer ER-, postmenopausal	Q 4 vs Q 1	0.84 (0.57-1.25)	breast disease, BMI, breastfeeding, educational level, family history of cancer, fibre Intake, folate Intake, follow-up time, height, HRT use, mammography, oc use, parity, physical activity, residence, total energy Intake, vitamin use	BRE80436
Sonestedt, 2007 BRE80147 Sweden	MDCS, Prospective Cohort, Age: 45-73 years, W	428/ 11 726 9.5 years	Cancer registry	Diet history questionnaire	Incidence, breast cancer, postmenopausal	25.9 vs 12.5 g/day	0.77 (0.57-1.05)	Age, Interviewer, method version, season of year, total energy Intake	Overlap with Ferrari, 2013 BRE80436
Giles, 2006 BRE22430 Australia	MCCS, Prospective Cohort, Age: 40-69 years, W, Postmenopausal	12 273 9.1 years	Pathology report + cancer registry	FFQ	Incidence, breast cancer, postmenopausal	per 1 sd/day	1.08 (0.92-1.26)	Age , energy Intake , HRT use, place of residence	Increment not provided
					Incidence, breast cancer ER+/PR+, postmenopausal	per 1 sd/day	1.36 (1.10-1.67)		
					Incidence, breast cancer ER-/PR-, postmenopausal	per 1 sd/day	0.65 (0.43-0.99)		
					Incidence, breast cancer ER+/PR-,	per 1 sd/day	1.01 (0.61-1.69)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Inclusion /exclusion
					postmenopausal				
Frazier, 2004 BRE02942 USA	NHS II, Historical Cohort, Age: 34-51 years, W, Registered nurses	361/ 47 355 9 years	All histology	FFQ	Incidence, breast cancer, premenopausal	27.5 vs 15.1 gm/day	0.81 (0.58-1.13)	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, energy Intake , family history, menopausal status, oc use, other anthropometric Index, other design Issue, parity/pregnancies	Overlap with Cho, 2003b BRE01651
Mattisson, 2004b BRE16042 Sweden	MDCS, Prospective Cohort, Age: 50- years, W, Postmenopausal	342/ 11 726 11 years	Partially histological - over 80%	7-day record + questionnaire	Incidence, Invasive & In situ breast cancer, postmenopausal	25.9 vs 12.5 g/day	0.58 (0.40-0.84)	Age , age at first child, age at menarche, educational level, energy Intake , height, HRT use, Interviewer, leisure time physical activity, other design Issue, other nutritional factors, season of Interview, waist circumference	Overlap with Ferrari, 2013 BRE80436
Frazier, 2003 BRE02941 USA	NHS, Nested Case Control, Age: 40-65 years, W,	121 700 10 years	All histology	FFQ	Incidence, breast cancer,	14.3 vs 5.6 g/day	0.78	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, family history, height, HRT use,	Holmes, 2004 BRE04010

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Inclusion /exclusion
	Registered nurses							menopausal status, nutrients, parity/pregnancies	
Kushi, 1995 BRE05142 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	339/ 34 388 6 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer ER+/PR+	≥21.8 vs ≤16.9 mg/day	0.92 (0.70-1.20)	Age , energy Intake	Overlap with Kushi L H, 1992 BRE05141
					Incidence, breast cancer ER+/PR-	≥21.8 vs ≤16 mg/day	1.24 (0.71-2.17)		
					Incidence, breast cancer ER-/PR-	≥21.8 vs ≤16 mg/day	0.98 (0.52-1.84)		
					Incidence, breast cancer ER-/PR+	≥21.8 vs ≤16 mg/day	1.48 (0.33-6.66)		
Giovannucci, 1993a BRE03262 USA	NHS, Nested Case Control, Age: 30-55 years, W, Registered nurses	392/ 786 controls 2 years	Medical records + death certificate	FFQ-semi-quantitative	Incidence, breast cancer,	Q 5 vs Q 1	0.62 (0.41-0.93)	Age	Holmes, 2004 BRE04010
Rohan, 1993 BRE17965 Canada	CNBSS, Nested Case Control, Age: 40-59 years, W, Screening Program	186 6 years	All histology	Dietary history questionnaire	Incidence, breast cancer,	per 12 g/day	0.85 (0.70-1.04)	Age , age at first child, age at menarche, benign breast disease, educational level, energy Intake , family history, menopausal status	Overlap with Terry, 2002 BRE12199
Willett, 1992 BRE13438	NHS, Prospective	1 439/ 89 494	Medical records + self-reported	FFQ-semi-quantitative	Incidence, breast cancer,	≥22 vs ≤11.9 g/day	1.02 (0.85-1.23)	Age , age at first child, age at	Holmes, 2004

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Inclusion /exclusion
USA	Cohort, Age: 30-55 years, W, Registered nurses	8 years			Incidence, breast cancer, postmenopausal	Q 5 vs Q 1	0.96 (0.75-1.25)	menarche, alcohol, benign breast disease, BMI, energy Intake , family history, menopausal status, nutrients, other design Issue, parity/pregnancies	BRE04010
					Incidence, breast cancer, premenopausal	Q 5 vs Q 1	1.06 (0.78-1.45)		

Figure 169 RR estimates of breast cancer by levels of fibre intake

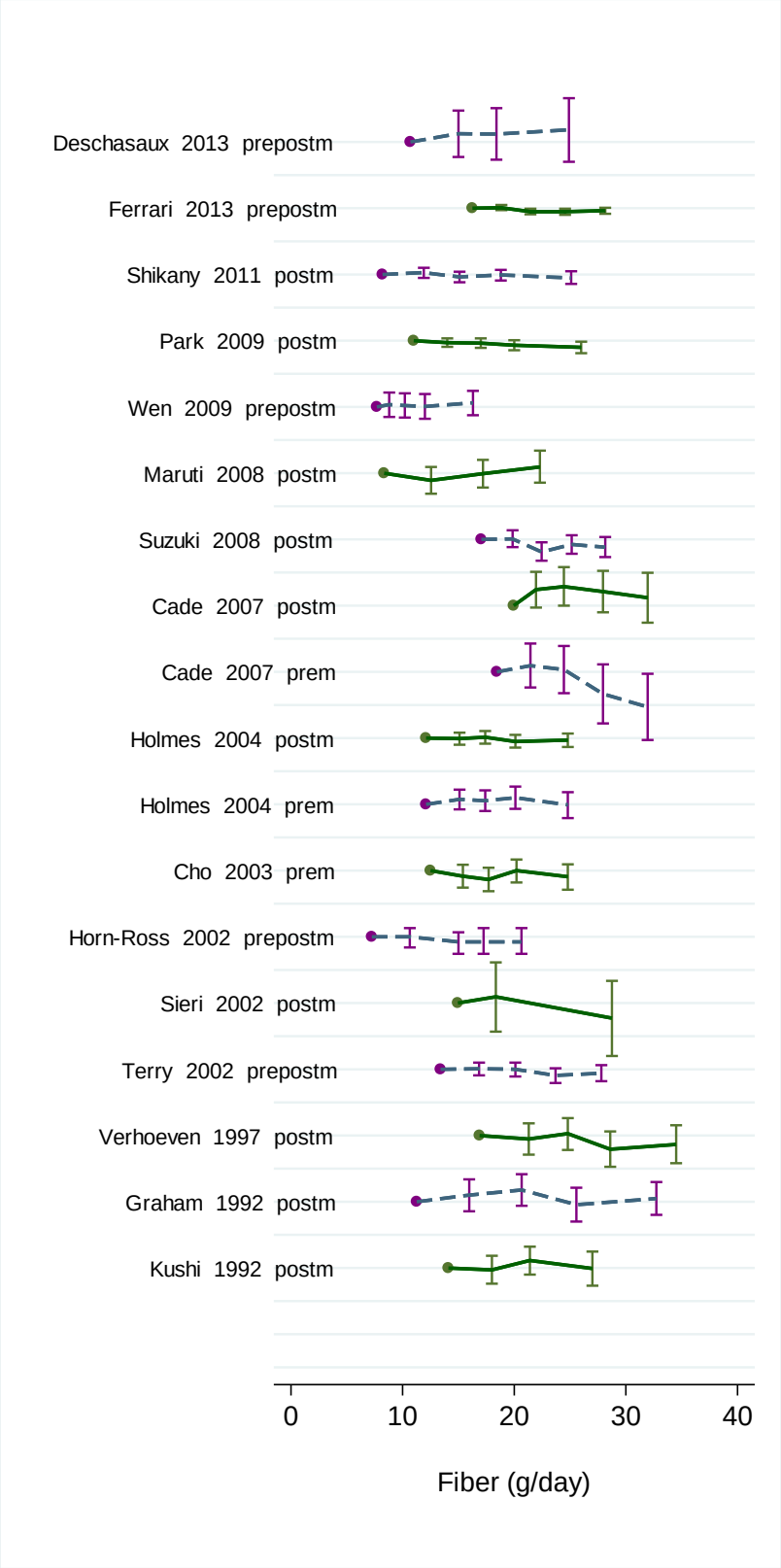


Figure 170 Relative risk of breast cancer for the highest compared with the lowest level of fibre intake

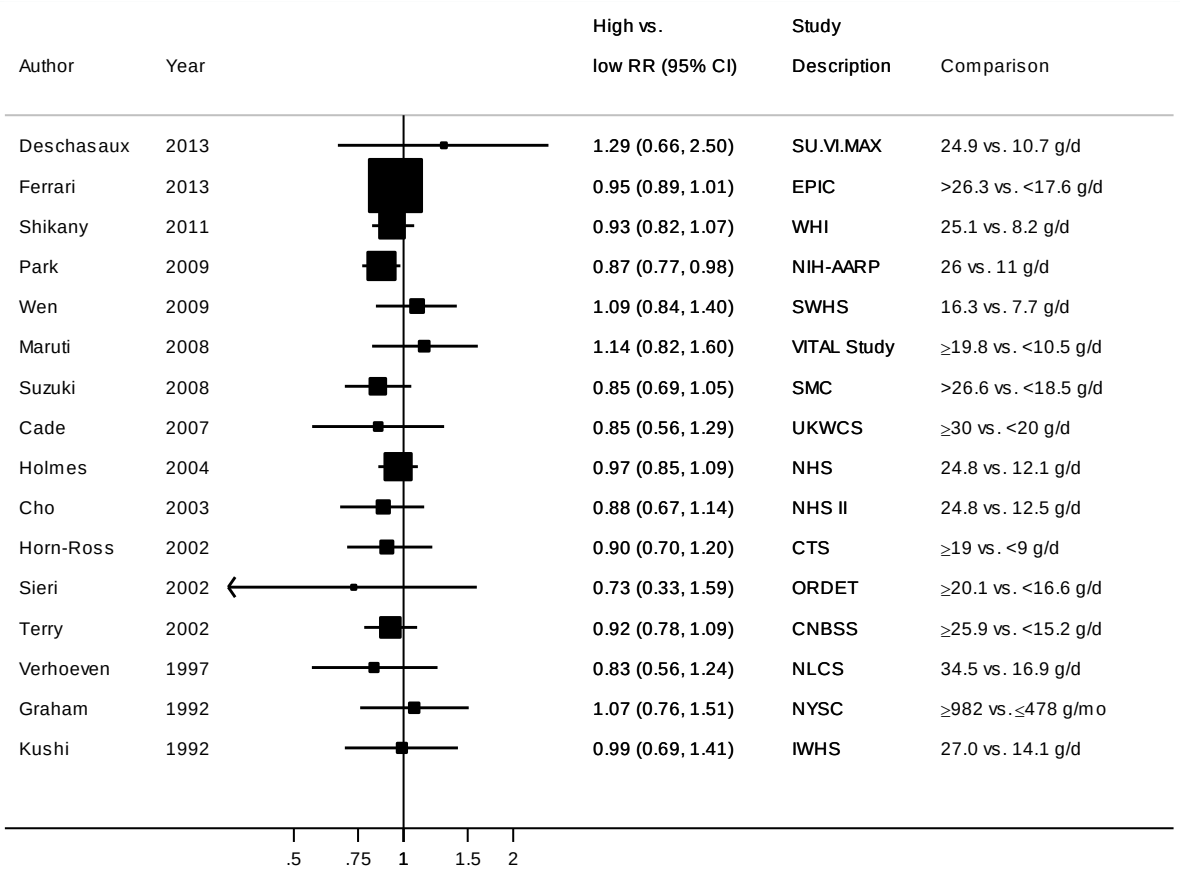


Figure 171 Relative risk of breast cancer for the highest compared with the lowest level of fibre intake, stratified by menopausal status

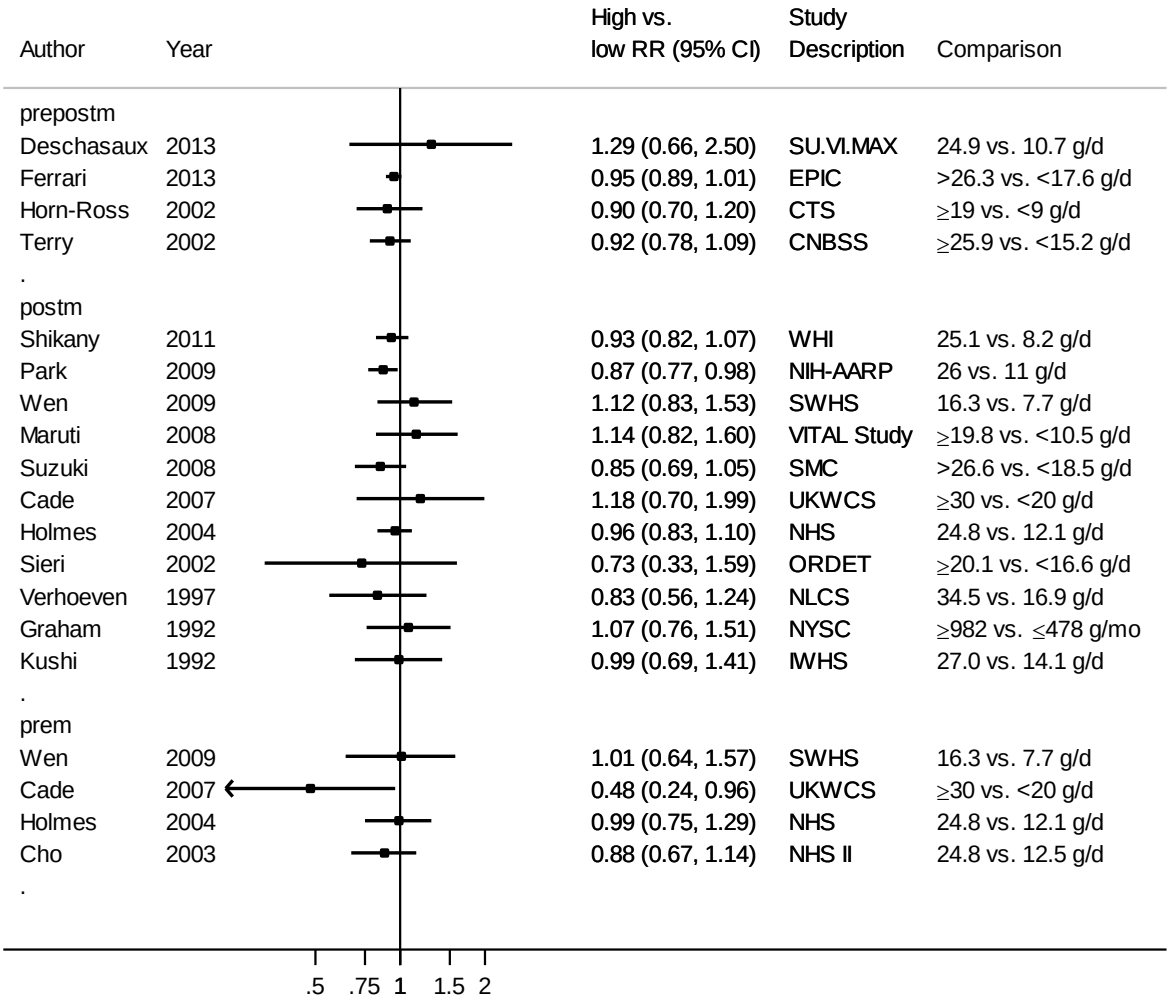


Figure 172 Relative risk of breast cancer for 10 g/day increase in fibre intake

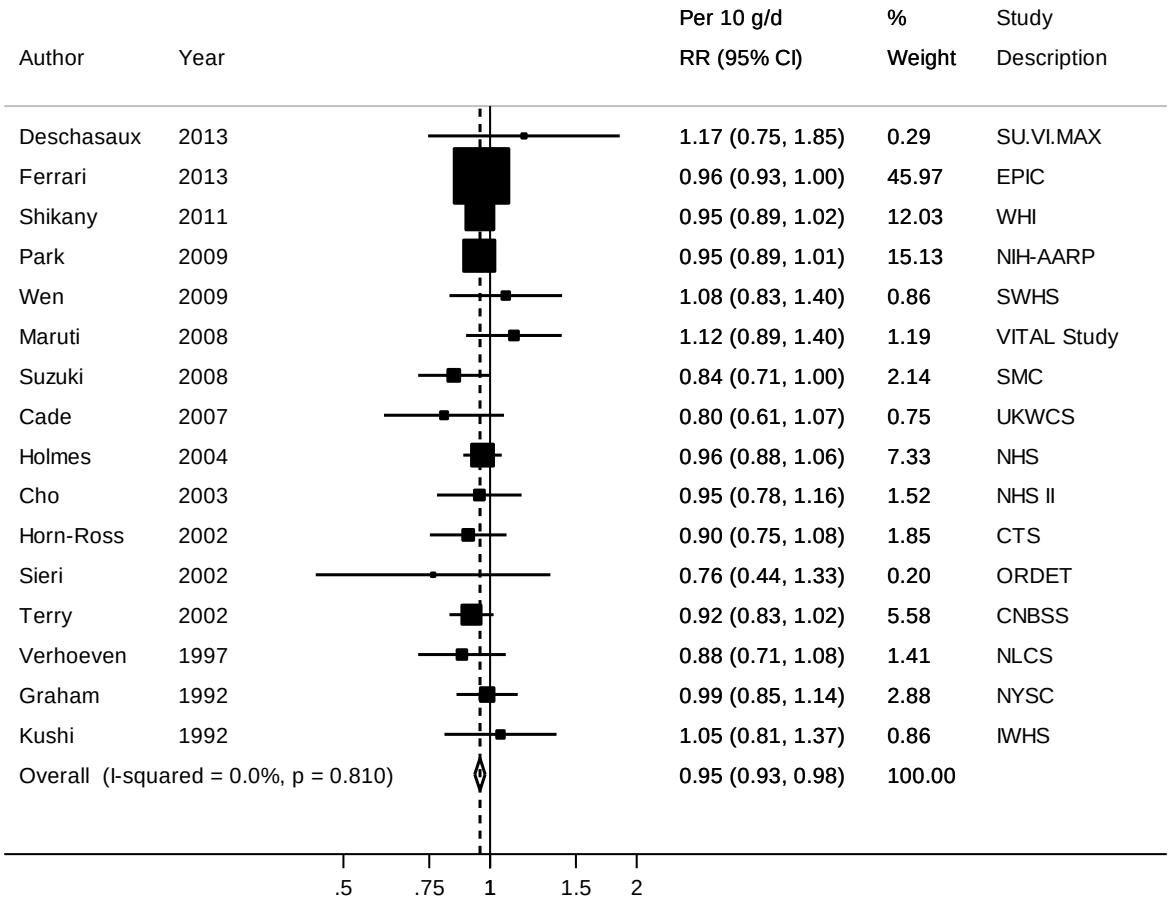


Figure 173 Relative risk of premenopausal breast cancer for 10 g/day increase in fibre intake

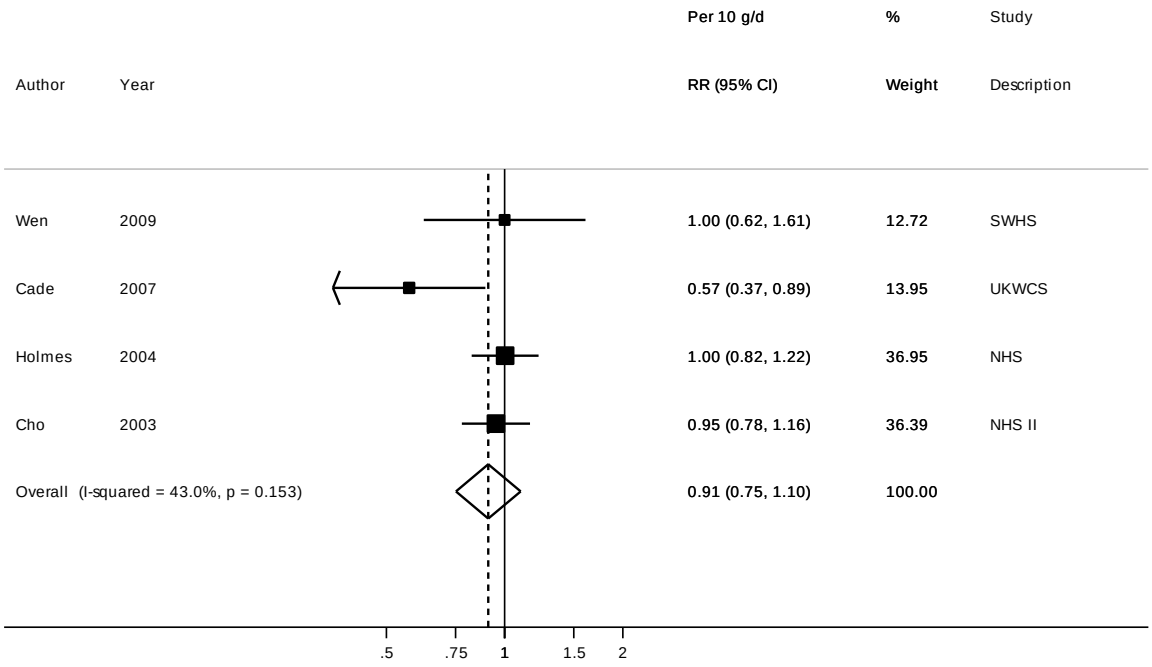


Figure 174 Relative risk of postmenopausal breast cancer for 10 g/day increase in fibre intake

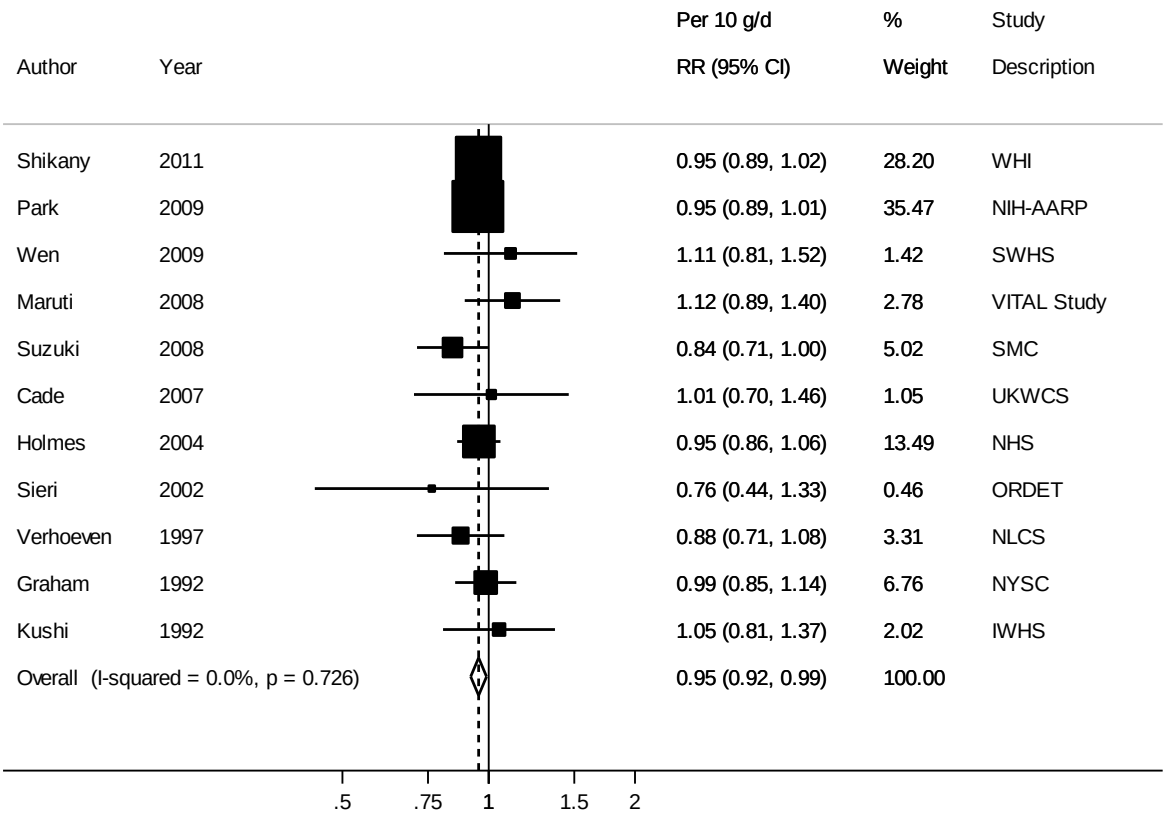


Figure 175 Relative risk of breast cancer for 10 g/day increase in fibre intake, stratified by geographic location

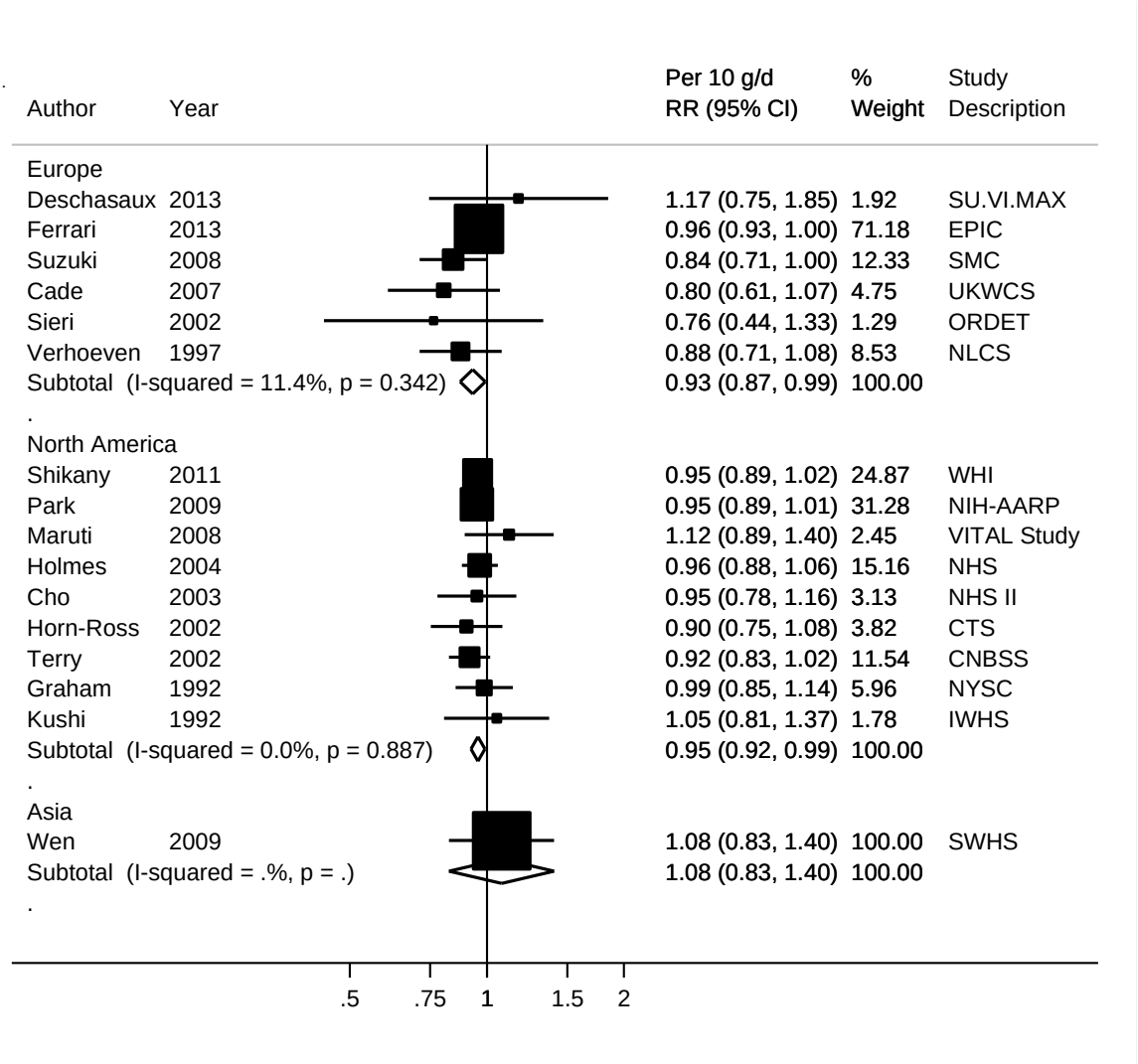


Figure 176 Funnel plot of studies included in the dose response meta-analysis of fibre intake and breast cancer

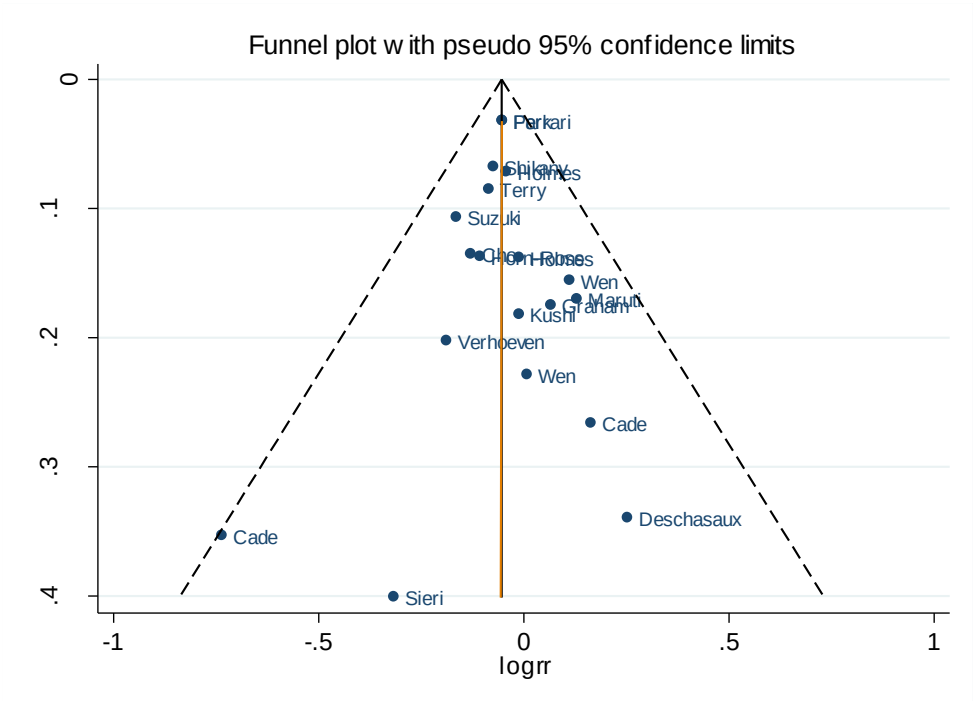


Figure 177 Funnel plot of studies included in the dose response meta-analysis of fibre intake and postmenopausal breast cancer

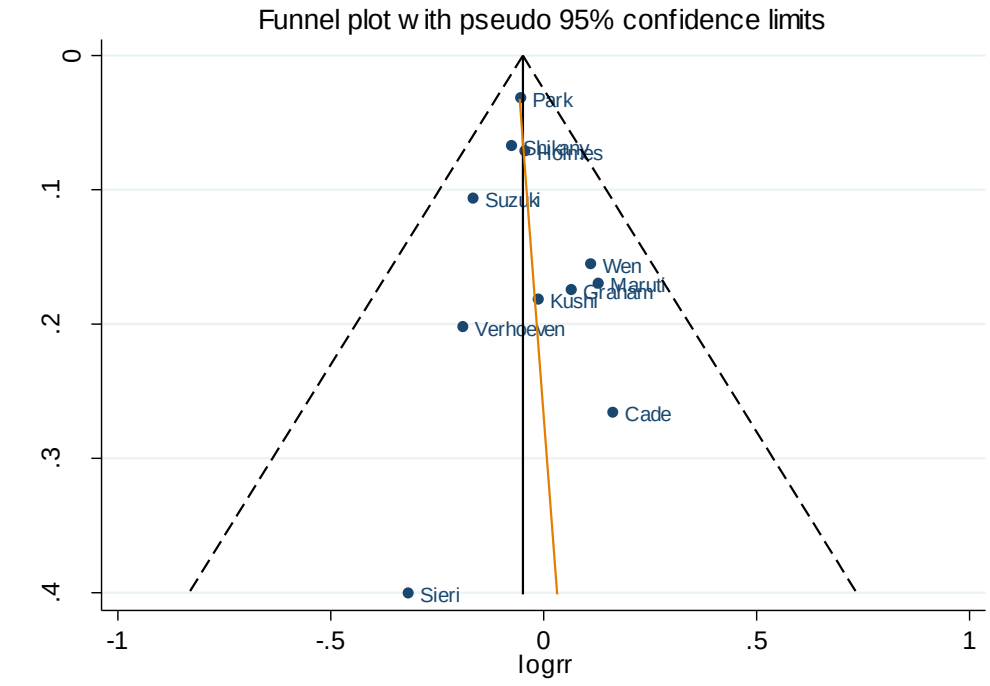
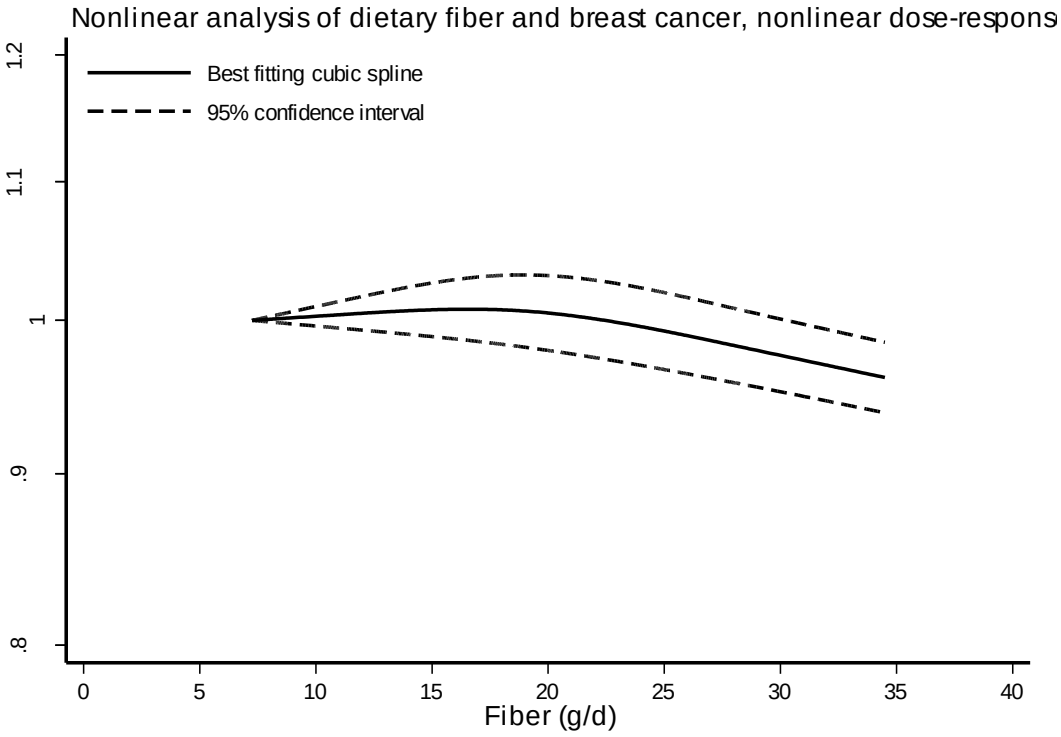


Figure 178 Fibre and breast cancer, nonlinear dose-response analysis



P nonlinearity=0.05

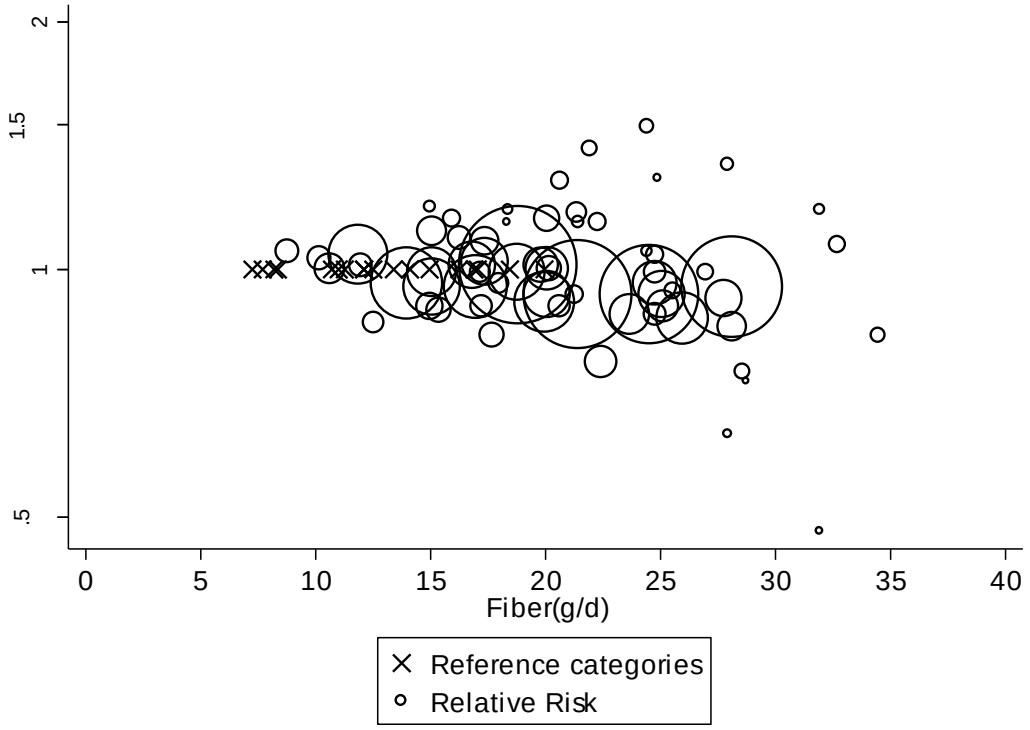
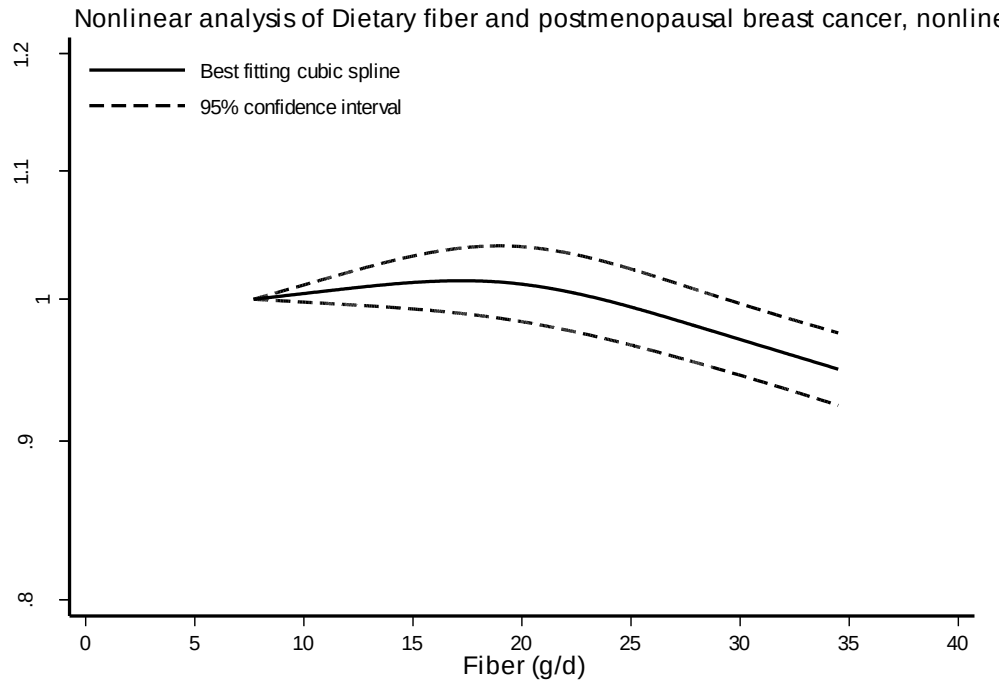


Table 113 Relative risk of breast cancer and fibre estimated using non-linear models

Fibre (g/day)	RR (95%CI)
7.25	1.00
10	1.00 (0.99-1.01)
15	1.01 (0.99-1.03)
20	1.01 (0.98-1.03)
25	0.99 (0.97-1.02)
30	0.98 (0.96-1.01)
35	0.96 (0.94-0.99)

Figure 179 Fibre and postmenopausal breast cancer, nonlinear dose-response analysis



P nonlinearity=0.001

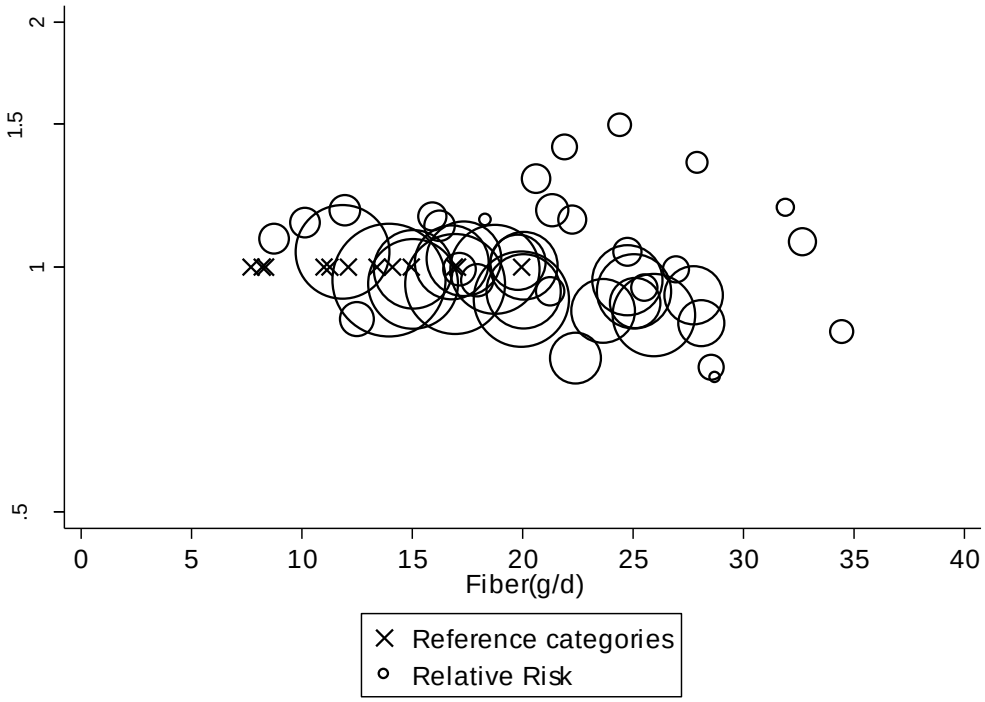

.5
1
1.5
2
0
5
10
15
20
25
30
35
40
Fiber(g/d)
Reference categories
Relative Risk

Table 114 Relative risks of postmenopausal breast cancer and fibre estimated using non-linear models

Fibre (g/day)	RR (95%CI)
7.7	1.00
10	1.00 (0.99-1.01)
15	1.01 (0.99-1.03)
20	1.01 (0.98-1.04)
25	0.99 (0.97-1.02)
30	0.98 (0.95-1.00)
35	0.95 (0.92-0.98)

5.1.2 Insoluble fibre

Seven studies on insoluble fibre intake and breast cancer risk were identified. Four studies investigated postmenopausal breast cancers, one was on premenopausal breast cancers, and two were on pre- and postmenopausal breast cancers combined. Study characteristics and results for all cancer types are shown in the Table.

Study quality:

Insoluble fibre intake was estimated from food intake assessed by FFQ in all, but one study (Deschasaux, 2014), which used repeated 24-hour recalls. One study used a combination of dietary assessment methods including FFQ, dietary records, and dietary interviews (Ferrari, 2013).

Loss to follow-up was low for the studies that reported such data, although some studies did not provide data.

Cancers were identified by record linkages to health registries, cancer registries, mortality registries, or death indexes.

All studies adjusted for at least age, and most of the studies adjusted for most of the established breast cancer risk factors, including: age, parity, age at menarche, age at menopause, physical activity, BMI, and alcohol consumption.

Breast cancer (any)

Six studies (14976 cases) were included in the dose-response meta-analysis. The summary RR for a 10 g/d increase in insoluble fibre intake was 0.97 (95% CI: 0.87-1.07) and there was low heterogeneity, I^2=30.0%, $p_{heterogeneity}$=0.21. There was no evidence of small study bias or publication bias with Egger's test, p=0.97. One large American study, the Women's Health Initiative (Shikany, 2011), contributed to 40% of the weight in the meta-analysis. The summary RR ranged from 0.94 (95% CI: 0.82-1.07) when the NIH-AARP Diet and Health Study (Park, 2009a) was excluded to 0.99 (95% CI: 0.89-1.10) when the Nurses' Health Study 2 (Cho, 2003b) was excluded.

Nonlinear dose-response analysis

There was no evidence of a nonlinear association, $p_{nonlinearity}=0.32$.

Table 115 Insoluble fibre intake and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	7
Studies included in forest plot of highest compared with lowest intake	Breast cancer: 6 Premenopausal: not enough studies Postmenopausal: not enough studies
Studies included in linear dose-response meta-analysis	Breast cancer: 6 Premenopausal: not enough studies Postmenopausal: not enough studies
Studies included in non-linear dose-response meta-analysis	Breast cancer: 6 Premenopausal: not enough studies Postmenopausal: not enough studies

Table 116 Insoluble fibre intake and breast cancer risk. Summary of the linear dose-response meta-analysis in the CUP (no dose-response meta-analysis was conducted in the 2005 SLR)

	Breast cancers (any)	Premenopausal	Postmenopausal
Increment unit used	10 g/day		
Studies (n)	6	-	-
Cases (total number)	14976	-	-
RR (95%CI)	0.97 (0.87-1.07)	-	-
Heterogeneity (I^2, p-	30.0%, p=0.21	-	-
P value Egger test	0.97	-	-

Stratified analyses

Geographic area	Asia	Europe	North-America
Studies (n)	-	1	5
RR (95%CI)	-	1.37 (0.66-2.83)	0.96 (0.86-1.07)
Heterogeneity (I^2, p- value)	-	-	36.2%, p=0.18

Table 117 Insoluble fibre and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Aune et al, 2012	6 5	-	North America, Europe	Incidence	High vs. low Per 10 g/d	0.96 (0.88-1.04) 0.96 (0.86-1.07)	- -	0%, p=0.55 36%, p=0.18

Table 118 Insoluble fibre intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Deschasaux, 2013 BRE80487 France	SU.VI.MAX, Prospective Cohort, Age: 47 years, W	167/ 4 684 12.6 years	Self-report/ medical records/histology	24 hour diet recall	Incidence, breast cancer	≥16.2 vs ≤10.4 g/day	1.32 (0.68-2.57)	Age-underlying cox models, alcohol, BMI, dietary pattern score, dietary records, educational level, family history of breast cancer, fat Intake, height, HRT use, Intervention group, menopausal status, non-alcohol energy Intake, number of children, physical activity, smoking status
Shikany, 2011 BRE80382 USA	Women's Health Initiative, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	6 098/ 148 767 8 years	Self-report verified by medical record	FFQ	Incidence, breast cancer	18.4 vs. 5.8 g/day	0.93 (0.82-1.06)	Age, age at first child birth, age at menarche, age at menopause, alcohol, BMI, educational level, energy Intake, ethnicity, family history of breast cancer, hormone use, HRT use, mammogram In the past 2 years, oral contraceptive history, parity, physical activity, smoking, trial assignment, trial assignment
Park, 2009a BRE80264 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W, Postmenopausal	5 461/ 185 598 7 years	Cancer registry	FFQ	Incidence, breast cancer	17 vs 6.8 g/day	1.03 (0.88-1.19)	Age, age at first child birth, age at menopause, alcohol Intake, BMI, breast biopsies, educational attainment, energy Intake, family history of cancer, fat Intake, fruits and vegetables Intake, menopausal hormone use,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								oophorectomy/hysterectomy, parity, physical activity, race, smoking status
Maruti, 2008a BRE80197 USA	VITAL, Prospective Cohort, Age: 50-76 years, W, Postmenopausal	455/ 28 586 5 years	Cancer registry	FFQ	Incidence, Invasive breast cancer, postmenopausal	14.6-44.2 vs ≤7.6 g/day	1.07 (0.78-1.49)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, BMI, breast biopsies, family history of cancer, height, mammography, menopausal hormone use, physical activity, race, total energy Intake
Cho, 2003b BRE01651 USA	NHS II, Prospective Cohort, Age: 26-46 years, W, Registered nurses	714/ 90 655 8 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, breast cancer, premenopausal	19 vs 9.5 g/day	0.81 (0.62-1.07)	Age at first child, age at menarche, alcohol, benign breast disease, BMI, family history, height, menopausal status, nutrients, oc use, parity/pregnancies, residual (willet), smoking habits
Terry, 2002 BRE12199 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	89 835 16.2 years	Partially histological - over 80%	FFQ	Incidence, Invasive & In situ breast cancer,	≥5.5 vs ≤2.7 g/day	0.89 (0.76-1.03)	Age , alcohol, benign breast disease, BMI, educational level, energy Intake , family history, HRT use, menopausal status, nutrients, oc use, other specified factor, other specified factor, parity/pregnancies, physical activity , recruitment center, smoking habits

Table 119 Insoluble fibre intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Lajous, 2008 BRE80218 France	E3N EPIC-France, Prospective Cohort, Age: 42-72 years, W, Postmenopausal	62 739 9 years	Cancer registry	Dietary history	Incidence, breast cancer, postmenopausal	Q 4 vs Q 1	0.99 (0.85-1.16)	Age, age at menarche, age at menopause, alcohol consumption, benign breast disease, BMI, breastfeeding, educational level, family history of cancer, fibre Intake, folate Intake, follow-up time, height, HRT use, mammography, oc use, parity, physical activity, residence, total energy Intake, vitamin use	
					Incidence, breast cancer ER-, postmenopausal	Q 4 vs Q 1	0.85 (0.58-1.25)		

Figure 180 RR estimates of breast cancer by levels of insoluble fibre intake

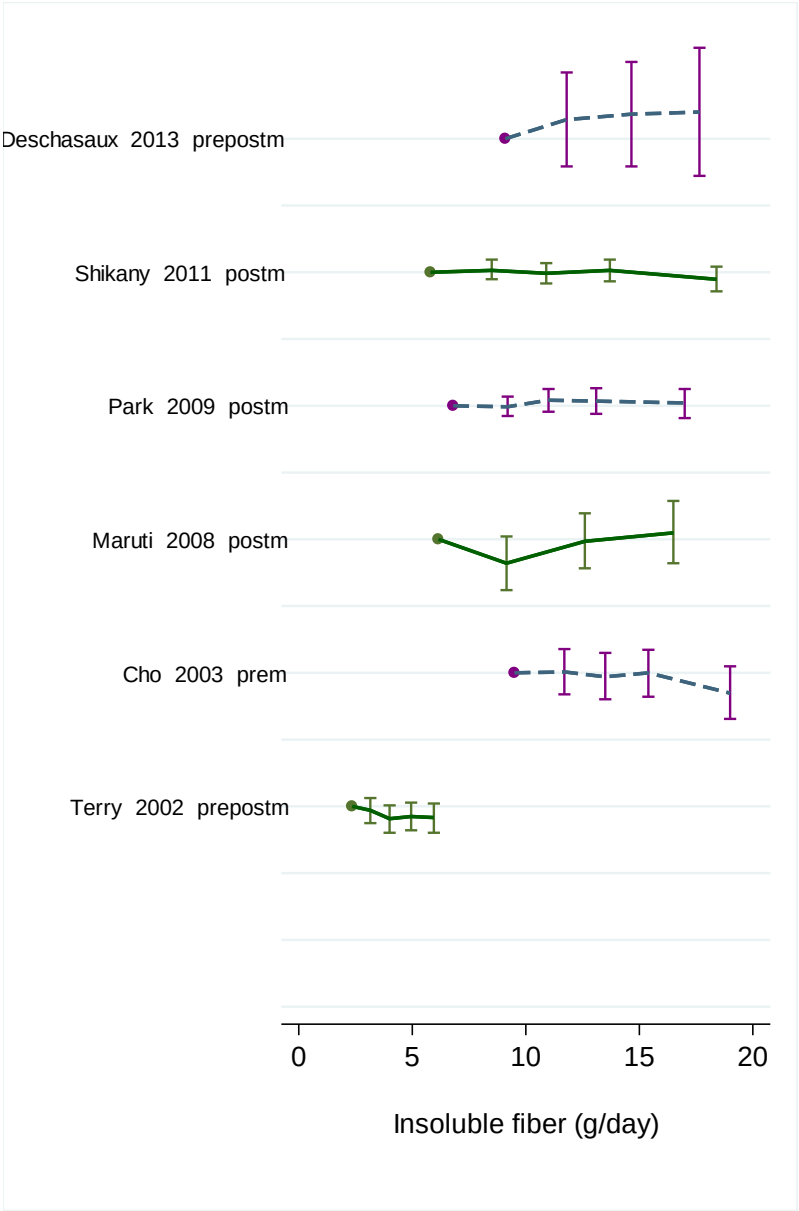


Figure 181 Relative risk of breast cancer for the highest compared with the lowest level of insoluble fibre intake

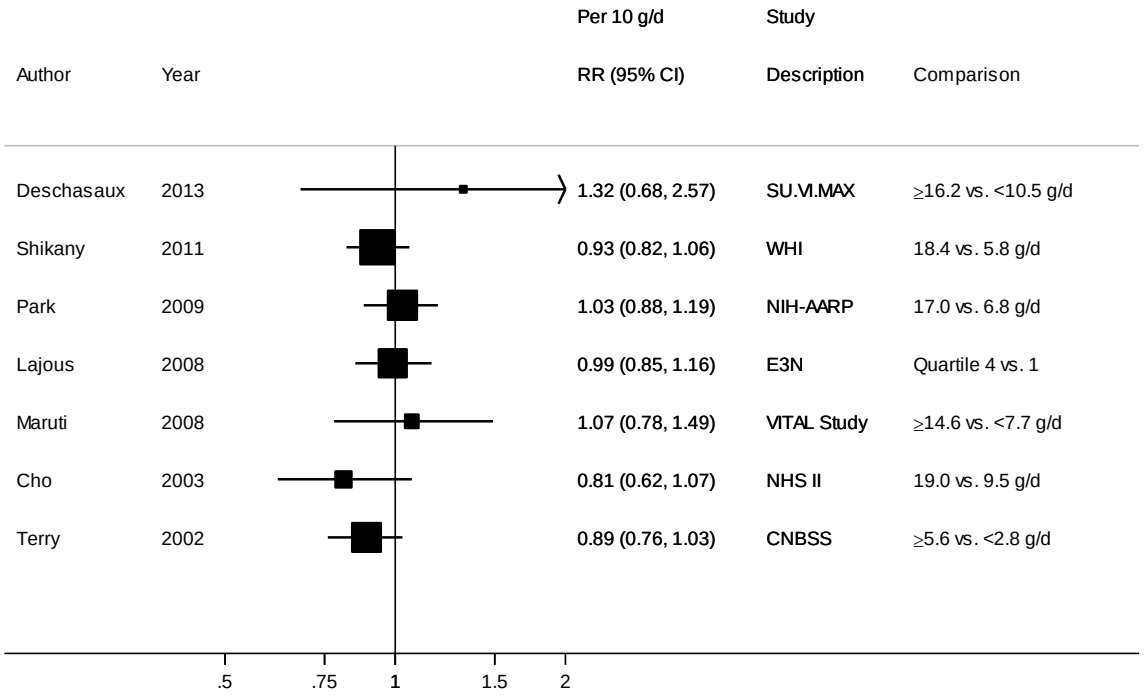


Figure 182 Relative risk of breast cancer for 10 g/day increase in insoluble fibre intake

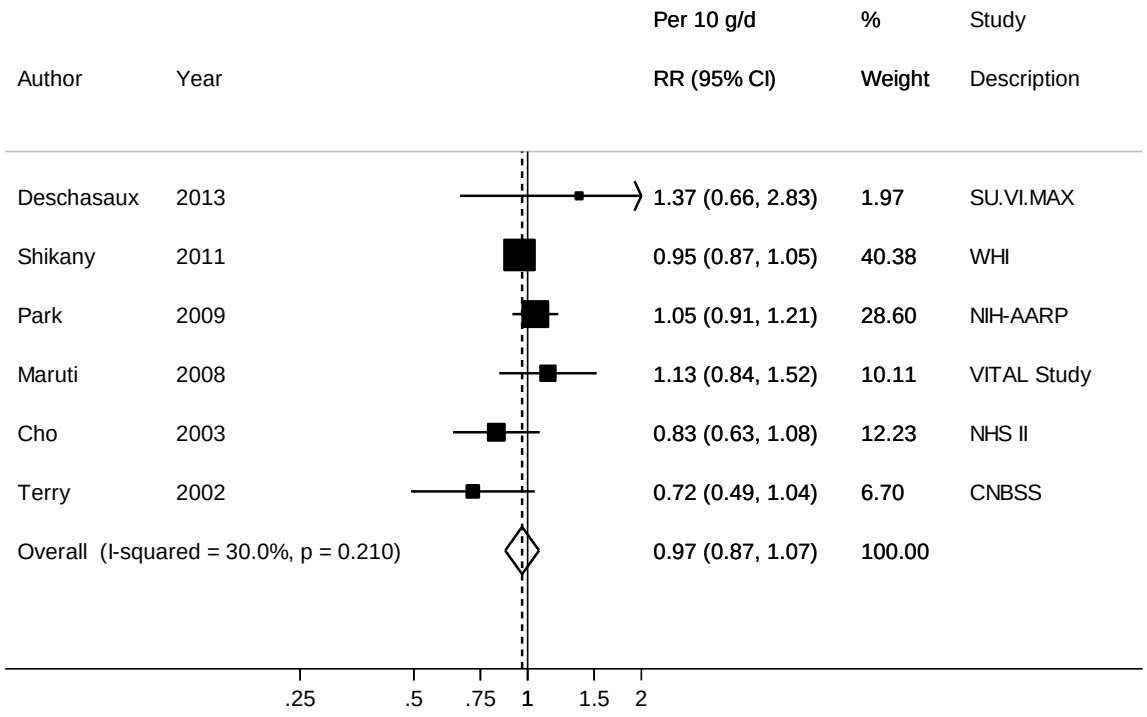


Figure 183 Relative risk of breast cancer for 10 g/day increase in insoluble fibre intake, stratified by geographic location

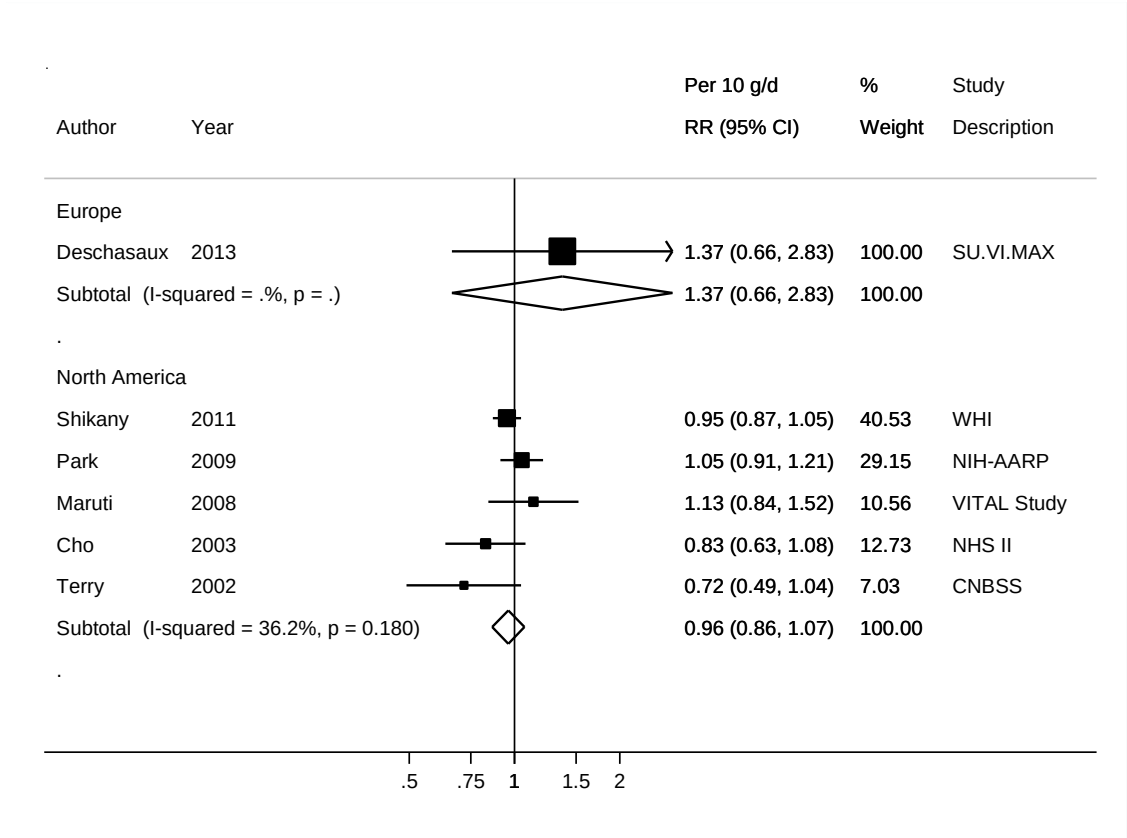


Figure 184 Funnel plot of studies included in the dose response meta-analysis of insoluble fibre intake and breast cancer

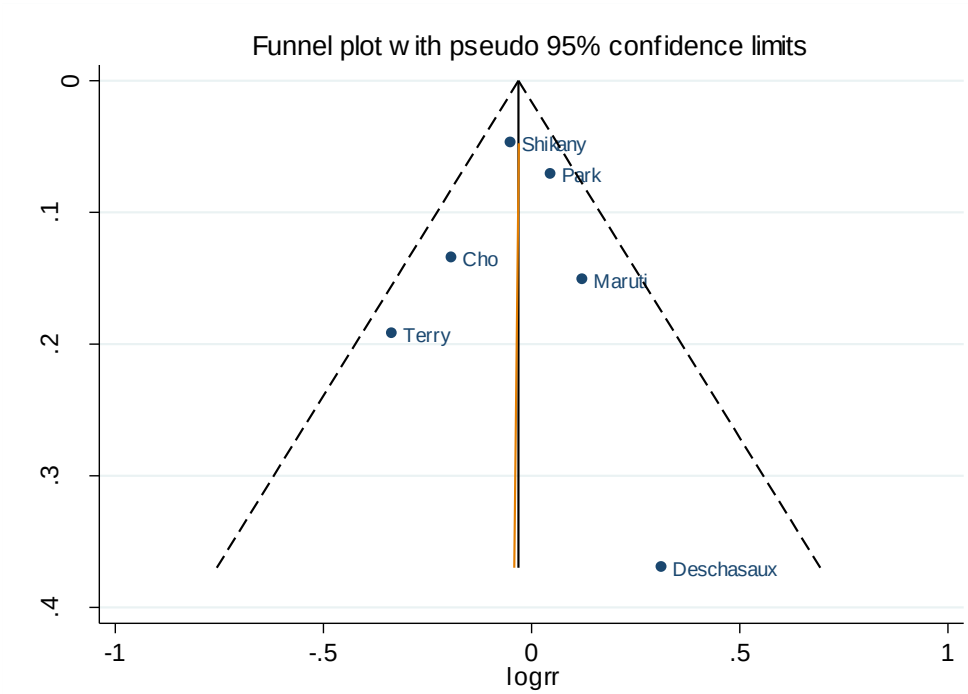
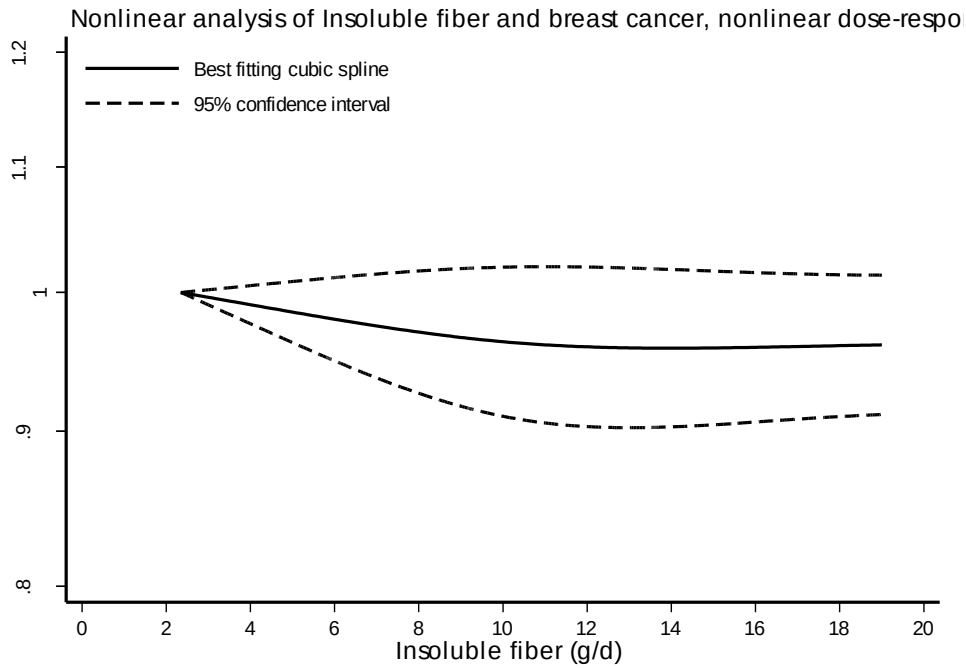


Figure 185 Insoluble fibre and breast cancer, nonlinear dose-response analysis



P nonlinearity=0.32

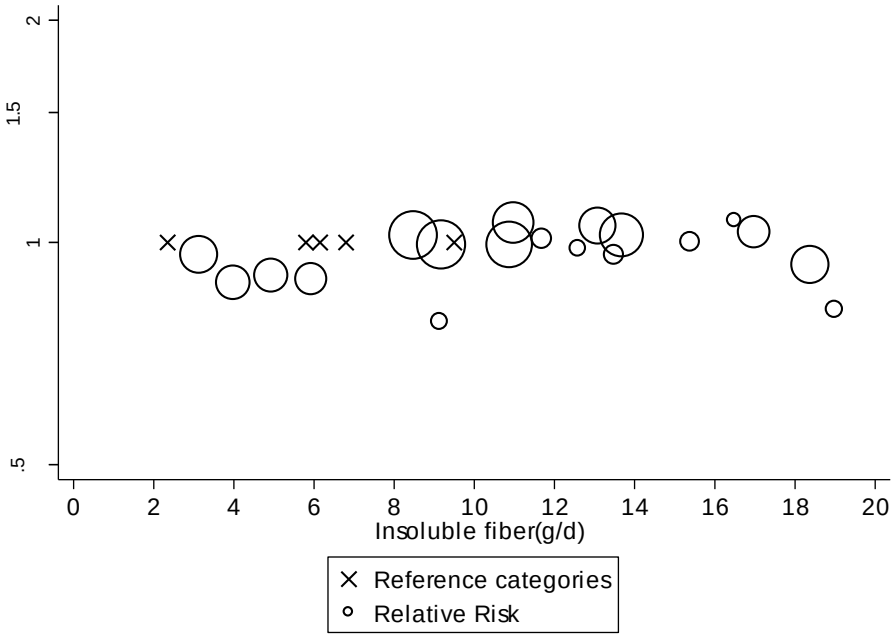


Table 120 Relative risk of breast cancer and insoluble fibre estimated using non-linear models

Insoluble fibre (g/day)	RR (95%CI)
2.35	1.00
4.0	0.99 (0.98-1.01)
6.0	0.98 (0.95-1.01)
8.0	0.97 (0.92-1.02)
10.0	0.96 (0.91-1.02)
12.0	0.96 (0.90-1.02)
14.0	0.96 (0.90-1.02)
16.0	0.96 (0.91-1.02)
18.0	0.96 (0.91-1.01)
20.0	0.96 (0.91-1.01)

5.1.2 Soluble fibre

Six studies on soluble fibre intake and breast cancer risk were identified. Two studies investigated postmenopausal breast cancers, one was on premenopausal breast cancers, and two were on pre- and postmenopausal breast cancers combined. Study characteristics and results for all cancer types are shown in the Table.

Study quality:

Soluble fibre intake was estimated from food intake assessed by FFQ in all, but one study (Deschasaux, 2014), which used repeated 24-hour recalls. One study used a combination of dietary assessment methods including FFQ, dietary records, and dietary interviews (Ferrari, 2013).

Loss to follow-up was low for the studies that reported such data, although some studies did not provide data.

Cancers were identified by record linkages to health registries, cancer registries, mortality registries, or death indexes.

All studies adjusted for at least age, and most of the studies adjusted for most of the established breast cancer risk factors, including: age, parity, age at menarche, age at menopause, physical activity, BMI, and alcohol consumption.

Breast cancer (any)

Five studies (14976 cases) were included in the dose-response meta-analysis. The summary RR for a 10 g/d increase in soluble fibre intake was 0.74 (95% CI: 0.63-0.88) and there was no evidence of heterogeneity, I^2=0%, $p_{heterogeneity}$=0.76. There was no evidence of small study bias or publication bias with Egger's test, p=0.29. One large American study, the Women's Health Initiative (Shikany, 2011), contributed 40% of the weight in the meta-analysis. The summary RR ranged from 0.71 (95% CI: 0.57-0.88) when the Women's Health Initiative (Shikany, 2011) was excluded to 0.79 (95% CI: 0.65-0.98) when the NIH-AARP Diet and Health Study (Park, 2009a) was excluded.

Nonlinear dose-response analysis

There was indication of a nonlinear association, $p_{nonlinearity}$=0.03, with a suggestion of a threshold effect, with a significant reduction in risk at intakes of 8 g/d or higher.

Table 121 Soluble fibre intake and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	6
Studies included in forest plot of highest compared with lowest intake	Breast cancer: 6 Premenopausal: not enough studies Postmenopausal: not enough studies

Studies included in linear dose-response meta-analysis	Breast cancer: 5 Premenopausal: not enough studies Postmenopausal: not enough studies
Studies included in non-linear dose-response meta-analysis	Breast cancer: 5 Premenopausal: not enough studies Postmenopausal: not enough studies

Table 122 Soluble fibre intake and breast cancer risk. Summary of the linear dose-response meta-analysis in the CUP (no dose-response meta-analysis was conducted in the 2005 SLR)

	Breast cancers (any)	Premenopausal	Postmenopausal
Increment unit used	10 g/day		
Studies (n)	5	-	-
Cases (total number)	14976	-	-
RR (95%CI)	0.74 (0.63-0.88)	-	-
Heterogeneity (I^2, p-	0%, p=0.76	-	-
P value Egger test	0.29	-	-

Stratified analyses

Geographic area	Asia	Europe	North-America
Studies (n)	-	1	4
RR (95%CI)	-	2.16 (0.18-26.10)	0.74 (0.63-0.88)
Heterogeneity (I^2, p- value)	-	-	0%, p=0.77

Table 123 Soluble fibre and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Aune et al, 2012	5	-	North America, Europe	Incidence	High vs. low Per 10 g/d	0.91 (0.84-0.99) 0.74 (0.63-0.88)	- -	7%, p=0.36 0%, p=0.77

Table 124 Soluble fibre intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors
Deschasaux, 2013 BRE80487 France	SU.VI.MAX, Prospective Cohort, Age: 47 years, W	167/ 4 684 12.6 years	Self-report/ medical records/histology	24 hour diet recall	Incidence, breast cancer	≥4.2 vs ≤2.6 g/day	1.22 (0.67-2.22)	Age-underlying cox models, alcohol, BMI, dietary pattern score, dietary records, educational level, family history of breast cancer, fat Intake, height, HRT use, Intervention group, menopausal status, non-alcohol energy Intake, number of children, physical activity, smoking status
Shikany, 2011 BRE80382 USA	Women's Health Initiative, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	6 098/ 148 767 8 years	Self-report verified by medical record	FFQ	Incidence, breast cancer	6.7 vs 2.2 g/day	0.90 (0.79-1.03)	Age, age at first child birth, age at menarche, age at menopause, alcohol, BMI, educational level, energy Intake, ethnicity, family history of breast cancer, hormone use, HRT use, mammogram In the past 2 years, oral contraceptive history, parity, physical activity, smoking, trial assignment, trial assignment
Park, 2009a BRE80264 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W, Postmenopausal	5 461/ 185 598 7 years	Cancer registry	FFQ	Incidence, breast cancer	9 vs 3.8 g/day	0.83 (0.70-0.98)	Age, age at first child birth, age at menopause, alcohol Intake, BMI, breast biopsies, educational attainment, energy Intake, family history of cancer, fat Intake, fruits and vegetables Intake, menopausal hormone use, oophorectomy/hysterectomy, parity, physical activity, race,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors
								smoking status
Cho, 2003b BRE01651 USA	NHS II, Prospective Cohort, Age: 26-46 years, W, Registered nurses	714/ 90 655 8 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, breast cancer, premenopausal	7.4 vs 3.8 g/day	0.87 (0.67-1.13)	Age at first child, age at menarche, alcohol, benign breast disease, BMI, family history, height, menopausal status, nutrients, oc use, parity/pregnancies, residual (willet), smoking habits
Terry, 2002 BRE12199 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	2536/ 89 835 16.2 years	Partially histological - over 80%	FFQ	Incidence, Invasive & In situ breast cancer,	≥7.8 vs ≤4.5 g/day	0.90 (0.75-1.08)	Age , alcohol, benign breast disease, BMI, educational level, energy Intake , family history, HRT use, menopausal status, nutrients, oc use, other specified factor, other specified factor, parity/pregnancies, physical activity , recruitment center, smoking habits

Table 125 Soluble fibre intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Lajous, 2008 BRE80218 France	E3N EPIC-France, Prospective Cohort, Age: 42-72 years, W, Postmenopausal	62 739 9 years	Cancer registry	Dietary history	Incidence, breast cancer, postmenopausal	Q 4 vs Q 1	1.05 (0.89-1.23)	Age, age at menarche, age at menopause, alcohol consumption, benign breast disease, BMI, breastfeeding, educational level, family history of cancer, fibre Intake, folate Intake, follow-up time, height, HRT use, mammography, oc use, parity, physical activity, residence, total energy Intake, vitamin use	
					Incidence, breast cancer ER-, postmenopausal	Q 4 vs Q 1	1.23 (0.82-1.85)		

Figure 186 RR estimates of breast cancer by levels of soluble fibre intake

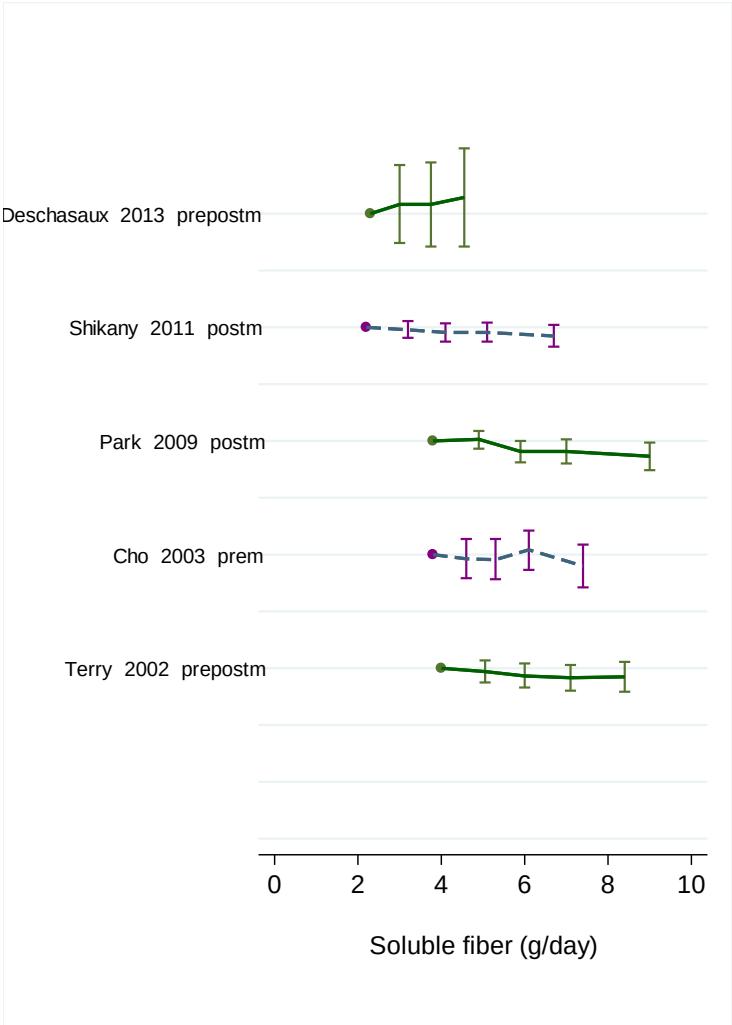


Figure 187 Relative risk of breast cancer for the highest compared with the lowest level of soluble fibre intake

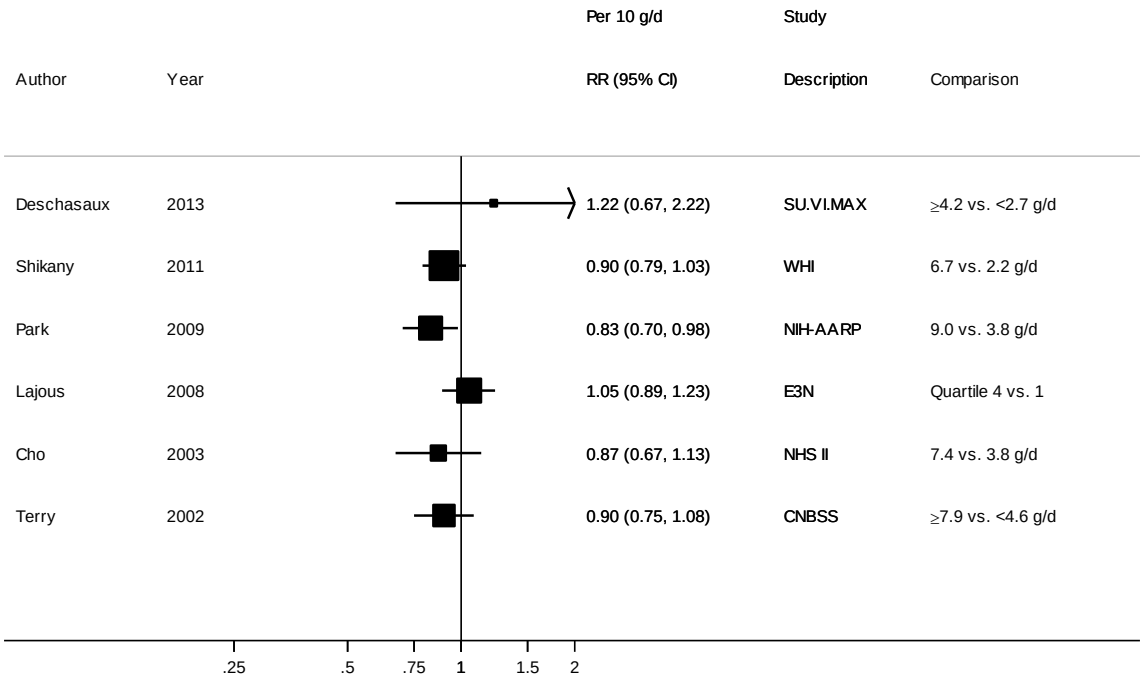


Figure 188 Relative risk of breast cancer for 10 g/day increase in soluble fibre intake

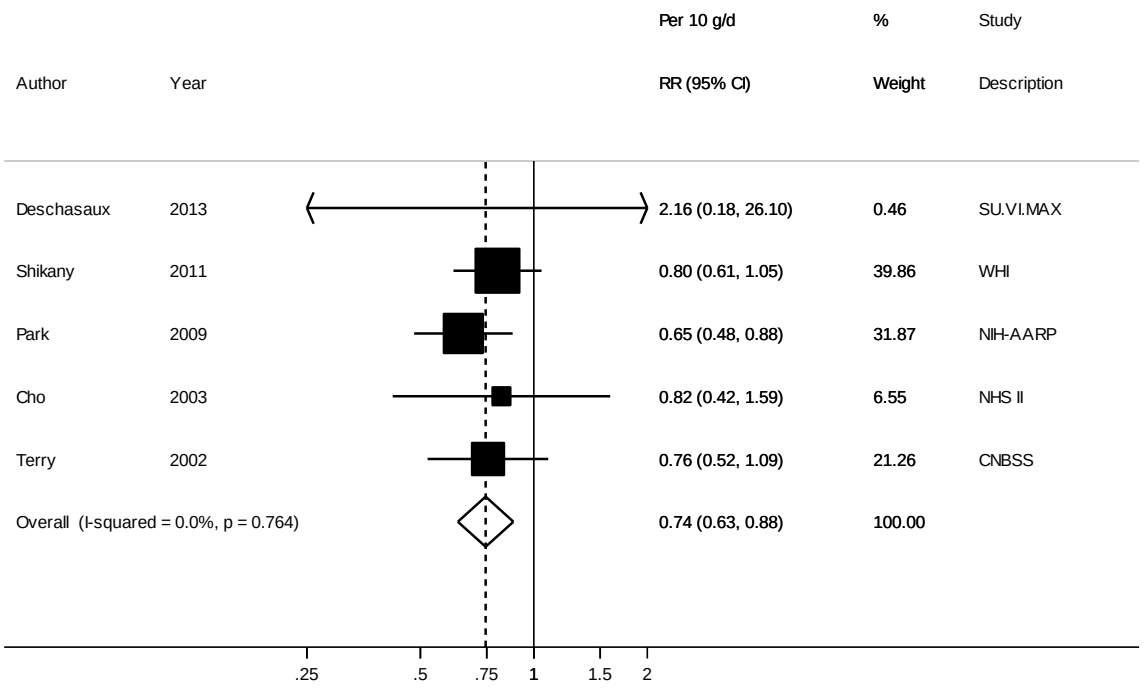


Figure 189 Relative risk of breast cancer for 10 g/day increase in soluble fibre intake, stratified by geographic region

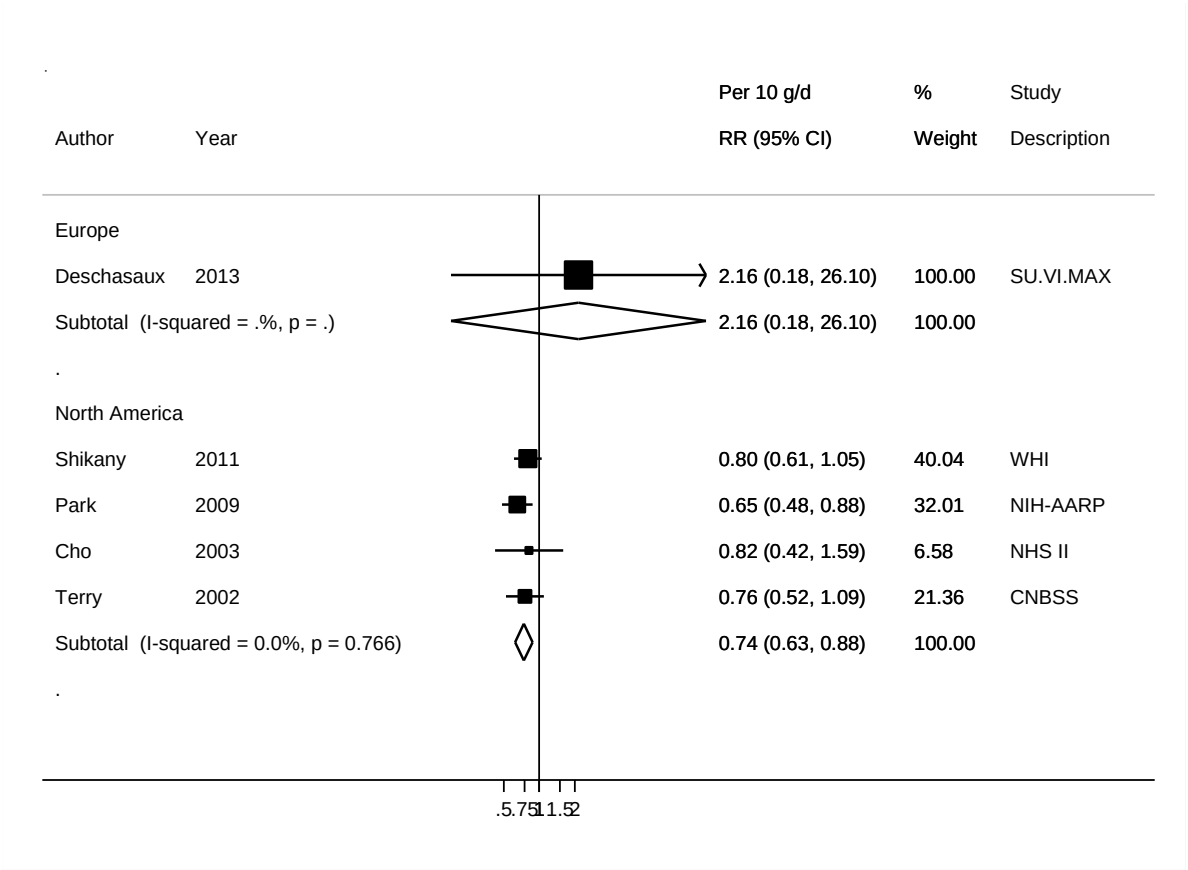


Figure 190 Funnel plot of studies included in the dose response meta-analysis of soluble fibre intake and breast cancer

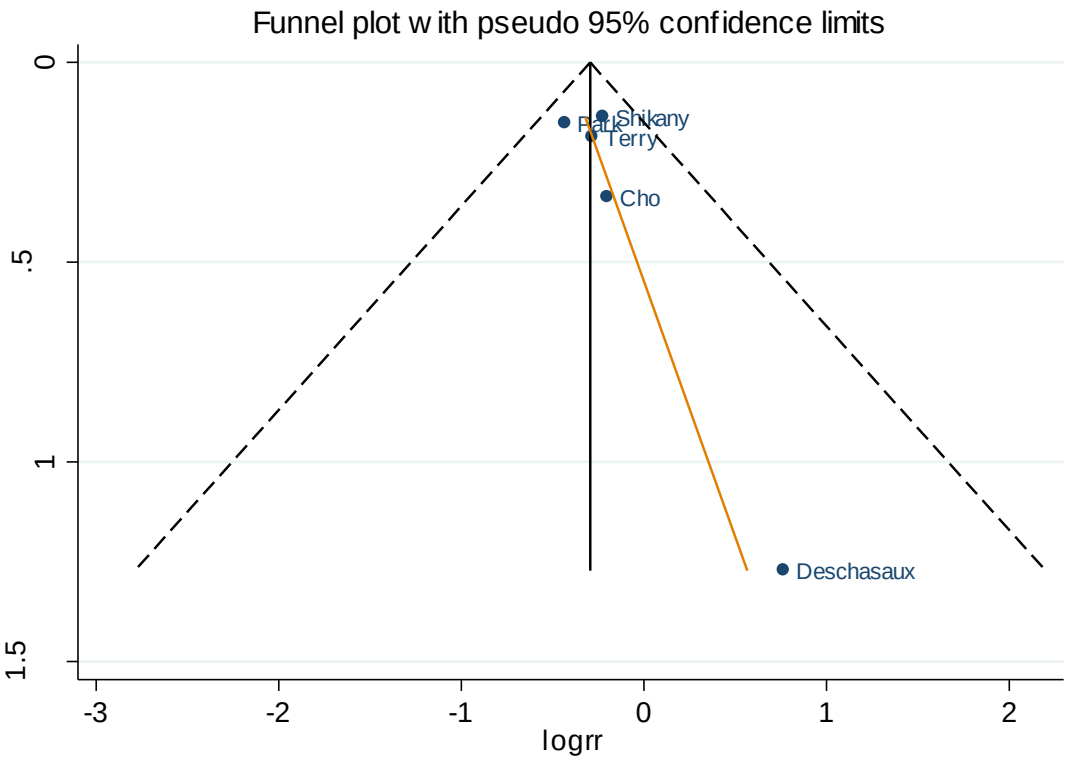
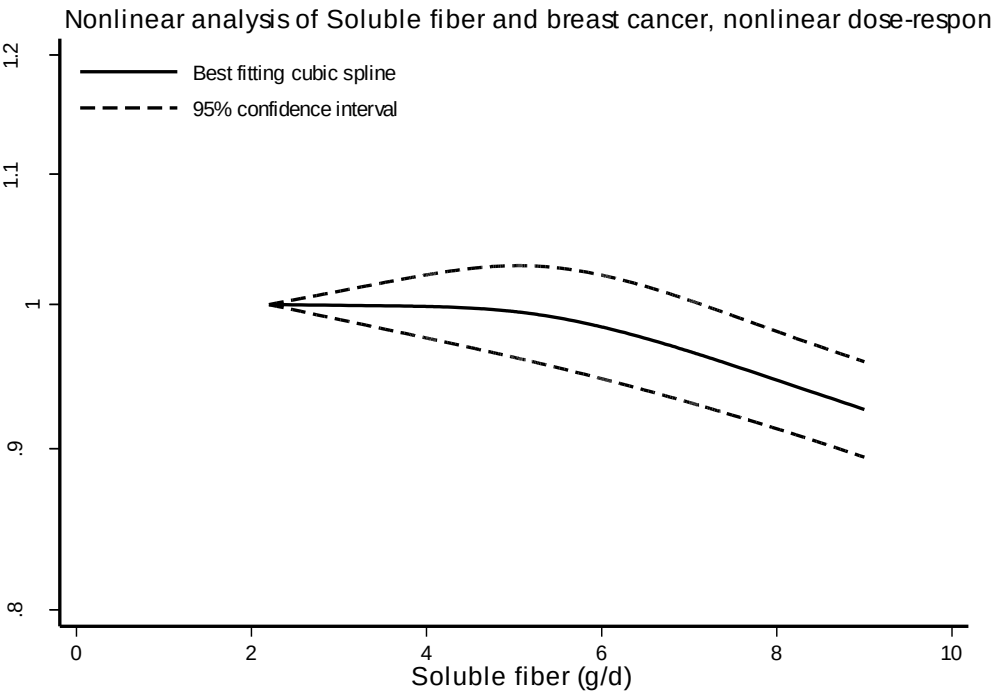


Figure 191 Soluble fibre and breast cancer, nonlinear dose-response analysis



P nonlinearity=0.03

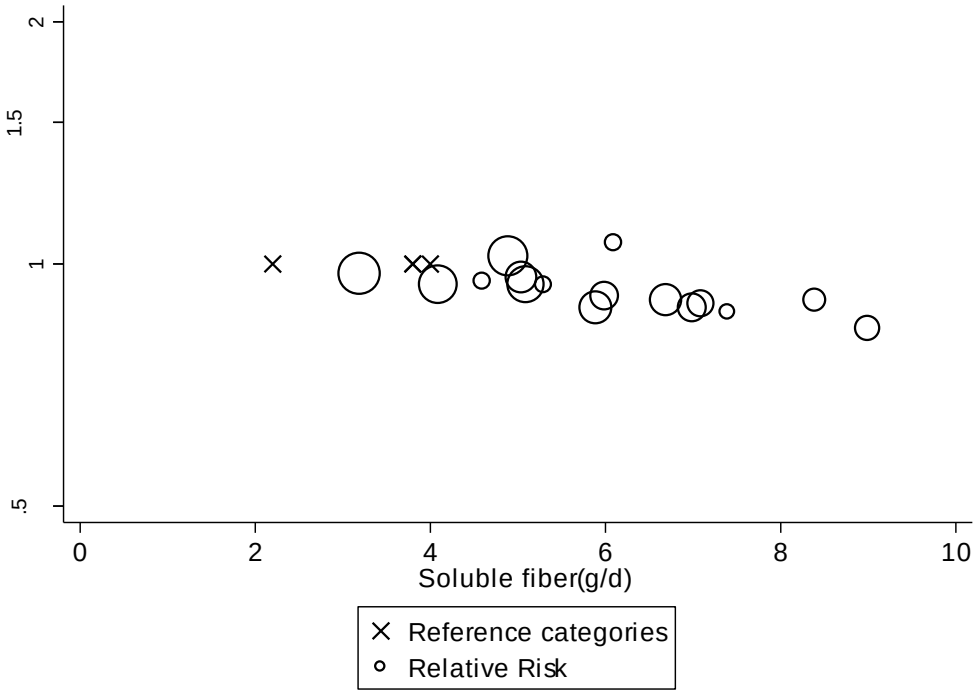


Table 126 Relative risk of breast cancer and soluble fibre estimated using non-linear models

Soluble fibre (g/day)	RR (95%CI)
2.2	1.00
4.0	1.00 (0.98-1.02)
6.0	0.98 (0.95-1.02)
8.0	0.94 (0.91-0.97)
9.0	0.93 (0.89-0.96)

5.1.2 Legume fibre

Five studies on legume fibre intake and breast cancer risk were identified. One study investigated postmenopausal breast cancers, one was on premenopausal breast cancers, and two were on pre- and postmenopausal breast cancers combined. Because of the limited number of studies it was not possible to conduct analyses by menopausal status. Study characteristics and results for all cancer types are shown in the Table.

Study quality:

Legume fibre intake was estimated from food intake assessed by FFQ in all, but one study (Deschasaux, 2014), which used repeated 24-hour recalls. One study used a combination of

dietary assessment methods including FFQ, dietary records, and dietary interviews (Ferrari, 2013).

Loss to follow-up was low for the studies that reported such data, although some studies did not provide data.

Cancers were identified by record linkages to health registries, cancer registries, mortality registries, or death indexes.

All studies adjusted for at least age, and most of the studies adjusted for most of the established breast cancer risk factors, including: age, parity, age at menarche, age at menopause, physical activity, BMI, and alcohol consumption.

Breast cancer (any)

Four studies (17918 cases) were included in the dose-response meta-analysis. The summary RR for a 10 g/d increase in legume fibre intake was 0.92 (95% CI: 0.72-1.17) and there was moderate heterogeneity, I^2=45.5%, $p_{heterogeneity}$=0.14. There was no evidence of small study bias or publication bias with Egger's test, p=0.41. One large European study, the EPIC study (Ferrari, 2013), contributed to 59% of the weight in the meta-analysis. The summary RR ranged from 0.70 (95% CI: 0.32-1.53) when the EPIC Study (Ferrari, 2013) was excluded to 0.99 (95% CI: 0.91-1.08) when the Nurses' Health Study (Cho, 2003b) was excluded.

Nonlinear dose-response analysis

There was indication of a nonlinear association, $p_{nonlinearity}$=0.003, and most of the reduction in risk was observed with intakes up to 6-8 grams per day and little further reductions in risk with higher intakes.

Table 127 Legume fibre intake and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	5
Studies included in forest plot of highest compared with lowest intake	Breast cancer: 4 Premenopausal: not enough studies Postmenopausal: not enough studies
Studies included in linear dose-response meta-analysis	Breast cancer: 4 Premenopausal: not enough studies Postmenopausal: not enough studies
Studies included in non-linear dose-response meta-analysis	Breast cancer: 4 Premenopausal: not enough studies Postmenopausal: not enough studies

Table 128 Legume fibre intake and breast cancer risk. Summary of the linear dose-response meta-analysis in the CUP (no dose-response meta-analysis was conducted in the 2005 SLR)

	Breast cancers (any)	Premenopausal	Postmenopausal
Increment unit used	10 g/day		
Studies (n)	4	-	-
Cases (total number)	17918	-	-
RR (95%CI)	0.92 (0.72-1.17)	-	-
Heterogeneity (I^2, p-	45.5%, p=0.14	-	-
P value Egger test	0.41	-	-

Stratified analyses

Geographic area	Asia	Europe	North-America
Studies (n)	-	2	2
RR (95%CI)	-	1.01 (0.92-1.11)	0.59 (0.21-1.64)
Heterogeneity (I^2, p- value)	-	0%, p=0.61	67.4%, p=0.08

Table 129 Legume fibre intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Deschasaux, 2013 BRE80487 France	SU.VI.MAX, Prospective Cohort, Age: 47 years, W	167/ 4 684 12.6 years	Self-report/ medical records/histology	24 hour diet recall	Incidence, breast cancer	≥5.2 vs ≤2.6 g/day	0.50 (0.29-0.88)	Age-underlying cox models, alcohol, BMI, dietary pattern score, dietary records, educational level, family history of breast cancer, fat Intake, height, HRT use, Intervention group, menopausal status, non-alcohol energy Intake, number of children, physical activity, smoking status
					Incidence, ductal carcinomas, postmenopausal	≥5.2 vs ≤2.6 g/day	0.42 (0.21-0.83)	
					Incidence, breast cancer, postmenopausal	≥5.2 vs ≤2.6 g/day	0.50 (0.26-0.97)	
					Incidence, breast cancer ER+, postmenopausal	≥5.2 vs ≤2.6 g/day	0.37 (0.18-0.76)	
					Incidence, breast cancer PR+, postmenopausal	≥5.2 vs ≤2.6 g/day	0.36 (0.16-0.81)	
Ferrari, 2013 BRE80436 Denmark,France,Germany,Greece,Italy,Netherlands,Norway, Spain,Sweden, UK	EPIC, Prospective Cohort, Age: 35-70 years, W	11 576/ 334 849 11.5 years	Cancer and pathology registry, active follow up, health Insurance record, mortality registry and contact of participants or next-of-kin	Questionnaire	Incidence, breast cancer	≥6.9 vs ≤2.5 g/day	0.90 (0.84-0.96)	Age, age at first child birth, age at menarche, alcohol, contraception, educational level, energy Intake, height, menopausal status, physical activity, smoking, study center, weight
					Incidence, breast cancer	per 5 g/day	0.85 (0.76-0.96)	
					Incidence, breast cancer	per 5 g/day	0.95 (0.91-0.98)	
					Incidence, breast cancer ER+/PR+	≥6.9 vs ≤2.5 g/day	0.92 (0.81-1.03)	
					Incidence, breast	≥6.9 vs ≤2.5	0.74 (0.59-0.93)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					cancer ER-/PR-	g/day		
Park, 2009a BRE80264 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W, Postmenopausal	5 461/ 185 598 7 years	Cancer registry	FFQ	Incidence, breast cancer	10.4 vs 2.9 g/day	1.09 (0.97-1.23) Ptrend:0.16	Age, age at first child birth, age at menopause, alcohol Intake, BMI, breast biopsies, educational attainment, energy Intake, family history of cancer, fat Intake, fruits and vegetables Intake, menopausal hormone use, oophorectomy/hysterectomy, parity, physical activity, race, smoking status
Cho, 2003b BRE01651 USA	NHS II, Prospective Cohort, Age: 26-46 years, W, Registered nurses	714/ 90 655 8 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, breast cancer, premenopausal	10.4 vs 3.3 g/day	0.97 (0.75-1.24)	Age at first child, age at menarche, alcohol, benign breast disease, BMI, family history, height, menopausal status, nutrients, oc use, parity/pregnancies, residual (willet), smoking habits

Table 130 Legume fibre intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Giles, 2006 BRE22430 Australia	MCCS, Prospective Cohort, Age: 40-69 years, W, Postmenopausal	12 273 9.1 years	Pathology report + cancer registry	FFQ	Incidence, breast cancer, postmenopausal	per 1 sd/day	1.07 (0.95-1.20)	Age , energy Intake , HRT use, place of residence	
					Incidence, breast cancer ER+/PR-, postmenopausal	per 1 sd/day	1.14 (0.81-1.61)		
					Incidence, breast cancer ER+/PR+, postmenopausal	per 1 sd/day	1.13 (0.97-1.32)		
					Incidence, breast cancer ER-/PR-, postmenopausal	per 1 sd	0.83 (0.58-1.19)		

Figure 192 RR estimates of breast cancer by levels of legume fibre intake

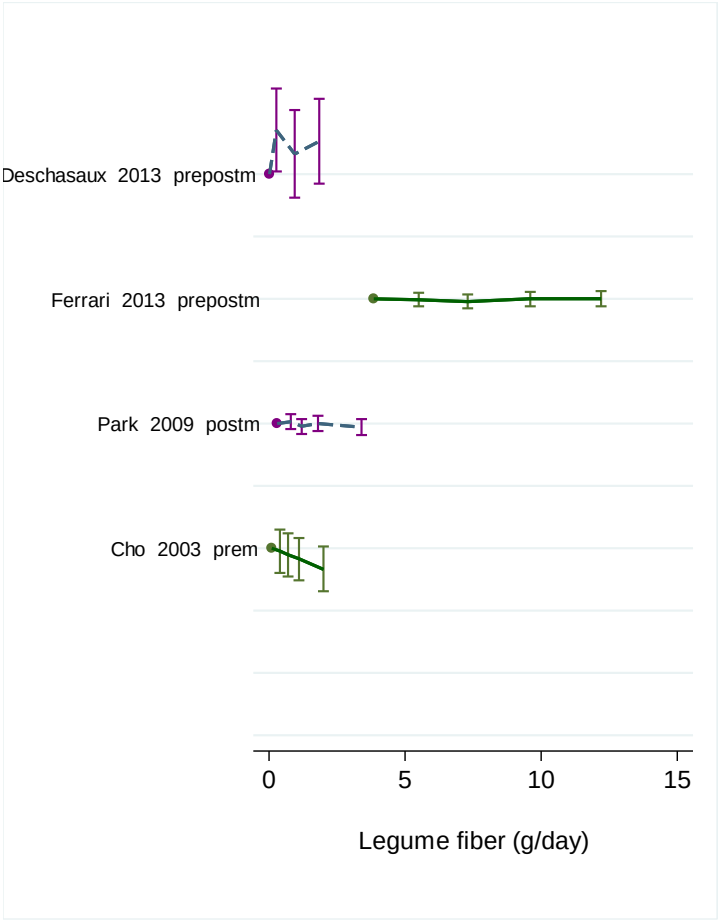


Figure 193 Relative risk of breast cancer for the highest compared with the lowest level of legume fibre intake

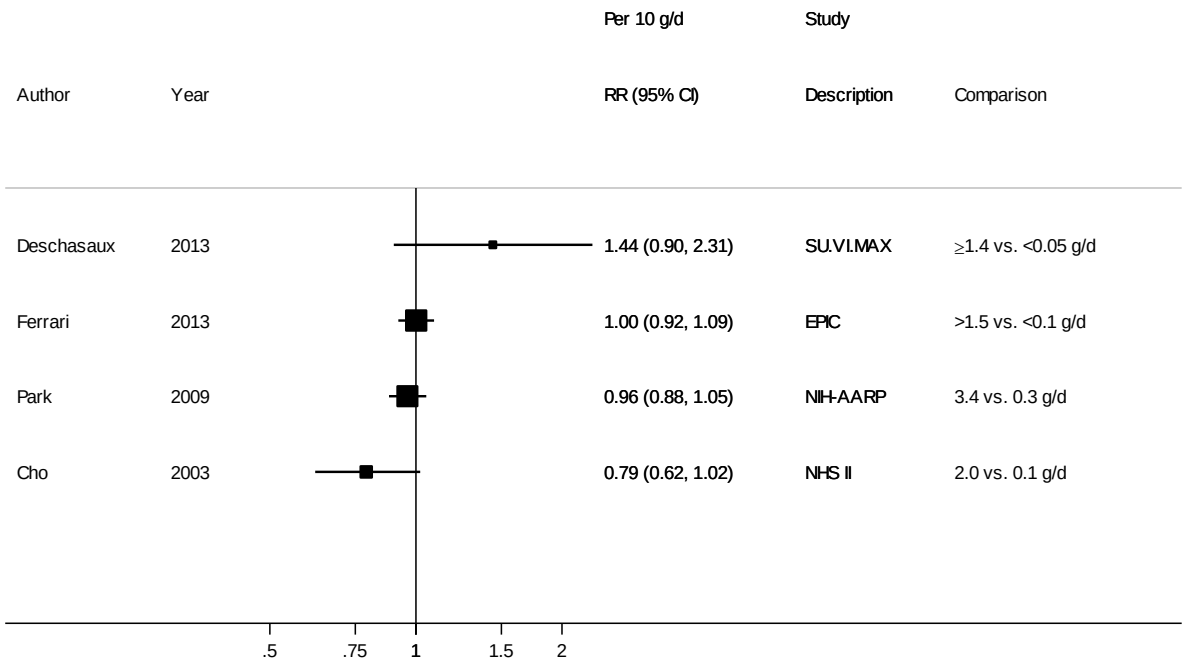


Figure 194 Relative risk of breast cancer for 10 g/day increase in legume fibre intake

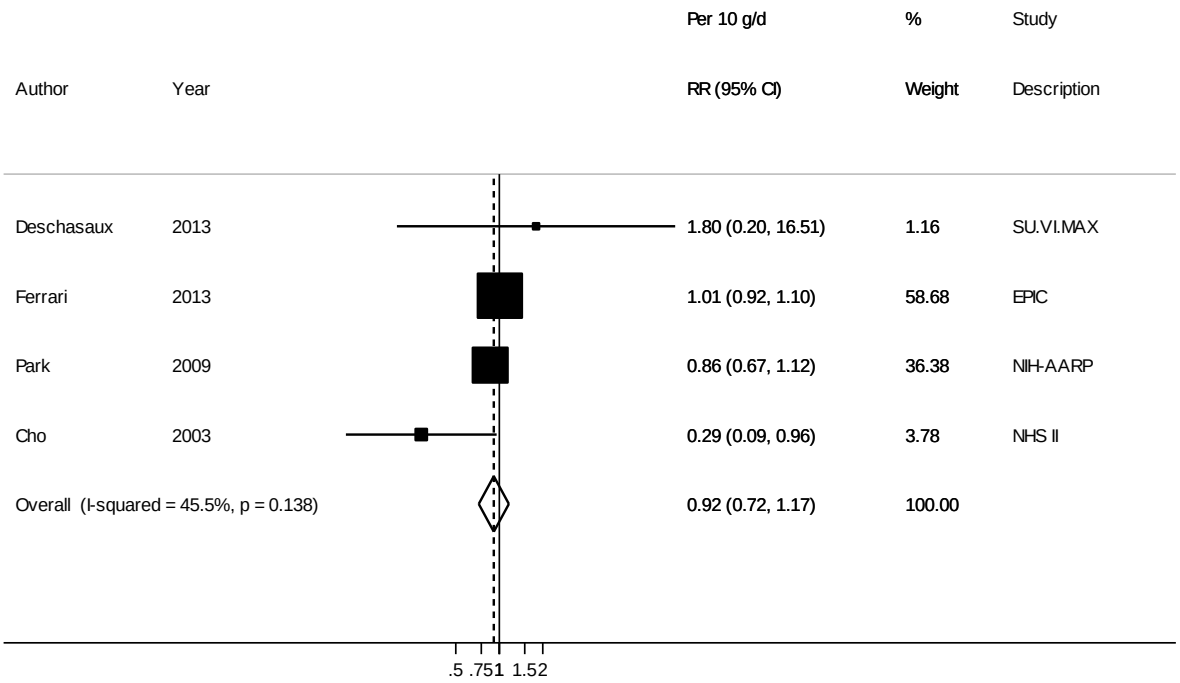


Figure 195 Relative risk of breast cancer for 10 g/day increase in legume fibre intake, stratified by geographic location

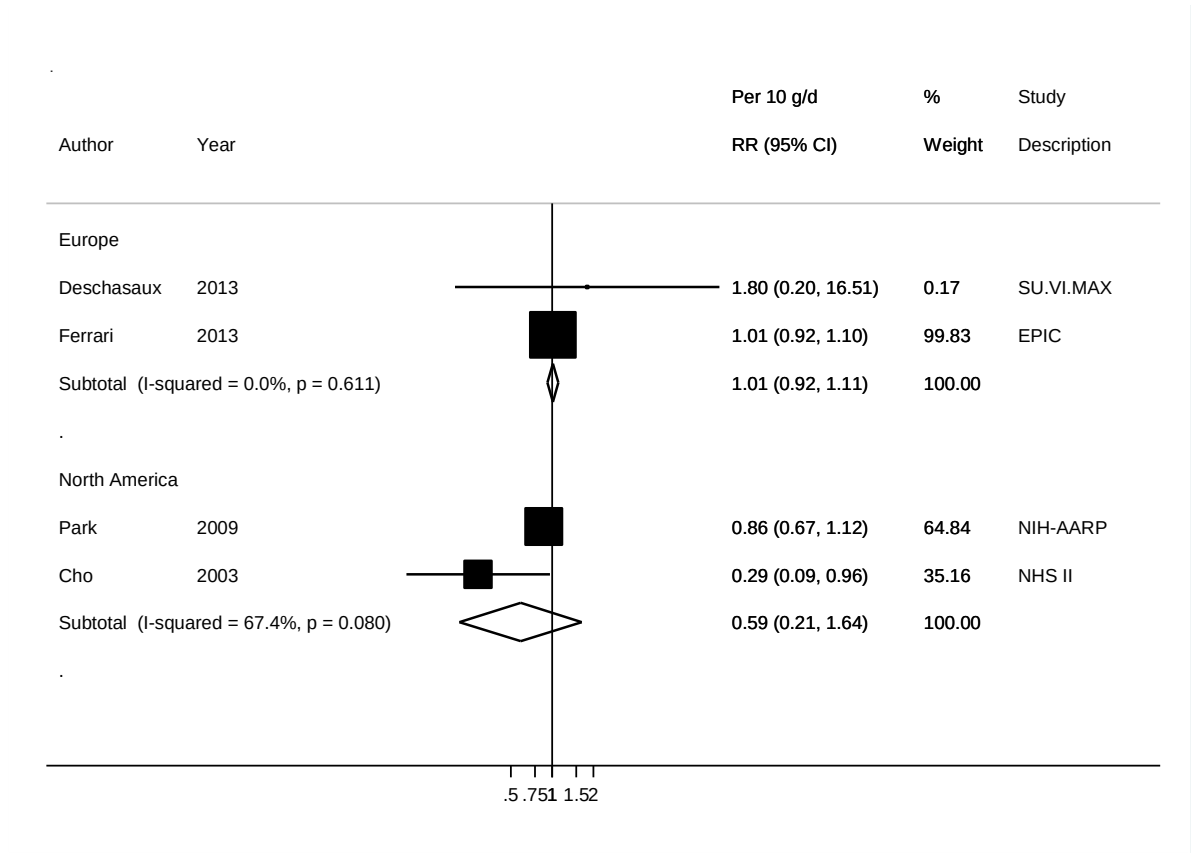


Figure 196 Funnel plot of studies included in the dose response meta-analysis of legume fibre intake and breast cancer

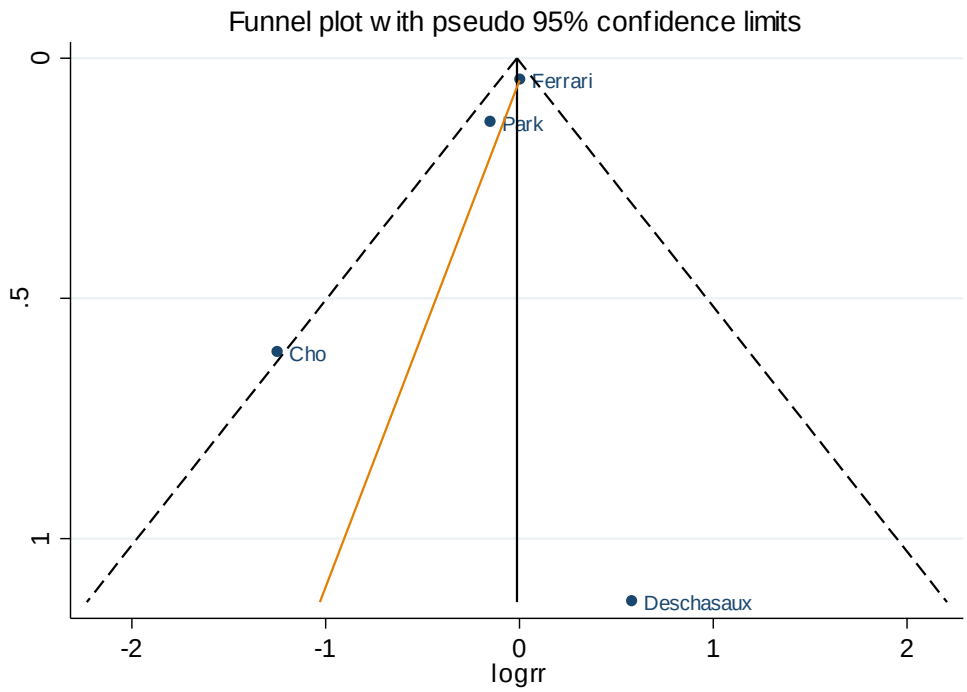
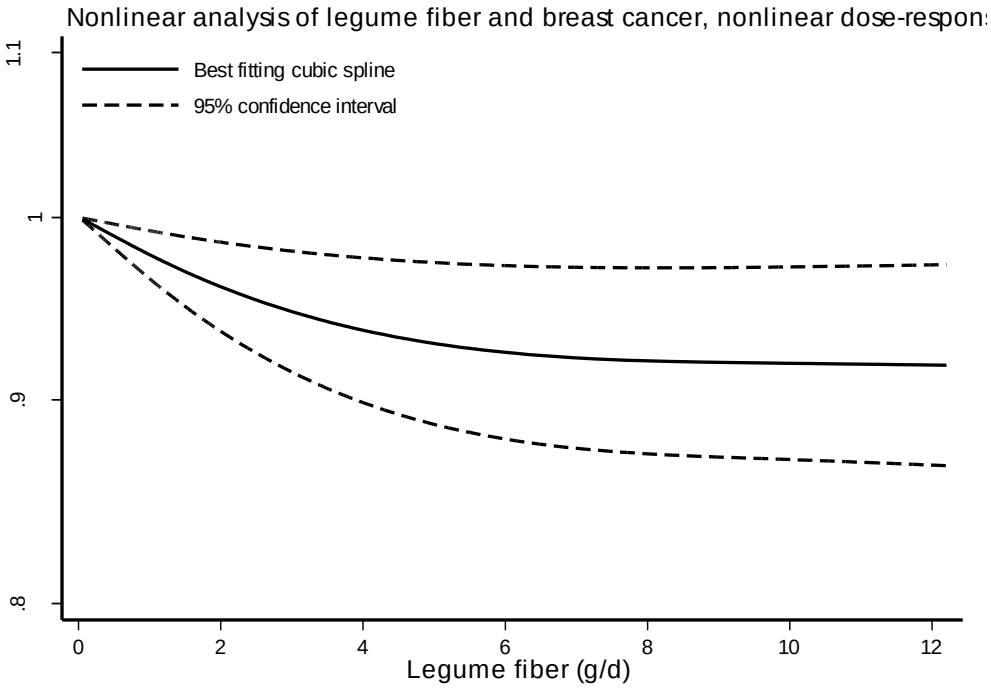


Figure 197 Legume fibre and breast cancer, nonlinear dose-response analysis



P nonlinearity=0.003

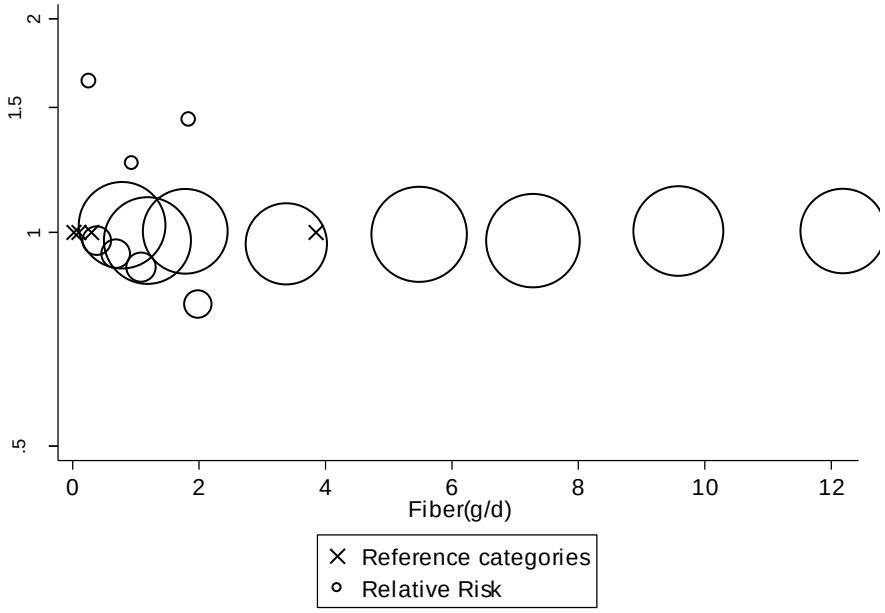


Table 131 Relative risk of breast cancer and legume fibre estimated using non-linear models

Legume fibre (g/day)	RR (95%CI)
0	1.00
2	0.96 (0.94-0.99)
4	0.94 (0.90-0.98)
6	0.93 (0.88-0.97)
8	0.92 (0.87-0.97)
10	0.92 (0.87-0.97)
12	0.92 (0.87-0.97)

5.1.2.1 Cereal fibre

Ten studies on cereal fibre intake and breast cancer risk were identified. Four studies investigated postmenopausal breast cancers, three were on premenopausal breast cancers, and three were on pre- and postmenopausal breast cancers combined. Study characteristics and results for all cancer types are shown in the Table.

Study quality:

Cereal fibre intake was estimated from food intake assessed by FFQ in all, but one study (Deschasaux, 2014), which used repeated 24-hour recalls. One study used a combination of dietary assessment methods including FFQ, dietary records, and dietary interviews (Ferrari, 2013).

Loss to follow-up was low for the studies that reported such data, although some studies did not provide data.

Cancers were identified by record linkages to health registries, cancer registries, mortality registries, or death indexes.

All studies adjusted for at least age, and most of the studies adjusted for most of the established breast cancer risk factors, including: age, parity, age at menarche, age at menopause, physical activity, BMI, and alcohol consumption.

Breast cancer (any)

Eight studies (26437 cases) were included in the dose-response meta-analysis. The summary RR for a 10 g/d increase in cereal fibre intake was 0.93 (95% CI: 0.84-1.03) and there was moderate heterogeneity, I^2=50.8%, $p_{heterogeneity}$=0.05. There was no evidence of small study bias or publication bias with Egger's test, p=0.93. One large European study, the EPIC study (Ferrari, 2013), contributed to 27% of the weight in the meta-analysis. The summary RR ranged from 0.91 (95% CI: 0.85-0.98) when the Nurses' Health Study (Holmes, 2004) was excluded to 0.95 (95% CI: 0.85-1.06) when the Swedish Mammography Cohort (Suzuki, 2008a) was excluded.

Nonlinear dose-response analysis

There was indication of a nonlinear association, $p_{nonlinearity}$=0.02, with a suggestion of a threshold effect, with a marginally significant reduction in risk at intakes of 20 g/d.

Premenopausal breast cancer

Three studies (1823 cases) were included in the dose-response meta-analysis of cereal fibre intake and premenopausal breast cancer. The summary RR per 10 g/d increase in cereal fibre intake was 0.82 (95% CI: 0.57-1.19) and there was high heterogeneity, I^2=60.7%, $p_{heterogeneity}$=0.08.

Postmenopausal breast cancer

Four studies (9923 cases) were included in the dose-response meta-analysis of cereal fibre intake and postmenopausal breast cancer. The summary RR per 10 g/d increase in cereal fibre intake was 0.97 (95% CI: 0.83-1.13), with low heterogeneity, I^2=59.8%, $p_{heterogeneity}$=0.06.

Table 132 Cereal fibre intake and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	10
Studies included in forest plot of highest compared with lowest intake	Breast cancer: 9 Premenopausal: 3 Postmenopausal: 5

Studies included in linear dose-response meta-analysis	Breast cancer: 8 Premenopausal: 3 Postmenopausal: 4
Studies included in non-linear dose-response meta-analysis	Breast cancer: 8 Premenopausal: not enough studies Postmenopausal: 4 (not enough studies)

Table 133 Cereal fibre intake and breast cancer risk. Summary of the linear dose-response meta-analysis in the CUP (no dose-response meta-analysis was conducted in the 2005 SLR)

	Breast cancers (any)	**Premenopausal**	**Postmenopausal**
Increment unit used	10 g/day		
Studies (n)	8	3	4
Cases (total number)	26437	1823	9923
RR (95%CI)	0.93 (0.84-1.03)	0.82 (0.57-1.19)	0.97 (0.83-1.13)
Heterogeneity (I^2, p-	50.8%, p=0.05	60.7%, p=0.08	59.8%, p=0.06
P value Egger test	0.93	-	-

Stratified analyses

Geographic area	**Asia**	**Europe**	**North-America**
Studies (n)	-	4	4
RR (95%CI)	-	0.90 (0.78-1.04)	0.96 (0.80-1.14)
Heterogeneity (I^2, p- value)	-	47.8%, p=0.13	59.6%, p=0.06

Table 134 Cereal fibre and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	**Number of studies**	**Total number of cases**	**Studies country, area**	**Outcome**	**Comparison**	**RR (95%CI)**	**P trend**	**Heterogeneity (I^2, p value)**
Meta-analyses								
Aune et al, 2012	6	14694	North America, Europe	Incidence	High vs. low Per 10 g/d	0.96 (0.90-1.02) 0.91 (0.79-1.04)	- -	5%, p=0.39 56%, p=0.05

Table 135 Cereal fibre intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors
Deschasaux, 2013 BRE80487 France	SU.VI.MAX, Prospective Cohort, Age: 47 years, W	167/ 4 684 12.6 years	Self-report/ medical records/histology	24 hour diet recall	Incidence, breast cancer	≥7.7 vs ≤4.3 g/day	1.43 (0.81-2.53)	Age-underlying cox models, alcohol, BMI, dietary pattern score, dietary records, educational level, family history of breast cancer, fat Intake, height, HRT use, Intervention group, menopausal status, non-alcohol energy Intake, number of children, physical activity, smoking status
Ferrari, 2013 BRE80436 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	11 576/ 334 849 11.5 years	Cancer and pathology registry, active follow up, health Insurance record, mortality registry and contact of participants or next-of-kin	Questionnaire	Incidence, breast cancer	≥10.9 vs ≤4.7 g/day	0.97 (0.91-1.04)	Age, age at first child birth, age at menarche, alcohol, contraception, educational level, energy Intake, height, menopausal status, physical activity, smoking, study center, weight
Park, 2009a BRE80264 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W, Postmenopausal	5 461/ 185 598 7 years	Cancer registry	FFQ	Incidence, breast cancer	8.9 vs 2.5 g/day	0.93 (0.85-1.02)	Age, age at first child birth, age at menopause, alcohol Intake, BMI, breast biopsies, educational attainment, energy Intake, family history of cancer, fat Intake, fruits and vegetables Intake, menopausal hormone use, oophorectomy/hysterectomy, parity, physical activity, race, smoking status

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors
Suzuki, 2008a BRE80148 Sweden	SMC, Prospective Cohort, Age: 60 years, W, Postmenopausal	1 284/ 51 823 8.3 years	Cancer registry	FFQ	Incidence, Invasive breast cancer	≥19.1 vs ≤11.9 g/day	0.91 (0.75-1.11)	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, benign breast disease, BMI, educational level, family history of cancer, fruit and vegetables Intake, fruit fibre Intake, height, menopausal status, other dietary fibre Intake, parity, postmenopausal hormone use, total energy Intake, total fat, use of oral contraception, vegetable fibre Intake
					Incidence, breast cancer ER+/PR+	≥19.1 vs ≤11.9 g/day	0.99 (0.77-1.29)	
					Incidence, Invasive breast cancer, PMH - never users	Q 4 vs Q 1	1.03 (0.79-1.35)	
					Incidence, Invasive breast cancer, PMH - ever users	Q 4 vs Q 1	0.44 (0.31-0.63)	
					Incidence, breast cancer ER+/PR+, PMH - never users	Q 4 vs Q 1	1.14 (0.80-1.64)	
					Incidence, breast cancer ER+/PR-	≥19.1 vs ≤11.9 g/day	0.86 (0.56-1.32)	
					Incidence, breast cancer ER+/PR+, PMH - ever users	Q 4 vs Q 1	0.41 (0.25-0.67)	
					Incidence, breast cancer ER-/PR-	≥19.1 vs ≤11.9 g/day	0.69 (0.39-1.24)	
					Incidence, breast cancer ER+/PR-, PMH - ever users	Q 4 vs Q 1	0.60 (0.30-1.21)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors
					Incidence, breast cancer ER+/PR-, PMH - never users	Q 4 vs Q 1	0.84 (0.45-1.55)	
					Incidence, breast cancer ER-/PR-, PMH - never users	Q 4 vs Q 1	0.87 (0.41-1.85)	
					Incidence, breast cancer ER-/PR-, PMH - ever users	Q 4 vs Q 1	0.23 (0.06-0.89)	
Cade, 2007 BRE20021 UK	UKWCS, Prospective Cohort, Age: 35-69 years, W	286/ 35 792 7.5 years	Nhs central registry	FFQ	Incidence, breast cancer, postmenopause	≥13 vs ≤3.9 g/day	1.15 (0.68-1.94)	Age , alcohol, BMI, energy Intake , HRT use, oc use, parity/pregnancies, physical activity , smoking habits
					Incidence, breast cancer, premenopause	≥13 vs ≤3.9 g/day	0.59 (0.32-1.10)	
Holmes, 2004 BRE04010 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	2 924/ 88 678 18 years	Medical records + self-reported	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	≥1 vs ≥-1 g/day	1.08 (0.96-1.22)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, energy Intake , family history, height, HRT use, menopausal status, other design Issue, parity/pregnancies
					Incidence, breast cancer, premenopausal	8.4 vs 2.4 g/day	0.99 (0.78-1.25)	
Cho, 2003b BRE01651 USA	NHS II, Prospective Cohort,	714/ 90 655 8 years	Medical records + self-reported +death	FFQ-semi-quantitative	Incidence, breast cancer, premenopausal	8.8 vs 3 g/day	0.91 (0.69-1.21)	Age at first child, age at menarche, alcohol, benign breast disease, BMI, family history, height,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors
	Age: 26-46 years, W, Registered nurses		certificate					menopausal status, nutrients, oc use, parity/pregnancies, residual (willet), smoking habits
Terry, 2002 BRE12199 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	89 835 16.2 years	Partially histological - over 80%	FFQ	Incidence, Invasive & In situ breast cancer,	≥5.6 vs ≤2.5 g/day	0.90 (0.78-1.04)	Age , alcohol, benign breast disease, BMI, educational level, energy Intake , family history, HRT use, menopausal status, nutrients, oc use, other specified factor, other specified factor, parity/pregnancies, physical activity , recruitment center, smoking habits

Table 136 Cereal fibre intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Hedelin, 2008 BRE80162 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	1 014/ 45 448 13 years	Cancer registry	FFQ	Incidence, Invasive breast cancer, postmenopausal	Q 4 vs Q 1	0.98 (0.81-1.19)	Age, age at first child, age at menarche, alcohol Intake, energy Intake, family history of cancer, ocp use, parity, saturated fat	No quantities
Giles, 2006 BRE22430 Australia	MCCS, Prospective Cohort, Age: 40-69 years, W, Postmenopausal	12 273 9.1 years	Pathology report + cancer registry	FFQ	Incidence, breast cancer, postmenopausal	per 1 sd/day	1.08 (0.95-1.23)	Age , energy Intake , HRT use, place of residence	No quantities
					Incidence, breast cancer ER+/PR-, postmenopausal	per 1 sd/day	1.24 (0.83-1.86)		
					Incidence, breast cancer ER+/PR+, postmenopausal	per 1 sd/day	1.17 (0.98-1.39)		
					Incidence, breast cancer ER-/PR-, postmenopausal	per 1 sd/day	0.78 (0.55-1.11)		

Figure 198 RR estimates of breast cancer by levels of cereal fibre intake

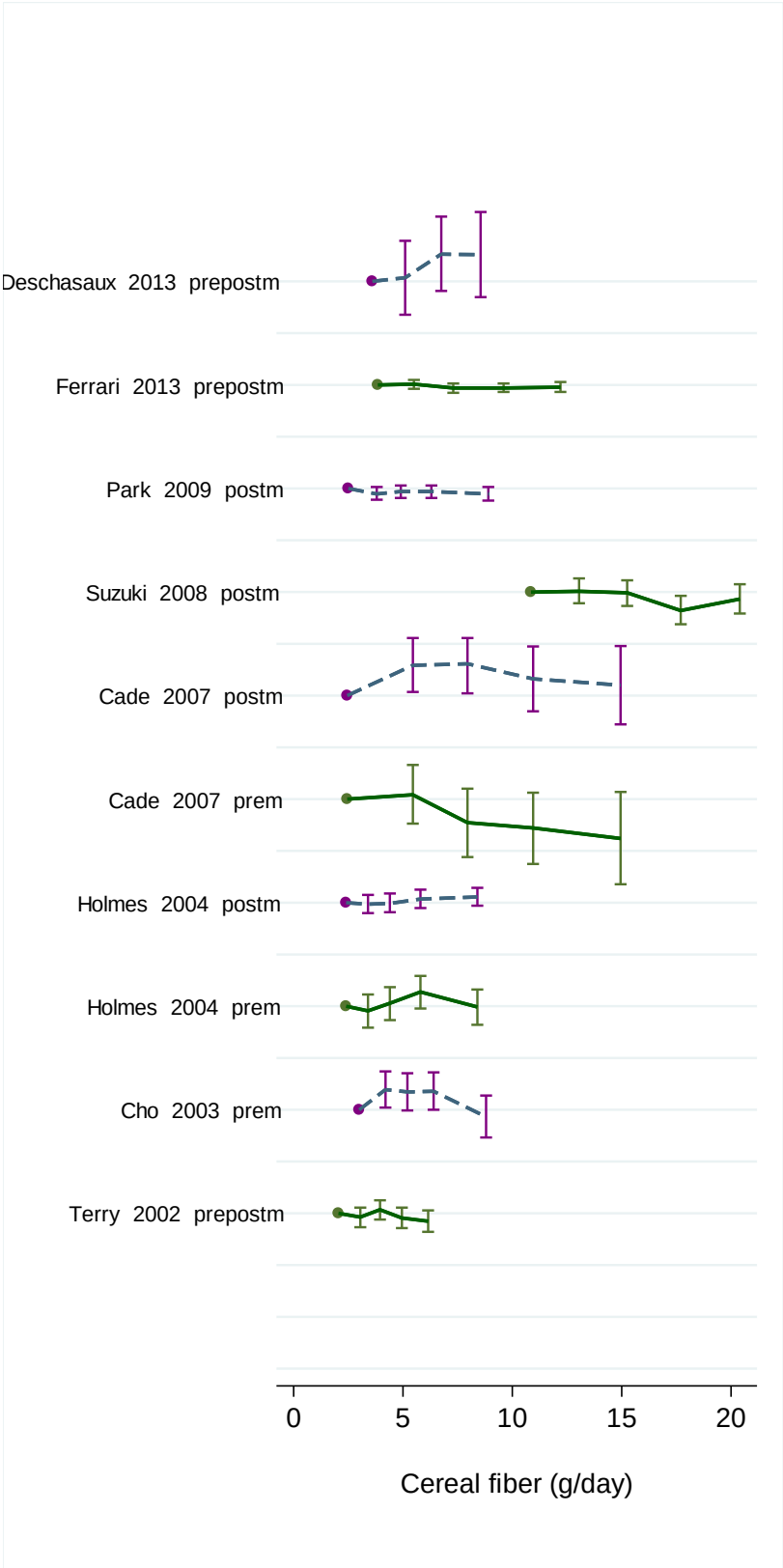


Figure 199 Relative risk of breast cancer for the highest compared with the lowest level of cereal fibre intake

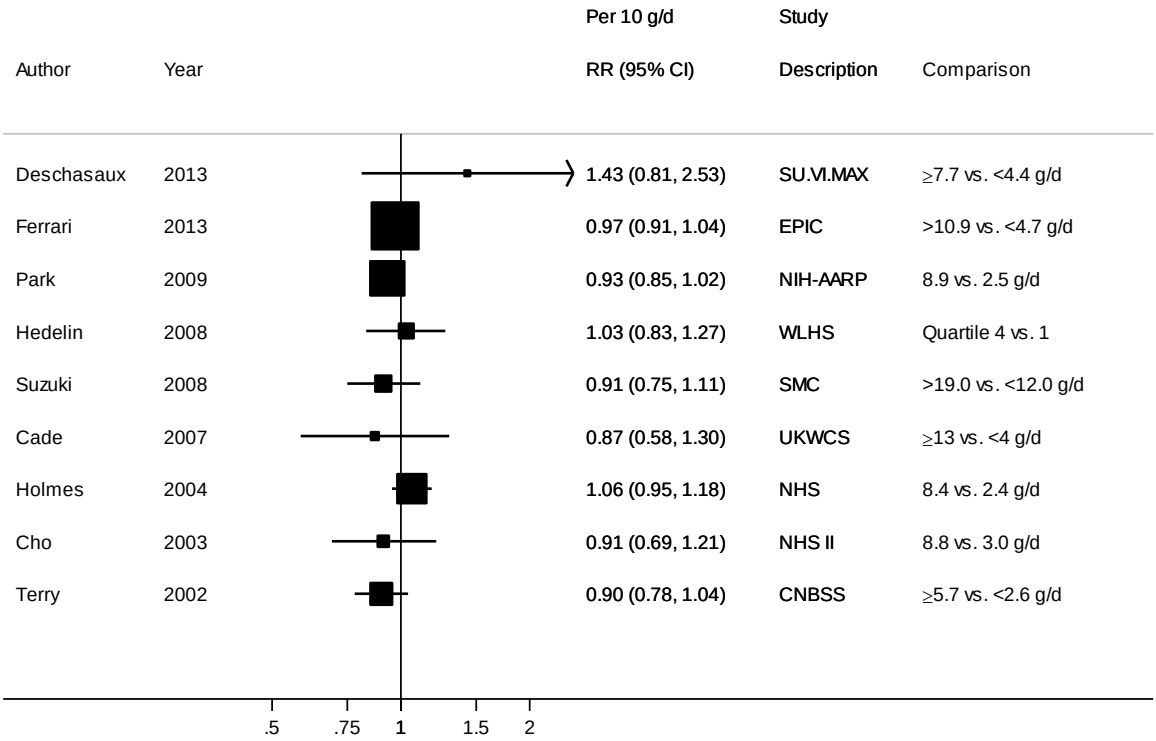


Figure 200 Relative risk of breast cancer for the highest compared with the lowest level of cereal fibre intake, stratified by menopausal status

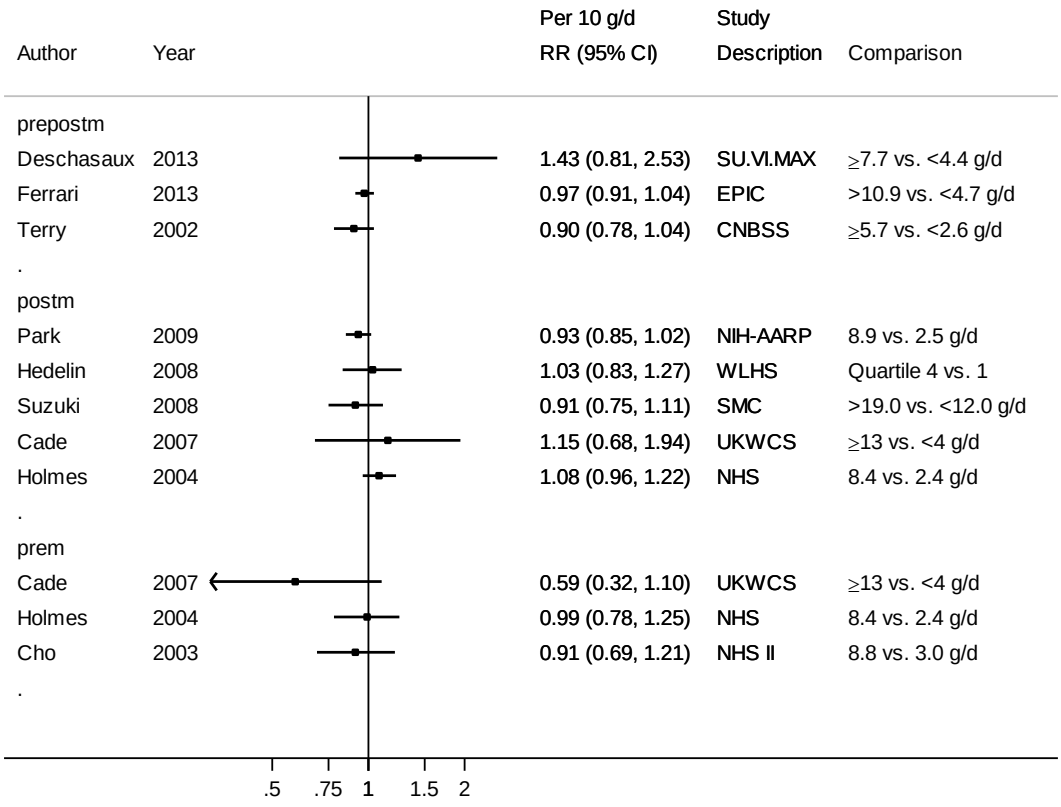


Figure 201 Relative risk of breast cancer for 10 g/day increase in cereal fibre intake

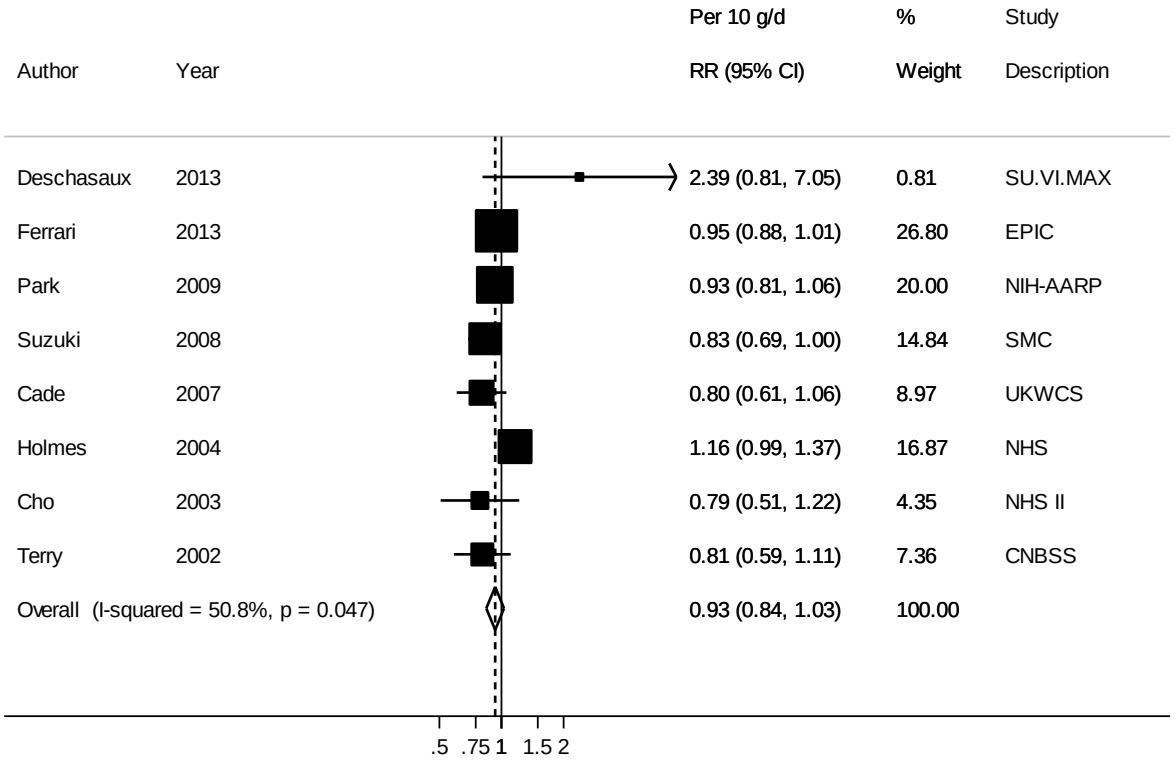


Figure 202 Relative risk of breast cancer for 10 g/day increase in cereal fibre intake, stratified by menopausal status

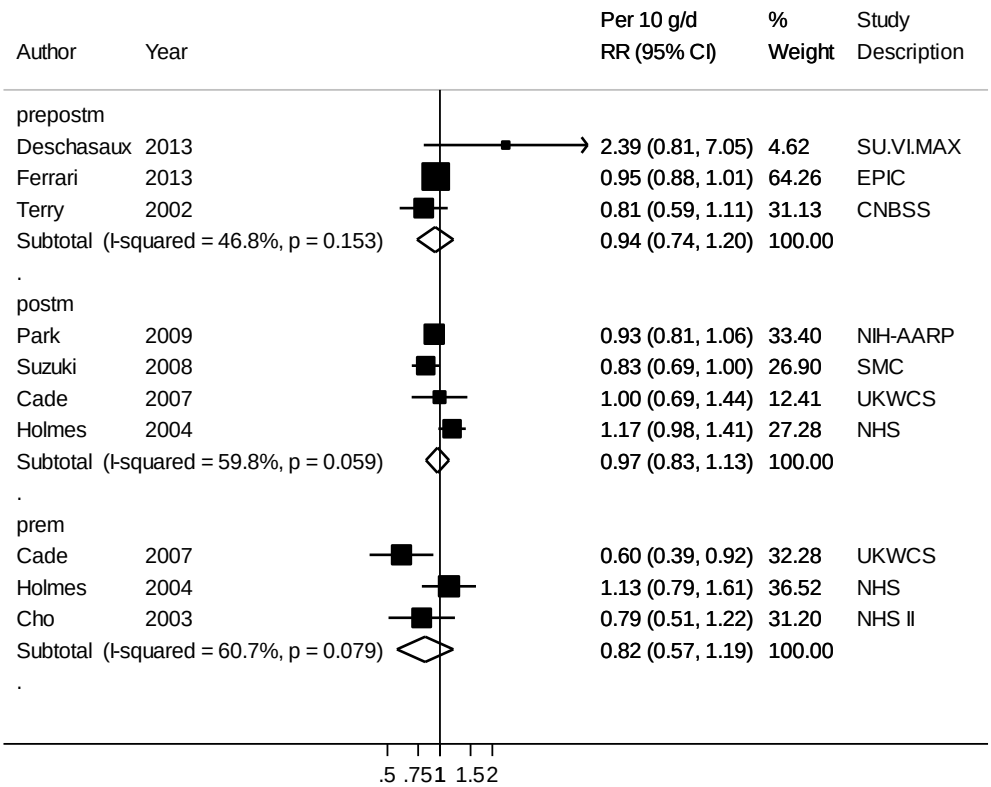


Figure 203 Relative risk of breast cancer for 10 g/day increase in cereal fibre intake, stratified by geographic location

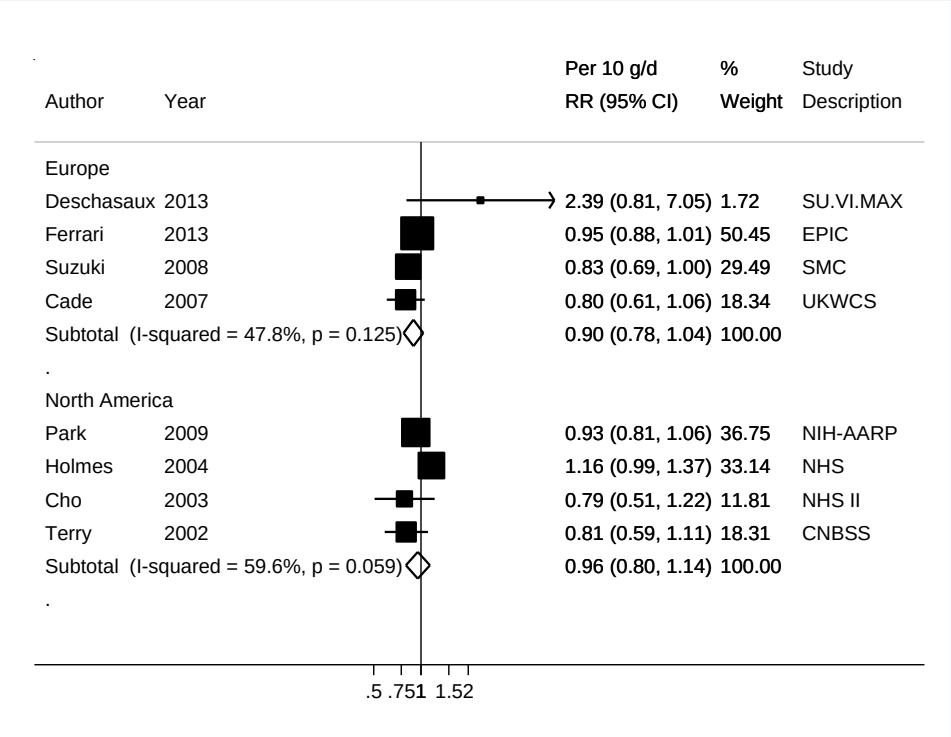


Figure 204 Funnel plot of studies included in the dose response meta-analysis of cereal fibre intake and breast cancer

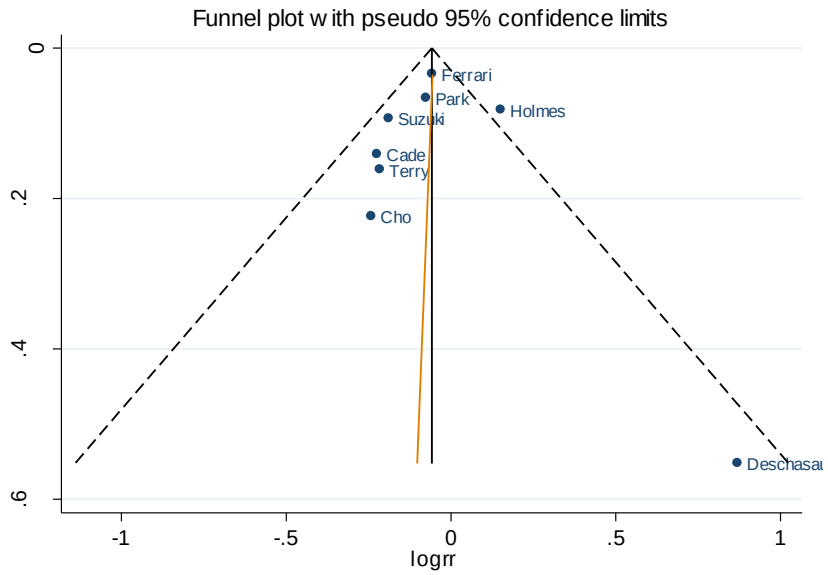
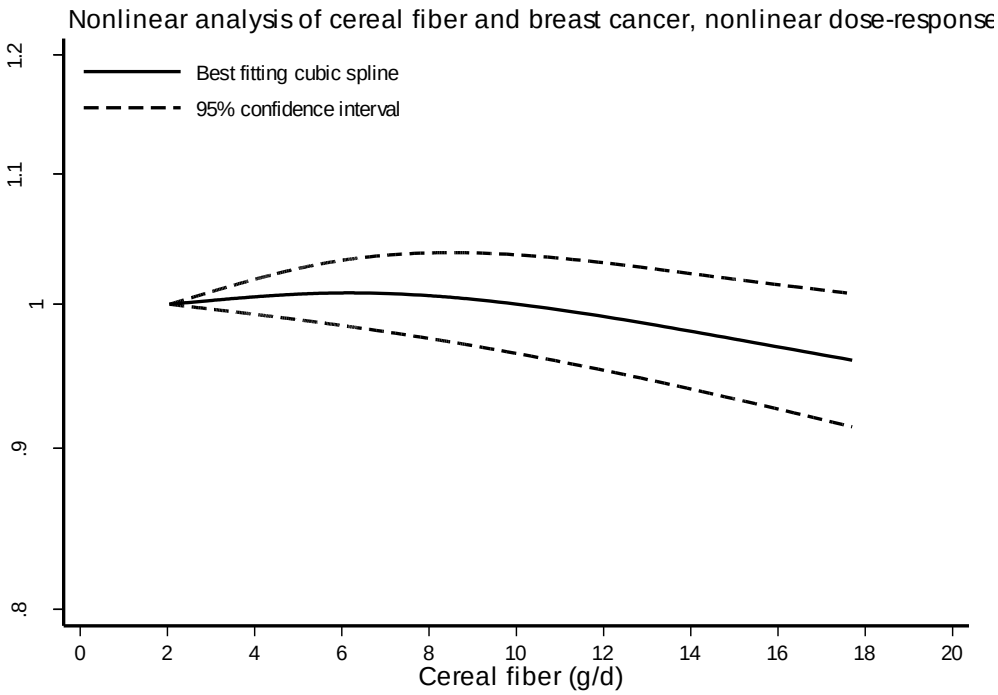


Figure 205 Cereal fibre and breast cancer, nonlinear dose-response analysis



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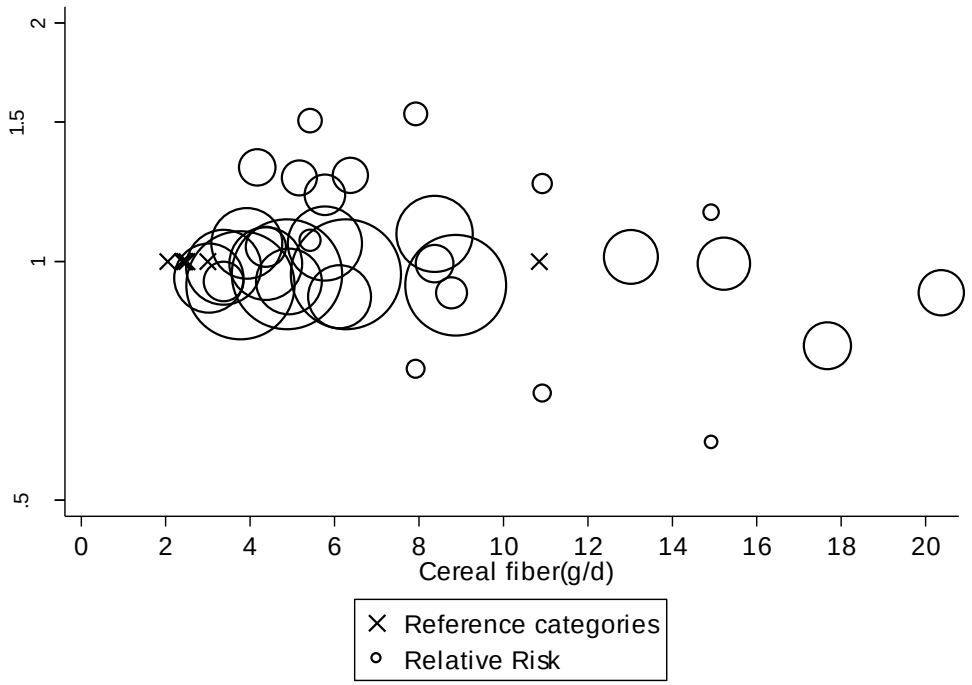
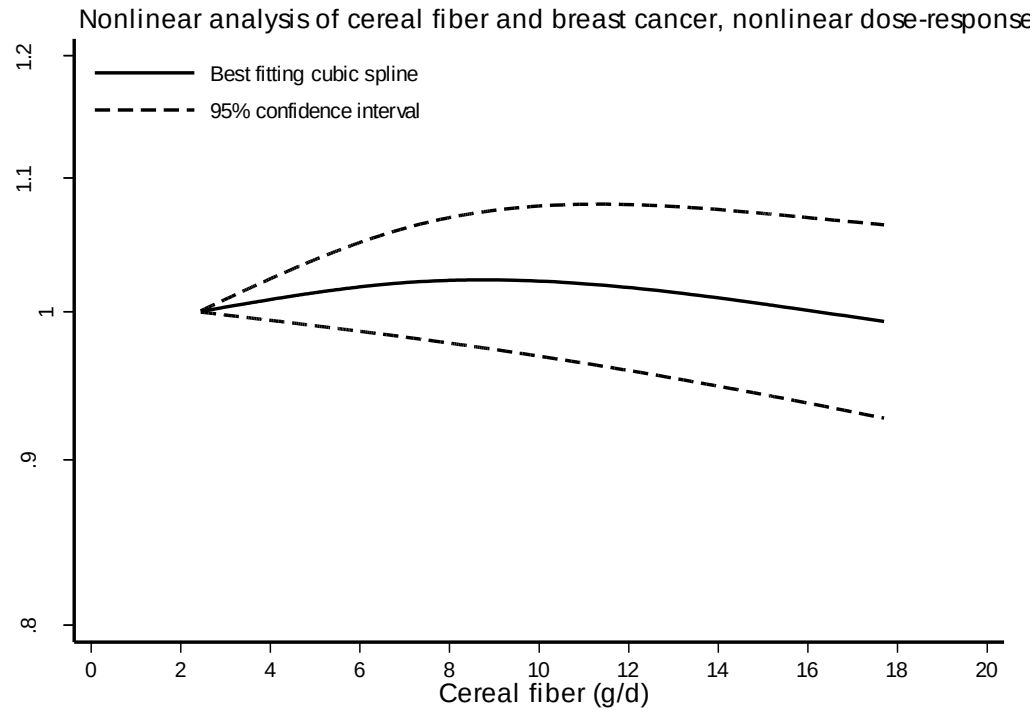


Table 137 Relative risk of breast cancer and cereal fibre estimated using non-linear models

Cereal fibre (g/day)	RR (95%CI)
2.05	1.00
4.0	1.01 (0.99-1.02)
6.0	1.01 (0.98-1.03)
8.0	1.01 (0.98-1.04)
10.0	1.00 (0.97-1.04)
12.0	0.99 (0.95-1.03)
14.0	0.98 (0.93-1.02)
16.0	0.97 (0.93-1.02)
18.0	0.96 (0.91-1.01)
20.0	0.95 (0.90-1.00)

Figure 206 Cereal fibre and postmenopausal breast cancer, nonlinear dose-response analysis



P nonlinearity=0.04

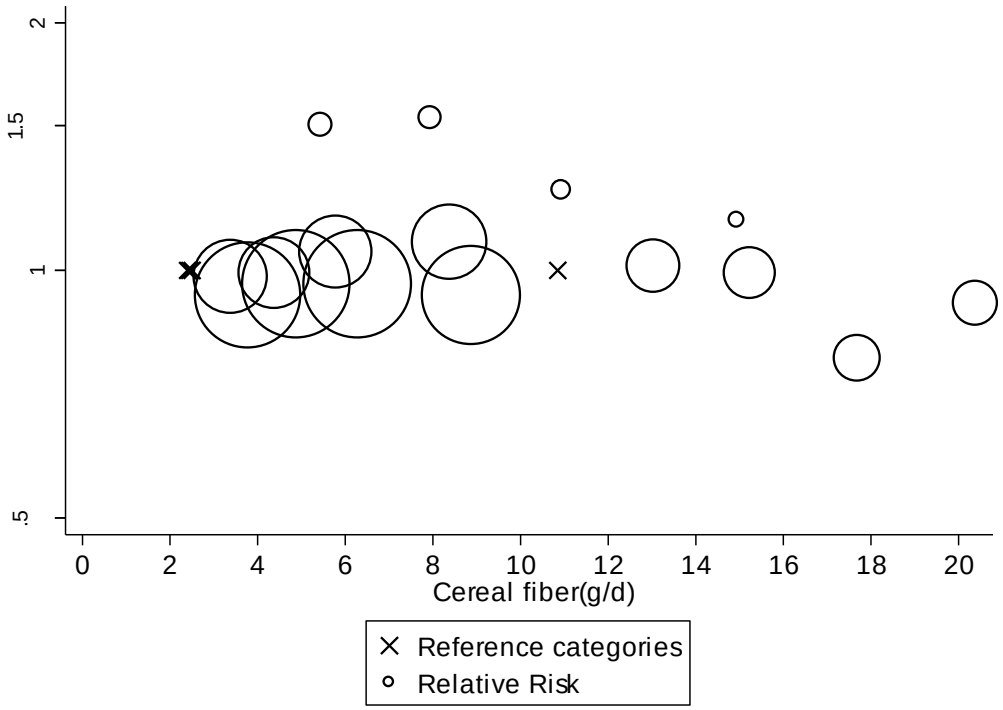


Table 138 Relative risk of postmenopausal breast cancer and cereal fibre estimated using non-linear models

Cereal fibre (g/day)	RR (95%CI)
2.4	1.00
4.0	1.01 (0.99-1.02)
6.0	1.02 (0.99-1.05)
8.0	1.02 (0.98-1.07)
10.0	1.02 (0.96-1.08)
12.0	1.02 (0.96-1.08)
14.0	1.01 (0.94-1.07)
16.0	1.00 (0.94-1.07)
18.0	0.99 (0.93-1.06)
20.0	0.98 (0.91-1.06)

5.1.2.2 Vegetable fibre

Ten studies on vegetable fibre intake and breast cancer risk were identified. Four studies investigated postmenopausal breast cancers, three were on premenopausal breast cancers, and three were on pre- and postmenopausal breast cancers combined. Study characteristics and results for all cancer types are shown in the Table.

Study quality:

Vegetable fibre intake was estimated from food intake assessed by FFQ in all, but one study (Deschasaux, 2014), which used repeated 24-hour recalls. One study used a combination of dietary assessment methods including FFQ, dietary records, and dietary interviews (Ferrari, 2013).

Loss to follow-up was low for the studies that reported such data, although some studies did not provide data.

Cancers were identified by record linkages to health registries, cancer registries, mortality registries, or death indexes.

All studies adjusted for at least age, and most of the studies adjusted for most of the established breast cancer risk factors, including: age, parity, age at menarche, age at menopause, physical activity, BMI, and alcohol consumption.

Breast cancer (any)

Eight studies (26437 cases) were included in the dose-response meta-analysis. The summary RR for a 10 g/d increase in vegetable fibre intake was 0.92 (95% CI: 0.80-1.06) and there was high heterogeneity, I^2=61.6%, $p_{heterogeneity}$=0.01. There was no evidence of small study bias or publication bias with Egger's test, p=0.90. One large European study, the EPIC study (Ferrari, 2013), contributed to 24% of the weight in the meta-analysis. The summary RR ranged from 0.88 (95% CI: 0.77-0.99) when the NIH-AARP Diet and Health Study (Park, 2009a) was excluded to 0.95 (95% CI: 0.81-1.13) when the EPIC Study (Ferrari, 2013) was excluded.

Nonlinear dose-response analysis

There was no evidence of a nonlinear association, $p_{nonlinearity}$=0.31, with a suggestion of a threshold effect, with significantly reduced risk at intakes of 8 g/d.

Premenopausal breast cancer

Three studies (1823 cases) were included in the dose-response meta-analysis of vegetable fibre intake and premenopausal breast cancer. The summary RR per 10 g/d increase in vegetable fibre intake was 0.94 (95% CI: 0.74-1.19) and there was no heterogeneity, I^2=0%, $p_{heterogeneity}$=0.72.

Postmenopausal breast cancer

Four studies (9923 cases) were included in the dose-response meta-analysis of vegetable fibre intake and postmenopausal breast cancer. The summary RR per 10 g/d increase in vegetable

fibre intake was 1.03 (95% CI: 0.85-1.25), with low heterogeneity, I^2=42.7%, $p_{heterogeneity}$=0.16.

Nonlinear dose-response analysis

The test for nonlinearity was not significant, $p_{nonlinearity}$=0.12, and the association was significant at 6 grams per day and above.

Table 139 Vegetable fibre intake and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	10
Studies included in forest plot of highest compared with lowest intake	Breast cancer: 9 Premenopausal: 3 Postmenopausal: 4
Studies included in linear dose-response meta-analysis	Breast cancer: 8 Premenopausal: 3 Postmenopausal: 4
Studies included in non-linear dose-response meta-analysis	Breast cancer: 8 Premenopausal: not enough studies Postmenopausal: not enough studies

Table 140 Vegetable fibre intake and breast cancer risk. Summary of the linear dose-response meta-analysis in the CUP (no dose-response meta-analysis was conducted in the 2005 SLR)

	Breast cancers (any)	**Premenopausal**	**Postmenopausal**
Increment unit used	10 g/day		
Studies (n)	8	3	4
Cases (total number)	26437	1823	9923
RR (95%CI)	0.92 (0.80-1.06)	0.94 (0.74-1.19)	1.03 (0.85-1.25)
Heterogeneity (I^2, p-	61.6%, p=0.01	0%, p=0.72	42.7%, p=0.16
P value Egger test	0.90	-	-

Stratified analyses

Geographic area	**Asia**	**Europe**	**North-America**
Studies (n)	-	4	4
RR (95%CI)	-	0.84 (0.51-1.36)	0.96 (0.84-1.09)
Heterogeneity (I^2, p- value)	-	65.5%, p=0.03	41.7%, p=0.16

Table 141 Vegetable fibre and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Aune et al, 2012	6	14 694	North America, Europe	Incidence	High vs. low	0.99 (0.92-1.07)	-	15%, p=0.32
					Per 10 g/d	0.97 (0.55-1.12)	-	39%, p=0.14

Table 142 Vegetable fibre intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Deschasaux, 2013 BRE80487 France	SU.VI.MAX, Prospective Cohort, Age: 47 years, W	167/ 4 684 12.6 years	Self-report/ medical records/ histology	24 hour diet recall	Incidence, breast cancer	≥5.2 vs ≤2.6 g/day	0.50 (0.29-0.88)	Age-underlying cox models, alcohol, BMI, dietary pattern score, dietary records, educational level, family history of breast cancer, fat Intake, height, HRT use, Intervention group, menopausal status, non-alcohol energy Intake, number of children, physical activity, smoking status
					Incidence, ductal carcinomas, postmenopausal	≥5.2 vs ≤2.6 g/day	0.42 (0.21-0.83)	
					Incidence, breast cancer, postmenopausal	≥5.2 vs ≤2.6 g/day	0.50 (0.26-0.97)	
					Incidence, breast cancer ER+, postmenopausal	≥5.2 vs ≤2.6 g/day	0.37 (0.18-0.76)	
					Incidence, breast cancer PR+, postmenopausal	≥5.2 vs ≤2.6 g/day	0.36 (0.16-0.81)	
Ferrari, 2013 BRE80436 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	11 576/ 334 849 11.5 years	Cancer and pathology registry, active follow up, health Insurance record, mortality registry and contact of participants or next-of-kin	Questionnaire	Incidence, breast cancer	≥6.9 vs ≤2.5 g/day	0.90 (0.84-0.96)	Age, age at first child birth, age at menarche, alcohol, contraception, educational level, energy Intake, height, menopausal status, physical activity, smoking, study center, weight
					Incidence, breast cancer	per 5 gday	0.85 (0.76-0.96)	
					Incidence, breast cancer	per 5 gday	0.95 (0.91-0.98)	
					Incidence, breast cancer ER+/PR+	≥6.9 vs ≤2.5 g/day	0.92 (0.81-1.03)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					Incidence, breast cancer ER-/PR-	≥6.9 vs ≤2.5 g/day	0.74 (0.59-0.93)	
Park, 2009a BRE80264 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W, Postmenopausal	5 461/ 185 598 7 years	Cancer registry	FFQ	Incidence, breast cancer	10.4 vs 2.9 g/day	1.09 (0.97-1.23) Ptrend:0.16	Age, age at first child birth, age at menopause, alcohol Intake, BMI, breast biopsies, educational attainment, energy Intake, family history of cancer, fat Intake, fruits and vegetables Intake, menopausal hormone use, oophorectomy/hysterectomy, parity, physical activity, race, smoking status
Suzuki, 2008a BRE80148 Sweden	SMC, Prospective Cohort, Age: 60 years, W, Postmenopausal	1 248/ 51 823 8.3 years	Cancer registry	FFQ	Incidence, Invasive breast cancer	≥2.67 vs ≤0.93 g/day	0.92 (0.72-1.18)	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, benign breast disease, BMI, cereal fibre, educational level, family history of cancer, fruit and vegetables Intake, fruit fibre Intake, height, menopausal status, other dietary fibre Intake, parity, postmenopausal
					Incidence, breast cancer ER+/PR+	≥2.67 vs ≤0.93 g/day	0.85 (0.61-1.18)	
					Incidence, breast cancer ER+/PR-	≥2.67 vs ≤0.93 g/day	1.03 (0.59-1.80)	
					Incidence, breast cancer ER-/PR-	≥2.67 vs ≤0.93 g/day	0.84 (0.40-1.77)	
					Incidence, Invasive breast cancer, pmh -	Q 4 vs Q 1	0.65 (0.46-0.90)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					never users			hormone use, total energy Intake, total fat, use of oral contraception
					Incidence, Invasive breast cancer, PMH - ever users	Q 4 vs Q 1	1.39 (0.89-2.17)	
Cade, 2007 BRE20021 UK	UKWCS, Prospective Cohort, Age: 35-69 years, W	286/ 35 792 7.5 years	NHS central registry	FFQ	Incidence, breast cancer, postmenopause	≥8 vs ≤2.9 g/day	1.20 (0.74-1.94)	Age, alcohol, BMI, energy Intake , HRT use, oc use, parity/pregnancies, physical activity , smoking habits
					Incidence, breast cancer, premenopause	≥7 vs ≤2.9 g/day	1.26 (0.73-2.18)	
Holmes, 2004 BRE04010 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	2 924/ 88 678 18 years	Medical records + self-reported	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	≥1 vs ≥-1 g/day	0.94 (0.82-1.08)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, energy Intake , family history, height, HRT use, menopausal status, other design Issue, parity/pregnancies
					Incidence, breast cancer, premenopausal	10.2 vs 3.6 g/day	0.95 (0.72-1.25)	
Cho, 2003b BRE01651 USA	NHS II, Prospective Cohort, Age: 26-46 years, W, Registered nurses	714/ 90 655 8 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, breast cancer, premenopausal	10.4 vs 3.3 g/day	0.97 (0.75-1.24)	Age at first child, age at menarche, alcohol, benign breast disease, BMI, family history, height, menopausal status, nutrients, oc use, parity/pregnancies, residual (willet), smoking habits

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Terry, 2002 BRE12199 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	89 835 16.2 years	Partially histological - over 80%	FFQ	Incidence, Invasive & In situ breast cancer,	≥11 vs ≤5.3 g/day	0.90 (0.75-1.08)	Age , alcohol, benign breast disease, BMI, educational level, energy Intake , family history, HRT use, menopausal status, nutrients, oc use, other specified factor, other specified factor, parity/pregnancies, physical activity , recruitment center, smoking habits

Table 143 Vegetable fibre intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Hedelin, 2008 BRE80162 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	1 014/ 45 448 13 years	Cancer registry	FFQ	Incidence, Invasive breast cancer, postmenopausal	Q 4 vs Q 1	0.98 (0.81-1.19)	Age, age at first child, age at menarche, alcohol Intake, energy Intake, family history of cancer, ocp use, parity, saturated fat	Only high vs. low analysis, No quantities
Giles, 2006 BRE22430 Australia	MCCS, Prospective Cohort,	12 273 9.1 years	Pathology report + cancer registry	FFQ	Incidence, breast cancer, postmenopausal	per 1 sd/day	1.07 (0.95-1.20)	Age , energy Intake , HRT use, place of residence	No quantities

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Age: 40-69 years, W, Postmenopausal				Incidence, breast cancer ER+/PR-, postmenopausal	per 1 sd/day	1.14 (0.81-1.61)		
					Incidence, breast cancer ER+/PR+, postmenopausal	per 1 sd/day	1.13 (0.97-1.32)		
					Incidence, breast cancer ER-/PR-, postmenopausal	per 1 sd	0.83 (0.58-1.19)		

Figure 207 RR estimates of breast cancer by levels of vegetable fibre intake

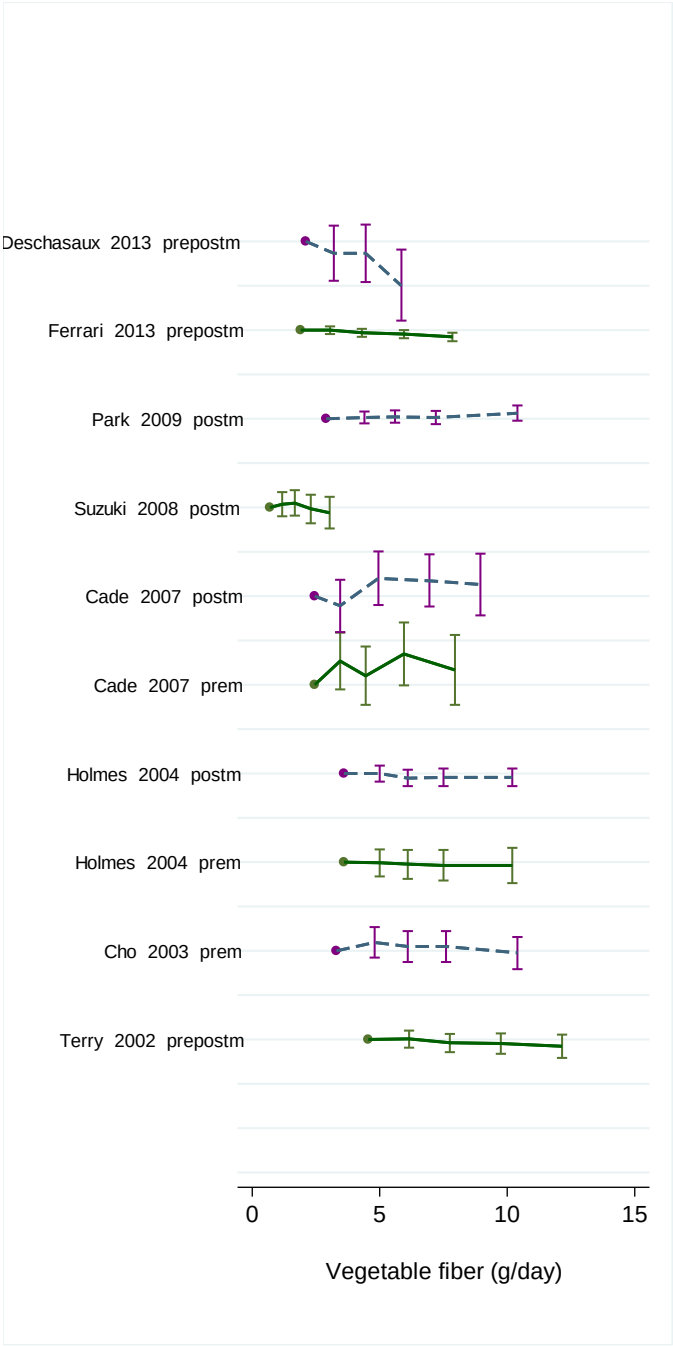


Figure 208 Relative risk of breast cancer for the highest compared with the lowest level of vegetable fibre intake

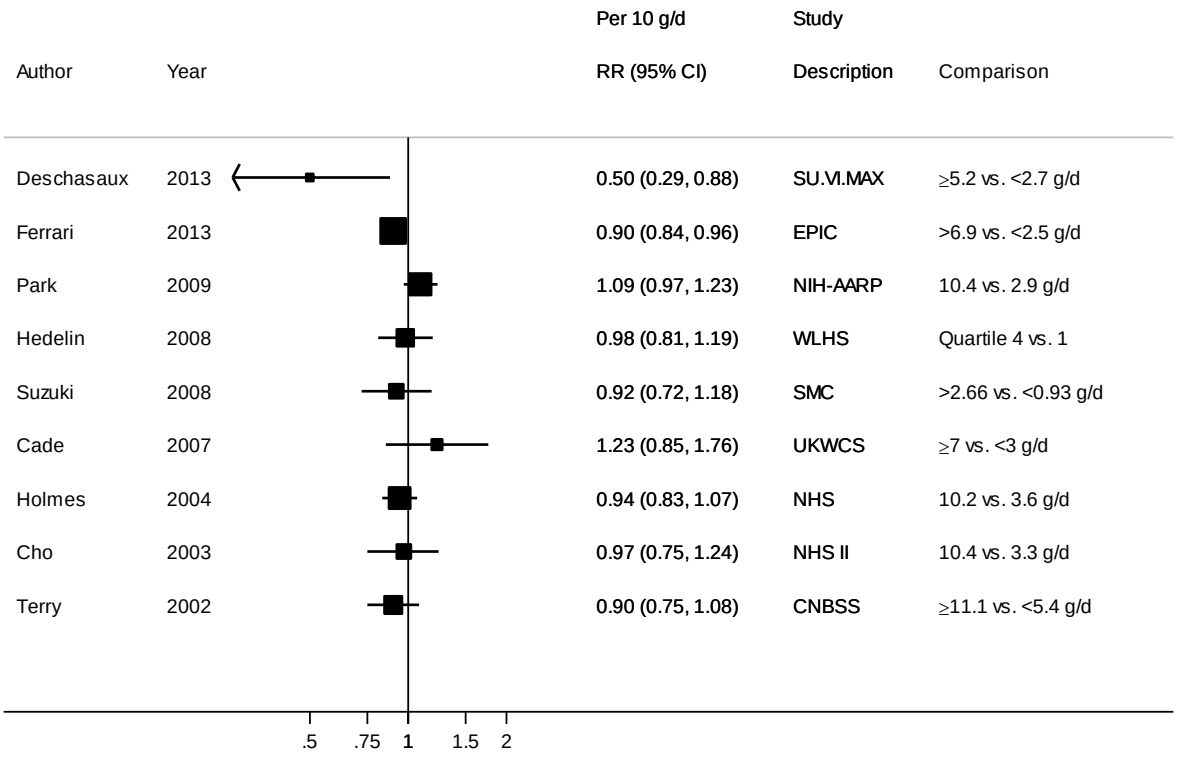


Figure 209 Relative risk of breast cancer for the highest compared with the lowest level of vegetable fibre intake, stratified by menopausal status

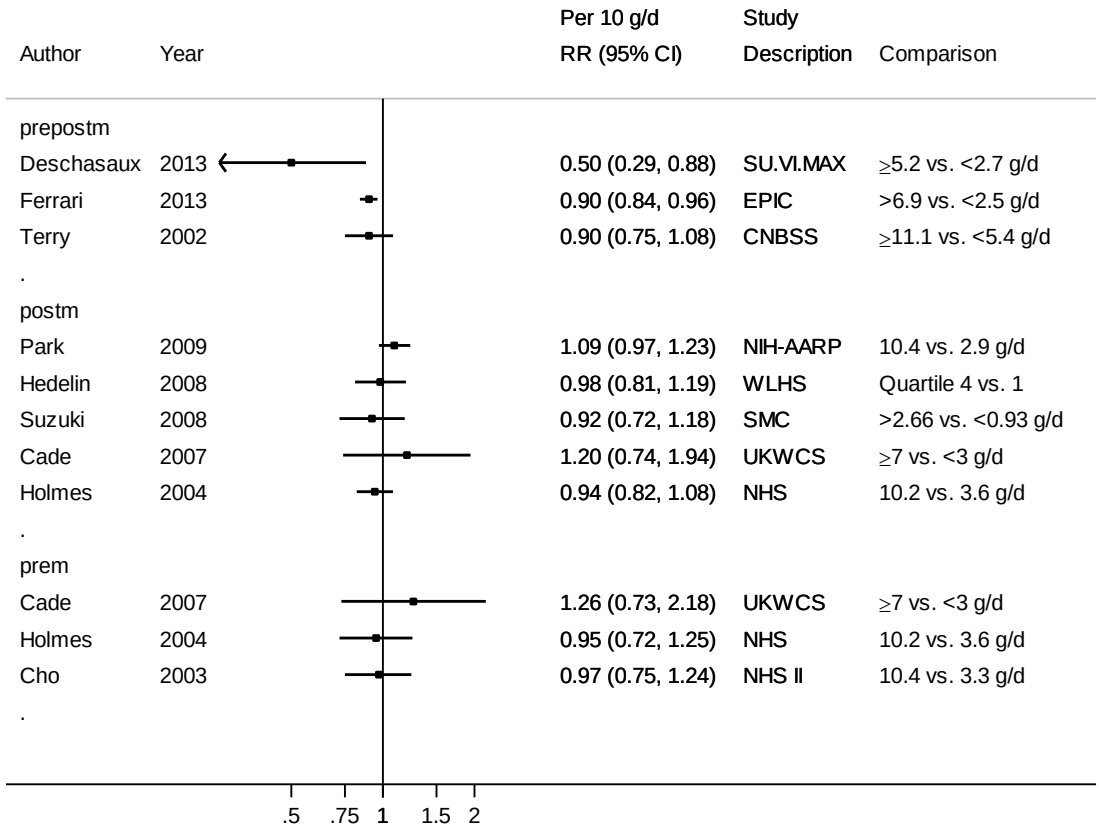


Figure 210 Relative risk of breast cancer for 10 g/day increase in vegetable fibre intake

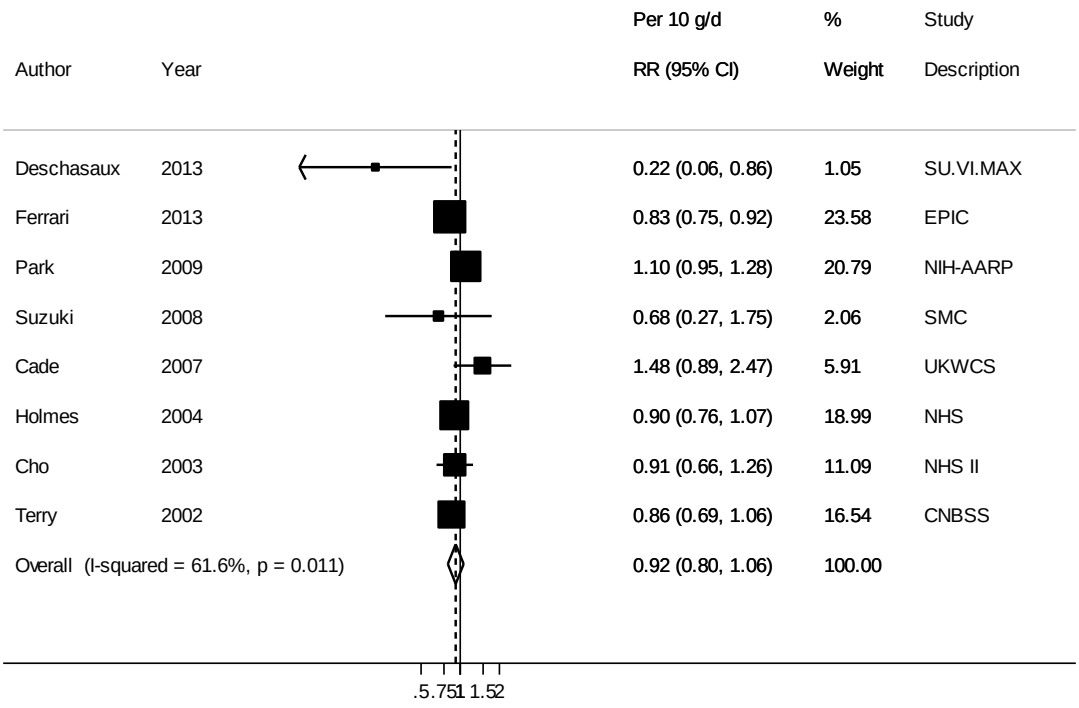


Figure 211 Relative risk of breast cancer for 10 g/day increase in vegetable fibre intake, stratified by menopausal status

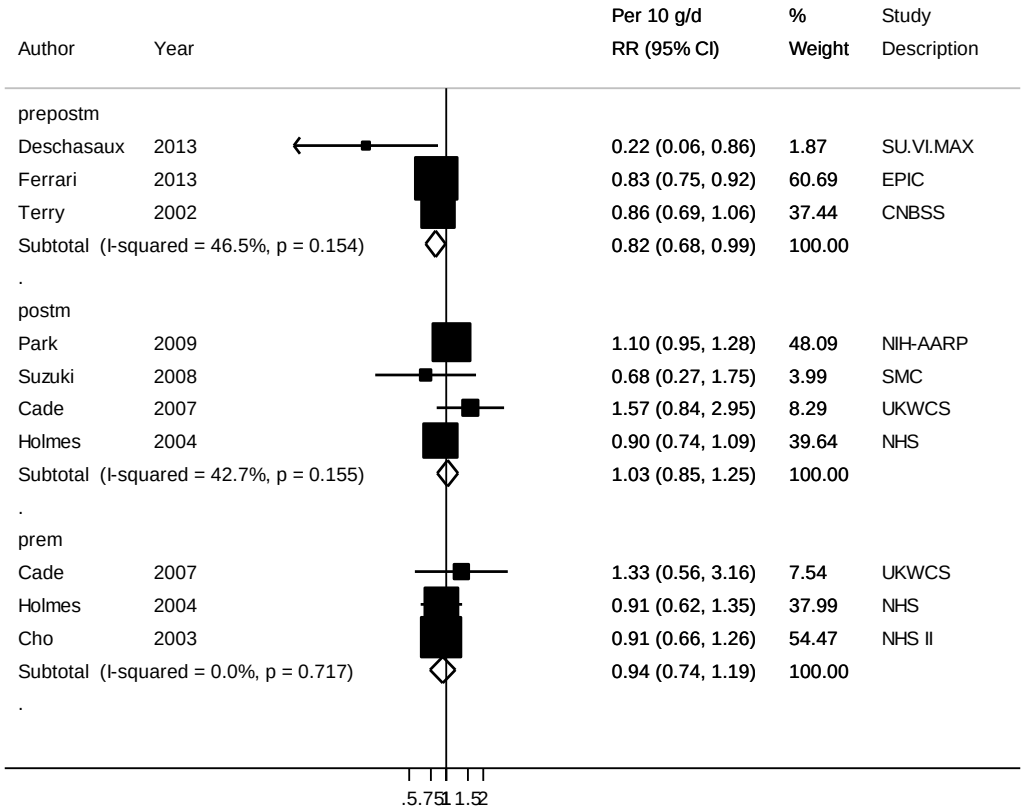


Figure 212 Funnel plot of studies included in the dose response meta-analysis of vegetable fibre intake and breast cancer

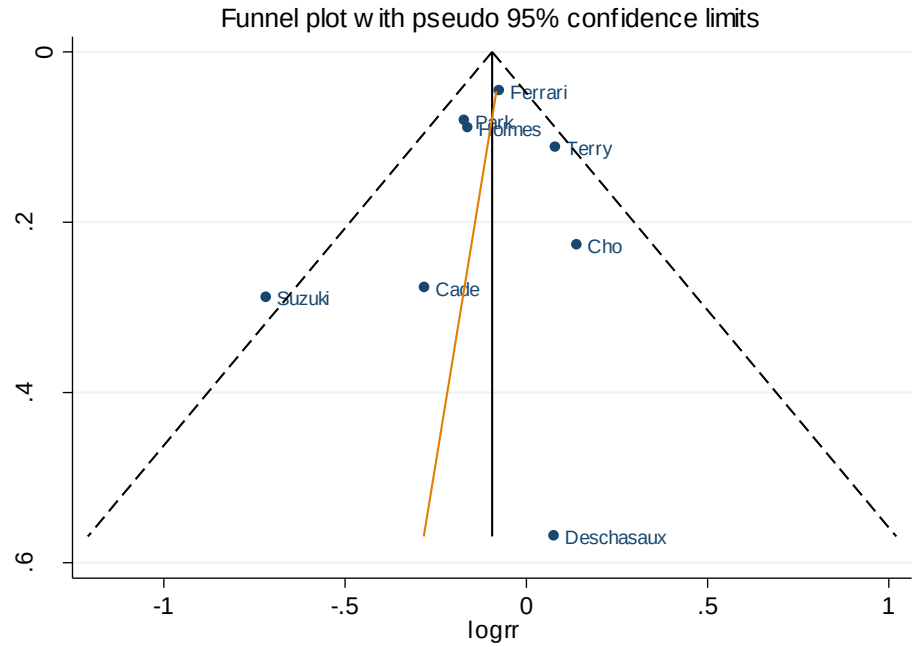
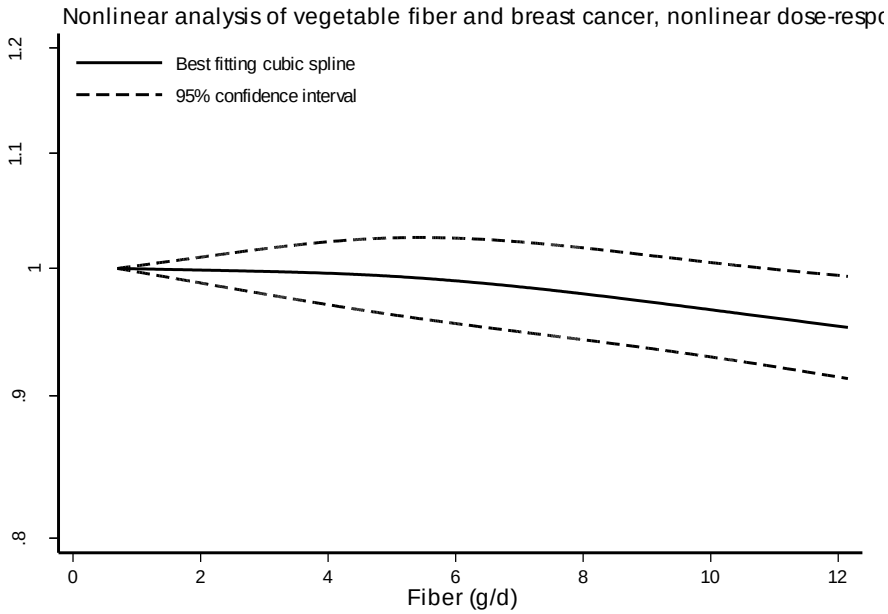


Figure 213 Vegetable fibre and breast cancer, nonlinear dose-response analysis



P nonlinearity=0.31

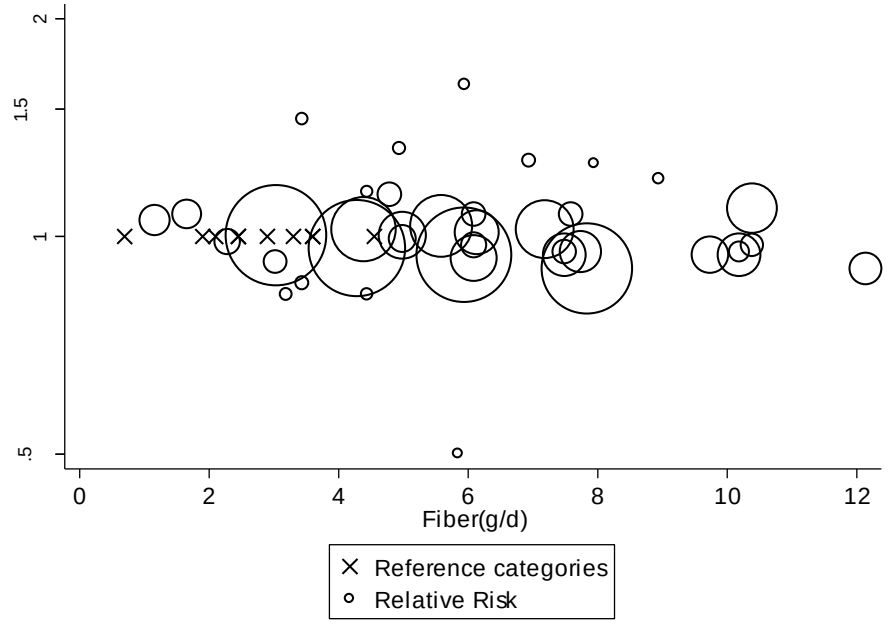
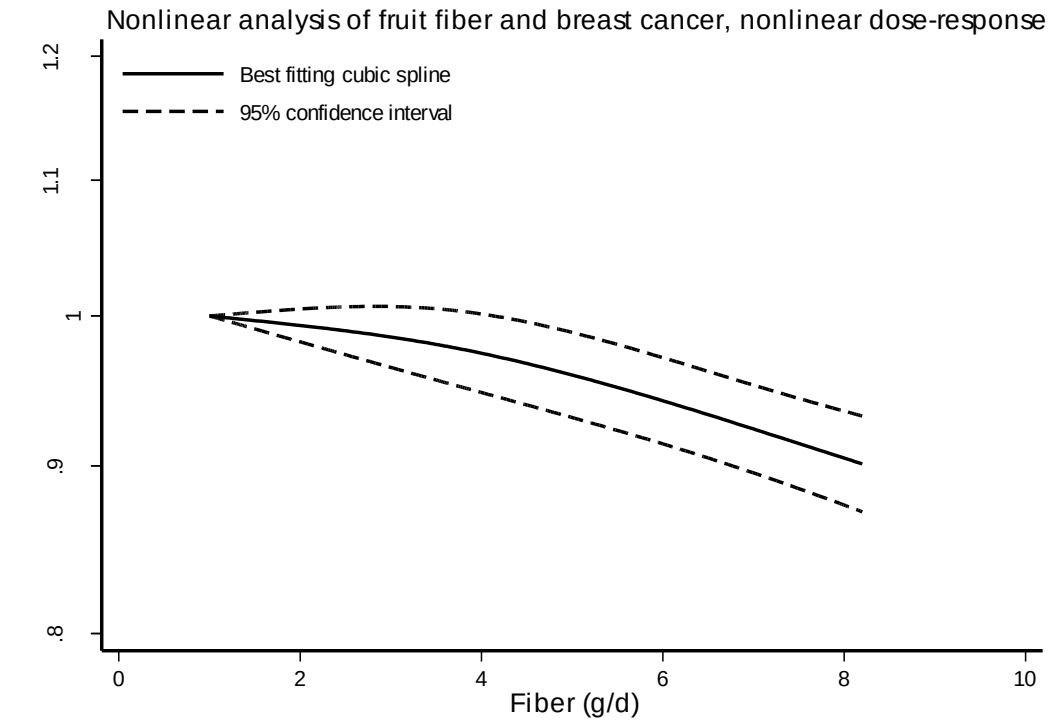


Table 144 Relative risk of breast cancer and vegetable fibre estimated using non-linear models

Vegetable fibre (g/day)	RR (95%CI)
0.7	1.00
2.0	1.00 (0.99-1.01)
4.0	1.00 (0.97-1.02)
6.0	0.99 (0.96-1.03)
8.0	0.98 (0.94-1.02)
10.0	0.97 (0.93-1.00)
12.0	0.95 (0.91-0.99)

Figure 214 Vegetable fibre and postmenopausal breast cancer, nonlinear dose-response analysis



P nonlinearity=0.12

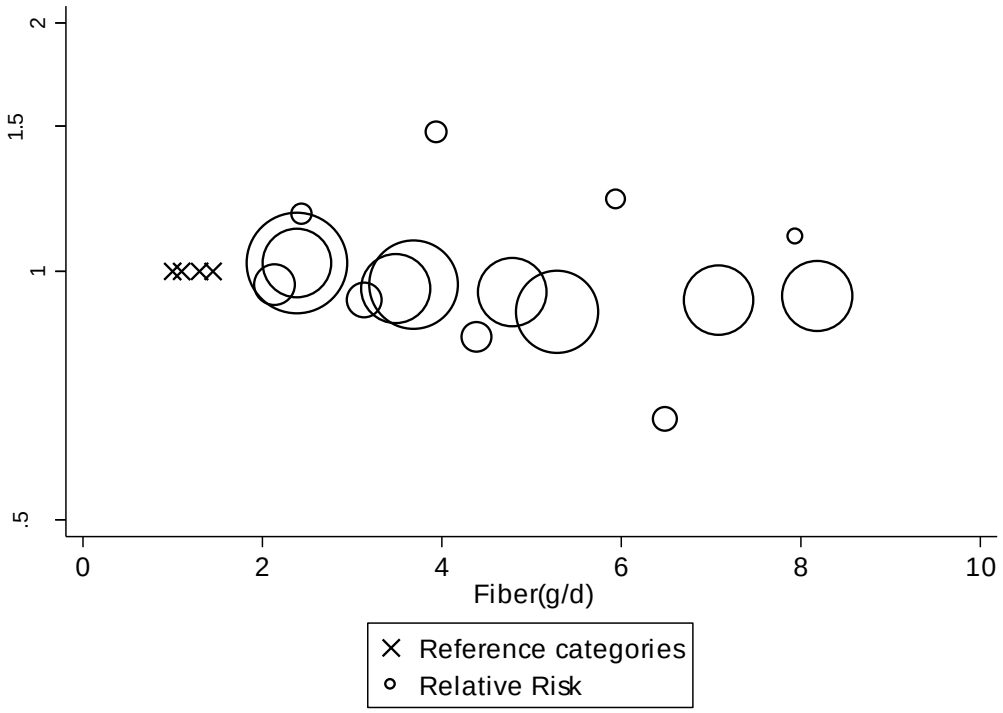


Table 145 Relative risk of postmenopausal breast cancer and vegetable fibre estimated using non-linear models

Vegetable fibre (g/day)	RR (95%CI)
1.0	1.00
2.0	0.99 (0.98-1.00)
4.0	0.97 (0.95-1.00)
6.0	0.94 (0.91-0.97)
8.0	0.91 (0.88-0.94)

5.1.2.3 Fruit fibre

Overall summary

Nine studies on fruit fibre intake and breast cancer risk were identified. Four studies investigated postmenopausal breast cancers, three were on premenopausal breast cancers, and three were on pre- and postmenopausal breast cancers combined. Study characteristics and results for all cancer types are shown in the Table.

Study quality:

Fruit fibre intake was estimated from food intake assessed by FFQ in all, but one study (Deschasaux, 2014), which used repeated 24-hour recalls. One study used a combination of dietary assessment methods including FFQ, dietary records, and dietary interviews (Ferrari, 2013).

Loss to follow-up was low for the studies that reported such data, although some studies did not provide data.

Cancers were identified by record linkages to health registries, cancer registries, mortality registries, or death indexes.

All studies adjusted for at least age, and most of the studies adjusted for most of the established breast cancer risk factors, including: age, parity, age at menarche, age at menopause, physical activity, BMI, and alcohol consumption.

Breast cancer (any)

Eight studies (26437 cases) were included in the dose-response meta-analysis. The summary RR for a 10 g/d increase in fruit fibre intake was 0.90 (95% CI: 0.82-1.00) and there was low heterogeneity, I^2=31.8%, $p_{heterogeneity}$=0.17. There was no evidence of small study bias or publication bias with Egger's test, p=0.46. One large European study, the EPIC study (Ferrari, 2013), contributed to 34% of the weight in the meta-analysis. The summary RR ranged from 0.87 (95% CI: 0.78-0.98) when the Canadian National Breast Screening Study (Terry, 2002) was excluded to 0.92 (95% CI: 0.84-1.00) when the Swedish Mammography Cohort (Suzuki, 2008a) was excluded.

Nonlinear dose-response analysis

There was indication of a nonlinear association, $p_{nonlinearity}$=0.002, with a suggestion of a threshold effect, with significantly reduced risk at intakes of 8 g/d.

Premenopausal breast cancer

Three studies (1823 cases) were included in the dose-response meta-analysis of fruit fibre intake and premenopausal breast cancer. The summary RR per 10 g/d increase in fruit fibre intake was 0.85 (95% CI: 0.51-1.36) and there was moderate heterogeneity, I^2=60.3%, $p_{heterogeneity}$=0.08.

Postmenopausal breast cancer

Four studies (9923 cases) were included in the dose-response meta-analysis of fruit fibre intake and postmenopausal breast cancer. The summary RR per 10 g/d increase in fruit fibre intake was 0.82 (95% CI: 0.70-0.97), with low heterogeneity, I^2=26.7%, $p_{heterogeneity}$=0.25.

Nonlinear dose-response analysis

The test for nonlinearity was not significant, $p_{nonlinearity}$=0.12, and there was a significant association from 6 grams per day and above.

Table 146 Fruit fibre intake and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	9
Studies included in forest plot of highest compared with lowest intake	Breast cancer: 8 Premenopausal: 3 Postmenopausal: 4
Studies included in linear dose-response meta-analysis	Breast cancer: 8 Premenopausal: 3 Postmenopausal: 4
Studies included in non-linear dose-response meta-analysis	Breast cancer: 8 Premenopausal: not enough studies Postmenopausal: 4 (not enough studies)

Table 147 Fruit fibre intake and breast cancer risk. Summary of the linear dose-response meta-analysis in the CUP (no dose-response meta-analysis was conducted in the 2005 SLR)

	Breast cancers (any)	Premenopausal	Postmenopausal
Increment unit used	10 g/day		
Studies (n)	8	3	4
Cases (total number)	26437	1823	9923
RR (95%CI)	0.90 (0.82-1.00)	0.83 (0.51-1.36)	0.82 (0.70-0.97)
Heterogeneity (I^2, p-	31.8%, p=0.17	60.3%, p=0.08	26.7%, p=0.25
P value Egger test	0.74	-	-

Stratified analyses

Geographic area	Asia	Europe	North-America
Studies (n)	-	4	4
RR (95%CI)	-	0.79 (0.58-1.08)	0.92 (0.81-1.06)
Heterogeneity (I^2, p- value)	-	44.3%, p=0.15	38.6%, p=0.18

Table 148 Fruit fibre and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	p trend	Heterogeneity (I^2, p value)
Meta-analyses								
Aune et al, 2012	6	14694	North America, Europe	Incidence	High vs. low	0.95 (0.86-1.06)	-	46%, p=0.10
					Per 10 g/d	0.88 (0.75-1.03)	-	48%, p=0.09

Table 149 Fruit fibre intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Deschasaux, 2013 BRE80487 France	SU.VI.MAX, Prospective Cohort, Age: 47 years, W	167/ 4 684 12.6 years	Self-report/ medical records/ histology	24 hour diet recall	Incidence, breast cancer	≥5 vs ≤2 g/day	1.07 (0.64-1.79)	Age-underlying cox models, alcohol, BMI, dietary pattern score, dietary records, educational level, family history of breast cancer, fat Intake, height, HRT use, Intervention group, menopausal status, non-alcohol energy Intake, number of children, physical activity, smoking status
Ferrari, 2013 BRE80436 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	11 576/ 334 849 11.5 years	Cancer and pathology registry, active follow up, health Insurance record, mortality registry and contact of participants or next-of-kin	Questionnaire	Incidence, breast cancer	≥6.9 vs ≤2.2 g/day	0.97 (0.91-1.04)	Age, age at first child birth, age at menarche, alcohol, contraception, educational level, energy Intake, height, menopausal status, physical activity, smoking, study center, weight
Park, 2009a BRE80264 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W, Postmenopausal	5 461/ 185 598 7 years	Cancer registry	FFQ	Incidence, breast cancer	8.2 vs 1.1 g/day	0.93 (0.82-1.05)	Age, age at first child birth, age at menopause, alcohol Intake, BMI, breast biopsies, educational attainment, energy Intake, family history of cancer, fat Intake, fruits and

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								vegetables Intake, menopausal hormone use, oophorectomy/hysterectomy, parity, physical activity, race, smoking status
Suzuki, 2008a BRE80148 Sweden	SMC, Prospective Cohort, Age: 60 years, W, Postmenopausal	1 284/ 51 823 8.3 years	Cancer registry	FFQ	Incidence, Invasive breast cancer	≥5.2 vs ≤1.6 g/day	0.66 (0.47-0.93)	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, benign breast disease, BMI, cereal fibre, educational level, family history of cancer, fruit and vegetables Intake, height, menopausal status, other dietary fibre Intake, parity, postmenopausal hormone use, total energy Intake, total fat, use of oral contraception, vegetable fibre Intake
					Incidence, breast cancer ER+/PR+	≥5.2 vs ≤1.6 g/day	0.62 (0.39-0.97)	
					Incidence, breast cancer ER+/PR-	≥5.2 vs ≤1.6 g/day	0.60 (0.29-1.22)	
					Incidence, breast cancer ER-/PR-	≥5.2 vs ≤1.6 g/day	0.50 (0.18-1.39)	
					Incidence, Invasive breast cancer, PMH - never users	Q 4 vs Q 1	0.57 (0.36-0.89)	
					Incidence, Invasive breast cancer, PMH - ever users	Q 4 vs Q 1	0.77 (0.47-1.28)	
Cade, 2007 BRE20021 UK	UKWCS, Prospective Cohort, Age: 35-69	286/ 35 792 7.5 years	NHS central registry	FFQ	Incidence, breast cancer, postmenopause	≥7 vs ≤1.9 g/day	1.10 (0.66-1.84)	Age , alcohol, BMI, energy Intake , HRT use, oc use, parity/pregnancies,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	years, W				Incidence, breast cancer, premenopause	≥6 vs ≤1.9 g/day	0.81 (0.44-1.49)	physical activity , smoking habits
Holmes, 2004 BRE04010 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	2 924/ 88 678 18 years	Medical records + self-reported	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	≥1 vs ≥-1 g/day	0.92 (0.81-1.04)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, energy Intake , family history, height, HRT use, menopausal status, other design Issue, parity/pregnancies
					Incidence, breast cancer, premenopausal	7.1 vs 1.3 g/day	0.86 (0.67-1.10)	
Cho, 2003b BRE01651 USA	NHS II, Prospective Cohort, Age: 26-46 years, W, Registered nurses	714/ 90 655 8 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, breast cancer, premenopausal	6.2 vs 1.1 g/day	1.13 (0.88-1.46)	Age at first child, age at menarche, alcohol, benign breast disease, BMI, family history, height, menopausal status, nutrients, oc use, parity/pregnancies, residual (willet), smoking habits
Terry, 2002 BRE12199 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	89 835 16.2 years	Partially histological - over 80%	FFQ	Incidence, Invasive & In situ breast cancer,	≥6.6 vs ≤1.9 g/day	1.07 (0.92-1.25)	Age , alcohol, benign breast disease, BMI, educational level, energy Intake , family history, HRT use, menopausal status, nutrients, oc use, other specified factor, other specified factor, parity/pregnancies, physical activity ,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								recruitment center, smoking habits

Table 150 Fruit fibre intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Giles, 2006 BRE22430 Australia	MCCS, Prospective Cohort, Age: 40-69 years, W, Postmenopausal	12 273 9.1 years	Pathology report + cancer registry	FFQ	Incidence, breast cancer, postmenopausal	per 1 sd/day	1.00 (0.88-1.13)	Age , energy Intake , HRT use, place of residence	Size of standard deviation not provided

Figure 215 RR estimates of breast cancer by levels of fruit fibre intake

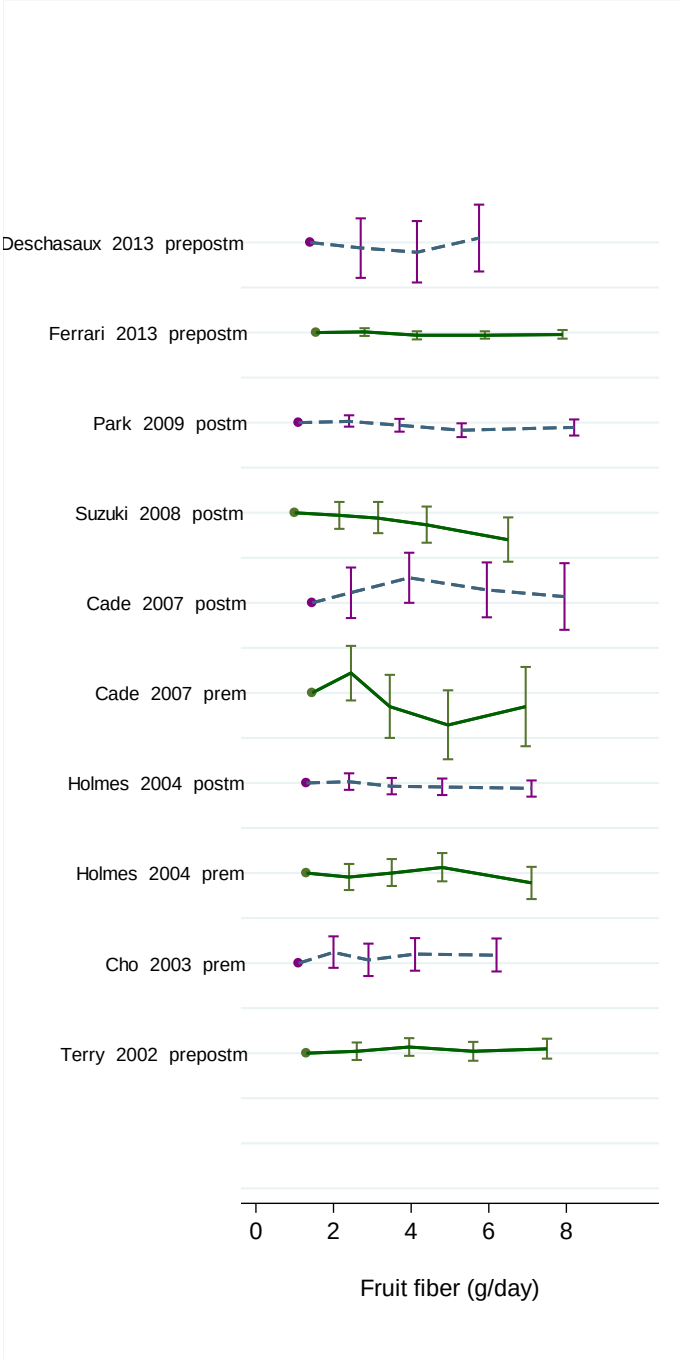


Figure 216 Relative risk of breast cancer for the highest compared with the lowest level of fruit fibre intake

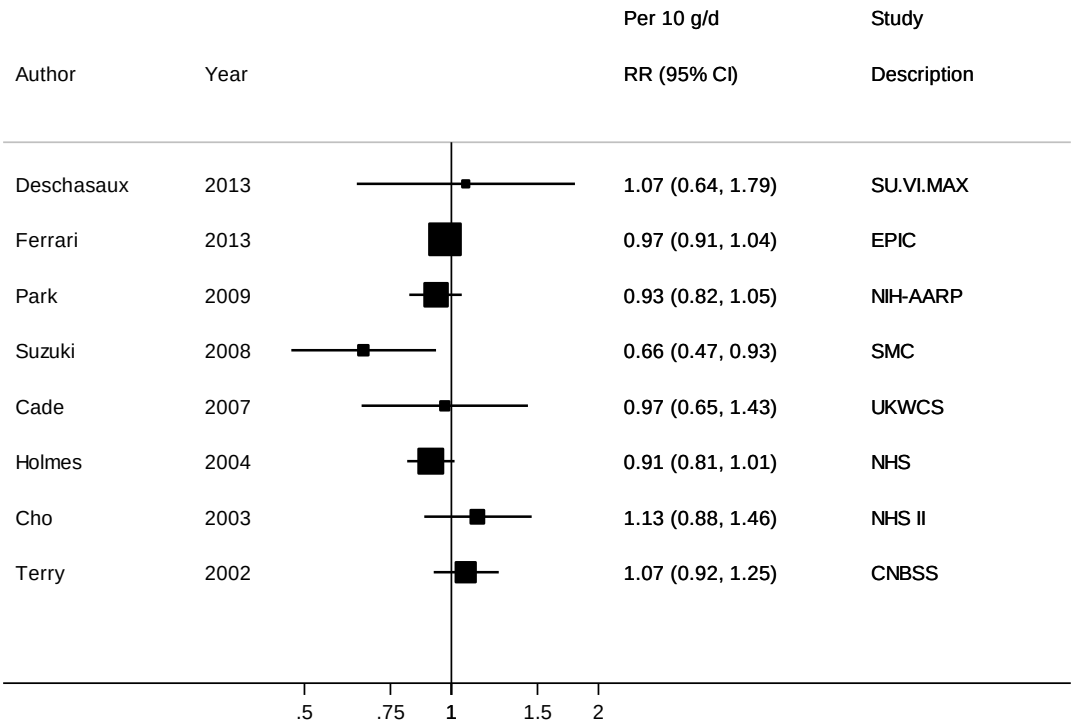


Figure 217 Relative risk of breast cancer for the highest compared with the lowest level of fruit fibre intake, stratified by menopausal status

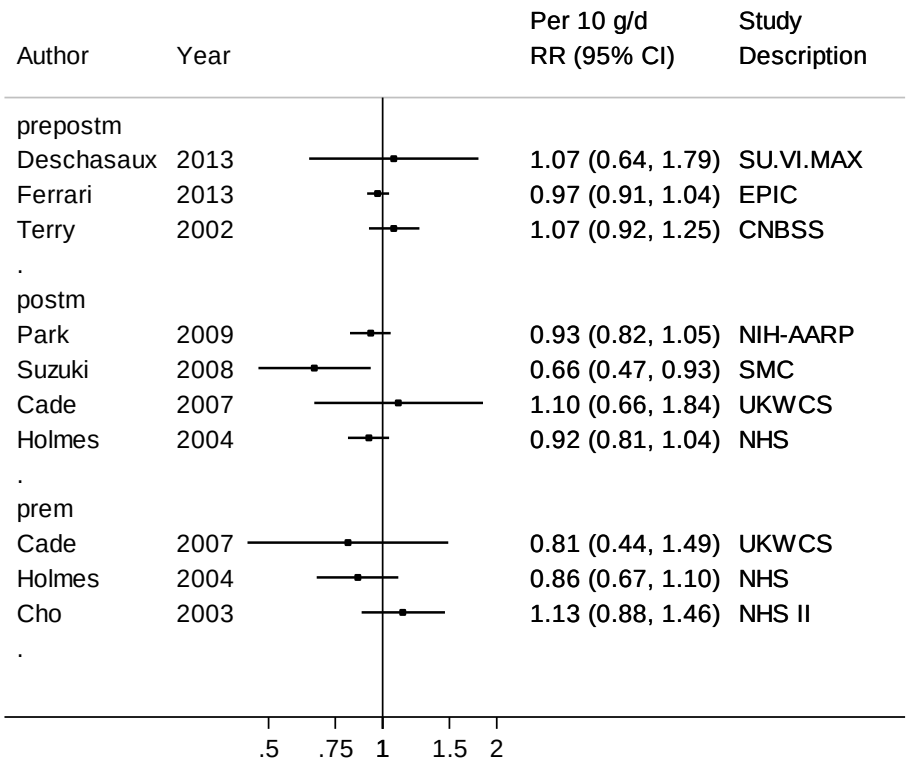


Figure 218 Relative risk of breast cancer for 10 g/day increase in fruit fibre intake

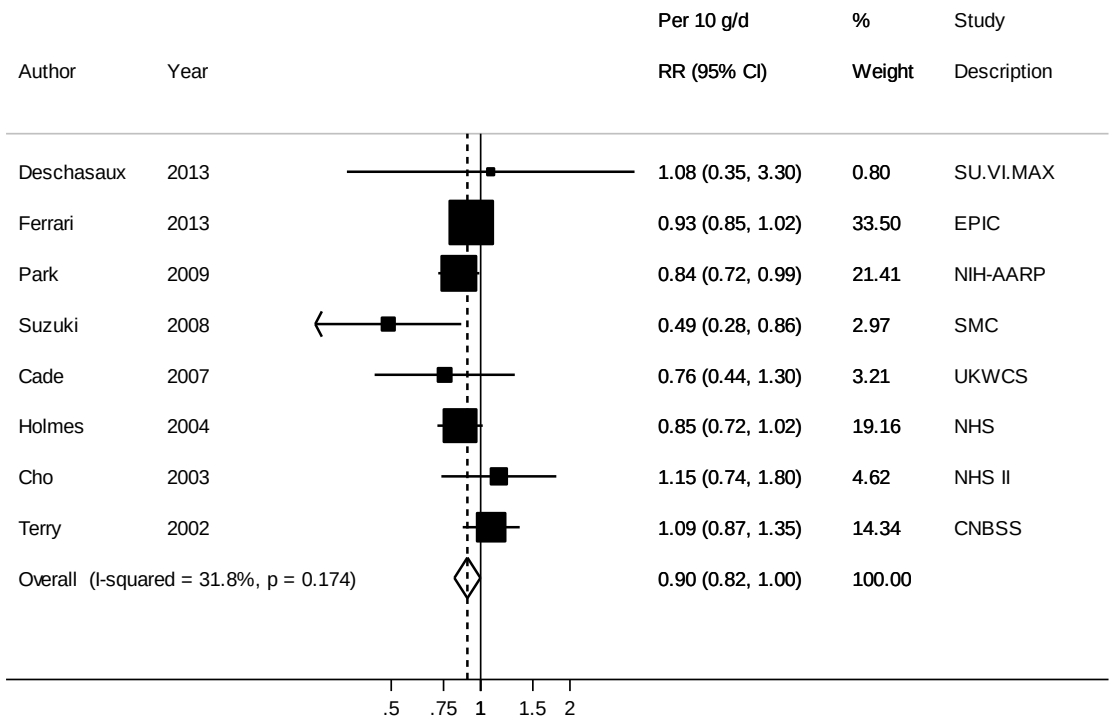


Figure 219 Relative risk of breast cancer for 10 g/day increase in fruit fibre intake, stratified by menopausal status

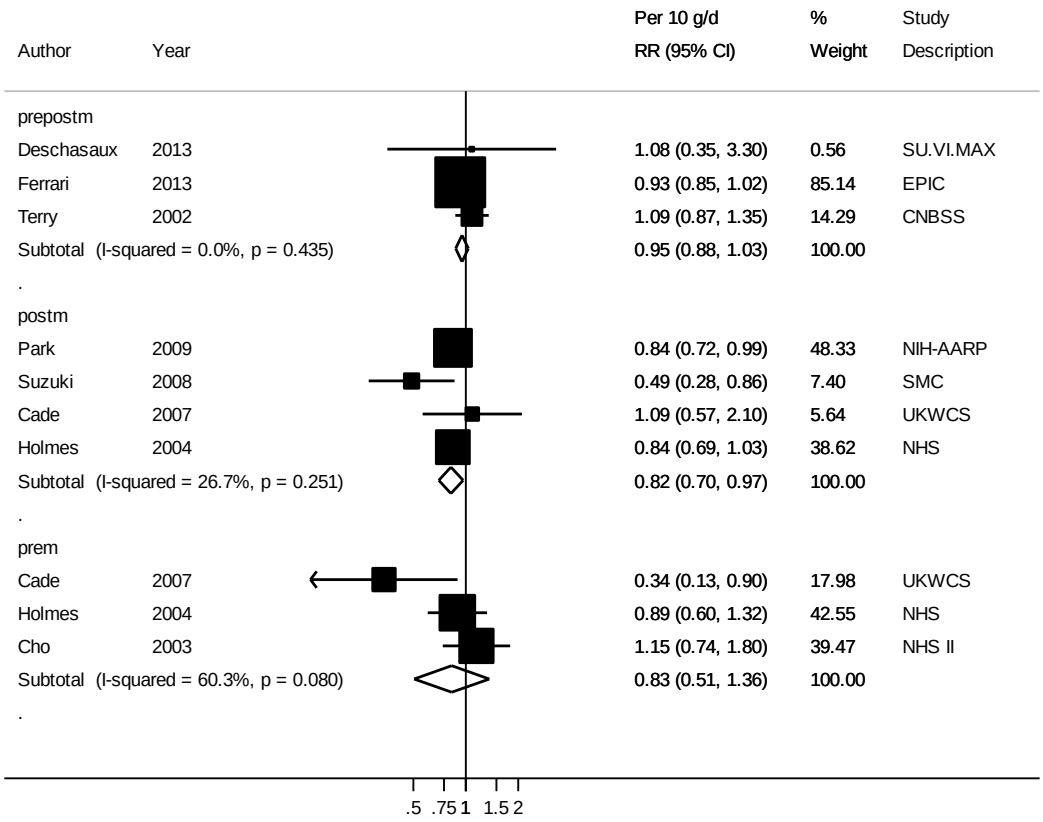


Figure 220 Relative risk of breast cancer for 10 g/day increase in fruit fibre intake, stratified by geographic region

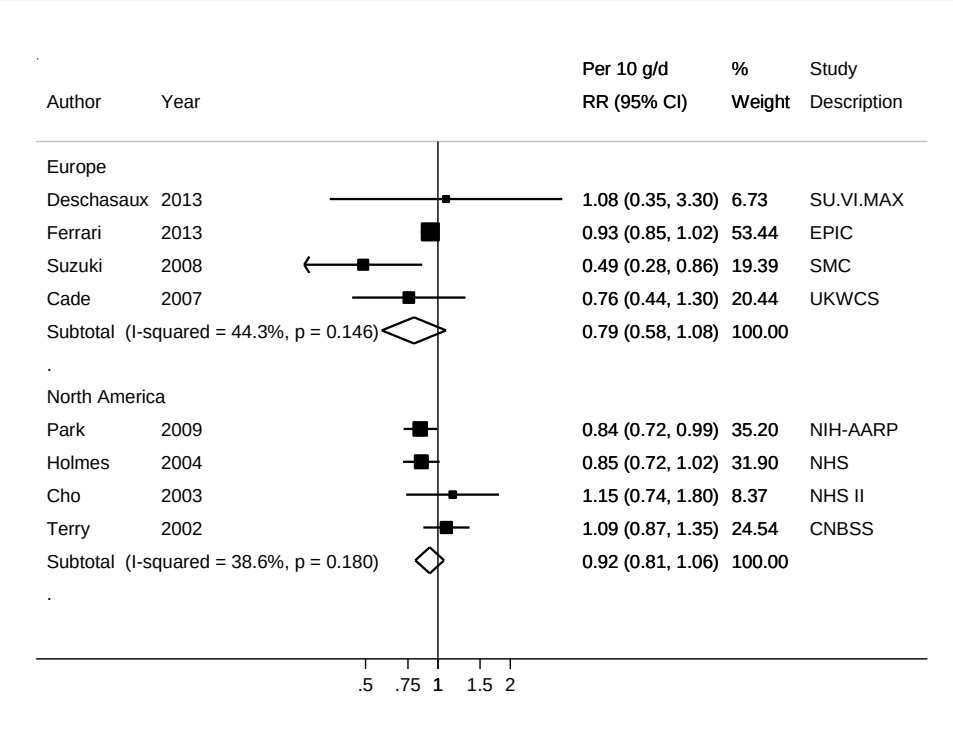


Figure 221 Funnel plot of studies included in the dose response meta-analysis of fruit fibre intake and breast cancer

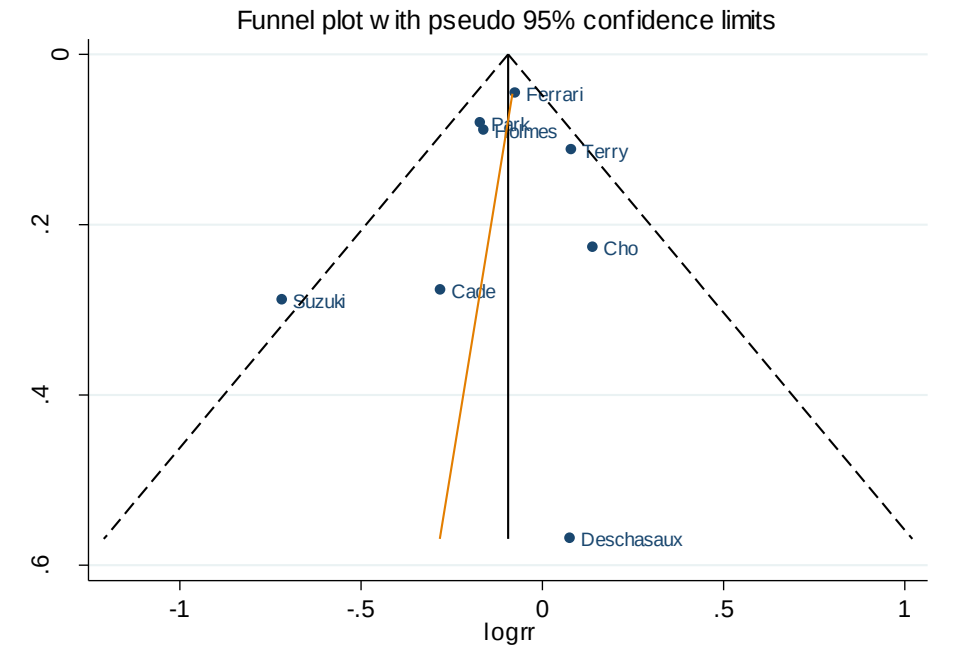
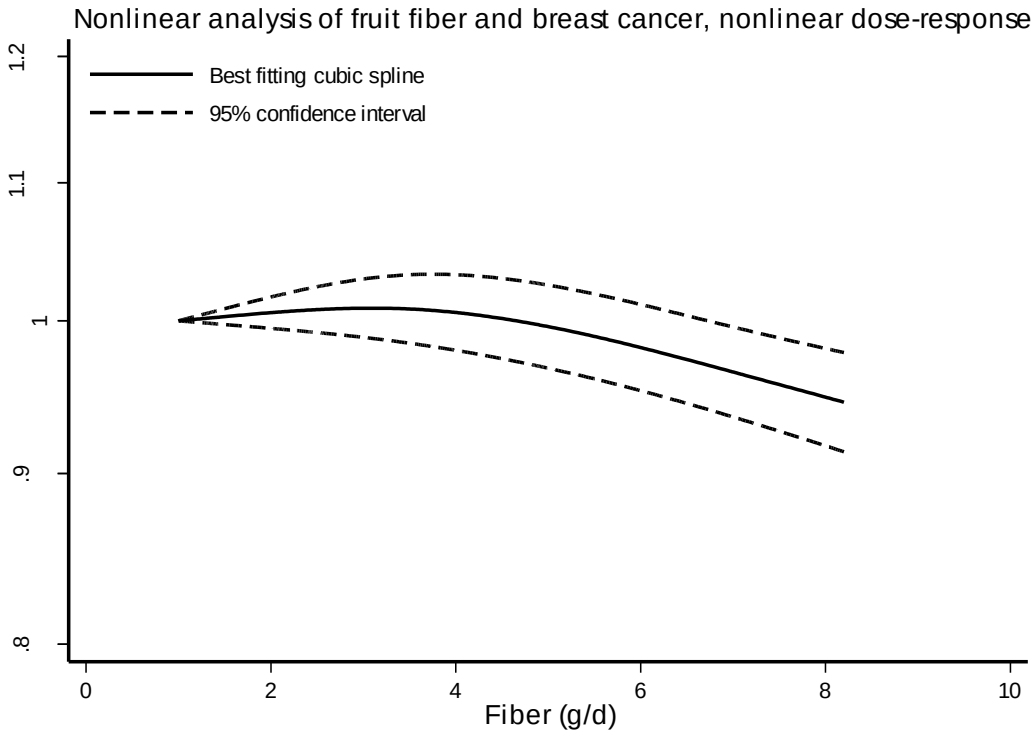


Figure 222 Fruit fibre and breast cancer, nonlinear dose-response analysis



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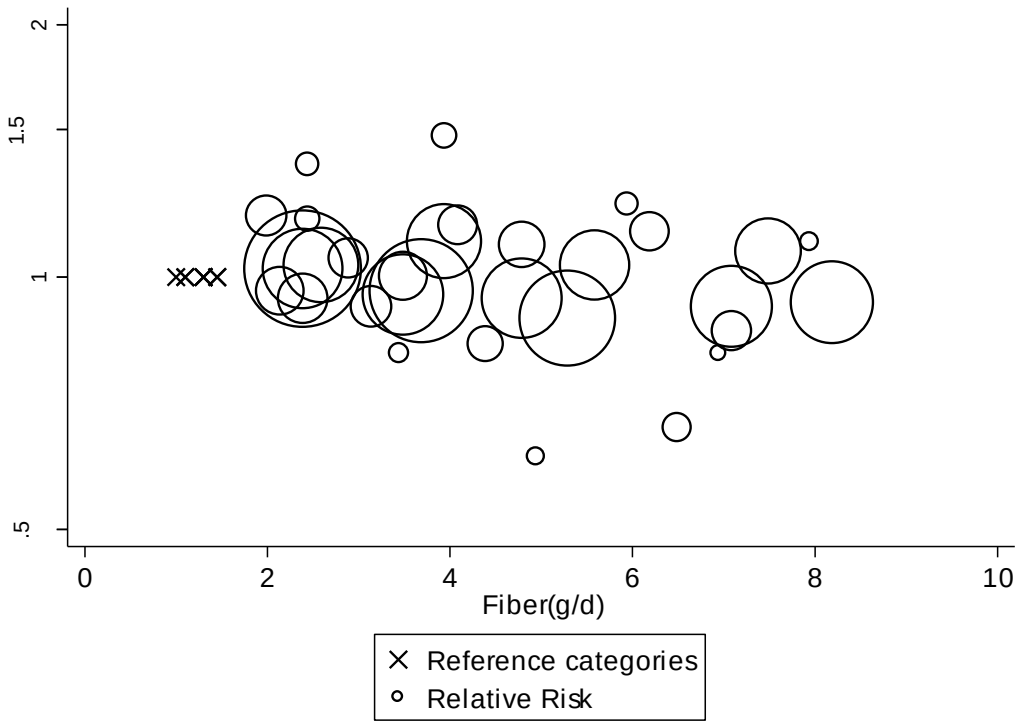
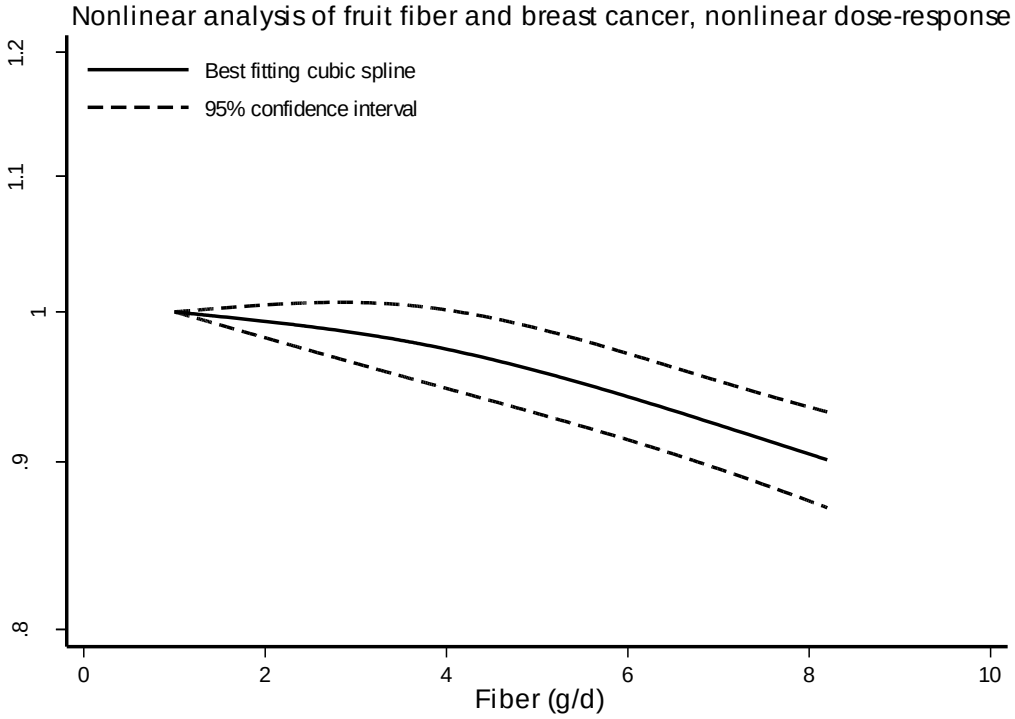


Table 151 Relative risk of breast cancer and fruit fibre estimated using non-linear models

Fruit fibre (g/day)	RR (95%CI)
1.0	1.00
2.0	1.01 (0.99-1.02)
4.0	1.01 (0.98-1.03)
6.0	0.98 (0.95-1.01)
8.0	0.95 (0.92-0.98)

Figure 223 Fruit fibre and postmenopausal breast cancer, nonlinear dose-response analysis



P nonlinearity=0.12

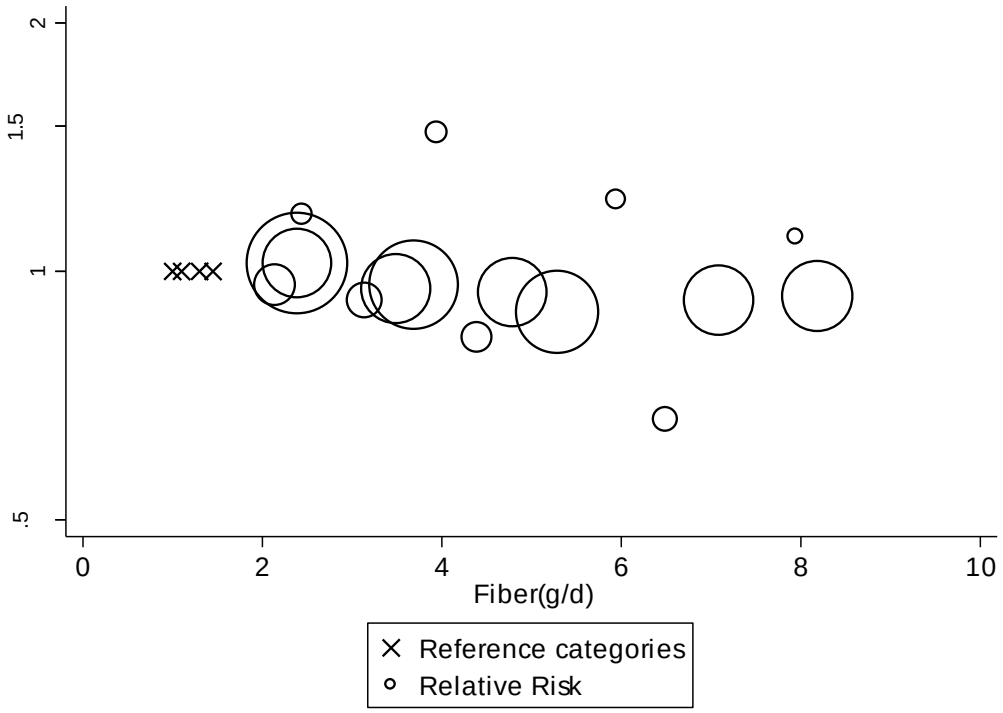


Table 152 Relative risk of postmenopausal breast cancer and fruit fibre estimated using non-linear models

Fruit fibre (g/day)	RR (95%CI)
1.0	1.00
2.0	0.99 (0.98-1.00)
4.0	0.97 (0.95-1.00)
6.0	0.94 (0.91-0.97)
8.0	0.91 (0.88-0.94)

5.1.5.1 Glycaemic Index

Cohort studies

Overall summary

Sixteen publications from 12 cohort studies on diet glycaemic index score (GI) and breast cancer risk were identified. From the 16 publications, three publications (EPIC Italy, Sieri, 2013; E3N, Lajous, 2008 and DCH, Nielsen 2005) are not counted among the 12 cohort studies as these are from cohorts that participated in EPIC (Romieu, 2012) , which is counted as one cohort study. Two other publications from the NHSII reported on glycaemic index of diet during adolescence and breast cancer risk during adulthood (Linos, 2010; Frazier, 2004).

Dose-response meta-analyses were conducted for studies that reported associations with pre- and postmenopausal breast cancers combined (Any breast cancer), premenopausal breast cancers and postmenopausal breast cancers. Only a few studies investigated the association of glycaemic index and breast cancer by cancer hormone receptor status, and dose-response meta-analysis was not conducted.

Table 153 Glycaemic index and breast cancer. Number of studies in the CUP SLR by analysis

Analysis	Number
Studies identified Total	12 (16 publications)
Studies included in forest plot of highest compared with lowest GI	
Any breast cancer	6
Premenopausal	7
Postmenopausal	11
Studies included in linear dose-response meta-analysis	
Any breast cancer	5
Premenopausal	6
Postmenopausal	10

Table 154 Summary of results of the dose-response meta-analyses on glycaemic index and breast cancer risk in the CUP SLR (no meta-analysis of cohort studies in 2005 SLR)

	CUP SLR		
	Any breast cancer	**Pre-menopausal breast cancer**	**Post-menopausal breast cancer**
Increment unit	Per 10 units/day		
Studies (n)	5	6	10
Cases	17 767	21 859	37 846
RR (95%CI)	1.02 (0.96-1.10)	1.01 (0.93-1.10)	1.06 (1.02-1.10)
Heterogeneity (I^2, p-value)	51.9%, 0.08	34%, 0.18	18.9%, 0.27
P value Egger test	0.593	0.001	0.866

Breast cancer (any)

Six studies on glycaemic index intake and risk of any breast cancer were identified. Five studies reported the data needed for dose-response meta-analysis. No association was observed. High heterogeneity was observed mainly due to the increased risk showed in the Italian ORDET study (Sieri, 2007).

There was no statistical evidence of small study or publication bias. However, only five studies were included in the analysis and the funnel plot shows asymmetry driven by the ORDET study (Sieri, 2007).

Premenopausal breast cancer

Seven studies on premenopausal breast cancer were identified. Six studies were included in the dose-response meta-analysis. No association was observed. The excluded study

(Higginbotham, 2004) reported a positive but not significant relative risk when comparing the highest to the lowest quintile of diet glycaemic index.

There was moderate heterogeneity driven by the Italian ORDET study (Sieri, 2007) and a study in Chinese women (Wen, 2009) that reported significant increases in breast cancer risk in premenopausal women with increasing levels of dietary glycaemic index score (Note: the Chinese study also investigated carbohydrate intake and found a positive association, see corresponding section).

There is statistical evidence of small study bias (p=0.01). The figure is asymmetric toward the right (driven by Sieri, 2007 and Wen, 2009). Exclusion of these studies did not substantially modify the overall results.

Postmenopausal breast cancer

Twelve studies were identified and ten studies could be included in the dose-response meta-analysis. A positive significant association was observed. The studies excluded from the meta-analysis reported a positive non-significant dose-response relationship (RR for one SD increment=1.19 (95% CI 0.93-1.52) (Giles, 2006, Australia) and a non significant inverse relationship when comparing the highest to the lowest quintile (Higginbotham, 2004).

There was moderate heterogeneity and no significant evidence of publication bias.

Breast cancer by hormone receptor status

Seven studies (including E3N that is also in EPIC) reported on the association of glycaemic index and breast cancer by hormone receptor status. There were maximum four studies in each subgroup investigated and not enough data to do dose-response meta-analysis. The relative risk for the highest compared to the lowest level of glycaemic index are shown in a forest plot. Overall, no significant associations of glycaemic index with breast cancer subgroups defined by hormone receptor status were observed and no clear pattern emerged.

Sensitivity analyses:

Subgroup and sensitivity analyses were not conducted due to low number of studies.

Non-linear dose-response meta-analysis:

Not conducted due to low number of studies.

Study quality:

No issues relevant to study quality were identified in the studies included in the dose-response meta-analysis. In two studies (Sieri, 2007; Wen, 2009) the number of premenopausal breast cancer cases was below 200 cases and the associations were stronger than in all studies on average.

Most studies investigated invasive breast cancer as outcome. In situ breast cancers were included in five studies, but the number of these cases was in general low (Jonas, 2003; Holmes, 2004; Higginbotham, 2004; Larsson, 2009c; Shikany, 2011). The WHI study (Shikany, 2011) was the only study that reported for in situ and invasive cancers. The RRs for all breast cancers in this study were included in the dose-response meta-analysis.

Follow-up was through cancer registries or active follow-up with medical confirmation and there was no report of important losses to follow-up.

All studies adjusted for main confounders.

Two studies were in populations recruited through cancer screenings (Silvera, 2005; Larsson, 2009c). One study included participants in randomized controlled trials and an observational study (WHI, Skihany, 2011). There was no difference in cumulative incidence of breast cancer in the groups in trial or observational study, and the associations in the paper are for all women combined.

Diet glycaemic index during adolescence and breast cancer risk during adulthood

Glycaemic index of the diet during adolescence was positively significantly related to increased breast cancer risk in an initial analysis in the Nurses' Health Study II (Frazier, 2004). However, no association was observed in the most recent analysis (Linos, 2010). In this cohort, 39,268 premenopausal women aged 34 to 53 years completed a 124-item food frequency questionnaire on their diet during high school in 1998; 455 incident cases of invasive breast cancer were diagnosed up to 2005. The multivariable-adjusted RR for the highest compared to the lowest quintile of diet glycaemic index was 1.18 (95% CI 0.88-1.58) p trend=0.37 (Linos, 2010).

Table 155 Glycaemic index and breast cancer risk. Main characteristics of studies included in linear dose-response meta-analyses.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Farvid, 2015b BRE80569 USA	NHS II, Prospective Cohort, Age: 27-44 years, W	2 833/ 90 488 20 years	Self-reported/death certificate/ medical records	FFQ (Diet at early adulthood-baseline)	Incidence, Invasive breast cancer	57.9 vs 49.7 units/day	1.03 (0.91–1.16) Ptrend:0.66	Age, age at menarche, age at menopause, alcohol intake, benign breast disease, BMI at age 18 years, weight gain since 18, height, energy intake, family history of breast cancer, HRT use, oral contraceptive use, menopause status, parity and age at first birth, race, smoking	All data available
		1 659/			Premenopause		1.05 (0.90–1.23) Ptrend:0.37		
		875/			Postmenopause		1.08 (0.87–1.35) Ptrend:0.84		
		1 571/			ER+/PR+		1.09 (0.93–1.28)		(No dose-response by hormone receptor status)
		429/			ER-/PR-		0.95 (0.69–1.30)		
Romieu, 2012 BRE80418 Denmark,France ,Germany,Greec e,Italy,Netherlan ds,Norway,Spai n,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	11 576/ 334 849 11.5 years	Cancer and pathology registry, active follow up, health Insurance record, mortality registry and contact of participants or next-of-kin	FFQ, diet history, 7-day food diary (depending on the cohort)	Incidence,all breast cancers	≥59 vs ≤52.6 units/day	1.05 (0.99-1.12) Ptrend:0.066	Age at first child birth, age at menarche, age at menopause, alcohol Intake, educational level, energy Intake, ever used contraceptive pills, ever used hormones, fibre Intake, height, menopausal status, physical	Midpoints of GL categories for pre-and postmenopausal cancers (No dose-response by hormone receptor status)
						per 5 units	1.03 (1.00-1.05)		
		2 827/			Premenopause	≥59 vs ≤52.6 units/day	1.02 (0.90-1.16) Ptrend:0.947		
		5 872/			Postmenopause		1.07 (0.99-1.17) Ptrend:0.073		
		493/			Postmenopause ER-/PR-		1.23 (0.92-1.65) Ptrend:0.241		
		1 053/			All, ER-/PR-		1.04 (0.86-1.26)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
							Ptrend:0.851	activity, smoking status, study centre, weight	
		658/			Postmenopause ER-		1.21 (0.93-1.56) Ptrend:0.151		
		1 443/			All, ER-		1.04 (0.88-1.24) Ptrend:0.902		
		3 004/			Postmenopause ER+		1.44 (0.89-2.34) Ptrend:0.304		
		5 823/			All, ER+		1.01 (0.90-1.14) Ptrend:0.874		
		176/			All, ER-/PR-/HER2+		1.01 (0.93-1.10) Ptrend:0.639		
		224/			All, ER-/PR-/HER2-		1.03 (0.65-1.65) Ptrend:0.546		
Shikany, 2011 BRE80382 USA	Women's Health Initiative, Follow-up of RCT and observational study (OS), Age: 50-79 years, W, Postmenopausal	6 098/ 148 767 8 years	Self-report verified by medical record	FFQ	Incidence, breast cancer	57 vs 47.8 units/day	1.01 (0.91-1.12) Ptrend:0.74	Age, age at first child birth, age at menarche, age at menopause, alcohol, BMI, educational level, energy intake, ethnicity, family history of breast cancer, hormone use, HRT use, mammogram in the past 2 years, parity, oral contraceptive	
							0.98 (0.88-1.10) Ptrend:0.33		
		1 162/			Incidence, in situ breast cancer		1.05 (0.90-1.22) Ptrend:0.41		
					Incidence, invasive breast cancer		1.01 (0.71-1.43) Ptrend:0.61		
		3 016/			All, ER+/PR+		1.07 (0.74-1.52) Ptrend:0.32		
		664/			All, ER+/PR-		1.18 (0.88-1.58)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
							Ptrend:0.37	use, physical activity, smoking, trial assignment	
		616/			All, ER-/PR+		1.68 (0.93-3.02) Ptrend:0.07		
George, 2009b BRE80456 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, Postmenopausal women	5 478/ 183 535 6.89 years	Linkage with 11 state cancer registry databases	Validated FFQ	Incidence, breast cancer	56.56-83.94 vs 33.61-50.43 units/day	1.05 (0.97-1.15) Ptrend:0.129	Age, alcohol consumption, BMI, educational level, ethnicity, family history of cancer, marital status, menopausal oestrogen use, physical activity, smoking, total energy Intake	Midpoints of categories, cases and person-years per quintile
Larsson, 2009c BRE80248 Sweden	SMC, Prospective Cohort, Age: 54 years, Postmenopausal women	2 952/ 61 433 17.4 years	Cancer registry	FFQ	Incidence, breast cancer	≥83.4 vs ≤75.7 units/day	1.08 (0.96-1.21) Ptrend:0.20	Age, age at first child birth, age at menarche, age at menopause, alcohol intake, BMI, height, dietary fibre, educational level, family history of cancer, HRT use, OC use, parity, total energy intake	Midpoints of categories, person-years per quintile (No dose-response by hormone receptor status)
		1 286/			ER+/PR+		0.89 (0.74-1.06) Ptrend:0.32		
		417/			ER+/PR-		1.44 (1.06-1.97) Ptrend:0.01		
		266/			ER-/PR-		1.29 (0.85-1.96) Ptrend:0.62		
Wen, 2009	SWHS,	616/	Cancer registry	Quantitative	Incidence,	76.8 vs 63.9	1.03 (0.79-1.34)	Age, age at first	Cases and

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
BRE80209 China	Prospective Cohort, Age: 40-70 years, W	73 328 7.35 years		FFQ	Invasive & In situ breast cancer	units/day	Ptrend:0.472	child birth, benign breast disease, BMI, educational level, energy intake, family history of cancer, physical activity	person-years per quintile
		190/			Premenopausal		1.19 (0.73-1.94) Ptrend:0.256		
		426/			Postmenopausal		0.96 (0.70-1.31) Ptrend:0.093		
Sieri, 2007 BRE80142 Italy	ORDET, Prospective Cohort, Age: 34-70 years	289/ 8 926 11.5 years	Cancer registry	Semi-quantitative FFQ	Incidence, Invasive & In situ breast cancer	≥57.6 vs ≤53.4 units/day	1.57 (1.04-2.36) Ptrend:0.04	Age, age at menarche, alcohol intake, educational level, energy intake, fibre Intake, height, parity, oral contraceptive use, saturated fat intake, smoking status, weight	Midpoints of exposure and person-years per quintile
		146/			Premenopausal		1.82 (1.01-3.27)		
		128/			Postmenopausal		1.12 (0.62-2.02)		
Silvera, 2005 BRE24119 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W, Screening Program	1 450/ 49 111 16.6 years	Cancer registry + death certificate	FFQ	Incidence, breast cancer	≥96.1 vs ≤60 units/day	0.88 (0.63-1.22) Ptrend:0.38	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, energy intake , family history, mammography, menopausal status, OC use, HRT use, other nutritional	For pre- and postmenopausal, distribution of cases and person-years per quintile
					Premenopausal	≥92.1 vs ≤63 units/day	0.78 (0.52-1.16) Ptrend:0.12		
					Postmenopausal		1.87 (1.18-2.97)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
							Ptrend:0.01	factors, parity/pregnancies, recruitment center	
Holmes, 2004 BRE04010 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	2 924/ 88 678 18 years	Medical records + self-reported	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	81 vs 69 units/day	1.15 (1.02-1.30) Ptrend:0.02	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, energy intake , family history, height, HRT use, menopausal status, parity/ pregnancies	Cases and person-years per quintile
		852/			Premenopausal		1.02 (0.82-1.28) Ptrend:0.68		
Jonas, 2003 BRE04456 USA	CPS II, Prospective Cohort, Age: 50-74 years, W, Postmenopausal	1 442/ 70 888 5 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	85 vs 65 units/day	1.03 (0.87-1.22) Ptrend:0.706	Age , age at first child, age at menarche, age at menopause, alcohol, anthropometry, anthropometry, benign breast disease, BMI, educational level, energy Intake , ethnicity, family history, height, HRT use, OC use, other hormonal	Q2 and Q4 score estimated as midpoints of medians of adjacent quintiles

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								variables, parity/pregnancies, physical activity , smoking habits	

Table 156 Glycaemic index and breast cancer risk. Main characteristics of studies excluded from linear dose-response meta-analyses.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Sieri, 2013 BRE80408 Italy	EPIC-Italy, Prospective Cohort, Age: 50 years, W	879/ 26 066 11 years	Cancer registry	FFQ	Incidence, breast cancer	57 vs 50 units/day	1.07 (0.86-1.33) Ptrend:0.362	Age at menarche, alcohol, BMI, educational level, parity, menopausal status, non-alcohol energy, recreational activity, intakes of saturated fat, fibre smoking, sport, work - physical activity	Included in EPIC (Romieu, 2012)
		391/			Premenopause		1.05 (0.76-1.47) Ptrend:0.799		
		419/			Postmenopause		1.05 (0.76-1.43) Ptrend:0.408		
Linos, 2010 BRE80298 USA	NHS II, Prospective Cohort, Age: 34-53 years, W, Premenopausal	455/ 39 268 7.8 years	Follow up questionnaires, medical records	Semi-quantitative FFQ	Incidence, Invasive breast cancer	58.4 vs 51.6 units/day	1.18 (0.88-1.58) Ptrend:0.37	Age, age at first child birth, age at menarche, alcohol consumption, benign breast disease, BMI,	Diet in adolescence

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								energy Intake, family history of cancer, menopausal status, OC use, parity, weight gain	
Lajous, 2008 BRE80218 France	E3N EPIC-France, Prospective Cohort, Age: 42-72 years, W, Postmenopausal	1 812/ 62 739 9 years	Cancer registry	Dietary history	Incidence, breast cancer, postmenopausal	65.6 vs 44.3 units/day	1.14 (0.99-1.32) Ptrend:0.06	Age, age at menarche, age at menopause, alcohol consumption, benign breast disease, BMI, breastfeeding, educational level, family history of cancer, fibre Intake, folate Intake, follow-up time, height, HRT use, mammography, OC use, parity, physical activity, residence, total energy intake, vitamin use	Included in EPIC (Romieu, 2012)
							1.05 (0.88-1.27) Ptrend:0.59		
		1 083/			ER+, postmenopausal		0.91 (0.63-1.32) Ptrend:0.98		
		279/			ER-, postmenopausal		0.94 (0.75-1.17) Ptrend:0.29		
		814/			PR+, postmenopausal		0.97 (0.74-1.27) Ptrend:0.83		
		511/			PR-, postmenopausal		1.14 (0.99-1.32) Ptrend:0.06		
					ER-/PR-, postmenopausal		1.05 (0.88-1.27) Ptrend:0.59		
Giles, 2006 BRE22430 Australia	MCCS, Prospective Cohort,	12 273 9.1 years	Pathology report + cancer registry	FFQ	Incidence, breast cancer, postmenopausal	per 1 SD	0.98 (0.88-1.10)	Age , energy intake , HRT use, place of	GI not expressed in g/d

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 40-69 years, W, Postmenopausal				ER+/PR+, postmenopausal		0.91 (0.77-1.07)	residence	
					ER+/PR-, postmenopausal		0.80 (0.57-1.12)		
					ER-/PR-, postmenopausal		0.98 (0.74-1.29)		
Nielsen, 2005 BRE23581 Denmark	DCH, Prospective Cohort, Age: 50-65 years, W, Postmenopausal	23 870 6.6 years	All histology	FFQ	Incidence, breast cancer, postmenopausal	per 10 units/day	0.94 (0.80-1.10)	Alcohol, BMI, educational level, HRT use, parity/pregnancies	Included in EPIC
					ER+, postmenopausal		0.86 (0.71-1.04)		
					ER-, postmenopausal		1.46 (1.01-2.11)		
Frazier, 2004 BRE02942 USA	NHS II, Historical Cohort, Age: 34-51 years, W, Registered nurses	361/ 47 355 9 years	All histology	FFQ	Incidence, breast cancer, premenopausal	83.5 vs 73.6 units/day	1.47 (1.04-2.08) Ptrend:0.01	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, energy Intake , family history, menopausal status, OC use, other anthropometric Index, other design Issue, parity/pregnancies	Diet in adolescence

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Higginbotham, 2004 BRE15353 USA	WHS, Prospective Cohort, Age: 45- years, W, Elderly	897/ 38 446 6.8 years	Partially histological - over 80%	FFQ-semi-quantitative	All breast cancers	Q5 vs Q1	1.01 (0.76-1.35) Ptrend:0.96	Age, age at first child, age at menarche, alcohol, BMI, energy from fat, energy Intake , family history, HRT use, OC use, other nutritional factors, other nutritional factors, parity/ pregnancies, physical activity , smoking habits	No measure of glycaemic index
		338/			Premenopausal		0.89 (0.67-1.17) Ptrend:0.39		
		559/			Postmenopausal		1.29 (0.92-1.81) Ptrend:0.06		
Cho, 2003b BRE01651 USA	NHS II, Prospective Cohort, Age: 26-46 years, W, Registered nurses	714/ 90 655 8 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, breast cancer, premenopausal	82 vs 70 units/day	1.05 (0.83-1.33) Ptrend:0.97	Age at first child, age at menarche, alcohol, benign breast disease, BMI, family history, height, menopausal status, nutrients, OC use, parity/pregnancies, smoking habits	Superseded by Farvid, 2015b

Figure 224 RR estimates of breast cancer by levels of dietary glycaemic index

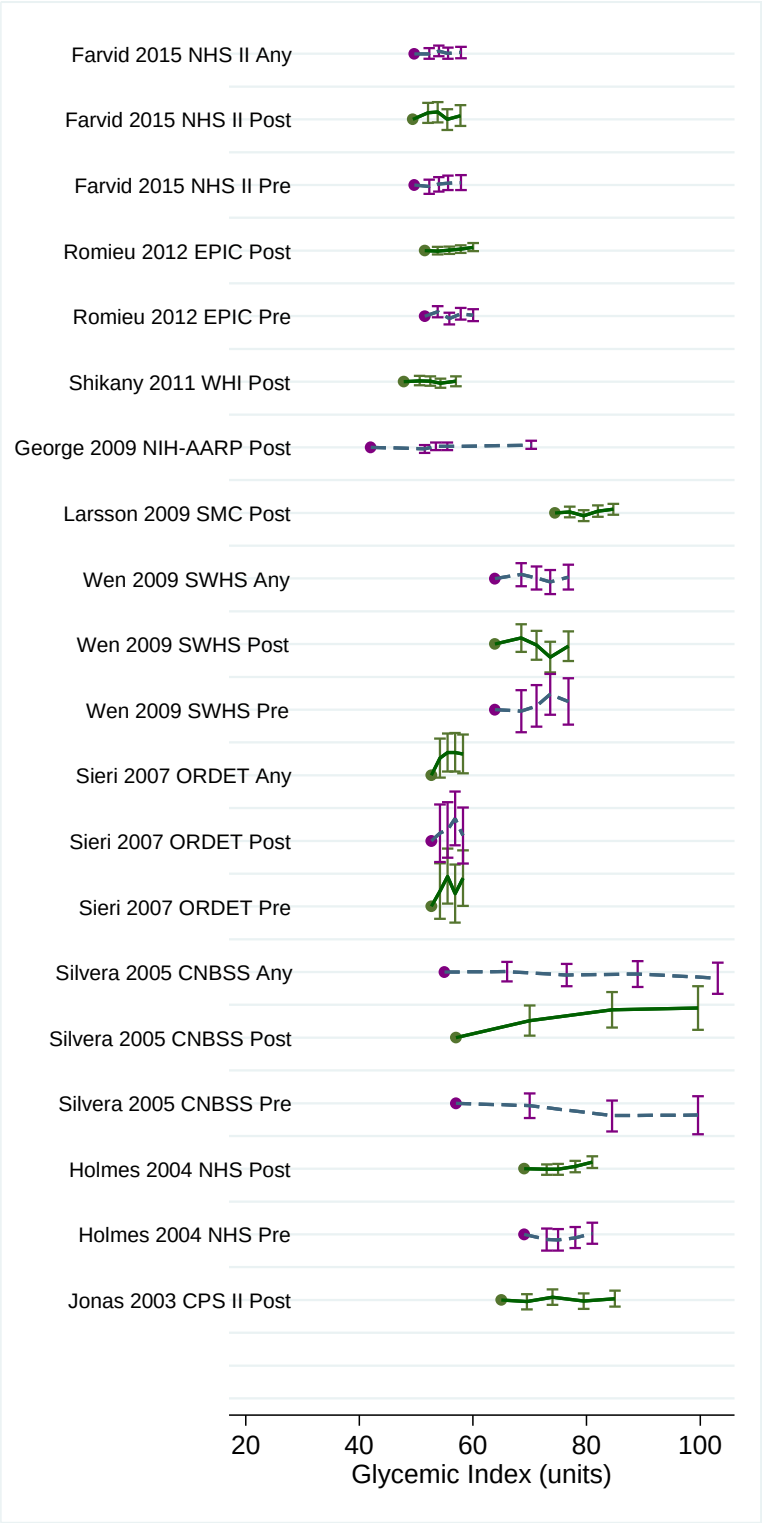


Figure 225 RR (95% CI) of breast cancer for the highest compared with the lowest diet glycaemic index score by menopausal status

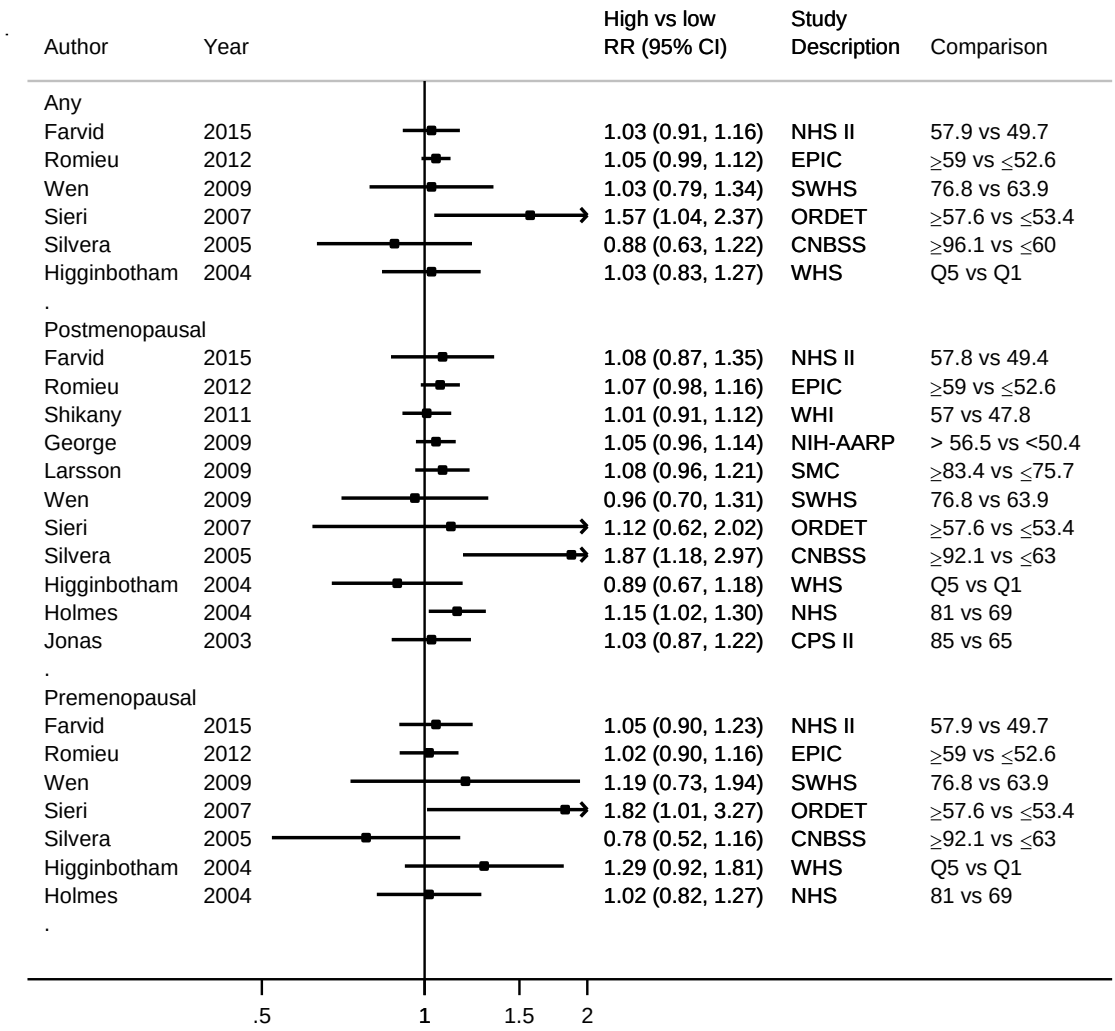
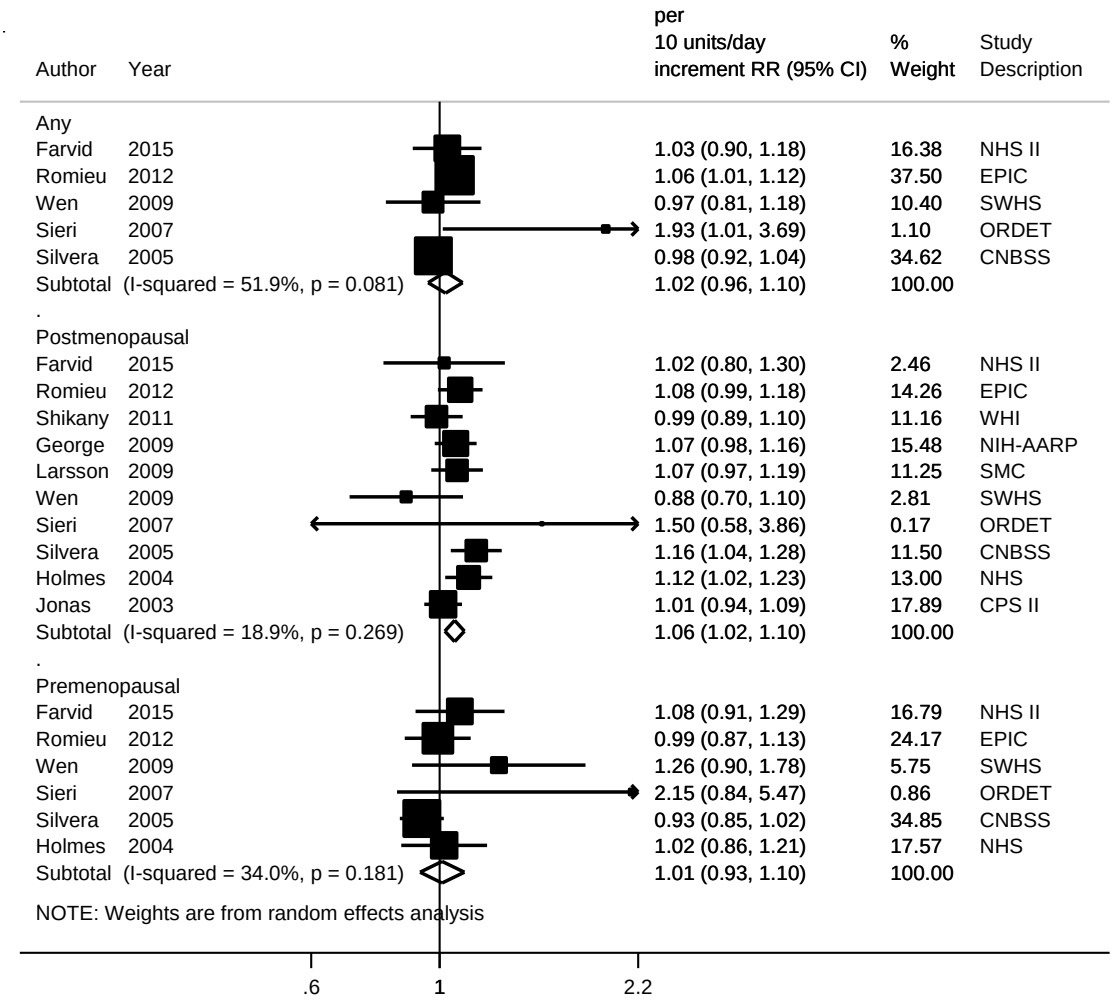


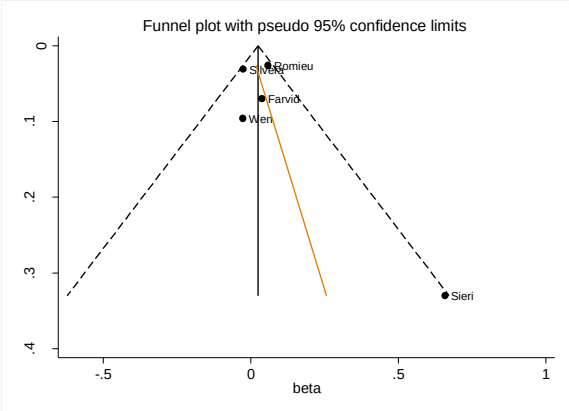
Figure 226 RR (95% CI) of breast cancer for 10 units/day increment of Glycaemic index by menopausal status



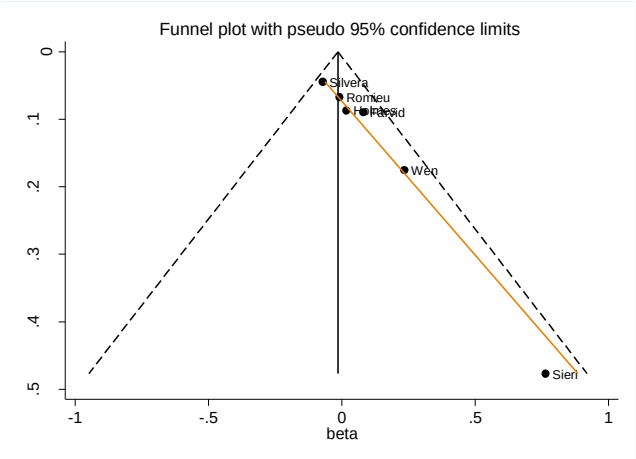
Note: Not included in the figure, in Giles, 2006 RR for 1 SD = 0.98 (0.88-1.10)

Figure 227 Funnel plot of studies included in the dose response meta-analysis of diet glycaemic index and breast cancer

Any breast cancer



Premenopausal breast cancer



Postmenopausal breast cancer

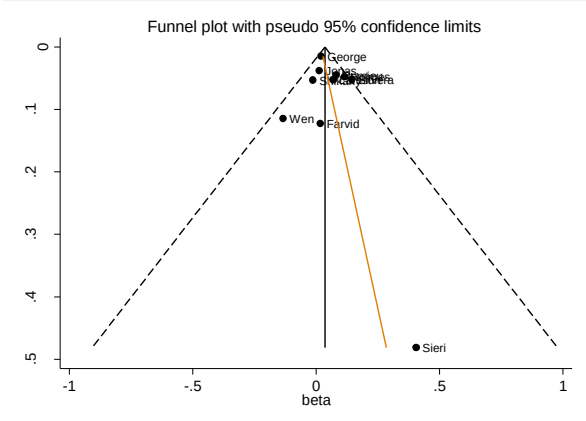
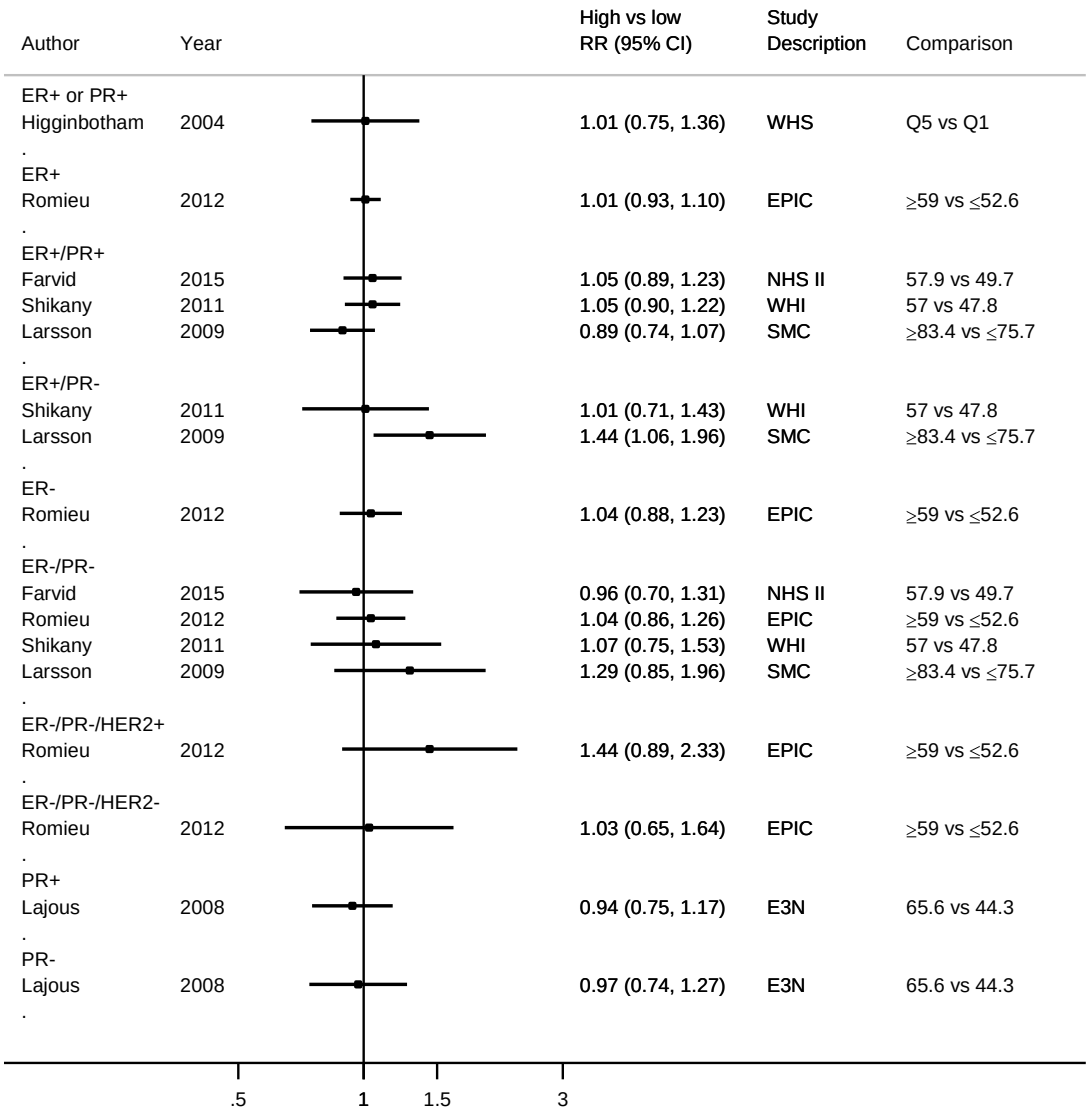


Figure 228 RR (95% CI) of breast cancer for the highest compared with the lowest level of diet glycaemic index by hormone receptor status



Note: not shown in the figure: MCS (Giles, 2006), the RR for 1 SD increment were 0.91 (95% CI 0.77-1.07) for ER+/PR+ breast cancer, 0.80 (95% CI 0.57-1.12) for ER+/PR- and 0.98 (95% CI 0.74-1.29) for ER-/PR- breast cancer (p test heterogeneity=0.65).

5.1.5.2 Glycaemic Load

Cohort studies

Overall summary

Sixteen publications from 12 cohort studies on diet glycaemic load score (GL) and breast cancer risk were identified. From the 16 publications, three publications (EPIC Italy, Sieri, 2013; E3N, Lajous, 2008 and DCH, Nielsen 2005) are not counted among the 12 cohort studies as these are from cohorts that participated in EPIC (Romieu, 2012) , which is counted as one cohort study. Dose-response meta-analyses were conducted for studies that reported associations with pre- and postmenopausal breast cancers combined (Any breast cancer), premenopausal breast cancers (Pre) and postmenopausal breast cancers (Post). Only a few studies investigated the association of glycaemic load and breast cancer by cancer hormone receptor status, and dose-response meta-analysis was not conducted.

Table 157 Glycaemic load and breast cancer. Number of studies in the CUP SLR by analysis

Analysis	Number
Studies identified Total	12 (16 publications)
Studies included in forest plot of highest compared with lowest GL	
Any breast cancer	6
Premenopausal	7
Postmenopausal	10
Studies included in linear dose-response meta-analysis	
Any breast cancer	6
Premenopausal	7
Postmenopausal	10

Table 158 Summary of results of the dose-response meta-analyses on glycaemic load and breast cancer risk in the CUP SLR (no meta-analysis of cohort studies in 2005 SLR)

	CUP SLR		
	Any breast cancer	**Pre-menopausal breast cancer**	**Post-menopausal breast cancer**
Increment unit	Per 50 units/day		
Studies (n)	6	7	10
Cases	17767	22573	37846
RR (95%CI)	1.02 (0.93-1.11)	1.07 (0.92-1.24)	1.02 (0.99-1.06)
Heterogeneity (I^2, p-value)	58.7, 0.03	71.8%, 0.0002	3.2%, p=0.41
P value Egger test	0.43	0.01	0.94

Breast cancer (any)

Six studies on glycaemic load intake and risk of any breast cancer were identified. All studies reported the data needed for dose-response meta-analysis. No association was observed. High heterogeneity was observed mainly due to the results of the Italian ORDET study (Sieri, 2007).

Two cohort studies, EPIC Italy (Sieri, 2013) and E3N (Lajous, 2008) participating in EPIC were not included in the counts as separated studies, and were not included in the dose-response meta-analysis.

There was no statistical evidence of publication bias. Only six studies were included in the analysis and the funnel plot shows asymmetry driven by the ORDET study (Sieri, 2007).

Premenopausal breast cancer

Seven studies on premenopausal breast cancer were identified. All were included in the dose-response meta-analysis. No association was observed. There was high heterogeneity driven by the Italian ORDET study (Sieri, 2007) and a study in Chinese women (Wen, 2009) that reported significant increases in breast cancer risk in premenopausal women with increasing levels of dietary glycaemic load score (Note: the Chinese study also investigated carbohydrate intake and found a positive association, see corresponding section).

There is statistical evidence of small study bias (p=0.01)

Postmenopausal breast cancer

Eleven studies were identified and ten studies could be included in the dose-response meta-analysis. No association was observed. The study excluded from the meta-analysis (Giles, 2006, Australia) reported a positive non-significant dose-response relationship (RR for one SD increment=1.19 (95% CI 0.93-1.52).

There was low heterogeneity and no significant evidence of publication bias.

Breast cancer by hormone receptor status

Seven studies reported on the association of glycaemic load and breast cancer by hormone receptor status. There were maximum two studies in each subgroup investigated and no dose-response meta-analysis was conducted. The relative risk for the highest compared to the lowest level of glycaemic load are shown in a figure. Overall, no significant associations with breast cancer subgroups defined by hormone receptor status were observed with the exception of a study in postmenopausal Swedish women (Larsson, 2009c) in which there was a significant positive association for ER+/PR- breast cancers.

Sensitivity analyses:

Subgroup and sensitivity analyses were not conducted due to low number of studies

Non-linear dose-response meta-analysis:

Not conducted due to low number of studies

Study quality:

No issues relevant to study quality were identified in the studies included in the dose-response meta-analysis. In two studies (Sieri, 2007; Wen, 2009) the number of premenopausal breast cancer cases was below 200 cases and the associations were stronger than in all studies on average.

The studies used published tables to derive glycaemic load. In most studies each unit of dietary insulin load indicates the equivalent amount of insulin produced by 1 kcal of glucose.

In two studies the equivalent was for 1 kcal of white bread (Holmes, 2004; Larsson, 2009c). Ranges of intake are overlapping across studies.

Most studies investigated invasive breast cancer as outcome. In situ breast cancers were included in five studies, but the number of these cases was in general low (Jonas, 2003; Holmes, 2004; Higginbotham, 2004; Larsson, 2009c; Shikany, 2011). The WHI study (Shikany, 2011) was the only study that reported for in situ and invasive cancers. The RR for the highest compared to the lowest dietary glycaemic load were 1.40 (95% CI 0.94–2.13) p trend= 0.07 for in situ breast cancer, 1.02 (95% CI 0.84–1.23) p trend= 0.77 for invasive and 1.08 (0.92–1.29) p trend= 0.27 for all breast cancer. The RRs for all breast cancers in this study were included in the dose-response meta-analysis. In the WHS (Higginbotham, 2004) the RR for the highest compared to the lowest quintile was 0.96 (95% CI 0.70–1.33; *P* for trend = 0.63) when the analyses were restricted to invasive cancers. Follow-up was through cancer registries or active follow-up with medical confirmation and there was no report of important losses to follow-up.

All studies adjusted for main confounders.

Two studies were in populations recruited through cancer screenings (Silvera, 2005; Larsson, 2009c). On study included participants in randomized controlled trials and an observational study (WHI, Skihany, 2011). There was no difference in cumulative incidence of breast cancer in the groups in trial or observational study, and the associations in the paper are for all women combined.

Diet glycaemic load during adolescence and breast cancer risk during adulthood

Glycaemic load of the diet during adolescence was not significantly related to breast cancer incidence in the Nurses' Health Study II (Linos, 2010; Frazier, 2004). A number of 39,268 premenopausal women aged 34 to 53 years completed a 124-item food frequency questionnaire on their diet during high school in 1998; 455 incident cases of invasive breast cancer were diagnosed up to 2005. The multivariable-adjusted RR for the highest compared to the lowest quintile of diet glycaemic load was 0.89 (95% CI 0.66-1.20) p trend=0.33 (Linos, 2010).

Table 159 Glycaemic load and breast cancer risk. Main characteristics of studies included in linear dose-response meta-analyses.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Farvid, 2015b BRE80569 USA	NHS II, Prospective Cohort, Age: 27-44 years, W	2 833/ 90 488 20 years	Self-reported/death certificate/ medical records	FFQ (Diet at early adulthood-baseline)	Incidence, Invasive breast cancer	148.6 vs 95.6	0.94 (0.84-1.07) Ptrend:0.31	Age, age at menarche, age at menopause, alcohol intake, benign breast disease, BMI at age 18 years, weight gain since 18, height, energy intake, family history of breast cancer, HRT use, oral contraceptive use, menopause status, parity and age at first birth, race, smoking	All data available
		1 547/			Premenopause	148.6 vs 95.6	0.93 (0.79–1.09) Ptrend:0.37		
		919/			Postmenopause	147.8 vs 94.1	0.95 (0.76–1.18) Ptrend:0.86		
Romieu, 2012 BRE80418 Denmark,France ,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	11 576/ 334 849 11.5 years	Cancer and pathology registry, active follow up, health Insurance record, mortality registry and contact of participants or next-of-kin	FFQ, diet history, 7-day food diary (depending on the cohort)	Incidence,all breast cancers	≥137.9 vs ≤101.7	1.07 (1.00-1.14) Ptrend:0.110	Age at first child birth, age at menarche, age at menopause, alcohol Intake, educational level, energy Intake, ever used contraceptive pills, ever used hormones, fibre Intake, height, menopausal status, physical	Midpoints of GL categories for pre-and postmenopausal cancers
						per 25 score	1.01 (0.99-1.04)		
		2 827/			Premenopause	≥137.9 vs ≤101.7	1.04 (0.91-1.20) Ptrend:0.843		
		5 872/			Postmenopause		1.09 (0.99-1.20) Ptrend:0.093		
		493/			Postmenopause ER-/PR-		1.48 (1.07-2.05) Ptrend:0.010		
		1 053/			All, ER-/PR-		1.17 (0.94-1.46) Ptrend:0.111		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		658/			Postmenopause ER-		1.36 (1.02-1.82) Ptrend:0.012	activity, smoking status, study centre, weight	
		1 443/			All, ER-		1.16 (0.96-1.41) Ptrend:0.047		
		3 004/			Postmenopause ER+		1.00 (0.87-1.14) Ptrend:0.840		
		5 823/			All, ER+		1.01 (0.92-1.11) Ptrend:0.657		
		176/			All, ER-/PR-/HER2+		1.48 (0.87-2.52) Ptrend:0.075		
		224/			All, ER-/PR-/HER2-		1.35 (0.83-2.19) Ptrend:0.251		
Shikany, 2011 BRE80382 USA	Women's Health Initiative, Follow-up of RCT and observational study (OS), Age: 50-79 years, W, Postmenopausal	6 098/ 148 767 8 years	Self-report verified by medical record	FFQ	Incidence, breast cancer	150.4 vs 52.9	1.08 (0.92-1.29) Ptrend:0.27	Age, age at first child birth, age at menarche, age at menopause, alcohol, BMI, educational level, energy intake, ethnicity, family history of breast cancer, hormone use, HRT use, mammogram in the past 2 years, parity, oral contraceptive use, physical activity, smoking, trial assignment	
							1.05 (0.97-1.13) Ptrend:0.27		
		1 162/			Incidence, in situ breast cancer		1.40 (0.94-2.13) Ptrend:0.07		
					Incidence, invasive breast cancer		1.02 (0.84-1.23) Ptrend:0.77		
		3 016/			All, ER+/PR+		0.81 (0.63-1.04) Ptrend:0.07		
		664/			All, ER+/PR-		0.60 (0.33-1.09) Ptrend:0.14		
		616/			All, ER-/PR+		1.68 (0.93-3.02) Ptrend:0.07		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
George, 2009b BRE80456 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, Postmenopausal women	5 478/ 183 535 6.89 years	Linkage with 11 state cancer registry databases	Validated FFQ	Incidence, breast cancer	135.31-583.68 vs 4.61-66.91	0.96 (0.81-1.12) Ptrend:0.495	Age, alcohol consumption, BMI, educational level, ethnicity, family history of cancer, marital status, menopausal oestrogen use, physical activity, smoking, total energy Intake	Midpoints of categories, cases and person-years per quintile
Larsson, 2009c BRE80248 Sweden	SMC, Prospective Cohort, Age: 54 years, Postmenopausal women	2 952/ 61 433 17.4 years	Cancer registry	FFQ	Incidence, breast cancer	≥200 vs ≤163	1.13 (1.00-1.29) Ptrend:0.05	Age, age at first child birth, age at menarche, age at menopause, alcohol intake, BMI, height, dietary fibre, educational level, family history of cancer, HRT use, OC use, parity, total energy intake	Midpoints of categories, person-years per quintile
		1 286/			ER+/PR+		0.94 (0.77-1.13) Ptrend:0.59		
		417/			ER+/PR-		1.81 (1.29-2.53) Ptrend:0.0008		
		266/			ER-/PR-		1.23 (0.79-1.90) Ptrend:0.45		
Wen, 2009 BRE80209 China	SWHS, Prospective Cohort, Age: 40-70 years, W	616/ 73 328 7.35 years	Cancer registry	Quantitative FFQ	Incidence, Invasive & In situ breast cancer	239.4 vs 163.8	1.07 (0.82-1.39) Ptrend:0.552	Age, age at first child birth, benign breast disease, BMI, educational level, energy	Cases and person-years per quintile
		190/			Premenopausal	239.4 vs 163.8	1.53 (0.96-2.45) Ptrend:0.008		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		426/			Postmenopausal	239.4 vs 163.8	0.91 (0.67-1.25) Ptrend:0.291	intake, family history of cancer, physical activity	
Sieri, 2007 BRE80142 Italy	ORDET, Prospective Cohort, Age: 34-70 years	289/ 8 926 11.5 years	Cancer registry	Semi-quantitative FFQ	Incidence, Invasive & In situ breast cancer	≥133.8 vs ≤103.2	2.53 (1.54-4.16) Ptrend:0.001	Age, age at menarche, alcohol intake, educational level, energy intake, fibre Intake, height, parity, oral contraceptive use, saturated fat intake, smoking status, weight	Midpoints of exposure and person-years per quintile
		146/			Premenopausal		3.89 (1.81-8.34)		
		128/			Postmenopausal		1.67 (0.80-3.46)		
Silvera, 2005 BRE24119 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W, Screening Program	1 450/ 49 111 16.6 years	Cancer registry + death certificate	FFQ	Incidence, breast cancer	≥175.1 vs ≤119	0.95 (0.79-1.14) Ptrend:0.70	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, energy intake , family history, mammography, menopausal status, OC use, HRT use, other nutritional factors, parity/pregnancies, recruitment center	For pre- and postmenopausal, distribution of cases and person-years per quintile
					Premenopausal	≥169.1 vs ≤125	0.96 (0.76-1.22) Ptrend:0.44		
					Postmenopausal	≥169.1 vs ≤125	1.08 (0.82-1.41) Ptrend:0.68		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Higginbotham, 2004 BRE15353 USA	WHS, Prospective Cohort, Age: 45- years, W, Elderly	897/ 38 446 6.8 years	Partially histological - over 80%	FFQ-semi-quantitative	All breast cancers	143 vs 92	1.01 (0.76-1.35) Ptrend:0.96	Age, age at first child, age at menarche, alcohol, BMI, energy from fat, energy Intake , family history, HRT use, OC use, other nutritional factors, other nutritional factors, parity/ pregnancies, physical activity , smoking habits	Cases and person-years per quintile
		338/			Premenopausal		1.27 (0.79-2.03) Ptrend:0.27		
		559/			Postmenopausal		0.90 (0.63-1.31) Ptrend:0.40		
Holmes, 2004 BRE04010 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	2 924/ 88 678 18 years	Medical records + self-reported	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	186 vs 116	1.03 (0.90-1.16) Ptrend:0.51	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, energy intake , family history, height, HRT use, menopausal status, parity/ pregnancies	Cases and person-years per quintile
		852/			Premenopausal		0.87 (0.70-1.12) Ptrend:0.26		
Jonas, 2003 BRE04456 USA	CPS II, Prospective Cohort, Age: 50-74 years,	1 442/ 70 888 5 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	147 vs 83	0.90 (0.76-1.08) Ptrend:0.679	Age , age at first child, age at menarche, age at menopause, alcohol,	Q2 and Q4 score estimated as midpoints of medians of adjacent

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	W, Postmenopausal							anthropometry, anthropometry, benign breast disease, BMI, educational level, energy Intake , ethnicity, family history, height, HRT use, OC use, other hormonal variables, parity/pregnancies, physical activity , smoking habits	quintiles

Table 160 Glycaemic load and breast cancer risk. Main characteristics of studies excluded from linear dose-response meta-analyses.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Sieri, 2013 BRE80408 Italy	EPIC-Italy, Prospective Cohort, Age: 50 years,	879/ 26 066 11 years	Cancer registry	FFQ	Incidence, breast cancer	190 vs 120	1.45 (1.06-1.99) Ptrend:0.029	Age at menarche, alcohol, BMI, educational	Included in EPIC (Romieu, 2012)

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	W	391/			Premenopause	196 vs 125	1.39 (0.87-2.22) Ptrend:0.109	level, parity, menopausal status, non-alcohol energy, recreational activity, intakes of saturated fat, fibre smoking, sport, work - physical activity	
		419/			Postmenopause	184 vs 114	1.53 (0.96-2.43) Ptrend:0.085		
Linos, 2010 BRE80298 USA	NHS II, Prospective Cohort, Age: 34-53 years, W, Premenopausal	455/ 39 268 7.8 years	Follow up questionnaires, medical records	Semi-quantitative FFQ	Incidence, Invasive breast cancer	203 vs 142	0.89 (0.66-1.20) Ptrend:0.33	Age, age at first child birth, age at menarche, alcohol consumption, benign breast disease, BMI, energy Intake, family history of cancer, menopausal status, OC use, parity, weight gain	Diet in adolescence
Lajous, 2008 BRE80218 France	E3N EPIC-France, Prospective Cohort, Age: 42-72 years, W, Postmenopausal	1 812/ 62 739 9 years	Cancer registry	Dietary history	Incidence, breast cancer, postmenopausal	165 vs 84	1.11 (0.96-1.29) Ptrend:0.14	Age, age at menarche, age at menopause, alcohol consumption, benign breast disease, BMI, breastfeeding, educational	Included in EPIC (Romieu, 2012)
							1.08 (0.95-1.23) Ptrend:0.24		
		1 083/			ER+, postmenopausal		0.91 (0.75-1.11) Ptrend:0.37		
		279/			ER-,		1.55 (1.07-2.25)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					postmenopausal		Ptrend:0.03	level, family history of cancer, fibre Intake, folate Intake, follow-up time, height, HRT use, mammography, OC use, parity, physical activity, residence, total energy intake, vitamin use	
		814/			PR+, postmenopausal		0.94 (0.75-1.17) Ptrend:0.47		
		511/			PR-, postmenopausal		1.16 (0.88-1.54) Ptrend:0.21		
					ER-/PR-, postmenopausal		1.71 (1.13-2.57) Ptrend:0.01		
Giles, 2006 BRE22430 Australia	MCCS, Prospective Cohort, Age: 40-69 years, W, Postmenopausal	12 273 9.1 years	Pathology report + cancer registry	FFQ	Incidence, breast cancer, postmenopausal	per 1 sd score	1.19 (0.93-1.52)	Age , energy intake , HRT use, place of residence	GL not expressed in g/d
					ER+/PR+, postmenopausal		1.11 (0.78-1.59)		
					ER+/PR-, postmenopausal		1.32 (0.60-2.90)		
					ER-/PR-, postmenopausal		0.81 (0.46-1.44)		
Nielsen, 2005 BRE23581 Denmark	DCH, Prospective Cohort, Age: 50-65 years, W, Postmenopausal	23 870 6.6 years	All histology	FFQ	Incidence, breast cancer, postmenopausal	per 100 score	1.04 (0.90-1.19)	Alcohol, BMI, educational level, HRT use, parity/pregnancies	Included in EPIC
					ER+, postmenopausal		0.99 (0.84-1.17)		
					ER-,		1.17 (0.86-1.59)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					postmenopausal				
Frazier, 2004 BRE02942 USA	NHS II, Historical Cohort, Age: 34-51 years, W, Registered nurses	361/ 47 355 9 years	All histology	FFQ	Incidence, breast cancer, premenopausal	289 vs 202	1.23 (0.91-1.67) Ptrend:0.14	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, energy Intake , family history, menopausal status, OC use, other anthropometric Index, other design Issue, parity/pregnancies	Diet in adolescence
Cho, 2003b BRE01651 USA	NHS II, Prospective Cohort, Age: 26-46 years, W, Registered nurses	714/ 90 655 8 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, breast cancer, premenopausal	211 vs 138	1.06 (0.78-1.45) Ptrend:0.96	Age at first child, age at menarche, alcohol, benign breast disease, BMI, family history, height, menopausal status, nutrients, OC use, parity/pregnancies, smoking habits	Superseded by Farvid, 2015b

Figure 229 RR estimates of breast cancer by levels of dietary glycaemic load

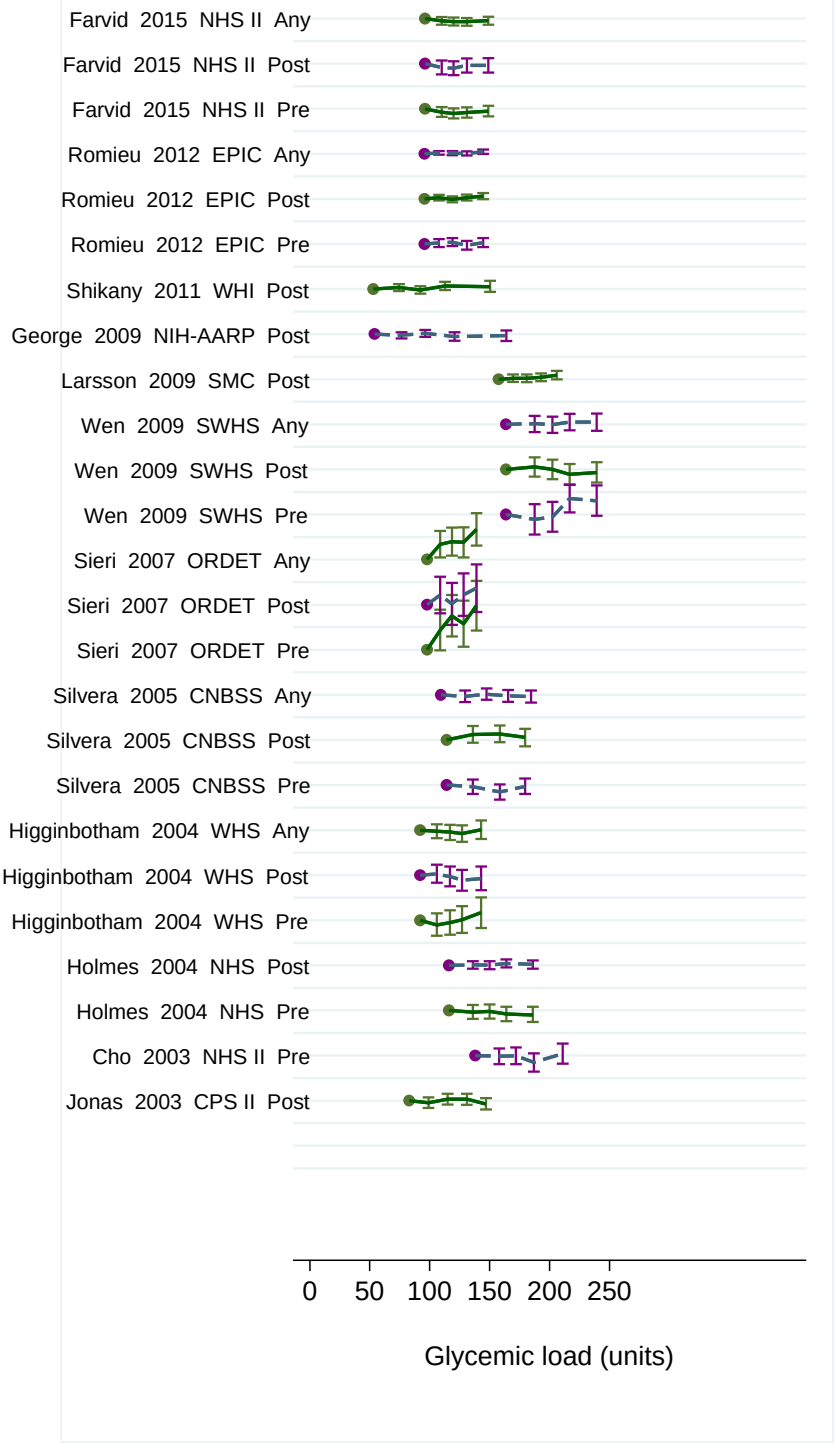


Figure 230 RR (95% CI) of breast cancer for the highest compared with the lowest diet glycaemic load score by menopausal status

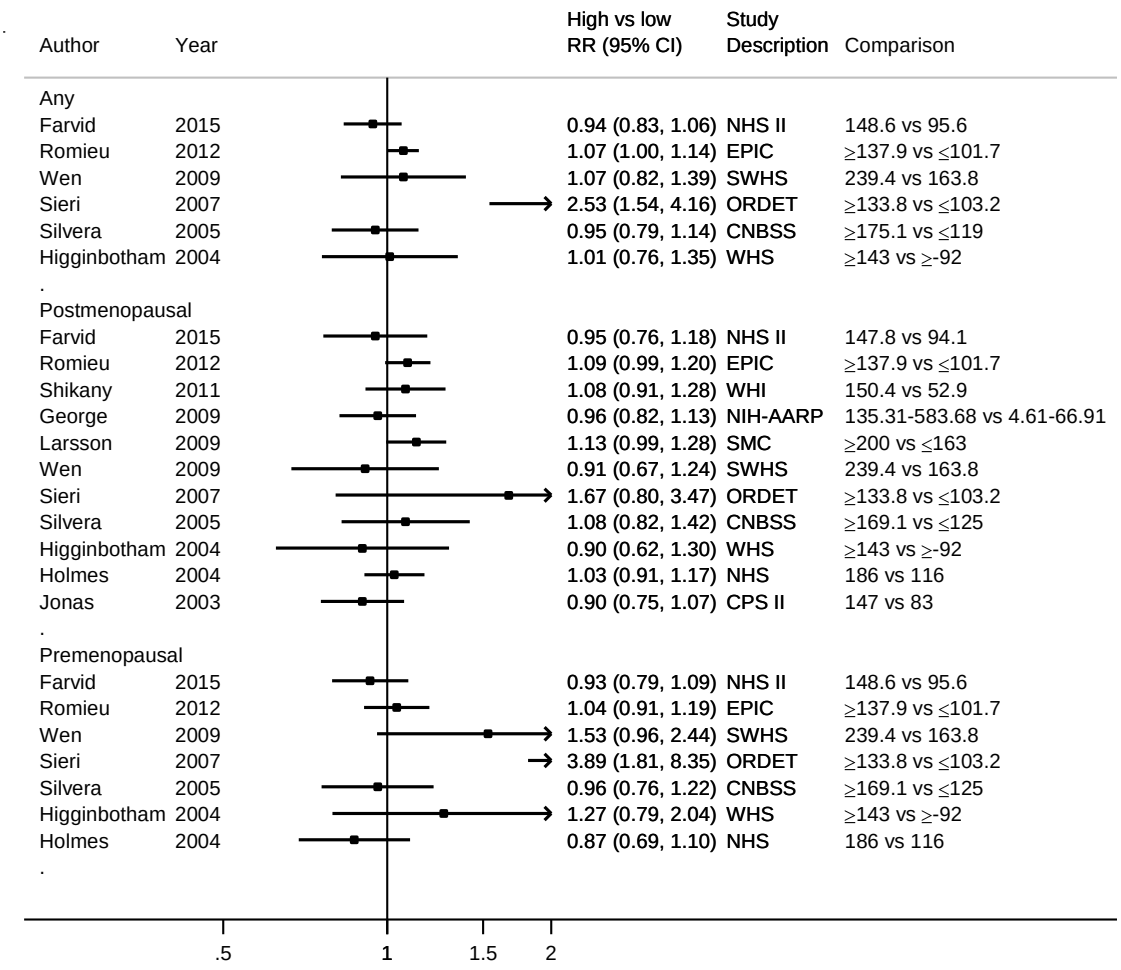
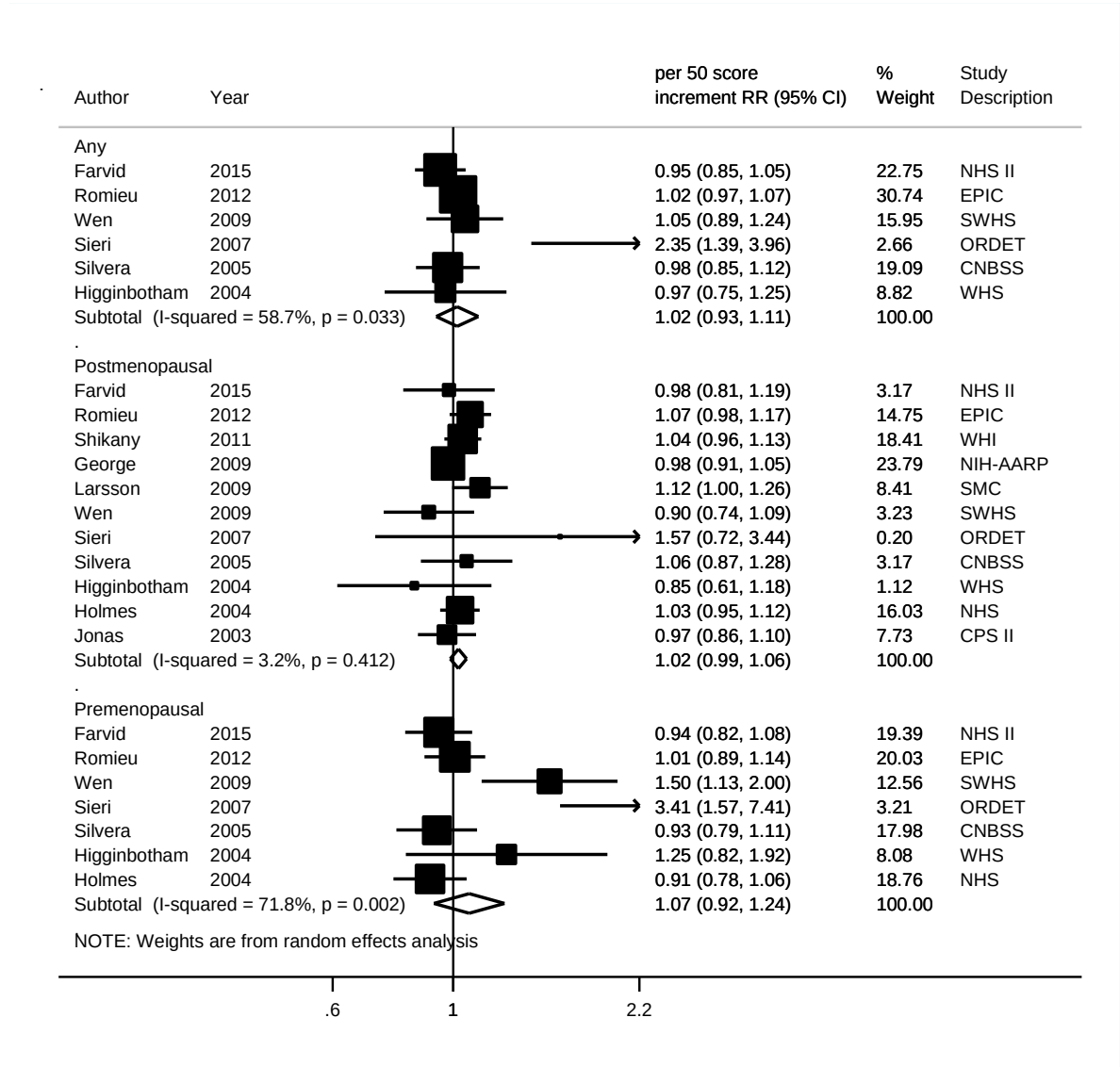


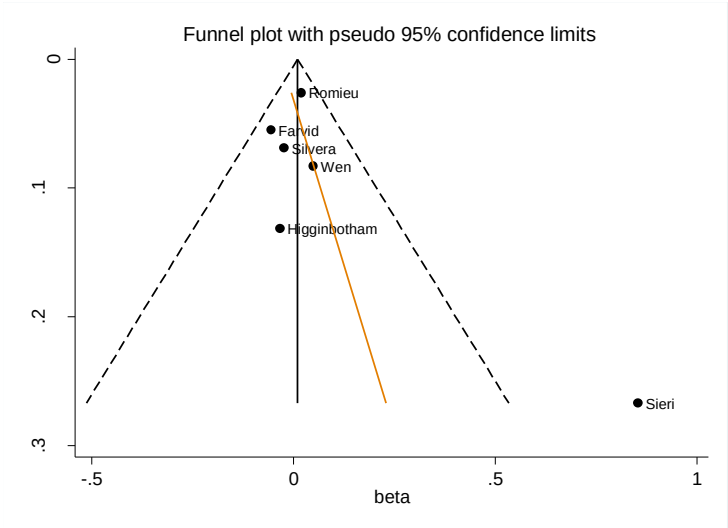
Figure 231 RR (95% CI) of breast cancer for 50 g/day increment by menopausal status



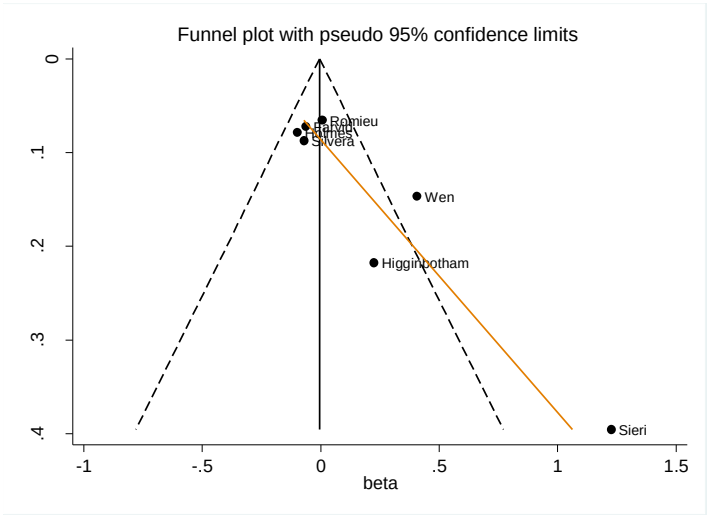
Note: Not included in the figure, in Giles, 2006 RR for 1 SD = 1.08 (0.92–1.29) p trend= 0.27

Figure 232 Funnel plot of studies included in the dose response meta-analysis of diet glycaemic load and breast cancer

Any breast cancer



Premenopausal breast cancer



Postmenopausal breast cancer

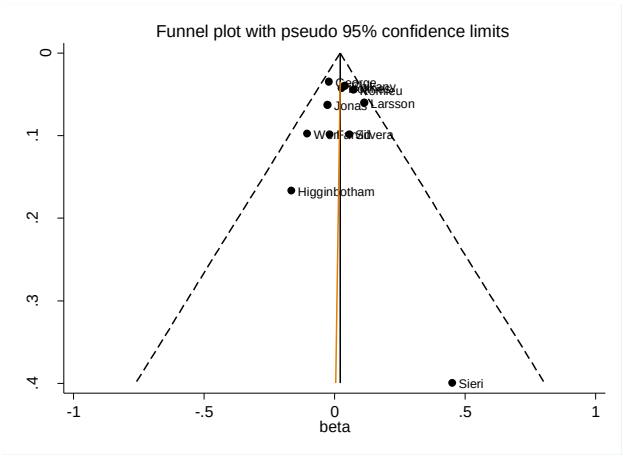
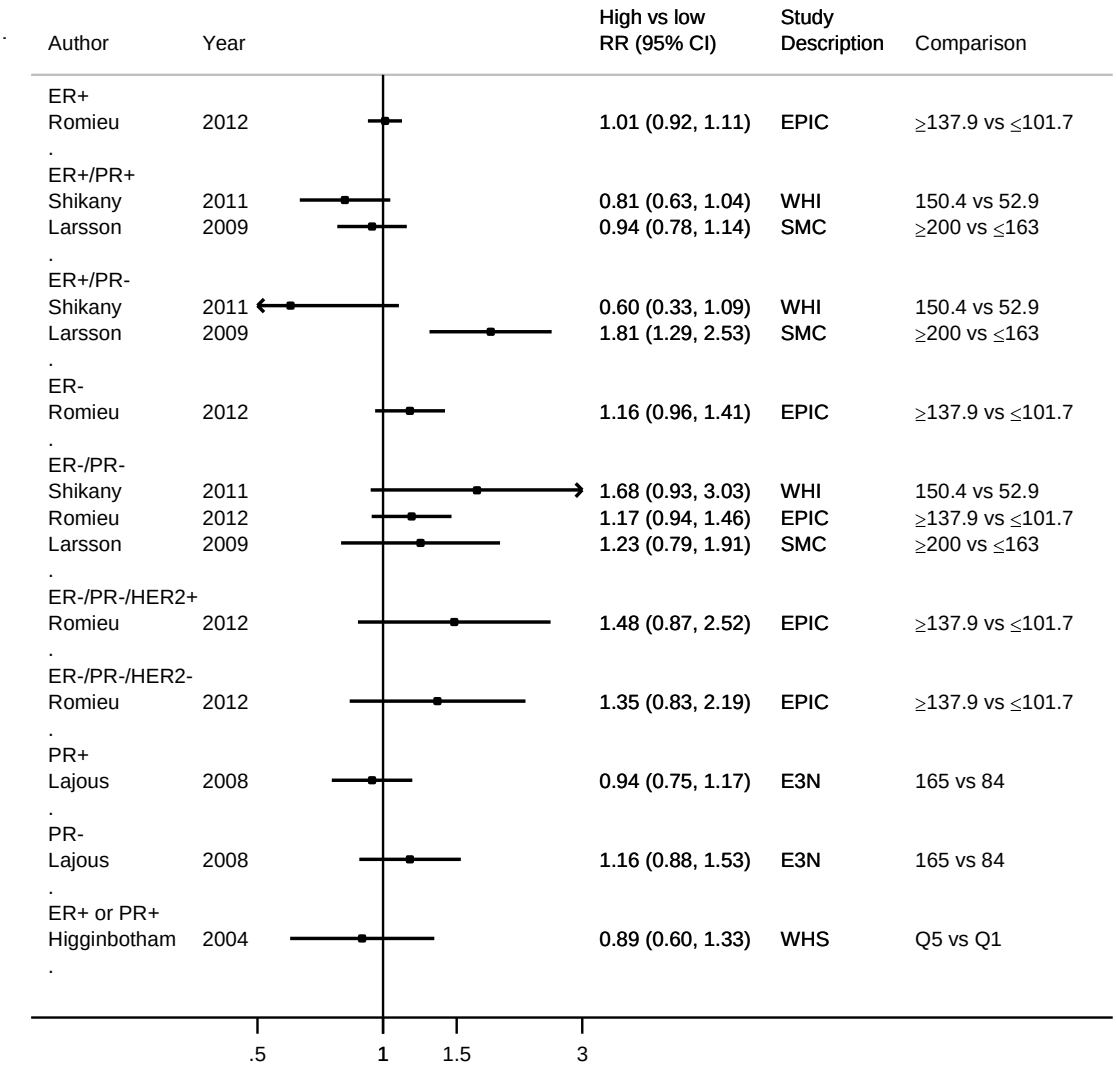


Figure 233 RR (95% CI) of breast cancer for the highest compared with the lowest level of diet glycaemic load by hormone receptor status



Note: not shown in the figure: MCS (Giles, 2006), the RR for 1 SD increment were 1.11 (95% CI 0.78-1.59) for ER+/PR+ breast cancer, 1.32 (95% CI 0.60-2.90) for ER+/PR- and 0.81 (95% CI 0.46-1.44) for ER-/PR- breast cancer (p test heterogeneity=0.55).

5.2.1 Total fat

7.1.0.1 Energy from fat

Randomised control trials

Five publications from two dietary interventional trials – Women's Health Initiative-Dietary Modification Trial (WHI DM trial) (Thomson, 2014a; Caan, 2009; Prentice, 2007; Prentice, 2006) and Canadian Diet and Breast Cancer Prevention Trial (CDBCP trial) (Martin, 2011), that comprised a low-fat diet were identified (see section 1.4 Low fat diet).

Cohort studies

Overall summary

Studies that measured total fat as an absolute intake (g/day) or as a relative intake expressed as a percentage of the total energy intake (% of energy) was considered together to facilitate a comprehensive review.

Fifty-one publications from 34 studies that examined total fat intake and/or percentage of energy from fat were identified. Three pooled analyses, two from the Pooling Project (Smith-Warner, 2001b, eight cohorts; Hunter, 1996, seven cohorts) and one from the UK Dietary Cohort Consortium (Key, 2011, four cohorts) were identified.

Dose-response meta-analyses were conducted to examine the associations of total fat intake (per 20g/day and per 5 % of energy) with risk of breast cancer and postmenopausal breast cancer.
Notes on method:

Models adjusted for total energy intake were selected, which represents an increase in total fat intake while keeping the total energy intake constant. If studies provided results both from the food diaries and the FFQs, results from the food diaries were used.

Table 161 Summary of results of the dose-response meta-analysis in the CUP SLR

	Breast cancer	**Premenopausal breast cancer**	**Postmenopausal breast cancer**
Total fat intake Increment unit used	Per 20g/day	Per 20g/day	Per 20g/day
Studies (n)	12[1]	1	17[1,3]
Cases	16 404	432	9 612
RR (95%CI)	1.02 (0.97-1.07)	1.12 (0.92-1.39)	1.08 (1.00-1.17)
Heterogeneity (I^2, p-value)	27%, 0.23	-	65%, 0.01
P value Egger test	0.85	-	0.69
Percentage of energy from fat Increment unit used	Per 5% of energy	Per 5% of energy	Per 5% of energy

Studies (n)	13[2]	2	10[3]
Cases	17 807	1 511	12 547
RR (95%CI)	1.01 (0.99-1.02)	1.01 (0.97-1.05)	1.00 (0.97-1.03)
Heterogeneity (I^2, p-value)	0%, 0.63	0%, 0.44	61%, 0.02
P value Egger test	0.50	-	0.71

[1]Included the Pooling Project (Hunter, 1996, seven cohorts).
[2]Included the Pooling Project (Smith-Warner, 2001b, eight cohorts).
[3]Included the UK Cohort Consortium (Key, 2011, four cohorts).

Breast cancer

Summary

Main results:

Twelve out of 23 studies (23 publications) on total fat intake and thirteen out of 19 studies (11 publications) on percentage of energy from fat could be included in the dose-response meta-analyses, respectively.

There was no significant association for total fat, as intake or percentage of energy, and breast cancer risk (summary RR per 20g/day=1.02, 95% CI=0.97-1.07; summary RR per 5% of energy=1.01, 95% CI=0.99-1.02, respectively), with low heterogeneity between studies (I^2=27%, P=0.23; I^2=0%, P=0.63, respectively).

There was no evidence of significant publication or small studies bias (P for Egger's test=0.85 and 0.50, respectively).

Eleven and six studies were excluded from the analysis of total fat intake and percentage of energy from fat, respectively. In six studies on total fat and percentage of energy (Key, 2011, four cohorts; Thiebaut, 2001; Byrne, 1996), the study populations overlapped with other studies that were already included in the analyses. Three studies on total fat intake (Martin, 2011; Horn-Ross, 2002; Toniolo, 1994) did not provide sufficient data for analysis. Non-significant inverse (Horn-Ross, 2002) and positive (Martin, 2011; Toniolo, 1994) associations were reported.

Two studies (Kinlen, 1982; Iso, 2007) were on breast cancer mortality. A non-significant inverse association was reported for those who modified their total fat intake according to medical advice compared with those who did not (Iso, 2007) and an inverse association (95% CI or P-value not reported) for high fat intake and standardised mortality ratio was observed in non-meat eating women of five enclosed religious orders compared with the general publication (Kinlen, 1982).

Four studies reported results by hormone receptor status, which were displayed in the highest compared with the lowest forest plot. Total fat intake was positively associated with ER-positive (Sieri, 2014; Martin, 2011) and ER+PR+ or ER+PR- (Sieri, 2014; Kushi, 1995) breast cancers (RR estimates ranged from 1.05 to 1.27); and inversely associated with ER-

negative (Sieri, 2014; Martin, 2011) and ER-PR- (Sieri, 2014; Kushi, 1995) or ER-PR+ (Kushi, 1995) breast cancers (RR estimates ranged from 0.47 to 0.84).

Sensitivity analyses:

The summary RR became borderline significant when Jones, 1987 was omitted (summary RR per 20g/day=1.02, 95% CI=1.00-1.05; I^2=0%, P=0.63) in influence analysis, which could be influenced by EPIC (Sieri, 2014) that contributed 81% weight in the analysis excluding Jones, 1987 (graph not shown). The summary RR did not change materially when studies were omitted in turn in influence analysis of percentage energy from fat.

Subgroup analyses by geographic location, exposure assessment, and confounder adjustment mostly showed similar non-significant associations. For total fat intake, borderline significant positive associations were observed among the European studies and the studies that adjusted for main confounding factors. In these analyses, EPIC (Sieri, 2014) contributed 91% and 82% weight, respectively.

Non-linear dose-response meta-analysis:

There was no evidence of significant non-linear relationship between total fat intake or percentage of energy from fat and breast cancer risk (P for non-linearity=0.31 and 0.27, respectively) (graphs not shown).

Study quality:

Most studies were from North America or Europe. One study was from Japan (Wakai, 2005) and one of Singaporean Chinese (Gago-Dominguez, 2003). Most studies used FFQs to assess total fat intake. Other studies used dietary questionnaires (Knekt, 1990) or a 24-hour recall (Jones, 1987). EPIC (Sieri, 2014; Sieri, 2008) used different methods (FFQs, dietary questionnaires).

There is some suggestion that measurement errors may attenuate the association. EPIC (Sieri, 2014) showed a significant positive association when calibrated (dietary questionnaires against 24-hour dietary recalls) total fat intake data was used (RR per 20% increase of calibrated fat intake = 1.06, 95% CI=1.01-1.12 vs. RR for non-calibrated fat intake=1.02, 95% CI=1.00-1.04), although not for percentage of energy from fat (RR per 20% increase =1.04, 95% CI=0.98-1.09 vs. RR=1.02, 95% CI= 0.99-1.04, respectively) (Sieri, 2008); the RRs in the Pooling Project when corrected for measurement error was 1.07 (95% CI=0.86-1.34) per 25 g/day increase of fat intake (Hunter, 1996) and 1.03 (95% CI=0.97-1.08) per 5% of energy (Smith-Warner, 2001b); the consortium of four cohorts based in the UK (Key, 2011, UKDCC) observed non-significant associations using data from FFQs or food diaries; and on average, studies that used FFQs or other methods found similar non-significant results in the present review.

Case ascertainment was through cancer registries or confirmed through medical records. All studies were adjusted for age, BMI, alcohol intake, and reproductive factors, apart from Gaard, 1995 that did not adjust for any reproductive factors, and Knekt, 1990 and Jones, 1987 that did not adjust for alcohol consumption.

Table 162 Total fat intake and percentage of energy from fat and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	23 (23 publications) total fat intake 19 (11 publications) percentage of energy from fat
Studies included in forest plot of highest compared with lowest exposure	15 (9 publications) total fat intake 6 (6 publications) percentage of energy from fat
Studies included in linear dose-response meta-analysis	12 (6 publications) total fat intake 13 (6 publications) percentage of energy from fat
Studies included in non-linear dose-response meta-analysis	7 (7 publications) total fat intake 6 (6 publications) percentage of energy from fat

Note: Include cohort, and nested case-control designs

Table 163 Total fat intake and percentage of energy from fat and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR		**CUP**	
Increment unit used	**Per 20g/day**	**Per 5%**	**Per 20g/day**	**Per 5%**
Studies (n)	4	2	12[1]	13[2]
Cases	2 292	3 008	16 404	17 807
RR (95%CI)	1.01 (0.96-1.07)	0.96 (0.93-0.99)	1.02 (0.97-1.07)	1.01 (0.99-1.02)
Heterogeneity (I^2, p-value)	70%	0%	27%, 0.23	0%, 0.63
P value Egger test	-		0.85	0.50
Stratified analyses in the CUP				
Increment unit used	**Per 20g/day**	**Per 20g/day**	**Per 5% of energy**	**Per 5% of energy**	**Per 5% of energy**
Geographic location	**Europe**	**North America**	**Europe**	**North America**	**Asia**
Studies (n)	6	5	3	8	2
Cases	12 547	3 704	9 329	8 035	443
RR (95%CI)	1.02 (1.00-1.05)	1.01 (0.92-1.11)	1.01 (0.98-1.03)	1.01 (0.98-1.04)	0.99 (0.93-1.06)
Heterogeneity (I^2, p-value)	0%, 0.63	54%, 0.05	0%, 0.68	41%, 0.10	0%, 0.65

Increment unit used	**Per 20g/day**	**Per 20g/day**	**Per 5% of energy**	**Per 5% of energy**
Adjustment for age, BMI, alcohol intake, reproductive factors	**Adjusted**	**Not adjusted**	**Adjusted**	**Not adjusted**
Studies (n)	9	3	12	1
Cases	16 016	388	17 721	86
RR (95%CI)	1.02 (1.00-1.05)	1.02 (0.78-1.33)	1.01 (0.99-1.02)	0.95 (0.86-1.06)
Heterogeneity (I^2, p-value)	0%, 0.70	66%, 0.05	0%, 0.69	-
Exposure assessment methods	**FFQs**	**Other methods**	**FFQs**	**Other methods**
Studies (n)	13	3	15	2
Cases	6 859	10 202	11 259	7 205
RR (95%CI)	1.02 (0.97-1.08)	0.98 (0.85-1.13)	1.01 (0.99-1.03)	1.00 (0.97-1.04)
Heterogeneity (I^2, p-value)	2%, 0.38	55%, 0.11	0%, 0.50	14%, 0.28

[1]Included the Pooling Project (Hunter, 1996, seven cohorts).

[2]Included the Pooling Project (Smith-Warner, 2001b, eight cohorts).

Table 164 Total fat intake and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Turner, 2011	29 studies (1 pooled study of prospective studies, 18 cohorts*, 10 case-control studies)	31 201 any breast cancer	China, France, Germany, Greece, Italy, the Netherlands, USA, Uruguay, Singapore, Sweden	Incidecne, any breast cancer	Highest vs lowest total fat intake (52 studies)	1.01 (0.99-1.03) Ptrend: >0.05	-
					Cohort studies (n=25)	1.01 (0.99-1.03) Ptrend: >0.05	-
					Case-control studies (n=27)	1.07 (0.99-1.15) Ptrend: 0.08	-

*All cohort studies identified were included in the present review

Table 165 Total fat intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Sieri, 2014 BRE80546 France, Italy, Spain, UK, Netherlands, Greece, Germany, Sweden, Denmark,	EPIC, Prospective Cohort, Age: 20-70 years, W	10 062/ 337 327 11.5 years	Cancer and mortality registries, health Insurance & pathology records, active follow up	FFQ, diet history, 7-day food diary	Incidence, breast cancer	117 vs 43 g/day	1.08 (0.97-1.21) Ptrend:0.22	Age, BMI, educational level, energy from alcohol, HRT use, menopausal status, non-alcohol energy, pregnancies,	Estimated dose-response results per 20g/day

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Norway								smoking status, study center	
						per 20 %	1.02 (1.00-1.04)		
						Calibrated data: per 20 %	1.06 (1.01-1.12)		
		3 540/			Incidence, breast cancer ER+/PR+	117.3 vs 43.2 g/day	1.20 (1.00-1.45) Ptrend:0.21		
						per 20 %	1.03 (0.99-1.07)		
		1 072/			Incidence, breast cancer ER+/PR-	117.3 vs 43.2 g/day	1.11 (0.79-1.56) Ptrend:0.35		
						per 20 %	1.05 (0.98-1.12)		
		1 018/			Incidence, breast cancer ER-/PR-	117.3 vs 43.2 g/day	0.79 (0.56-1.11) Ptrend:0.13		
						per 20 %	0.96 (0.90-1.03)		
		3 155/			Incidence, breast cancer unknown ER/PR status	117.3 vs 43.2 g/day	1.15 (0.94-1.40) Ptrend:0.09		
						per 20 %	1.03 (0.99-1.07)		
		539/			Incidence, breast cancer HER-2 +	119.6 vs 44.5 g/day	1.34 (0.84-2.14) Ptrend:0.59		
						per 20 %	0.99 (0.91-1.09)		
		1 720/			Incidence, breast cancer HER-2 -	119.6 vs 44.5 g/day	1.28 (0.98-1.68) Ptrend:0.14		
						per 20 %	1.05 (1.00-1.11)		
		5 756/			Incidence, breast cancer HER-2	119.6 vs 44.5 g/day	1.06 (0.92-1.22) Ptrend:0.42		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
					unknown	per 20 %	1.02 (0.99-1.05)		
		5 615/			Incidence, breast cancer ER+	117.3 vs 43.2 g/day	1.16 (1.00-1.34) Ptrend:0.11		
						per 20 %	1.03 (1.00-1.06)		
		1 395/			Incidence, breast cancer ER-	117.3 vs 43.2 g/day	0.84 (0.63-1.13) Ptrend:0.18		
						per 20 %	0.98 (0.93-1.04)		
		3 761/			Incidence, breast cancer PR+	117.3 vs 43.2 g/day	1.17 (0.98-1.40) Ptrend:0.32		
						per 20 %	1.03 (0.99-1.06)		
		2 108/			Incidence, breast cancer PR-	117.3 vs 43.2 g/day	0.93 (0.73-1.19) Ptrend:0.66		
						per 20 % change	1.00 (0.96-1.05)		
Löf, 2007 BRE80144 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	974/ 44 569 13 years	Cancer registry	FFQ	Incidence, Invasive breast cancer	80.7 vs 30.8 g/day	1.02 (0.72-1.45) Ptrend:0.7	Age, age at first child birth, age at menarche, alcohol consumption, BMI, educational level, family history of cancer, non-alcohol energy, parity, use of oral contraception	
						per 10 g/day	1.04 (0.97-1.11)		
Hunter, 1996	The Pooling	4 980/	Self-reported	FFQ	Incidence, breast	Q5 vs Q1	1.05 (0.94-1.16)	Age at	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Canada, USA, the Netherlands, Sweden	Project Pooled study of 7 cohorts*, Age: 28-90 years, W (*AHS, CNBSS, IWHS, NLCS, NYSC, NHS(a), NHS(b), SMC),	337 819	and verified by medical records and/or record linkage with cancer registries		cancer		Ptrend:0.21	menarche, menopausal status, parity, age at birth of first child, BMI, height, education, history of benign breast disease, maternal history of breast cancer, history of breast cancer in a sister, OC use, fibre intake, alcohol intake, energy intake	
						per 25 g/day	1.02 (0.94-1.11)		
	AHS	153/ 15 172				-	-		
	CNBSS	514/ 56 837				per 25 g/day	1.21 (0.89-1.65)		
	IWHS	723/ 34 406				per 25 g/day	1.28 (1.03-1.59)		
	NLCS	434/ 62 412				per 25 g/day	0.90 (0.67-1.22)		
	NYSC	376/ 18 475				per 25 g/day	1.04 (0.88-1.22)		
	NHS(a)	1 094/ 89 046				per 25 g/day	0.97 (0.86-1.10)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	NHS(b)	911/ 68 817				per 25 g/day	0.93 (0.77-1.12)		
	SMC	775/ 61 471				per 25 g/day	0.98 (0.78-1.22)		
Gaard, 1995 BRE17516 Norway	Norway National Health Screening Service, 1974, Prospective Cohort, Age: 35-49 years, W, Screening Program	248/ 24 897 10 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer	≥61 vs ≤49.9 g/day	1.25 (0.86-1.81) Ptrend:0.18	Age , age-underlying cox models, BMI, energy Intake , height, menopausal status, smoking habits	
Knekt, 1990 BRE04898 Finland	Mobile Clinic Health Examination Survey, 1973, Prospective Cohort, Age: 20-69 years, W, Screening Program	3 988 20 years	All histology	Dietary history questionnaire	Incidence, breast cancer	≥97.3 vs ≤71.1 g/day	1.72 (0.61-4.82) Ptrend:0.10	Age , energy Intake	
Jones, 1987 BRE04461 USA	NHANES I, Prospective Cohort, Age: 25-74 years, W	86/ 5 485 10 years	Medical records + self-reported +death certificate	24h recall	Incidence, breast cancer	≥74 vs ≤37.9 g/day	0.34 (0.16-0.73)	Age , age at menarche, age at menopause, BMI, educational level, family history, menopausal	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								status	

Table 166 Percentage of energy from fat and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Farvid, 2014 BRE80577 USA	NHS II, Prospective Cohort, Age: 26-45 years, W	2 830/ 88 804 20 years	Self report verified by medical record and pathology report	Semi-quantitative FFQ	Incidence, breast cancer	38.6 vs 24.5 %	1.07 (0.95-1.21) Ptrend:0.1	Age, age at menarche, age at menopause, alcohol Intake, BMI, calendar year, energy, energy from protein, family history of breast cancer In first degree relatives, height, history of benign breast disease, hormone use, menopausal status, OC use, parity and age at first birth, race, smoking status and dose	
						per 5 %	1.03 (0.99-1.06)		
		1 544/			Incidence, breast	per 5 %	1.06 (1.01-1.11)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
					cancer ER+ & PR+				
		423/			Incidence, breast cancer ER- & PR-	per 5 %	1.01 (0.93-1.10)		
Sieri, 2008 BRE80202 Europe	EPIC, Prospective Cohort, Age: 20-70 years, W	7 119/ 319 826 8.8 years	Cancer registry / database / pathology reports	FFQ	Incidence, breast cancer	44.9 vs 28.9 % energy/day	1.04 (0.96-1.13) Ptrend:0.432	Age, alcohol Intake, centre location, educational attainment, energy Intake, height, menopausal status, smoking status, weight	
Wakai, 2005 BRE24482 Japan	JACC, Prospective Cohort, Age: 40-79 years, W, Previous study	129/ 26 291 7.6 days	Partially histological - over 80%	FFQ	Incidence, breast cancer	≥24.55 vs ≤18.43 %	0.80 (0.46-1.38) Ptrend:0.32	Age , age at first child, age at menarche, age at menopause, alcohol, BMI, educational level, energy Intake , family history, height, HRT use, other energy Index, other nutritional factors, other physical activity Index, parity/pregnancies, recruitment center, smoking habits	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Gago-Dominguez, 2003 BRE17518 China	SCHS, Prospective Cohort, Age: 45-74 years, W	314/ 63 257 5.3 years	Partially histological - over 80%	FFQ	Incidence, breast cancer	≥29.44 vs ≤21.87 %	0.94 (0.68-1.31) Ptrend:0.95	Age , alcohol, educational level, ethnicity, family history, menstrual characteristics , parity/pregnancies	
Smith-Warner, 2001b Canada, USA, the Netherlands, Sweden	The Pooling Project, Pooled study of 8 cohorts*, Age: 28-90 years, W (*AHS, CNBSS, IWHS, NHS(a), NHS(b), NLCS, NYSC, NYUWHS, SMC),	7 329/ 351 821	Self-reported and verified by medical records and/or record linkage with cancer registries	FFQ	Incidence, breast cancer	per 5% of energy	1.00 (0.9888-1.16) Ptrend:0.85	Percent of energy from protein, percent of energy from alcohol, age at menarche, parity, age at birth of first child, menopausal status at diagnosis, MHT use, OC use, history of benign breast disease, family history of breast cancer, smoking status, education, BMI, BMI-menopausal status at diagnosis interaction, height, fibre intake, energy	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								intake, monounsaturated fat, polyunsaturated fat	
	AHS	160/ 15 172				per 5% of energy	1.66 (0.77-3.55)		
	CNBSS	419/ 56 837				per 5% of energy	1.24 (0.87-1.75)		
	IWHS	1 130/ 34 406				per 5% of energy	1.19 (0.96-1.46)		
	NHS(a)	1 020/ 89 046				per 5% of energy	0.88 (0.73-1.06)		
	NHS(b)	1 638/ 68 817				per 5% of energy	1.04 (0.88-1.22)		
	NLCS	887/ 62 412				per 5% of energy	1.25 (1.02-1.53)		
	NYSC	367/ 18 475				per 5% of energy	0.84 (0.40-1.77)		
	NYUWHS	385/ 14 006				per 5% of energy	1.04 (0.82-1.32)		
	SMC	1 323/ 61 467				per 5% of energy	1.13 (0.94-1.35)		
Jones, 1987 BRE04461 USA	NHANES I, Prospective Cohort, Age: 25-74 years, W	86/ 5 485 10 years	Medical records + self-reported +death certificate	24h recall	Incidence, breast cancer	≥42 vs ≤29.9 %/day	0.66 (0.33-1.31)	Age , age at menarche, age at menopause, BMI, educational level, family history,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								menopausal status	

Table 167 Total fat intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Key, 2011 UK	UK Dietary Cohort Consortium Pooled study of 4 cohorts* Mean age: 56.4 ±9.7 years among cases, W (*EPIC-Norfolk; EPIC-Oxford; UKWCS; Whitehall II study)	657 cases/ 1 911 controls EPIC-Norfolk: 353 cases/1 252 controls EPIC-Oxford: 194 cases/ 194 cases UKWCS: 42 cases/202 controls Whitehall II study: 68 cases/263 controls	Record linkage with National Statistics and cancer registries	Food diary and FFQ	Incidence, breast cancer	Food diaries ≥94.7 vs ≤41.0 g/day	0.87 (0.54-1.41) Ptrend:0.392	Age, alcohol consumption, parity, menopausal status, current hormone replacement therapy use, physical activity, height, weight, and energy intake	Superseded by Sieri, 2014, BRE80546 (EPIC-Norfolk and EPIC-Oxford overlapped with Sieri, 2014)
						per 21.1 g/day	0.92 (0.77-1.11)		
						FFQs ≥108.5 vs ≤40.0 g/day	0.80 (0.50-1.30) Ptrend: 0.525		
						per 28.5 g/day	0.94 (0.76-1.15)		(Included in stratified analysis)

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Martin, 2011 BRE80323 Canada	CDBCPT, Nested Case Control, Age: 47 years, Participants of a breast cancer prevention RCT	220 cases/ 440 controls 10	Pathology	Food records, diet at baseline of RCT	Incidence, Invasive breast cancer	63 vs 46 g/day	1.10 (0.86-1.40)	Age, age at first child birth, age at menarche, family history of breast cancer, HRT use, menopausal status, number of childbirths, parity, randomisation, smoking	Excluded, two exposure categories only
		167 cases/ 334 controls			Incidence, breast cancer ER+	63 vs 46 g/day	1.27 (0.96-1.69)		
		42 cases/ 84 controls			Incidence, breast cancer ER-	63 vs 46 g/day	0.72 (0.39-1.31)		
Sieri, 2008 BRE80202 Europe	EPIC, Prospective Cohort, Age: 20-70 years, W	7 119/ 319 826 8.8 years	Cancer registry / database / pathology reports	FFQ	Incidence, breast cancer	113.4 vs 46 g/day	1.02 (0.90-1.17) Ptrend:0.601	Age, alcohol Intake, centre location, educational attainment, energy Intake, height, menopausal status, smoking status, weight	Publication superseded by Sieri, 2014
						per 20 %	1.02 (0.99-1.04)		
						per 20 % calibrated data	1.04 (0.98-1.10)		
Iso, 2007 BRE80427 Japan	JACC, Prospective Cohort,	99/ 15 years	Municipal resident registration	FFQ	Mortality, breast cancer	modified vs no change	1.00	Age, centre location	Results on breast cancer morality, not

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 40-79 years, W		records, death certificates						analysed
Bingham, 2003 BRE14387 UK	EPIC-UK, Nested Case Control, Age: 45-74 years, W	13 070 7 years	Partially histological - over 80%	7-day record + questionnaire	Incidence, Invasive breast cancer	Food diaries 92.4 vs 37.14 g/day	1.79 (0.89-3.56) Ptrend:0.051	Body weight, height, HRT use, menopausal status, parity/pregnancies, univariate partition	Study superseded by Sieri, 2014
						FFQs 113.38 vs 38.62 g/day	1.31 (0.65-2.64) Ptrend:0.520		
Frazier, 2003 BRE02941 USA	NHS, Nested Case Control, Age: 40-65 years, W, Registered nurses	121 700 10 years	All histology	FFQ, adolescent diet	Incidence, breast cancer	107.5 vs 35.5 g/day	0.92 Ptrend:0.32	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, family history, height, HRT use, menopausal status, nutrients, parity/pregnancies	Excluded, adolescent diet
Horn-Ross, 2002 BRE15412 USA	CTS, Prospective Cohort, Age: 21-103 years, W, Registered teachers	111 383 2 years	Partially histological - over 80%	FFQ	Incidence, Invasive breast cancer	≤75 vs ≤34 g/day	0.80 (0.60-1.20) Ptrend:0.4	Age , age at first child, age at menarche, BMI, energy Intake , ethnicity, family history, menopausal status, physical	Excluded, missing cases, non-cases, exposure levels per category

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								activity	
Thiebaut, 2001 BRE12244 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W, Registered teachers	65 879 3.4 years	Not specified	FFQ-semi-quantitative	Incidence, breast cancer	Q4 vs Q1	1.37 (0.99-1.89)	Age , age at menarche, age at menopause, alcohol, benign breast disease, BMI, educational level, energy Intake , family history, marital status	Study superseded by Sieri, 2014
Wolk, 1998 BRE13548 Sweden	SMC, Prospective Cohort, Age: 40-76 years, W, Screening Program	61 147 4.2 years	All histology	FFQ	Incidence, Invasive breast cancer	≥50.21 vs ≤40.29 g/day	1.00 (0.76-1.32) Ptrend:0.82	Age , age at first child, alcohol, BMI, educational level, energy Intake , family history, nutrients, parity/pregnancies, residual (willet)	Publication superseded by Hunter, 1996
Byrne, 1996 BRE05719 USA	NHEFS, Prospective Cohort, Age: 25-74 years, W	52/ 6 156 3.9 years	Medical records + death certificate	FFQ	Incidence, breast cancer	Q4 vs Q1	0.98 (0.40-2.20)	Age , residual (willet)	Follow-up study of NHANES I, superseded by Jones, 1987
Kushi, 1995 BRE05142 USA	IWHS, Prospective Cohort, Age: 55-69	329/ 34 388 6 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer ER+/PR+	≥72 vs ≤61 g/day	1.22 (0.94-1.59) Ptrend:0.14	Age , energy Intake	Results by hormone receptor status, not analysed

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	years, W	75/			Incidence, breast cancer ER+/PR-	≥72 vs ≤61 g/day	1.05 (0.61-1.81) Ptrend:0.86		
		14/			Incidence, breast cancer ER-/PR+	≥72 vs ≤61 g/day	0.47 (0.12-1.91) Ptrend:0.32		
		61/			Incidence, breast cancer ER-/PR-	≥72 vs ≤61 g/day	0.73 (0.38-1.38) Ptrend:0.38		
Toniolo, 1994 BRE12398 USA	NYUWHS, Nested Case Control, Age: 35-65 years, W	735 7 years	Medical records	FFQ-semi-quantitative	Incidence, Invasive breast cancer	123 vs 28 g/day	1.49 (0.89-2.48) Ptrend:0.09		Excluded, missing cases and non-cases per category
Giovannucci, 1993a BRE03262 USA	NHS, Nested Case Control, Age: 30-55 years, W, Registered nurses	392/ 786 controls 2 years	Medical records + death certificate	FFQ-semi-quantitative	Incidence, breast cancer	Q5 vs Q1	0.64 (0.43-0.96) Ptrend:0.07	Age , residual (willet)	Publication superseded by Hunter, 1996
						per 100 g/day	1.04 (0.64-1.68)		
Willett, 1992 BRE13438 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	1 439/ 89 494 8 years	Medical records + self-reported	FFQ-semi-quantitative	Incidence, breast cancer	≥82 vs ≤57.9 g/day	0.90 (0.77-1.07) Ptrend:0.47	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, energy Intake , family history, menopausal status, nutrients, other design Issue, parity/pregnanci	Publication superseded by Hunter, 1996

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								es	
Howe, 1991 BRE17622 canada	CNBSS, Nested Case Control, Age: 40-59 years, W, Screening Program	519/ 1182 controls 5 years	All histology	Dietary history questionnaire	Incidence, breast cancer	Q4 vs Q1	1.30 (0.90-1.88) Ptrend:.052	Age , energy Intake , recruitment center, time of recruitment	Publication superseded by Hunter, 1996
						per 77 g/day	1.35 (1.00-1.82)		
Willett, 1987b BRE13442 USA	NHS, Prospective Cohort, Age: 34-59 years, W, Registered nurses	601/ 89 538 4 years	Medical records + self-reported	FFQ-semi-quantitative	Incidence, breast cancer	Q5 vs Q1	0.82 (0.64-1.05) Ptrend:0.11	Age , age at first child, alcohol, benign breast disease, body weight, family history, menopausal status, smoking habits	Publication superseded by Hunter, 1996
Kinlen, 1982 BRE17702 Great Britain	Britain, 1978, Historical Cohort, Age: -85 years, W, Religious orders	31/ 2 813 66 years	Death certificate		Mortality, breast cancer	high vs low	0.57	Age	Results on breast cancer morality, not analysed

Table 168 Percentage of energy from fat and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Boeke, 2014a BRE80585 USA	NHS I and II, Prospective Cohort, Age: 25-55 years, W	9 979/ 182 671 30 years	Medical records, pathology reports, next of kin, death certificate, ndi	Semi-quantitative FFQ	Incidence, breast cancer	Q5 vs Q1	1.02 (0.96-1.10) Ptrend:0.88	Age, age at menarche, age at menopause, alcohol Intake, BMI at age 18 years, breastfeeding, calendar year, cohort, family history of breast cancer, height, history of benign breast disease, menopausal status, oral contraceptive use, parity and age at first birth, physical activity, postmenopausal hormone use, protein, total energy Intake, weight change	Superseded by Smith-Warner, 2001b
		1 529/			Mortality, breast cancer	Q5 vs Q1	0.85 (0.72-1.01) Ptrend:0.05		
Key, 2011 UK	UK Dietary Cohort Consortium Pooled study of 4 cohorts* Mean age: 56.4	657 cases/ 1 911 controls EPIC-Norfolk: 353 cases/1 252 controls	Record linkage with National Statistics and cancer registries	Food diary and FFQ	Incidence, breast cancer	Food diaries ≥40.3 vs ≤25.7% of energy	0.90 (0.66-1.23) Ptrend:0.504	Age, alcohol consumption, parity, menopausal status, current hormone	Superseded by Sieri, 2008 (EPIC-Norfolk and EPIC-Oxford

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	±9.7 years among cases, W (*EPIC-Norfolk; EPIC-Oxford; UKWCS; Whitehall II study)	EPIC-Oxford: 194 cases/ 194 cases UKWCS: 42 cases/202 controls Whitehall II study: 68 cases/263 controls						replacement therapy use, physical activity, height, weight, and energy intake	overlapped with Sieri, 2008)
						per 5.7 % of energy	0.97 (0.88-1.07)		
						FFQs ≥39.3 vs ≤24.2 % of energy	0.80 (0.59-1.09) Ptrend: 0.366		
						per 6.0% of energy	0.96 (0.87-1.05)		(Included in stratified analysis)
Thiebaut, 2001 BRE12244 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W, Registered teachers	65 879 3.4 years	Not specified	FFQ-semi-quantitative	Incidence, breast cancer	Q4 vs Q1	1.12 (0.92-1.37)	Age , age at menarche, age at menopause, alcohol, benign breast disease, BMI, density, educational level, family history, marital status	Superseded by Sieri, 2008
Holmes, 1999 BRE04008 USA	NHS, Prospective Cohort, Age: 30-55 years, W,	2 956/ 121 700 14 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, Invasive breast cancer	≥50.1 vs 30.1-35 %	0.96 (0.76-1.23) Ptrend:0.03	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease,	Superseded by Smith-Warner, 2001b

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Registered nurses							BMI, body weight, energy Intake , family history, height, HRT use, menopausal status, nutrients	
						per 5 % of total energy/day	0.97 (0.94-1.00)		
Byrne, 1996 BRE05719 USA	NHEFS, Prospective Cohort, Age: 25-74 years, W	52/ 6 156 3.9 years	Medical records + death certificate	FFQ	Incidence, breast cancer	≥36.6 vs ≤29.4 % of total energy	0.98 (0.50-2.10)	Age	Superseded by Jones, 1987, NHEFS was a follow-up study of NHANES I

Figure 234 RR estimates of breast cancer by levels of total fat intake and percentage of energy from fat

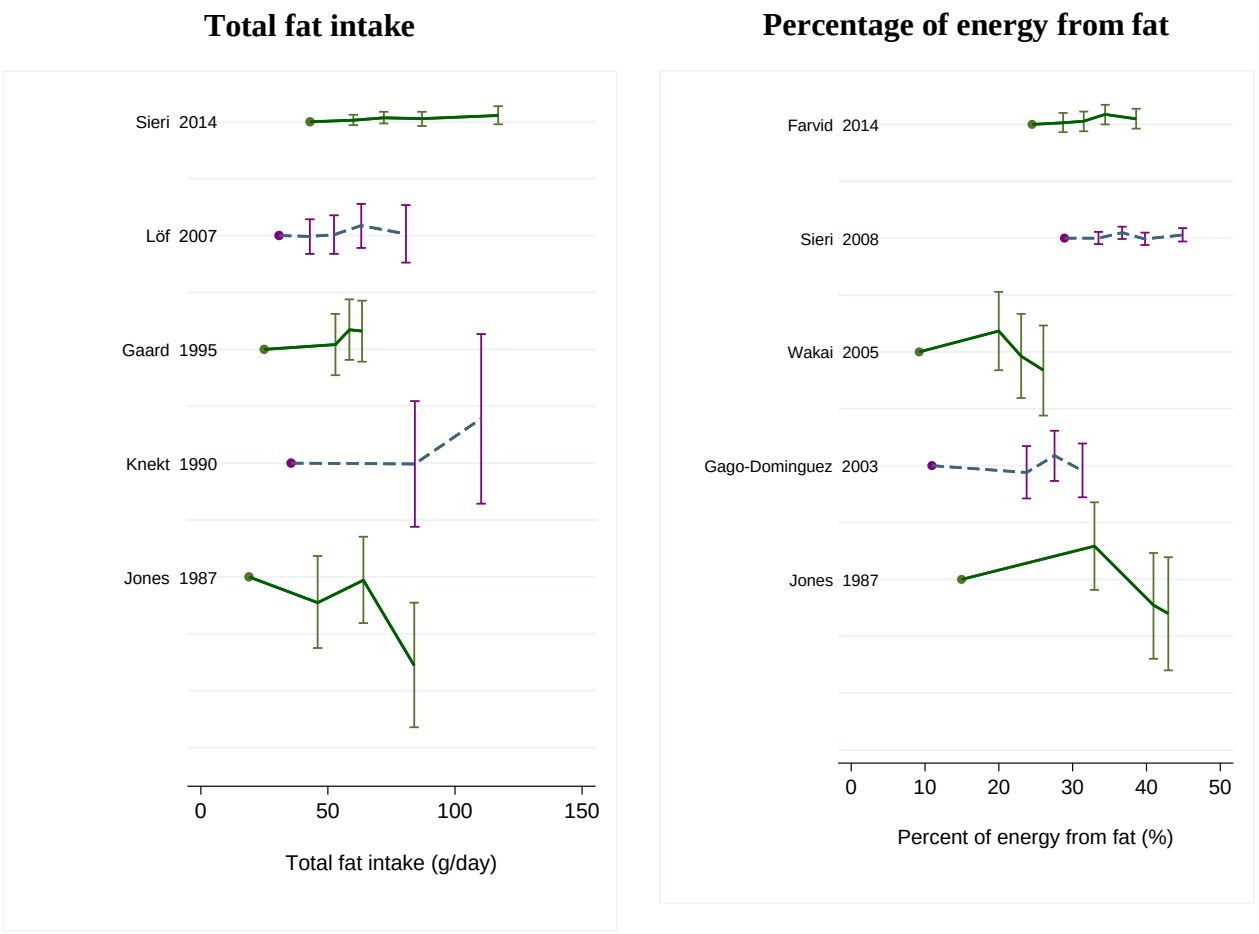


Figure 235 RR (95% CI) of breast cancer for the highest compared with the lowest total fat intake and percentage of energy from fat

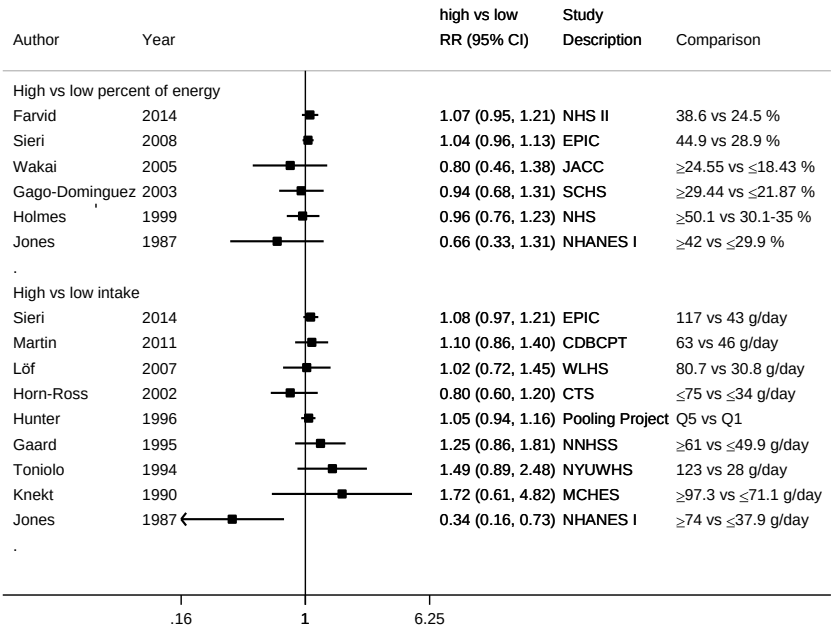


Figure 236 Relative risk of breast cancer for 20 g/day of total fat intake and 5% of energy from fat

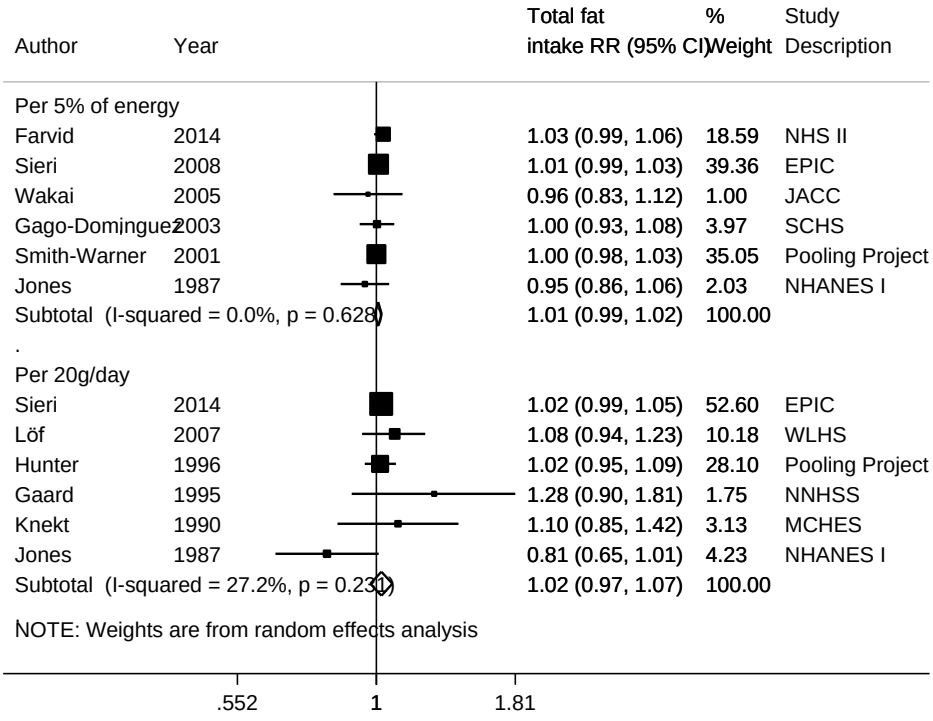


Figure 237 Funnel plot of studies included in the dose response meta-analysis of total fat intake and breast cancer

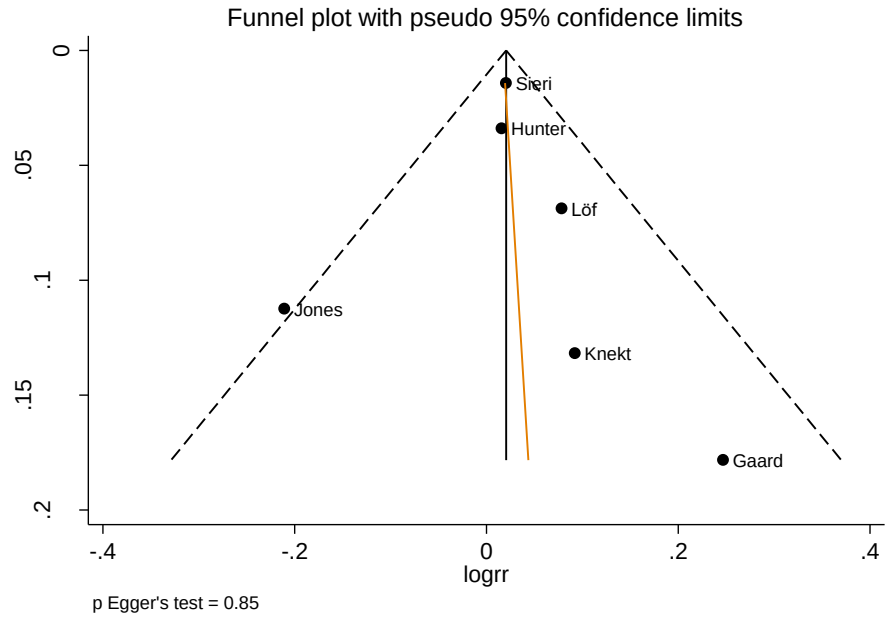


Figure 238 Funnel plot of studies included in the dose response meta-analysis of percentage of energy from fat and breast cancer

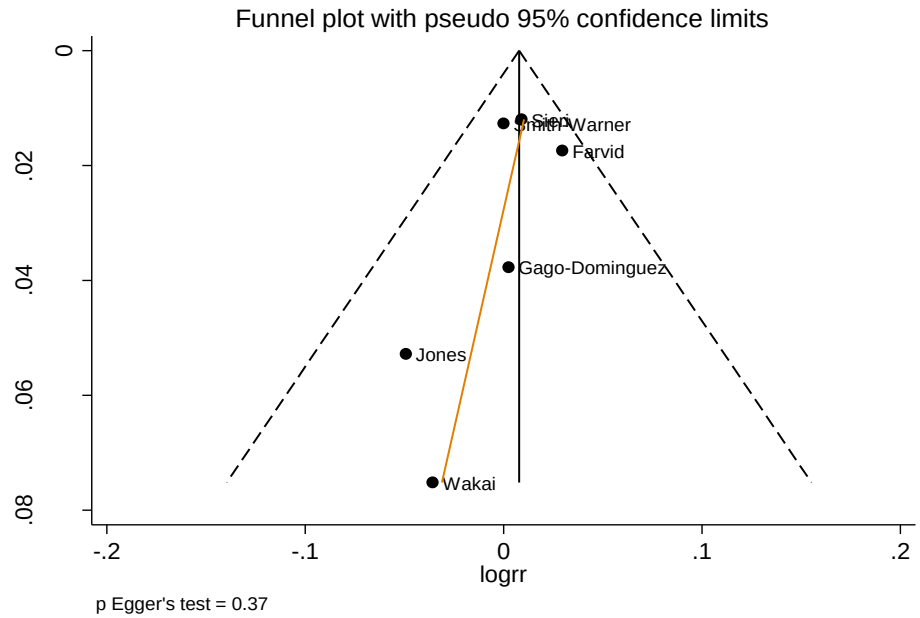


Figure 239 Relative risk of breast cancer for 20 g/day of total fat intake, by geographic location

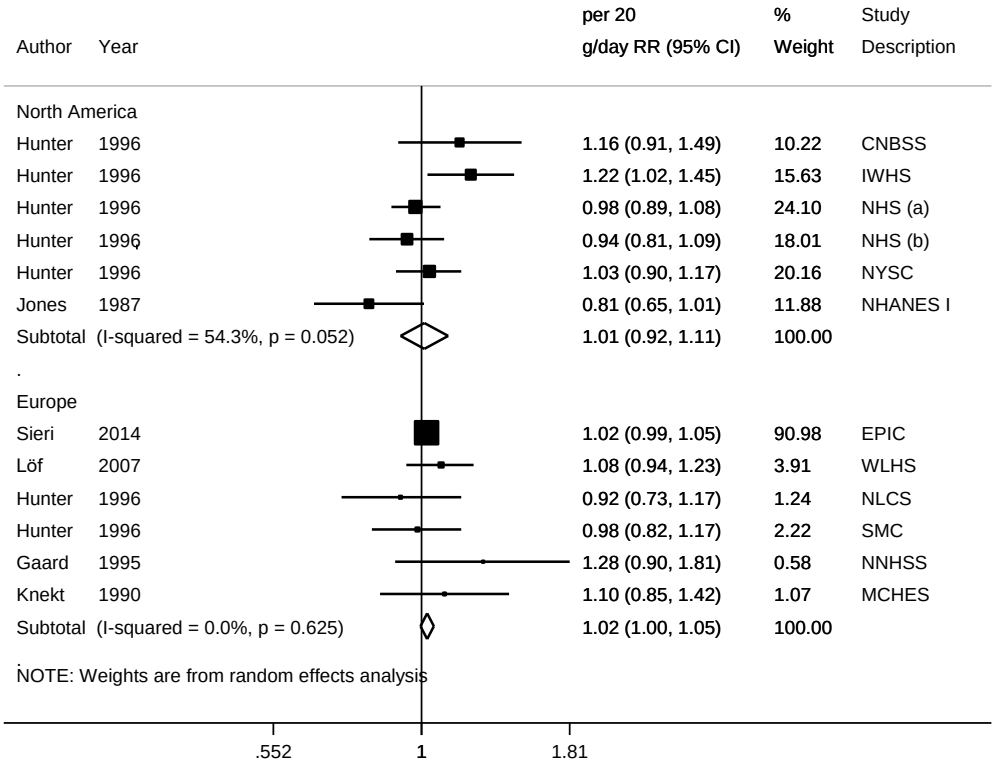


Figure 240 Relative risk of breast cancer for 5 % of energy from fat, by geographic location

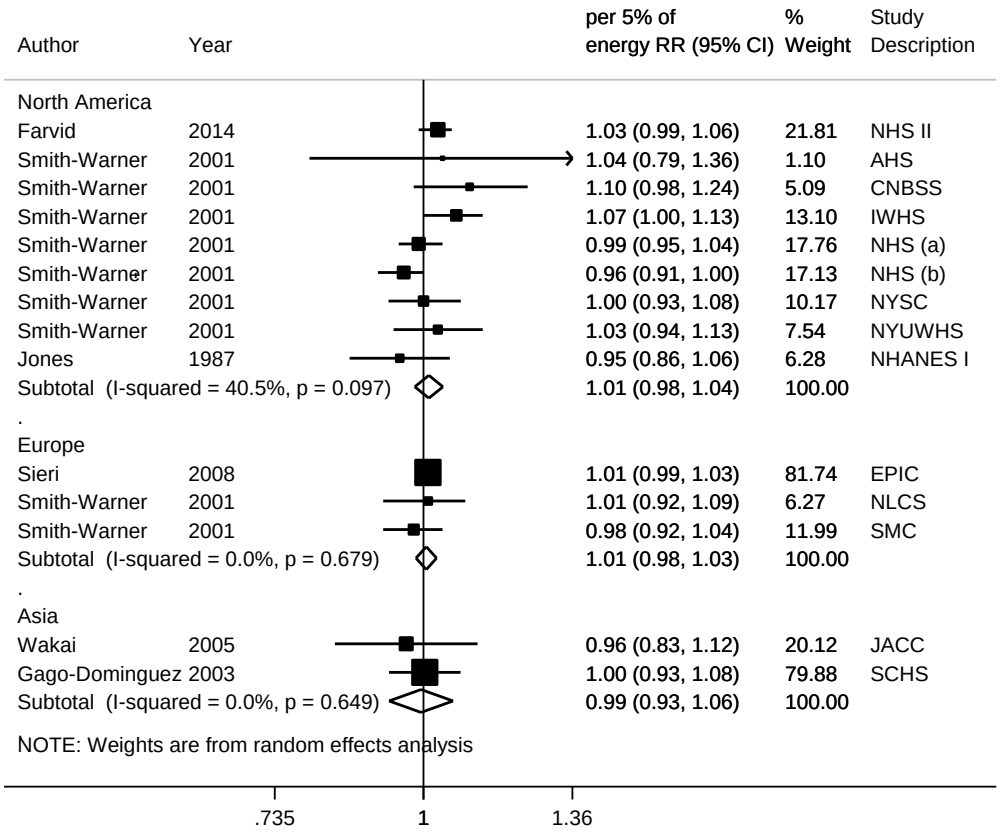


Figure 241 Relative risk of breast cancer for 20 g/day of total fat intake, by exposure assessment

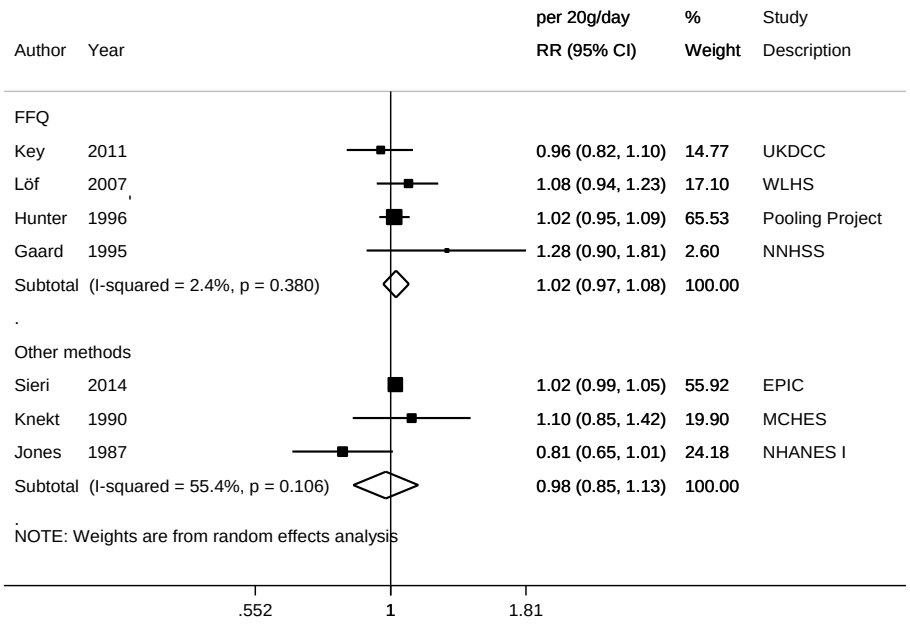


Figure 242 Relative risk of breast cancer for 5 % of energy from fat, by exposure assessment

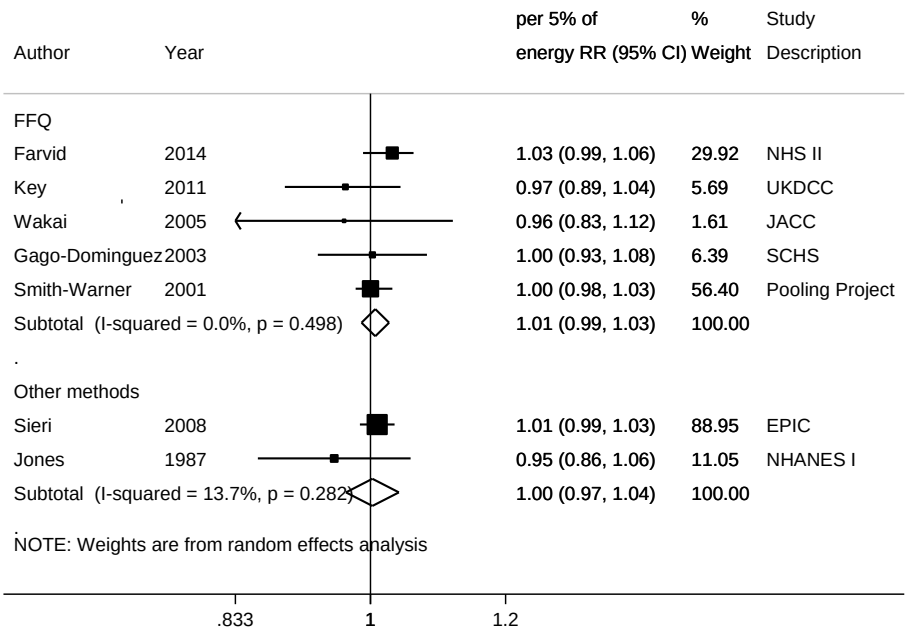
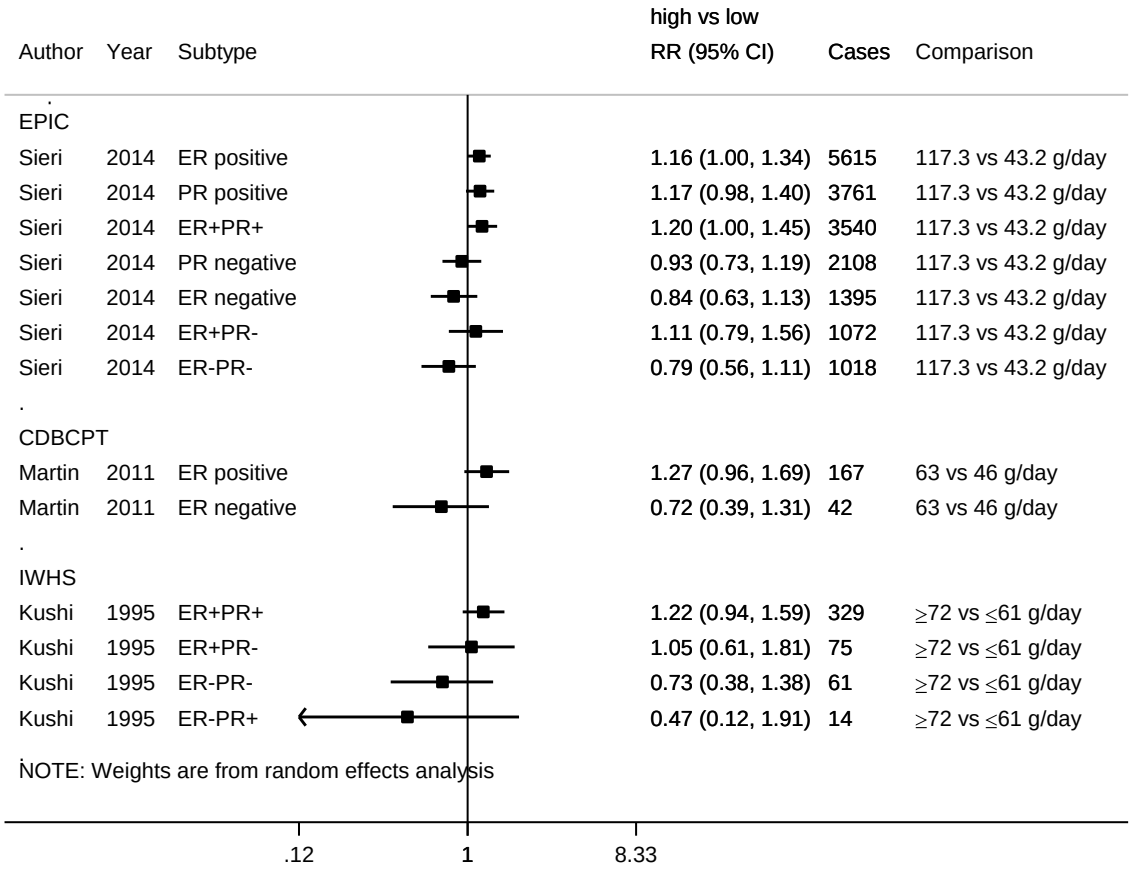


Figure 243 RR (95% CI) of hormone receptor defined breast cancer for the highest compared with the lowest total fat intake



Premenopausal breast cancer

Summary

Main results:

Three studies from five publications on total fat intake and two studies from three publications on percentage energy from fat were identified. No pooled studies were identified. Two studies on percentage energy from fat could be included in the dose-response meta-analysis.

There was no significant association for percentage of energy from fat and premenopausal breast cancer risk (summary RR per 5% of energy=1.01, 95% CI=0.97-1.05, I^2=0%, P=0.44).

One study (two publications) on fat intake during adolescence were excluded (Linos, 2010; Frazier, 2004). The publication (Linos, 2010) that used prospective data observed a positive association with a significant dose-response trend and the other publication (Frazier, 2004) with retrospective data which could be affected by recall bias observed a non-significant inverse association. Another excluded study (two publications) (Willett, 1992; Willett, 1987b) did not have sufficient data to be included in the analysis. A non-significant inverse association was observed (Willett, 1992).

One study (Farvid, 2014) reported non-significant results by hormone receptor status (RRs per 5% of energy=1.05, 95% CI= 0.99-1.12 for ER+PR+ and 1.01, 95% CI= 0.90-1.31 for ER-PR- premenopausal breast cancers).

Stratified analysis and non-linear dose-response meta-analysis was not conducted due to limited number of studies.

Study quality:

Only two American studies (NHS, NHS II) and one Swedish study (Lof, 2007a, WLHS) reported results. All studies used FFQs to assess total fat intake. Farvid, 2014 (NHS II) assessed premenopausal fat intake. Major confounding factors of breast cancer were adjusted for in the studies.

Table 169 Total fat intake and percentage of energy from fat and premenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	3 (5 publications) total fat intake 2 (3 publications) percentage of energy from fat
Studies included in forest plot of highest compared with lowest exposure	2 (2 publications) total fat intake 2 (2 publications) percentage of energy from fat
Studies included in linear dose-response meta-analysis	1 (1 publications) total fat intake 2 (2 publications) percentage of energy from fat

Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 170 Total fat intake and percentage of energy from fat and premenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR*		CUP	
Increment unit used	**Per 20g/day**	**Per 5%**	**Per 20g/day**	**Per 5%**
Studies (n)	-	-	1	2
Cases	-	-	432	1 511
RR (95%CI)	-	-	1.12 (0.92-1.39)	1.01 (0.97-1.05)
Heterogeneity (I^2, p-value)	-	-	-	0%, 0.44
P value Egger test	-	-	-	-

*No meta-analysis was conducted in the 2005 and 2008 SLR

Table 171 Total fat intake and premenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Turner, 2011	6 studies (2 cohorts*, 2 case-control studies)	>4 025 premenopausal breast cancer	Germany, USA	Incidence, premenoapausal breast cancer	Highest vs lowest total fat intake	0.97 (0.94-1.01) Ptrend: >0.05	-

*All cohort studies identified were included in the present review.

Table 172 Total fat intake and premenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Löf, 2007 BRE80144 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	432/ 44 569 13 years	Cancer registry	FFQ	Incidence, Invasive breast cancer, age < 50 years	80.7 vs 30.8 g/day	1.46 (0.87-2.47) Ptrend:0.1	Age, age at first child birth, age at menarche, alcohol consumption, BMI, educational level, family history of cancer, non-alcohol energy, parity, use of oral contraception	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
						per 10 g/day	1.06 (0.96-1.18)		

Table 173 Percentage of energy from fat and premenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Farvid, 2014 BRE80577 USA	NHS II, Prospective Cohort, Age: 26-45 years, W	1 511/ 88 804 20 years	Self report verified by medical record and pathology report	Semi-quantitative FFQ, premenopausal diet	Incidence, premenopausal breast cancer, premenopausal	38.5 vs 24.5 %	1.07 (0.91-1.26) Ptrend:0.4	Age, age at menarche, alcohol Intake, BMI, calendar year, energy, energy from protein, family history of breast cancer In first degree relatives, height, history of benign breast disease, OC use, parity and age at first birth, race, smoking status and dose	
						per 5 %	1.02 (0.97-1.06)		
		815/			Incidence, breast cancer ER+ & PR+,	per 5 %	1.05 (0.99-1.12)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
					premenopausal				
		237/			Incidence, breast cancer ER- & PR-, premenopausal	per 5 %	1.00 (0.90-1.13)		
Holmes, 1999 BRE04008 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	784/ 121 700 14 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, Invasive breast cancer, premenopausal	≥50.1 vs 30.1-35 %	1.03 (0.70-1.51) Ptrend:0.77	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, energy Intake , family history, height, HRT use, menopausal status, nutrients	
						per 5 % of total energy/day	0.99 (0.93-1.05)		

Table 174 Total fat intake and premenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Linos, 2010	NHS II,	455/	Follow up	Semi-	Incidence,	142 vs 105	1.35 (1.00-1.81)	Age, age at first	Excluded,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
BRE80298 USA	Prospective Cohort, Age: 34-53 years, W, Premenopausal	39 268 7.8 years (1998-2005)	questionnaires, medical records	quantitative FFQ, 124-item, adolescent diet assessed in 1998	Invasive breast cancer	g/day	Ptrend:0.05	child birth, age at menarche, alcohol consumption, benign breast disease, BMI, energy Intake, family history of cancer, menopausal status, OC use, parity, weight gain	adolescent diet
Frazier, 2004 BRE02942 USA	NHS II, Historical Cohort, Age: 34-51 years, W, Premenopausal	361/ 47 355 9 years (max) (1989-1998)	All histology	FFQ, 131-item adolescent diet assessed in 1998	Incidence, breast cancer,	140.7 vs 107 g/day	0.91 (0.67-1.24) Ptrend:0.68	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, energy Intake , family history, menopausal status, OC use, other anthropometric Index, other design Issue, parity/pregnancies	Excluded, adolescent diet
Willett, 1992 BRE13438 USA	NHS, Prospective Cohort,	527/ 89 494 8 years	Medical records + self-reported	FFQ-semi-quantitative	Incidence, breast cancer, premenopausal	Q5 vs Q1	0.96 (0.73-1.26) Ptrend:0.76	Age , age at first child, age at menarche,	Excluded, insufficient data

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 30-55 years, W, Registered nurses							alcohol, benign breast disease, BMI, energy Intake , family history, nutrients, other design Issue, parity/pregnancies	
Willett, 1987b BRE13442 USA	NHS, Prospective Cohort, Age: 34-59 years, W, Registered nurses	89 538 4 years	Medical records + self-reported	FFQ-semi-quantitative	Incidence, breast cancer, premenopausal	Q5 vs Q1	0.93 Ptrend:0.78	Age , age at first child, alcohol, benign breast disease, body weight, energy Intake , family history, menopausal status, smoking habits	Excluded, insufficient data

Table 175 Percentage of energy from fat and premenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Cho, 2003a BRE17370 USA	NHS II, Prospective Cohort,	714/ 90 655 8 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative, premenopausal	Incidence, Invasive breast cancer,	38 vs 24 %/day	1.25 (0.98-1.59) Ptrend:.06	Age , age at first child, age at menarche,	Superseded by Farvid, 2014 BRE80577

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 25-42 years, W, Premenopausal			diet	premenopausal			alcohol, benign breast disease, BMI, family history, height, menopausal status, multivariate partition, OC use, parity/pregnancies, smoking habits	

Figure 244 RR estimates of premenopausal breast cancer by levels of total fat intake and percentage of energy from fat

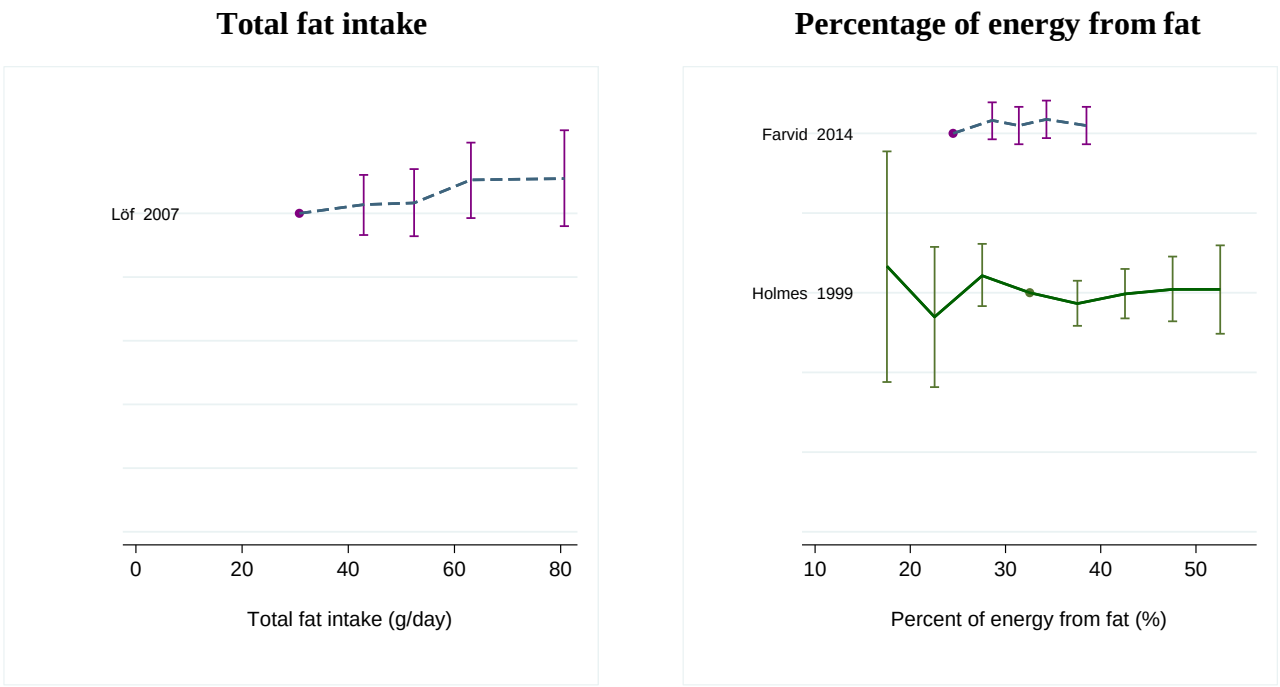


Figure 245 RR (95% CI) of premenopausal breast cancer for the highest compared with the lowest total fat intake and percentage of energy from fat

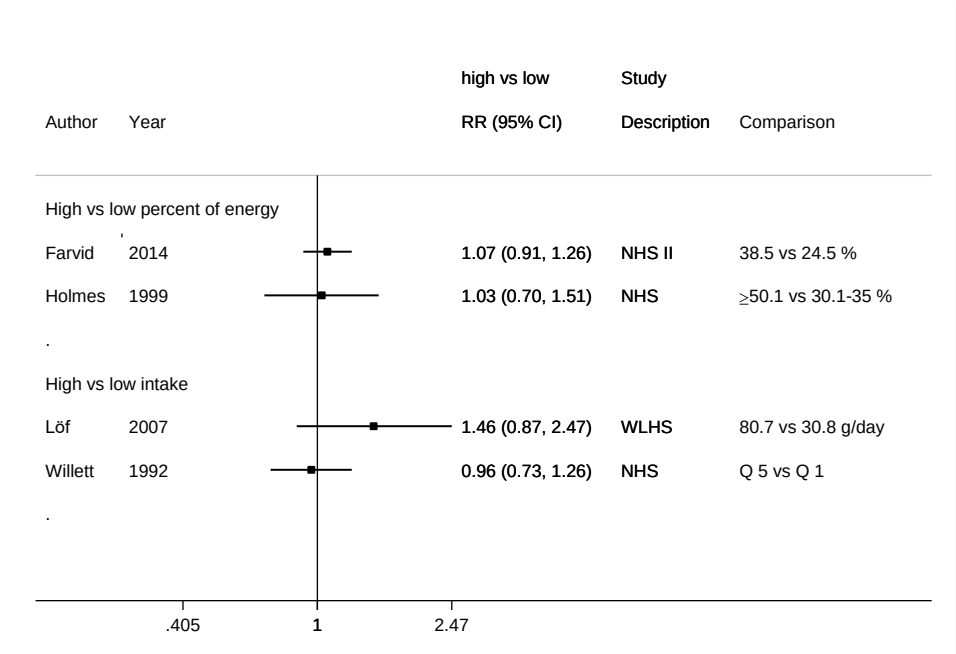
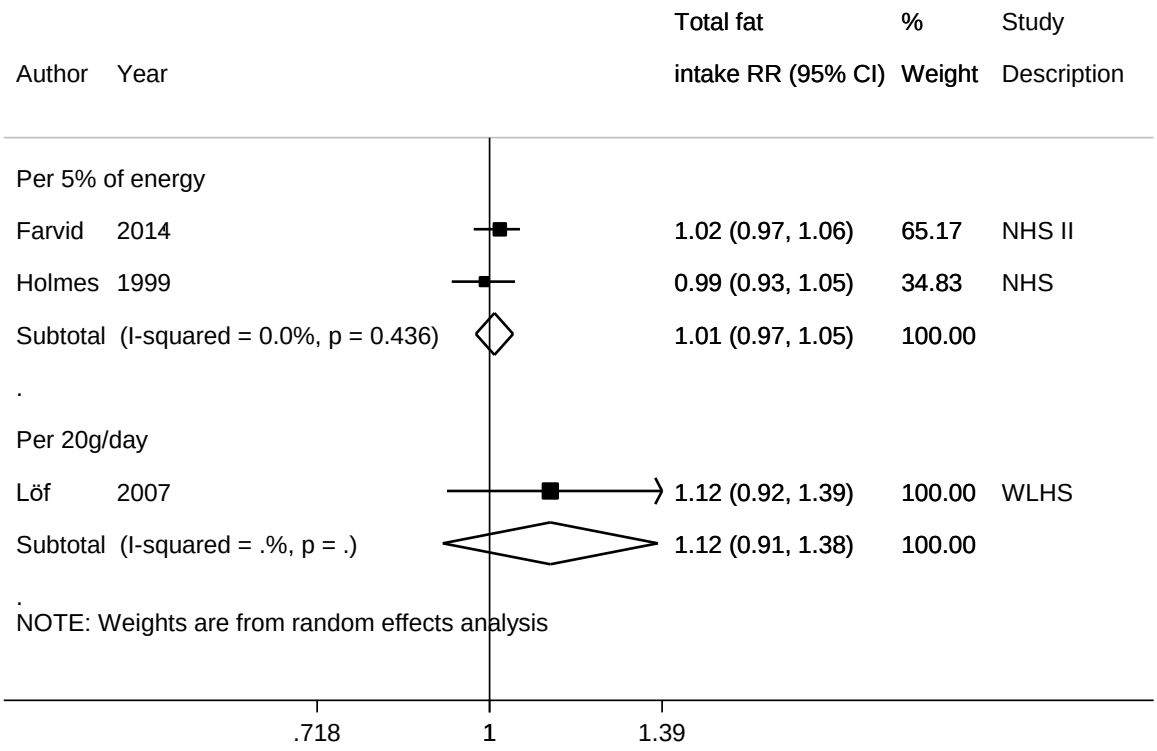


Figure 246 Relative risk of premenopausal breast cancer for 20 g/day of total fat intake and 5% of energy from fat



Postmenopausal breast cancer

Summary

Main results:

Seventeen out of 20 studies (21 publications) on total fat intake and 10 out of 14 studies (13 publications) on percentage of energy from fat could be included in the dose-response meta-analyses, respectively.

Total fat intake was borderline significantly positively associated with postmenopausal breast cancer risk (summary RR per 20g/day=1.08, 95% CI=1.00-1.17). For percentage of energy from fat, no significant association was observed (summary RR per 5% energy=1.00, 95% CI=0.97-1.03). There was evidence of high heterogeneity between studies (I^2=65%, P=0.01 and I^2=61%, P=0.01, respectively).

Subgroup analyses of total fat intake showed a significant positive association among the North American studies (summary RR for 20 g/day=1.09, 95% CI=1.01-1.17, I^2=77%, P<0.001) and not the European studies (summary RR=1.00, 95% CI=0.85-1.19, I^2=63%, P=0.05). Studies that used FFQs to assess total fat intake (eight out of 15 were North American studies) found a borderline significance positive association (summary RR=1.05, 95% CI=1.00-1.10) and studies that used other methods observed a non-significant positive association (summary RR=1.13, 95% CI=0.87-1.48, seven studies).

North American studies that reported on percentage of energy from fat observe no association on average (summary RR for 5% of energy=1.00, 95% CI=0.98-1.03, I^2=54%, P=0.07). For European studies, one study (Key, 2011, UKDCC) that pooled data from four UK cohorts observed a significant inverse association (RR=0.83, 95% CI=0.72-0.96).

The study population in one excluded study on total fat intake (Hartz, 2013) overlapped with another study that was already included in the meta-analysis. Two studies on total fat intake (Sieri, 2008; Sieri, 2002) and four on percentage of energy from fat (Prentice, 2013a; Velie, 2000; Kushi, 1992; Wirfalt, 2004) did not have sufficient data to be included in the meta-analyses. For the highest versus lowest fat intake comparison, non-significant associations that were positive in postmenopausal hormone non-users and inverse in postmenopausal hormone users (Sieri, 2008) and significantly positive overall (Sieri, 2002) were reported. For percentage of energy from fat, Prentice, 2013a reported a borderline significant positive association for a 40% increment in calibrated FFQ fat density (RR=1.05, 95% CI=1.00-1.09). When information from 4-day food records was used, the RR estimate was 1.19 (95% CI=1.00-1.41) (Prentice, 2013a). Two other studies (Velie, 2000; Kushi, 1992) reported non-significant positive associations and Wirfalt, 2004 reported no significant difference between mean percentage energy from fat in cases and non-cases.

Three studies reported results by breast cancer hormone receptor status, of which two with the highest compared with the lowest results were presented in the forest plot. Farvid, 2014 reported per increase of 5% of energy, RR estimates of 1.05 (95% CI=0.97-1.13) for ER+PR+ and 0.98 (95% CI=0.85-1.14) for ER-PR- postmenopausal breast cancers. No significant associations were observed in the other two studies (Park, 2012; Kim, 2006).

Sensitivity analyses:

Summary RR per 20 g/day increase of total fat intake ranged from 1.05 (95% CI=0.98-1.14) when Freedman, 2006 was omitted to 1.09 (95% CI=1.02-1.17) when Key, 2011 was omitted in influence analysis. The study of Freedman, 2006 (WHI-DM, non-intervention group) included only women with ≥32% calories from fat. Results in this study were adjusted for these selection criteria (Freedman, 2006). The summary RR did not change materially when studies were omitted in turn in influence analysis of percentage energy from fat.

Non-linear dose-response meta-analysis:

There was no evidence of non-linear relationship between total fat intake and postmenopausal breast cancer risk (P for non-linearity=0.35) (graph not shown). For percentage of energy from fat, the test of departure from linearity was significant (P for non-linearity=0.01). The curve showed an increase in risk with an increase percentage of energy from fat, which dropped after 30% where there were limited data points.

Study quality:

Most studies were from North America or Europe. One study was from Japan (Wakai, 2005). One study was of multi-ethnicity (Park, 2012). Key, 2011 included MHT non-users only.

There were more studies that used FFQs to assess total fat intake. One study (Barrett-Connor, 1993) used a 24-hour recall and observed a strong positive association. One study (Sonestedt, 2007) used diet history questionnaire. The summary RR did not change appreciably when these studies was omitted in influence.

In addition to Prentice, 2013a that could not be included in the meta-analysis (results mentioned above), Key, 2011 (UKDCC) and Freedman, 2006 (WHI-DM, non-intervention arm) were able to use data from both sources (FFQs and food diaries or food records) in the analysis. Stronger associations with data from food diaries or food records than data from FFQs were observed, although the results were inconsistent. Key, 2011 found a significant inverse association with total fat intake from food diaries (RR per 21.1g /day=0.70, 95% CI=0.52-0.95) but not from FFQs (RR per 28.5 g/day= 0.78, 95% CI=0.56-1.08). Freedman, 2006 found a significant positive association from food records (RR for the highest versus the lowest intake=2.09, 95% CI=1.21-3.61, P trend=0.08) but not from FFQ (RR=1.71, 95%CI=0.70-4.18, P trend=0.18). On average, positive associations were observed in the studies with data from FFQs or other methods in the present review.

Case ascertainment was through cancer registries or confirmed through medical records. All studies were adjusted for major confounding factors, apart from Graham, 1992 that did not adjust for alcohol or BMI, possibly because these factors were not significantly associated with breast cancer in this study.

Table 176 Total fat intake and percentage of energy from fat and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	20 (21 publications) total fat intake 14 (13 publications) percentage energy from fat
Studies included in forest plot of highest compared with lowest exposure	11 (11 publications) total fat intake 8 (8 publications) percentage energy from fat
Studies included in linear dose-response meta-analysis	17 (8 publications) total fat intake 10 (7 publications) percentage energy from fat
Studies included in non-linear dose-response meta-analysis	8 (8 publications) total fat intake Not enough studies on percentage energy from fat

Note: Include cohort, case-cohort, and nested case-control designs.

Table 177 Total fat intake and percentage of energy from fat and postmenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR		**CUP**	
Increment unit used	**Per 20g/day**	**Per 5%**	**Per 20g/day**	**Per 5%**
Studies (n)	5	2	17[1,2]	10[2]
Cases	2 007	2 150	9 612	12 547
RR (95%CI)	1.06 (0.99-1.14)	0.95 (0.92-0.98)	1.08 (1.00-1.17)	1.00 (0.97-1.03)
Heterogeneity (I^2, p-value)	65%	66%	65%, 0.01	61%, 0.02
P value Egger test	-	-	0.69	0.71

Stratified analyses in the CUP					
Increment unit used	**Per 20g/day**	**Per 20g/day**	**Per 5% of energy**	**Per 5% of energy**	**Per 5% of energy**
Geographic location	**Europe**	**North America**	**Europe**	**North America**	**Asia**
Studies (n)	7	7	4	5	1
Cases	2 052	5 981	286	12 185	76
RR (95%CI)	1.00 (0.85-1.19)	1.09 (1.01-1.17)	0.83 (0.72-0.96)	1.00 (0.98-1.03)	1.02 (0.85-1.23)

Heterogeneity (I^2, p-value)	63%, 0.05	77%, <0.001	-	54%, 0.07	-
Increment unit used	**Per 20g/day**	**Per 20g/day**	**Per 5% of energy**	**Per 5% of energy**	
Adjustment for age, BMI, alcohol intake, reproductive factors	**Adjusted**	**Not adjusted**	**Adjusted**	**Not adjusted**	
Studies (n)	17	-	9	1	
Cases	9 612	-	12 203	344	
RR (95%CI)	1.08 (1.00-1.17)	-	1.00 (0.97-1.03)	1.01 (0.94-1.08)	
Heterogeneity (I^2, p-value)	65%, 0.01	-	68%, 0.01	-	
Exposure assessment methods	**FFQs**	**Other methods**	**FFQs**	**Other methods**	
Studies (n)	15	7	10	4	
Cases	9 169	1 332	12 547	286	
RR (95%CI)	1.05 (1.00-1.10)	1.13 (0.87-1.48)	1.00 (0.98-1.02)	0.83 (0.72-0.96)	
Heterogeneity (I^2, p-value)	24%, 0.25	81%, 0.001	46%, 0.09	-	

[1]Included the Pooling Project (Hunter, 1996, seven cohorts).

[2]Included the UK Cohort Consortium (Key, 2011, four cohorts).

Table 178 Total fat intake and postmenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Turner, 2011	15 studies (12 cohorts, 3 case-control studies)	>13 460 postmenopausal breast cancer	Germany, Italy, The Netherlands, Singapore, Sweden, USA	Incidence, postmenoapausal breast cancer	Highest vs lowest total fat intake (21 studies)	1.04 (1.01-1.07) Ptrend: 0.004	-
					Cohort studies (n=16)	1.05 (1.01-1.08) Ptrend: 0.01	-

*All cohort studies identified were included in the present review.

Table 179 Total fat intake and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Sczaniecka, 2012 BRE80434 USA	VITAL, Prospective Cohort, Age: 50-76 years, W, Postmenopausal	772/ 30 252 6 years	Seer registry	Semi-quantitative FFQ	Incidence, breast cancer	≥73.9 vs ≤32.6 g/day	1.43 (0.95-2.14) Ptrend:0.10	Age, age at first child birth, age at menarche, age at menopause, alcohol, BMI, breast biopsies, educational level, energy, estrogen replacement therapy, exercise, family history of breast	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								cancer, fruits, height, history of hysterectomy, mammography, nsaid use, race, vegetable, years of combined hormone therapy	
Key, 2011 UK	UK Dietary Cohort Consortium Pooled study of 4 cohorts* Mean age: 56.4 ±9.7 years among cases, W (*EPIC-Norfolk; EPIC-Oxford; UKWCS; Whitehall II study)	286 cases/ 699 controls	Record linkage with National Statistics and cancer registries	Food diary and FFQ	Incidence, breast cancer, postmenopausal, not using HRT	Food diaries per 21.1 g/day	0.70 (0.52-0.95) Ptrend:<0.05	Age, alcohol consumption, parity, menopausal status, current hormone replacement therapy use, physical activity, height, weight, and energy intake	
						FFQs per 28.5 g/day	0.78 (0.56-1.08)		
Löf, 2007 BRE80144 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	542/ 44 569 13 years	Cancer registry	FFQ	Incidence, Invasive breast cancer, age >= 50 yrs	80.2 vs 30.8 g/day	0.76 (0.47-1.22) Ptrend:0.34	Age, age at first child birth, age at menarche, alcohol consumption, BMI, educational level, family history of cancer, non-	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								alcohol energy, parity, use of oral contraception	
						per 10 g/day	1.01 (0.93-1.11)		
Sonestedt, 2007 BRE80147 Sweden	MDCS, Prospective Cohort, Age: 45-73 years, W	428/ 11 726 9.5 years	Cancer registry	Diet history questionnaire	Incidence, breast cancer, postmenopausal	96.1 vs 62.5 g/day	1.21 (0.90-1.64) Ptrend:0.14	Age, Interviewer, method version, season of year, total energy Intake	
Thiébaut, 2007 BRE80012 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, Postmenopausal	3 501/ 188 736 4.4 years	Cancer registry	24h recall + FFQ	Incidence, Invasive breast cancer	90.5 vs 24.2 g/day	1.22 (1.03-1.45) Ptrend:0.013	Age at first child birth, age at menopause, alcohol energy, BMI, menopausal hormone use, non-alcohol energy, parity, smoking habits	
						per 2-fold	1.15 (1.05-1.26)		
Freedman, 2006 BRE80628 USA	WHI - DM (non-intervention group), Nested Case Control, Age: 50-79 years, W, Postmenopausal, women with ≥32% kcal from	603/ 1206 controls 6.92 years	Medical records and pathology reports	4-day food record & FFQ	Incidence, Invasive breast cancer, postmenopausal	93 vs 37.8 g/day	2.09 (1.21-3.61) Ptrend:0.008	Age at entry, breast biopsies, clinic, energy Intake, family history, HRT use, lenght of follow-up	
						118.9 vs 42.1 g/day	1.71 (0.70-4.18) Ptrend:0.18		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	fat								
Sieri, 2002 BRE20941 Italy	ORDET, Nested Case Control, Age: 41-70 years, W, Postmenopausal	56/ 214 controls 5.5 years	Cancer registry + death certificate	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	62.8-146.6 vs ≤54.3 g/day	3.47 (1.43-8.44) Ptrend:0.005	Birth cohort, educational level, parity/pregnancies, residual (willet)	
Hunter, 1996 Canada, USA, the Netherlands, Sweden	The Pooling Project Pooled study of 7 cohorts*, Age: 28-90 years, W (*AHS, CNBSS, IWHS, NLCS, NYSC, NHS(a), NHS(b), SMC),	3 465/	Self-reported and verified by medical records and/or record linkage with cancer registries	FFQ	Incidence, breast cancer, postmenopausal	per 25 g/day	1.01 (0.91-1.12) Ptrend:0.41	Age at menarche, menopausal status, parity, age at birth of first child, BMI, height, education, history of benign breast disease, maternal history of breast cancer, history of breast cancer in a sister, OC use, fibre intake, alcohol intake, energy intake	
Barrett-Connor, 1993 BRE00581 USA	Rancho Bernardo, 1972, Prospective Cohort, Age: 40-79 years, W	15/ 590 15 years	Medical records + death certificate	24h recall	Incidence, breast cancer, postmenopausal	per 28 g/day	2.01 (1.19-3.41)	Age , age at menopause, alcohol, BMI, parity/pregnancies	

Table 180 Percentage of energy from fat and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Farvid, 2014 BRE80577 USA	NHS II, Prospective Cohort, Age: 26-45 years, W	918/ 88 804 20 years	Self report verified by medical record and pathology report	Semi-quantitative FFQ, premenopausal diet	Incidence, postmenopausal breast cancer, postmenopausal	39 vs 24.6 % energy	1.02 (0.83-1.26) Ptrend:0.34	Age, age at menarche, age at menopause, alcohol Intake, BMI, calendar year, energy, energy from protein, family history of breast cancer In first degree relatives, height, history of benign breast disease, hormone use, OC use, parity and age at first birth, race, smoking status and dose	
						per 5 % energy	1.03 (0.97-1.09)		
		513/			Incidence, breast cancer ER+ & PR+, postmenopausal	per 5 % energy	1.05 (0.97-1.13)		
		136/			Incidence, breast cancer ER- & PR-, postmenopausal	per 5 % energy	0.98 (0.85-1.14)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Park, 2012 BRE80399 Hawaii	MEC, Prospective Cohort, Age: 45-75 years, Postmenopausal	3 885/ 85 089 12.4 years	Cancer registry	FFQ	Incidence, breast cancer	≥35.7 vs ≤23.4 % energy	0.94 (0.85-1.05) Ptrend:0.26	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, educational level, energy Intake, ethnicity, family history of breast cancer, HRT use, number of childbirths, smoking status, time, type of menopause	
		1 764/			Incidence, breast cancer ER+/PR+	≥35.7 vs ≤23.4 % energy	0.90 (0.77-1.06) Ptrend:0.08		
		350/			Incidence, breast cancer ER+/PR-	≥35.7 vs ≤23.4 % energy	1.12 (0.78-1.61) Ptrend:0.32		
		499/			Incidence, breast cancer ER-/PR-	≥35.7 vs ≤23.4 % energy	0.92 (0.69-1.23) Ptrend:0.54		
Key, 2011 UK	UK Dietary Cohort Consortium Pooled study of 4 cohorts* Mean age: 56.4 ±9.7 years among cases, W	286 cases/ 699 controls	Record linkage with National Statistics and cancer registries	Food diary and FFQ	Incidence, breast cancer, postmenopausal, not using HRT	Food diaries per 5.7 % energy	0.81 (0.69-0.95) Ptrend:<0.05	Age, alcohol consumption, parity, menopausal status, current hormone replacement therapy use, physical	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	(*EPIC-Norfolk; EPIC-Oxford; UKWCS; Whitehall II study)							activity, height, weight, and energy intake	
						FFQs per 6 % energy	0.89 (0.76-1.03)		
Thiébaut, 2007 BRE80012 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, Postmenopausal	3 501/ 188 736 4.4 years	Cancer registry	24h recall + FFQ	Incidence, Invasive breast cancer	40.1 vs 20.3 % energy	1.11 (1.00-1.24) Ptrend:0.017	Age at first child birth, age at menopause, alcohol energy, BMI, menopausal hormone use, non-alcohol energy, parity, smoking habits	
						per 2-fold	1.15 (1.05-1.26)		
Kim, 2006 BRE80115 USA	NHS, Prospective Cohort, W, Postmenopausal	3 537/ 121 701 20 years	Medical records	FFQ	Incidence, Invasive breast cancer	≥50.1 vs 30.1-35 % energy	1.01 (0.74-1.38) Ptrend:0.11	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, energy Intake , family history, height, HRT use, other design Issue, parity/pregnancies	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
						per 5 % energy	0.98 (0.95-1.00)		
		1 653/			Incidence, breast cancer ER+/PR+	≥45.1 vs 30.1-35 % energy	0.71 (0.50-1.00) Ptrend:0.55		
						per 5 % energy	0.98 (0.94-1.03)		
		477/			Incidence, breast cancer ER+/PR-	≥45.1 vs 30.1-35 % energy	1.36 (0.82-2.26) Ptrend:0.5		
						per 5 % energy	0.98 (0.90-1.07)		
		517/			Incidence, breast cancer ER-/PR-	≥45.1 vs 30.1-35 % energy	0.78 (0.49-1.24) Ptrend:0.27		
						per 5 % energy	0.95 (0.88-1.03)		
		83/			Incidence, breast cancer ER-/PR+	≥45.1 vs 30.1-35 % energy	0.80 (0.18-3.63) Ptrend:0.83		
						per 5 % energy	0.98 (0.80-1.20)		
Wakai, 2005 BRE24482 Japan	JACC, Prospective Cohort, Age: 40-79 years, W, Previous study	76/ 26 291 7.6 days	Partially histological - over 80%	FFQ	Incidence, breast cancer, postmenopausal	≥24.36 vs ≤18.37 % energy	0.99 (0.50-1.95) Ptrend:0.9	Age , age at first child, age at menarche, age at menopause, alcohol, BMI, educational level, energy Intake , family history, height, HRT use, other energy Index, other nutritional factors, other physical activity Index, parity/pregnancies, recruitment	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								center, smoking habits	
Graham, 1992 BRE03424 USA	NYSC Prospective Cohort, Age: 50-107 years, W, Postmenopausal	344/ 18 586 8 years	Partially histological - over 80%	FFQ	Incidence, breast cancer, postmenopausal	37-54 vs ≤26 % energy	1.00 (0.59-1.70)	Age , educational level	

Table 181 Total fat intake and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Hartz, 2013 BRE80483 USA	WHI, Prospective Cohort, Age: 55-70 years, W, Postmenopausal	147 202 8 years	Self reported/death certificate/ medical records	Questionnaire	Incidence, breast cancer, postmenopausal	per 1 SD	1.00 (0.97-1.03)	Age, alcohol, family history of prostate cancer, history of cancer, history of polyp diagnosis, medication, number of cigarettes smoked, osteoporosis, psychological character, race,	Superseded study by Freedman, 2006

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								study, weight	
Sieri, 2008 BRE80202 Europe	EPIC, Prospective Cohort, Age: 20-70 years, W	1 553/ 319 826 8.8 years	Cancer registry / database / pathology reports	FFQ	Incidence, breast cancer, HRT - no	113.4 vs 46 g/day	1.09 (0.88-1.36) Ptrend:0.74	Age, alcohol Intake, centre location, educational attainment, energy Intake, height, menopausal status, smoking status, weight	Excluded, missing cases and non-cases per category in subgroups
						per 20 %	1.02 (0.98-1.06)		
		1 909/			HRT - yes	113.4 vs 46 g/day	0.85 (0.69-1.05) Ptrend:0.127		
						per 20 %	0.98 (0.94-1.02)		
Mattisson, 2004a BRE17807 Sweden	MDCS, Prospective Cohort, Age: 50- years, W, Postmenopausal	342/ 11 726 7.6 years	Partially histological - over 80%	7-day record + questionnaire	Incidence, breast cancer, postmenopausal	100 vs 65 g/day	1.34 (0.94-1.90) Ptrend:0.018	Age , age at first child, age at menarche, educational level, energy Intake , height, HRT use, Interviewer, leisure time physical activity, other design Issue, other nutritional factors, residual (willet), season of Interview, smoking habits, waist	Superseded by Sonestedt, 2007

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								circumference	
Byrne, 2002 BRE01315 USA	NHS, Prospective Cohort, Age: 57 years, W, Postmenopausal	1 071/ 44 697 14 years	All histology	FFQ-semi-quantitative	Incidence, Invasive breast cancer, postmenopausal	Q5 vs Q1	0.94 (0.77-1.15) Ptrend:0.57	Age , age at first child, age at menopause, age at menopause, alcohol, BMI, density, family history, height, nutrients, parity/pregnancies	Superseded by Hunter, 1996, the Pooling Project
Voorrips, 2002 BRE13011 Netherlands	NLCS, Case Cohort, Age: 55-69 years, W, Postmenopausal	796/ 62 573 6.3 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	86 vs 61 g/day	1.16 (0.87-1.56) Ptrend:.23	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, educational level, energy Intake , family history, OC use, parity/pregnancies, smoking habits	Superseded by Hunter, 1996, the Pooling Project
Wirfält, 2002 BRE13504 Sweden	MDCS, Nested Case Control, Age: 50- years, W, Postmenopausal	237/ 673 controls 8 years	Partially histological - over 80%	7-day record + questionnaire	Incidence, breast cancer, postmenopausal	105 vs 69 g/day	1.51 (0.92-2.49) Ptrend:0.019	Age at first child, alcohol, BMI, educational level, energy Intake , height, HRT use, nutritional factors , waist	Superseded by Sonestedt, 2007

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								circumference	
van den Brandt, 1993 BRE16919 Netherlands	NLCS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	437/ 1 598 3.3 years	All histology	FFQ-semi-quantitative	Incidence, Invasive breast cancer, postmenopausal	highest vs lowest	1.08 (0.73-1.59) Ptrend:0.32	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, educational level, family history, OC use, parity/pregnancies, residual (willet), smoking habits	Superseded by Hunter, 1996, the Pooling Project
Graham, 1992 BRE03424 USA	NYSC, Prospective Cohort, Age: 50-107 years, W, Postmenopausal	344/ 18 586 8 years	Partially histological - over 80%	FFQ	Incidence, breast cancer, postmenopausal	2344-13422 vs 0-1268 g/month	0.99 (0.69-1.41)	Age , educational level	Superseded by Hunter, 1996, the Pooling Project
Kushi L H, 1992 BRE05141 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	459/ 34 388 4 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	80.7 vs 56.6 g/day	1.38 (0.86-2.21) Ptrend:0.18	Age , age at first child, age at menarche, age at menopause, age-underlying cox models, alcohol, benign breast disease, BMI, BMI, energy Intake , family history, whr	Superseded by Hunter, 1996, the Pooling Project

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Willett, 1992 BRE13438 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	774/ 89 494 8 years	Medical records + self-reported	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	Q5 vs Q1	0.91 (0.73-1.14) Ptrend:0.61	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, energy Intake , family history, nutrients, other design Issue, parity/pregnancies	Superseded by Hunter, 1996, the Pooling Project
Howe, 1991 BRE17622 Canada	CNBSS, Nested Case Control, Age: 40-59 years, W, Screening Program	287/ 56 837 5 years	All histology	Dietary history questionnaire	Incidence, breast cancer, postmenopausal	per 77 g/day	1.17 (0.79-1.72)	Age , energy Intake , recruitment center, time of recruitment	Superseded by Hunter, 1996, the Pooling Project
Willett, 1987b BRE13442 USA	NHS, Prospective Cohort, Age: 34-59 years, W, Registered nurses	89 538 4 years	Medical records + self-reported	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	Q5 vs Q1	0.77 Ptrend:0.22	Age , age at first child, alcohol, benign breast disease, body weight, energy Intake , family history, menopausal status, smoking habits	Superseded by Hunter, 1996, the Pooling Project

Table 182 Percentage of energy from fat and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Prentice, 2013a BRE80586 USA	WHI (DM-comparison group and OS), Prospective Cohort, Age: 50-79 years, W, Postmenopausal	5 061/ 103 426 16 years	Self-report verified by medical record	4-day food record & FFQ	Incidence, Invasive breast cancer, postmenopausal	per 40 % increase in fat density from FFQs, not calibrated	1.05 (1.01-1.09)	Age, cohort, date of enrolment, educational level, Gail model risk, participant type, postmenopausal hormone use, race/ethnicity, randomization group, recreational physical activity, smoking	Excluded, increment per 40% increase
						per 40 % increase in fat density from FFQs, calibrated	1.03 (0.99-1.07)		
						per 40 % increase in fat density from FFQs, not calibrated	1.04 (1.00-1.08)	As above, and BMI	
						per 40 % increase in fat density from FFQs, calibrated	1.05 (1.00-1.09)		
	WHI-DM comparison group	902 cases/ 1 059 controls			Incidence, Invasive breast cancer, postmenopausal	per 40 % increase in fat density from food records, not calibrated	1.23 (1.04-1.44)	Age, cohort, date of enrolment, educational level, Gail	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
						per 40 % increase in fat density from food records, calibrated	1.18 (0.99-1.39)	model risk, postmenopausal hormone use, race/ethnicity, randomization group, recreational physical activity, current smoking	
						per 40 % increase in fat density from food records, not calibrated	1.21 (1.03-1.43)	As above, and BMI	
						per 40 % increase in fat density from food records, calibrated	1.19 (1.00-1.41)		
Wirfalt, 2004 BRE17083 Sweden	MDCS, Nested Case Control, Age: 50- years, W, Postmenopausal	12 803 8 years	Partially histological - over 80%	7-day record + questionnaire	Incidence, breast cancer, postmenopausal	(mean exposure)			Excluded, mean exposure comparison only
Byrne, 2002 BRE01315 USA	NHS, Prospective Cohort, Age: 57 years, W, Postmenopausal	1 071/ 44 697 14 years	All histology	FFQ-semi-quantitative	Incidence, Invasive breast cancer, postmenopausal	per 5% energy	0.99 (0.94-1.04)	Age , age at first child, age at menopause, age at menopause, alcohol, BMI, energy Intake , family history,	Publication superseded by Kim, 2006

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								height, nutrients, parity/pregnancies	
Velie, 2000 BRE12851 USA	BCDDP, Prospective Cohort, W, Screening Program	996/ 40 022 5.3 years	Medical records + self-reported	FFQ	Incidence, breast cancer, postmenopausal	Q5 vs Q1	1.07 (0.86-1.32) Ptrend:0.51	Age at first child, age at menarche, alcohol, benign breast disease, BMI, educational level, energy Intake , family history, height, parity/pregnancies	Excluded, missing exposure levels
Holmes, 1999 BRE04008 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	1 913/ 121 700 14 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, Invasive breast cancer, postmenopausal	≥50.1 vs 30.1-35 % energy	1.01 (0.72-1.41) Ptrend:0.06	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, energy Intake , family history, height, HRT use, menopausal status, nutrients	Publication superseded by Kim, 2006
						per 5 % energy	0.96 (0.93-1.00)		
Kushi L H, 1992 BRE05141 USA	IWHS, Prospective Cohort, Age: 55-69	34 388 4 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	Q4 vs Q1	1.13 (0.84-1.51) Ptrend:0.31	Age , age at first child, age at menarche, age at menopause, age-	Excluded, missing exposure levels

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	years, W, Postmenopausal							underlying cox models, alcohol, benign breast disease, BMI, BMI at 18 years, density, energy Intake , family history, WHR	

Figure 247 RR estimates of postmenopausal breast cancer by levels of total fat intake and percentage of energy from fat

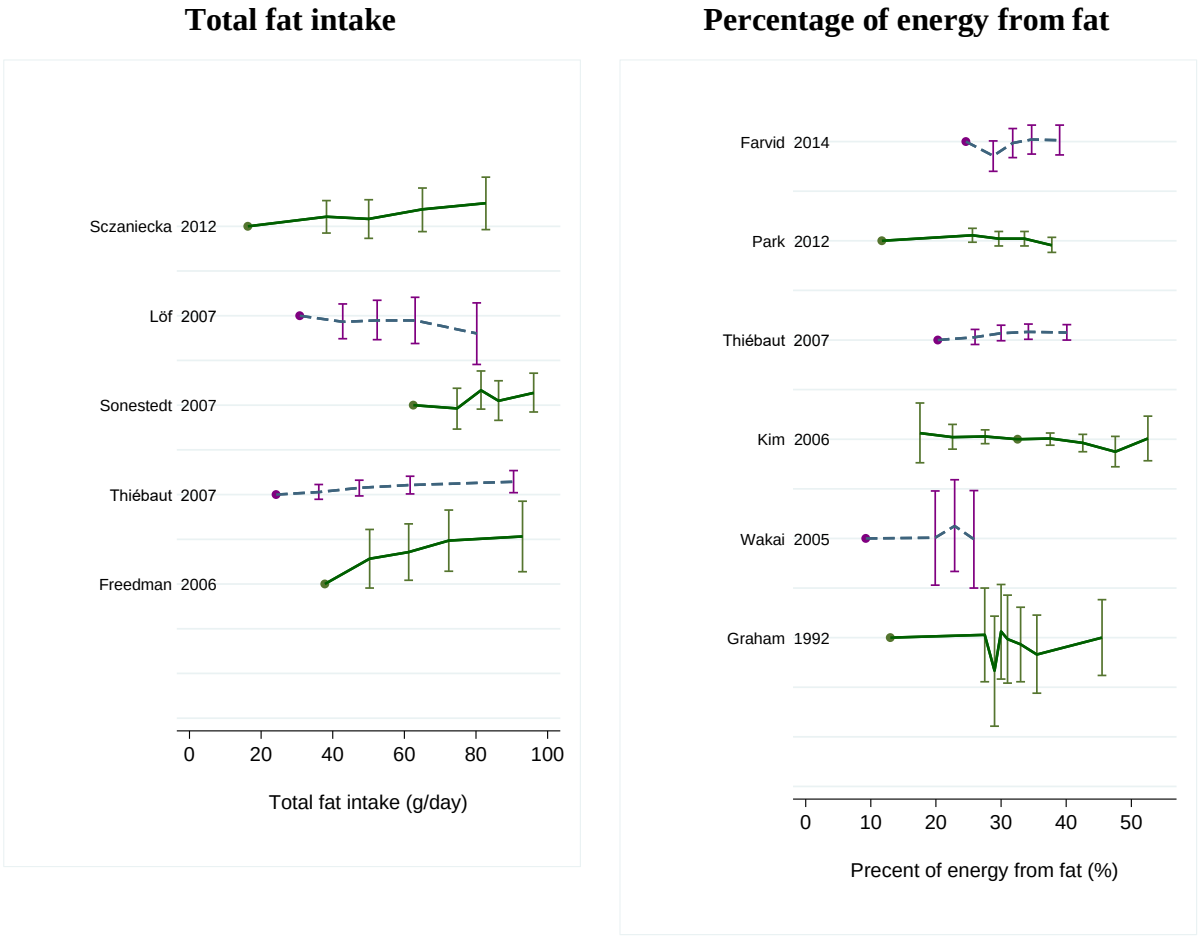


Figure 248 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest total fat intake and percentage of energy from fat

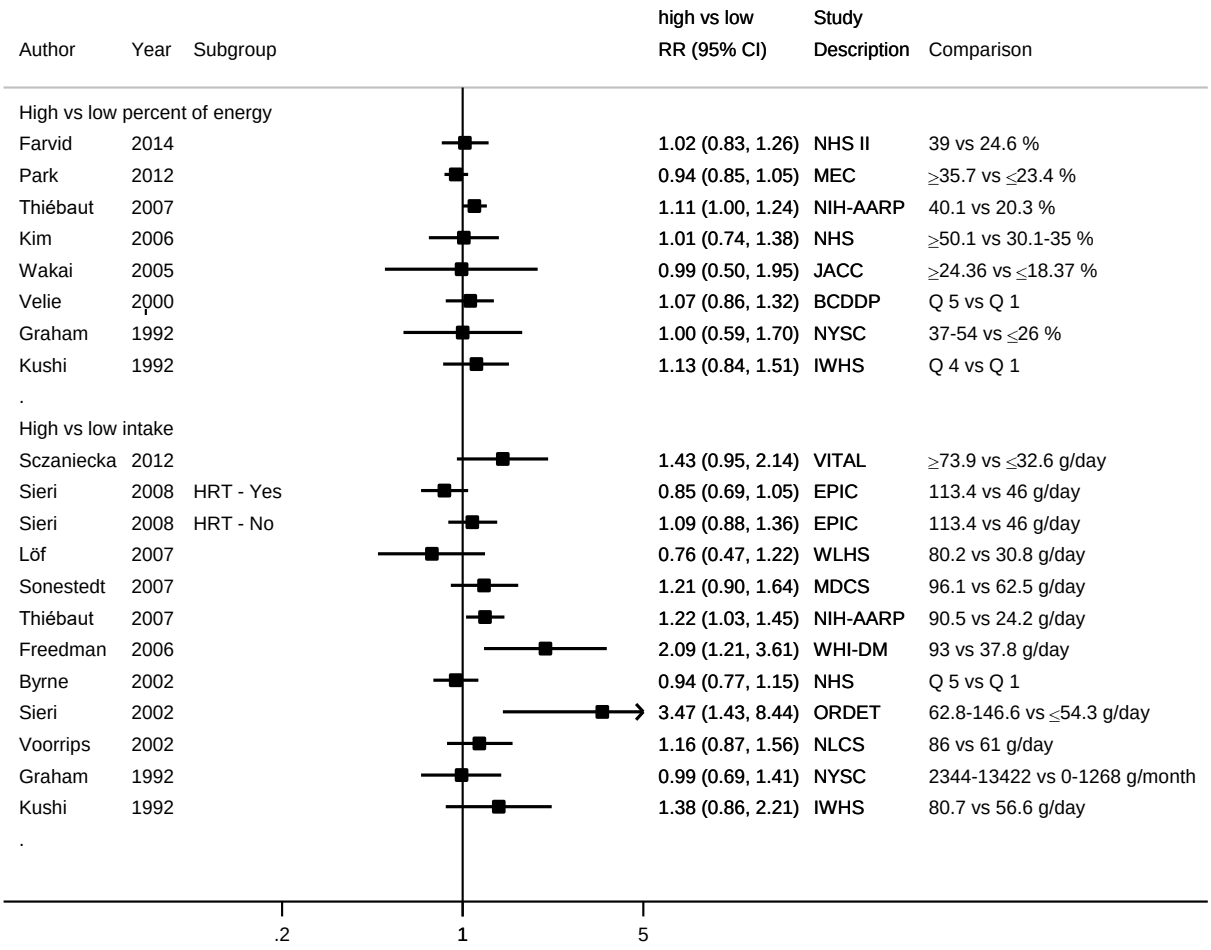


Figure 249 Relative risk of postmenopausal breast cancer for 20 g/day of total fat intake and 5% of energy from fat

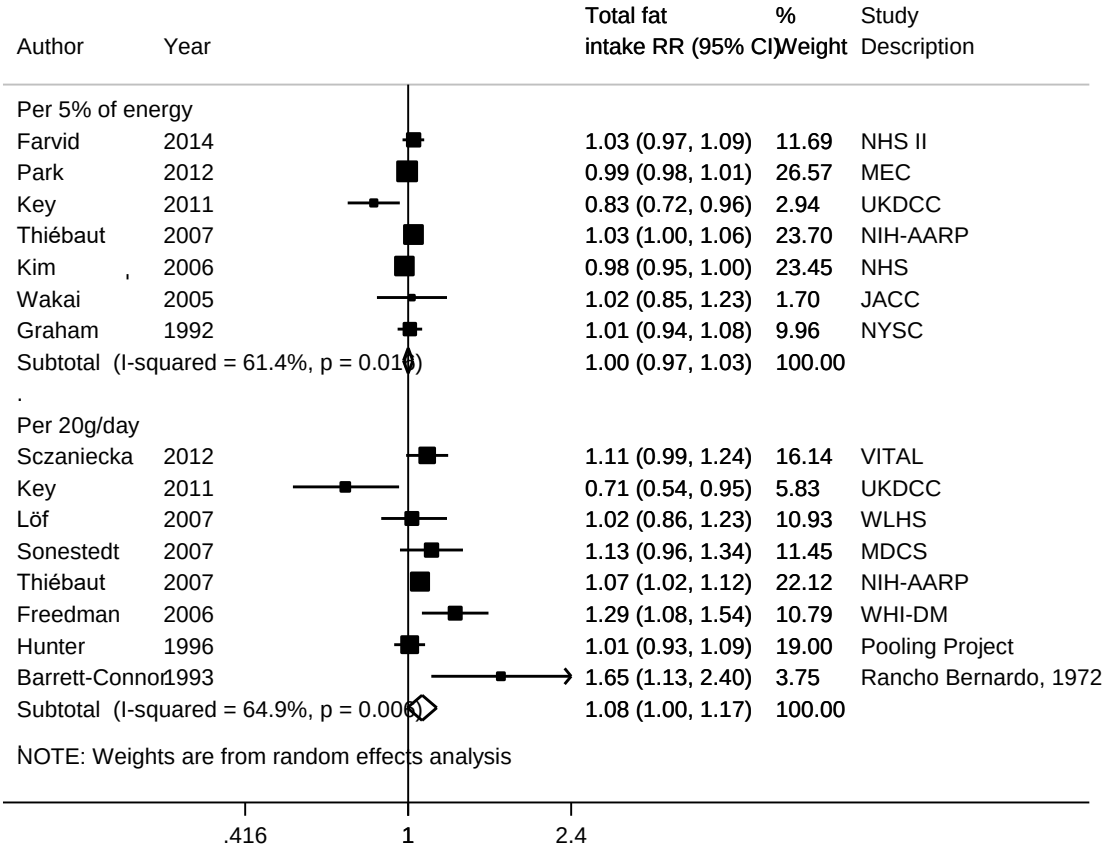


Figure 250 Funnel plot of studies included in the dose response meta-analysis of total fat intake and postmenopausal breast cancer

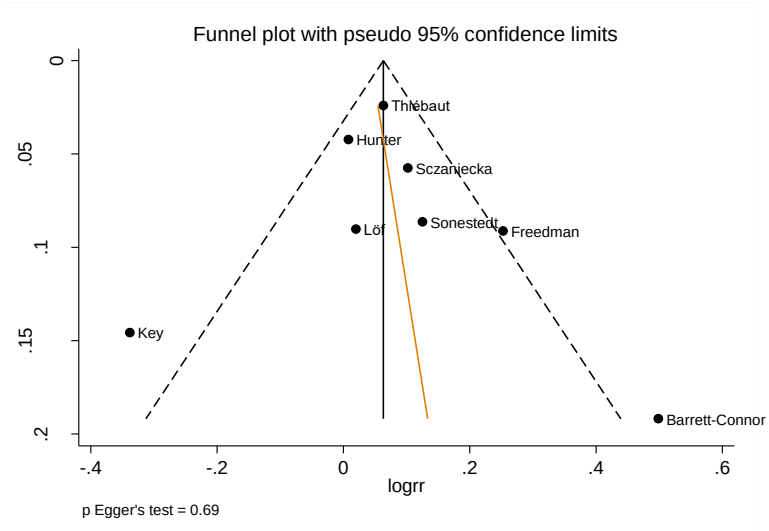


Figure 251 Funnel plot of studies included in the dose response meta-analysis of percentage of energy from fat and postmenopausal breast cancer

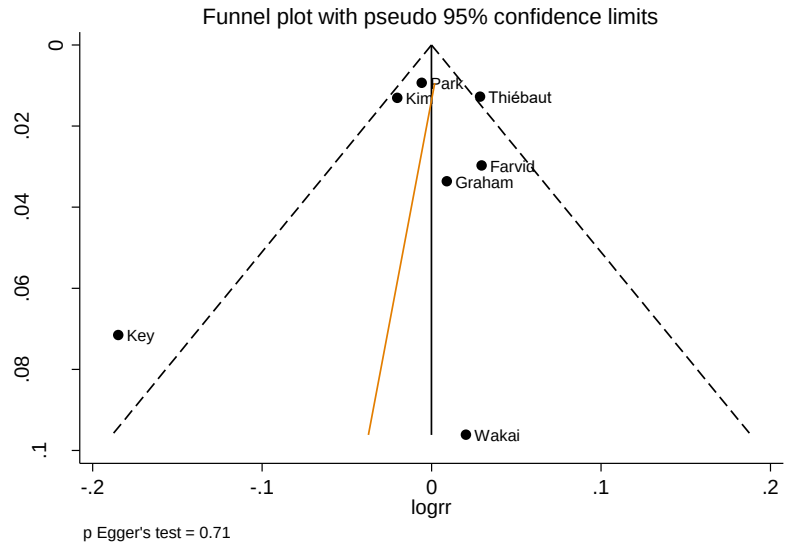


Figure 252 Relative risk of postmenopausal breast cancer for 20 g/day of total fat intake, by geographic location

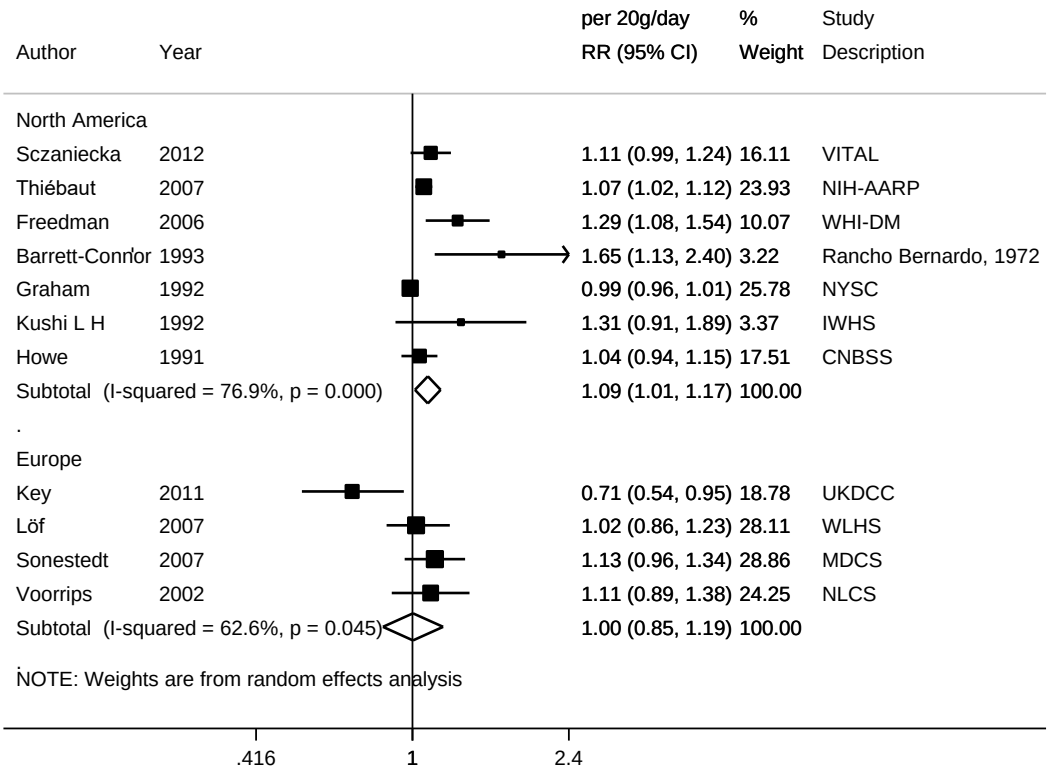


Figure 253 Relative risk of postmenopausal breast cancer for 5% of energy from fat, by geographic location

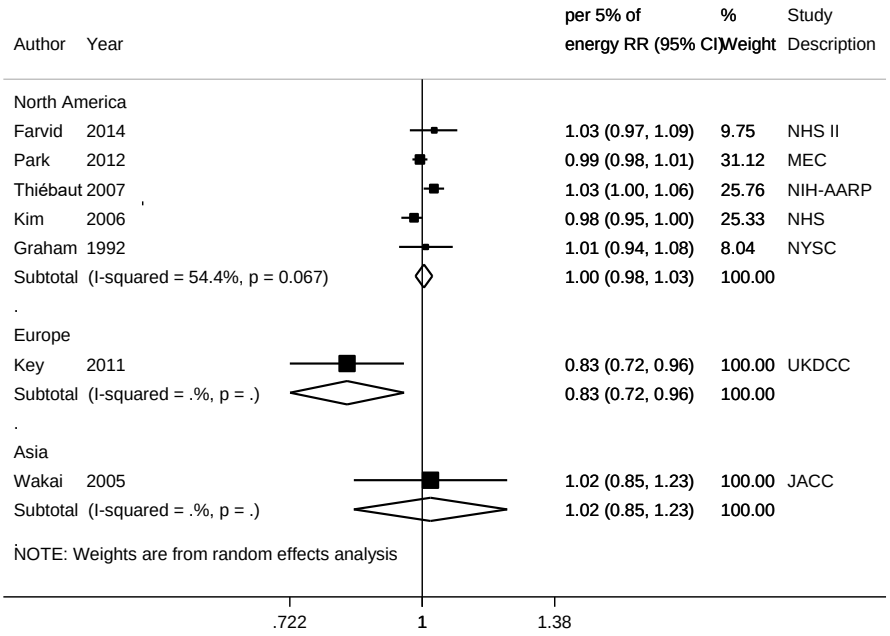


Figure 254 Relative risk of postmenopausal breast cancer for 20 g/day of total fat intake, by exposure assessment

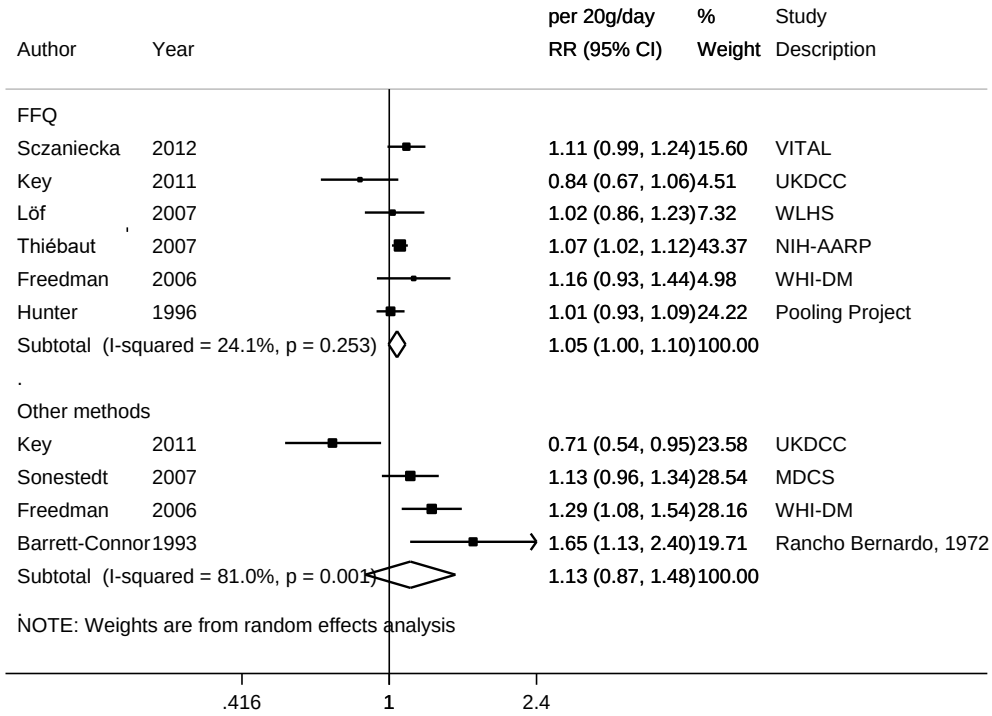


Figure 255 Relative risk of postmenopausal breast cancer for 5% of energy from fat, by exposure assessment

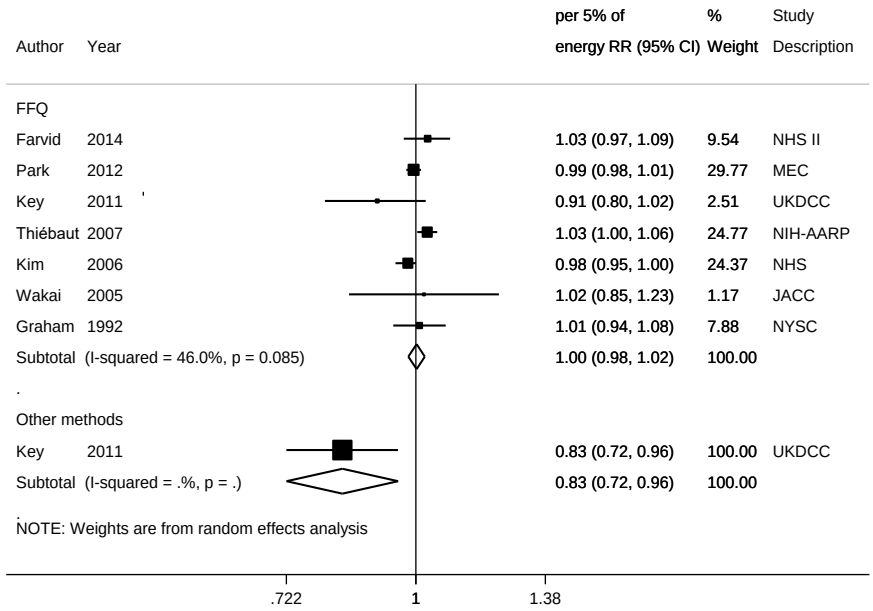
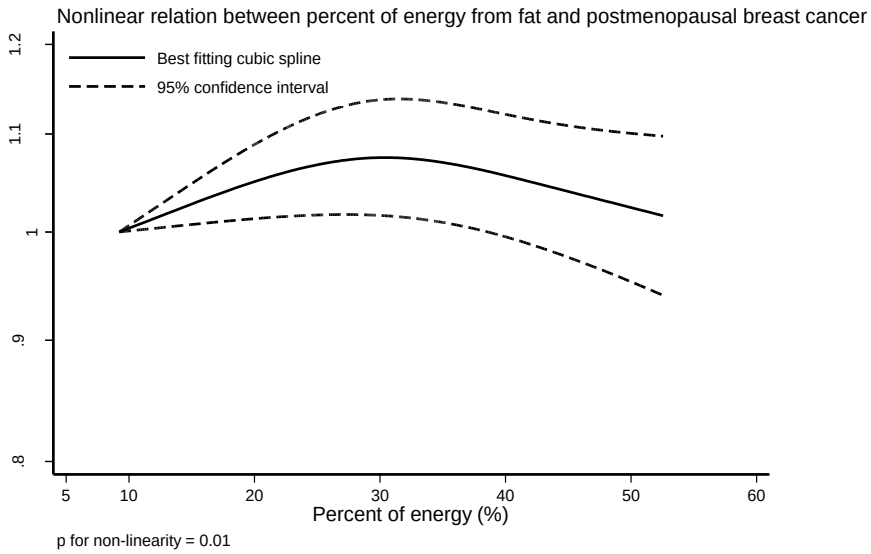


Figure 256 Non-linear dose-response meta-analysis of percentage of energy from fat and postmenopausal breast cancer



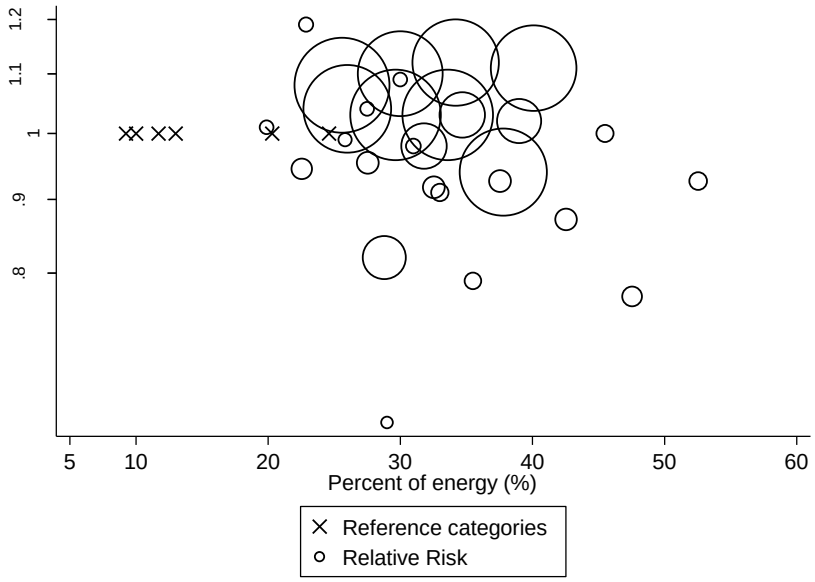
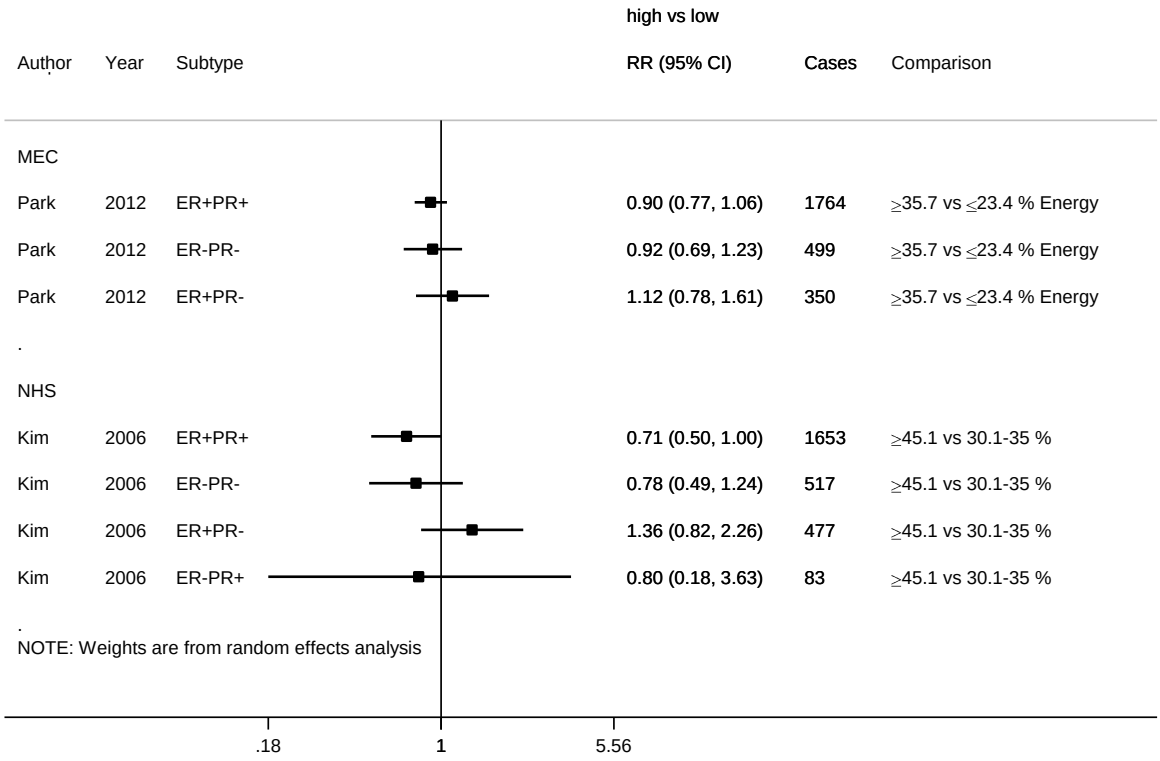


Table 183 Relative risk of postmenopausal breast cancer and percentage of energy from fat estimated using non-linear models

Percent of energy from fat (%)	RR (95%CI)
9.2	1
20.3	1.05 (1.01-1.09)
30.0	1.07 (1.02-1.14)
40.1	1.06 (1.00-1.12)

Figure 257 RR (95% CI) of hormone receptor defined postmenopausal breast cancer for the highest compared with the lowest percentage of energy from fat



5.2.2 Saturated fat

7.1.0.1 Energy from saturated fat

Cohort studies

Overall summary

Studies that measured saturated fat as an absolute intake (g/day) or a percentage of the total energy intake (% of energy) were reviewed together to facilitate a comprehensive review.

Forty-four publications from 32 studies that examined saturated fat intake and/or percentage of total energy from saturated fat were identified. Among which were three pooled analyses, two from the Pooling Project (Smith-Warner, 2001b, eight cohorts; Hunter, 1996, seven cohorts) and one from the UK Dietary Cohort Consortium (Key, 2011, four cohorts).

Dose-response meta-analyses were conducted to examine the associations of saturated fat intake (per 10g/day and per 5 % of energy) with risk of breast cancer and of premenopausal and postmenopausal breast cancer.

Notes on method:

As in the Pooling Project, results from the model that was mutually adjusted for other type of fat were selected if the studies presented such results. Models adjusted for total energy intake were selected, which represents an increase in saturated fat intake while keeping the total energy intake constant. If studies provided results both from the food diaries and the FFQs, results from the food diaries were used.

Table 184 Summary of results of the dose-response meta-analysis in the CUP SLR

	Breast cancer	**Premenopausal breast cancer**	**Postmenopausal breast cancer**
Saturated fat intake Increment unit used	Per 10g/day	Per 10g/day	Per 10g/day
Studies (n)	12[1]	2	11[3]
Cases	16 404	545	3 463
RR (95%CI)	1.04 (1.01-1.07)	0.95 (0.79-1.15)	1.07 (0.95-1.20)
Heterogeneity (I^2, p-value)	0%, 0.74	0%, 0.40	51%, 0.05
P value Egger test	0.42	-	1.00
Percentage of total energy from saturated fat Increment unit used	Per 5% of energy	Per 5% of energy	Per 5% of energy
Studies (n)	11[2]	6[2]	16[4]
Cases	17 592	>1511	>8 666
RR (95%CI)	1.06 (1.02-1.10)	1.07 (0.96-1.19)	1.01 (0.93-1.10)
Heterogeneity (I^2, p-value)	9%, 0.35	0%, 0.73	65%, 0.02
P value Egger test	-	-	0.52

[1]Included the Pooling Project (Hunter, 1996, seven cohorts).

[2]Included the Pooling Project (Smith-Warner, 2001b, eight cohorts, five in the analysis of premenopausal breast cancer).

[3]Included the UK Cohort Consortium (Key, 2011, four cohorts).

[4]Included the Pooling Project (Smith-Warner, 2001b, eight cohorts) and the UK Cohort Consortium (Key, 2011, four cohorts).

Breast cancer

Summary

Main results:

Twelve out of 22 studies (21 publications on saturated fat intake and eleven out of 17 studies (10 publications) on percentage of total energy from saturated fat identified could be included in the dose-response meta-analyses respectively.

Significant positive associations were observed for saturated fat, as intake or percentage of energy, and breast cancer risk (summary RR per 10g/day=1.04, 95% CI=1.01-1.07; summary RR per 5% of energy=1.06, 95% CI=1.02-1.10, respectively), with low heterogeneity between studies (I^2=0%, P=0.74; I^2=9%, P=0.35, respectively).

There was no evidence of significant publication or small studies bias (P for Egger's test=0.42 for studies on saturated fat intake).

Ten and six studies were excluded from the analysis of saturated fat intake and percentage of energy from saturated fat, respectively. In six studies on saturated fat (Key, 2011, EPIC-Norfolk, EPIC-Oxford, UKWCS, and WS II; Trichopoulou, 2010, EPIC-Greece; Thiebaut, 2001, E3N) and five on percentage of energy (Key, 2011; Thiebaut, 2001, see above for studies), the study populations overlapped with the multi-centre study that was already included in the analyses (Sieri, 2008, EPIC). The dietary intervention for breast cancer prevention was excluded because post-randomised saturated fat intake was examined (Martin, 2011, CDBCPT). Two studies on saturated fat intake (Horn-Ross, 2002, CTS; Toniolo, 1994 NYUWHS) did not provide sufficient data for analysis. Non-significant inverse (Horn-Ross, 2002) and positive (Toniolo, 1994) associations were reported. The Japanese study (Wakai, 2005, JACC) was excluded as percentage of energy from saturated fat was low (uppermost category ≥7.45 %) compared with other studies (lowermost category ≤8.3%). A non-significant inverse association was reported (Wakai, 2005).

One study nested within NHS and NHS II that reported results on preschool diet (age 3-5 years) and breast cancer risk in adulthood was excluded (Michels, 2006c). A non-significant positive association was observed.

One study reported that high saturated fat intake was associated with greater risk of ER+PR+ breast cancer (RR for the highest vs the lowest intake=1.28, 95% CI=1.09-1.52) but not ER-PR- breast cancer (RR=0.96, 95% CI=0.70-1.31) (Sieri, 2014).Sensitivity analyses:

Sieri, 2014 contributed 85% weight in the analysis of saturated fat intake. When this study was omitted in influence analysis, the association became non-significant (summary RR per 10g/day=1.02 (95% CI=0.96-1.09). For the analysis of percentage energy from saturated fat, the association became borderline significant when the larger studies (Sieri, 2008, EPIC 58% weight; Smith-Warner, 2001b, Pooling Project, 20% weight; Farvid, 2014, NHS II, 18% weight) was omitted in turn.

Subgroup analyses by geographic location, confounding adjustment, and methods of exposure assessment were conducted. Strong influence from individual studies or small numbers in the strata inhibited meaningful comparison. Significant positive associations were observed but became non-significant when the EPIC study (Sieri, 2014, 94% weight in the analysis of saturated fat intake among European studies) and the NHS II study (Farvid, 2014, 55% weight in the analysis of percentage of energy among North American studies) were omitted.

Non-linear dose-response meta-analysis:

There was no evidence of signficant non-linear relationship between saturated fat intake and breast cancer risk (P for non-linearity=0.19) (graph not shown). Non-linear analysis of percentage of saturated fat intake was not conductd because of insufficient data.

Study quality:

Saturated fat intake was assessed by a FFQ in most studies. Study centres within the EPIC study (Sieri, 2014; Sieri, 2008) used either a FFQ or a dietary history questionnaire. Knekt, 1990 used the dietary history method and Jones, 1987 used a 24-hour recall. There is some suggestion that measurement errors may slightly attenuate the association. In the EPIC study, RR estimates per 20% increase of calibrated saturated fat intake (dietary questionnaires against 24-hour dietary recalls) was 1.05 (95% CI=1.02-1.08) and of observed intake, 1.02, 95% CI=1.01-1.04) (Sieri, 2014) and RR estimates per 20% increase of calibrated saturated fat density was 1.04 (95% CI=1.00-1.07) and of observed density, 1.02 (95% CI=1.00-1.04) (Sieri, 2008), although in the Pooling Project, the RR estimates when corrected for measurement error were non-significant (RR per 10 g/day of intake=1.08, 95% CI=0.93-1.26, Hunter, 1996; RR per 5% of energy=1.06, 95% CI=0.92-1.24, Smith-Warner, 2001b); the consortium of four cohorts based in the UK (Key, 2011, UKDCC) observed non-significant associations using data from FFQs or food diaries; and on average, studies that used FFQs or other methods found similar non-significant results in the present review.

Case ascertainment was through cancer registries or confirmed through medical records. Most studies included in the analysis of percentage of energy from saturated fat were adjusted for age, BMI, alcohol intake, and reproductive factors (Sieri, 2008; Farvid, 2014; Smith-Warner, 2001b); the significant positive association remained when the Asian study of Singaporean Chinese (Gago-Dominguez, 2003) that did not adjust for alcohol intake was excluded. Multiple confounding factors were adjusted for in most studies of saturated fat intake (Sieri, 2014; Lof, 2007a; Hunter, 1996).

Table 185 Saturated fat intake and percentage of total energy from saturated fat and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	21 (20 publications) on saturated fat intake[1] 17 (10 publications) on percentage of energy from saturated fat[2]
Studies included in forest plot of highest compared with lowest exposure	11 on saturated fat intake 14 on percentage of energy from saturated fat
Studies included in linear dose-response meta-analysis	12[1] on saturated fat intake 11[2] on percentage of energy from saturated fat
Studies included in non-linear dose-response meta-analysis	7 on saturated fat intake

	Insufficient data

Note: Include cohort, and nested case-control designs

Table 186 Saturated fat intake and percentage of total energy from saturated fat and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR		CUP	
Increment unit used	**Per 10g/day**	**Per 5% of energy**	**Per 10g/day**	**Per 5% of energy**
Studies (n)	4	-	12[1]	11[2]
Cases	2 292	-	16 404	17 592
RR (95%CI)	0.97 (0.91-1.03)	-	1.04 (1.01-1.07)	1.06 (1.02-1.10)
Heterogeneity (I^2, p-value)	0%	-	0%, 0.74	9%, 0.35
P value Egger test	-	-	0.42	-
Stratified analysis in the CUP				
Increment unit used	**Per 10g/day**	**Per 10g/day**	**Per 5% of energy**	**Per 5% of energy**
Geographic location[3]	**Europe**	**North America**	**Europe**	**North America**
Studies (n)	6	5	3	7
Cases	12 446	3 704	9 329	7 949
RR (95%CI)	1.04 (1.02-1.07)	1.00 (0.90-1.12)	1.10 (0.99-1.21)	1.09 (1.02-1.17)
Heterogeneity (I^2, p-value)	0%, 0.88	43%, 0.12	40%, 0.19	0%, 0.72
Adjustment for age, BMI, alcohol intake, reproductive factors	**Adjusted**	**Not adjusted**	**Adjusted**	**Not adjusted**
Studies (n)	3	3	3	1
Cases	16 016	388	17 278	314
RR (95%CI)	1.04 (1.01-1.07)	0.98 (0.85-1.13)	1.06 (1.02-1.10)	0.93 (0.77-1.12)
Heterogeneity (I^2, p-value)	0%, 0.85	0%, 0.42	0%, 0.50	-
Exposure assessment	**FFQ**	**Food diaries/dietary**	**FFQ**	**FFQ/dietary history**

		history		
Studies (n)	4	3	4	1
Cases	6 859	10 202	11 130	7 119
RR (95%CI)	1.02 (0.95-1.08)	1.03 (0.96-1.11)	1.04 (0.96-1.13)	1.05 (1.00-1.10)
Heterogeneity (I^2, p-value)	0%, 0.76	14%, 0.31	46%, 0.14	-

[1]Included the Pooling Project (Hunter, 1996, seven cohorts).

[2]Included the Pooling Project (Smith-Warner, 2001b, eight cohorts).

[3]Also one Asian study (Gago-Dominguez, 2003) (RR per 5% of energy=0.93 (95% CI=0.77-1.12)

Table 187 Saturated fat intake and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Turner, 2011	29 studies (1 pooled study of prospective studies, 18 cohorts*, 10 case-control studies)	31 201 any breast cancer	China, France, Germany, Greece, Italy, the Netherlands, USA, Uruguay, Singapore, Sweden	Incidecne, any breast cancer	Highest vs lowest saturated fat intake (27 studies)	1.00 (0.95-1.05) Ptrend: >0.05	-
					Cohort studies (n=19)	0.99 (0.94-1.05) Ptrend: >0.05	-
					Case-control studies (n=8)	1.08 (0.94-1.24) Ptrend: >0.05	-

*All cohort studies identified were included in the present review, except for the study of Saadatian-Elahi, 2002 that was on biomarkers of fat intake.

Table 188 Saturated fat intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Sieri, 2014 BRE80546 France, Italy, Spain, UK, Netherlands, Greece, Germany, Sweden, Denmark, Norway	EPIC, Prospective Cohort, Age: 20-70 years, W	10 062/ 337 327 11.5 years	Cancer and mortality registries, health Insurance & pathology records, active follow up	FFQ, diet history, 7-day food diary	Incidence, breast cancer	48 vs 15 g/day	1.14 (1.03-1.26) Ptrend:0.006	Age, BMI, educational level, energy from alcohol, HRT use, menopausal status, non-alcohol energy, pregnancies, smoking status, study center
						per 20 %	1.02 (1.01-1.04)	
		3 540/			Incidence, breast cancer ER+/PR+	47.5 vs 15.4 g/day	1.28 (1.09-1.52) Ptrend:0.009	
						per 20 %	1.03 (1.01-1.06)	
		1 072/			Incidence, breast cancer ER+/PR-	47.5 vs 15.4 g/day	1.31 (0.97-1.77) Ptrend:0.05	
						per 20 %	1.06 (1.01-1.11)	
		1 018/			Incidence, breast cancer ER-/PR-	47.5 vs 15.4 g/day	0.96 (0.70-1.31) Ptrend:0.39	
						per 20 %	0.99 (0.94-1.04)	
		3 155/			Incidence, breast cancer unknown ER/PR status	47.5 vs 15.4 g/day	1.07 (0.90-1.27) Ptrend:0.19	
		539/			Incidence, breast cancer HER-2 +	48.6 vs 15.7 g/day	0.95 (0.62-1.46) Ptrend:0.86	
						per 20 %	0.98 (0.92-1.05)	
		1 720/			Incidence, breast	48.6 vs 15.7	1.29 (1.01-1.64)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					cancer HER-2 -	g/day	Ptrend:0.04	
						per 20 %	1.04 (1.00-1.09)	
		5 756/			Incidence, breast cancer HER-2 unknown	48.6 vs 15.7 g/day	1.14 (1.01-1.30) Ptrend:0.03	
		5 615/			Incidence, breast cancer ER+	47.5 vs 15.4 g/day	1.26 (1.11-1.44) Ptrend:0.001	
						per 20 %	1.03 (1.01-1.05)	
		1 395/			Incidence, breast cancer ER-	47.5 vs 15.4 g/day	0.98 (0.75-1.27) Ptrend:0.62	
						per 20 %	1.01 (0.97-1.06)	
		3 761/			Incidence, breast cancer PR+	47.5 vs 15.4 g/day	1.26 (1.07-1.48) Ptrend:0.01	
						per 20 %	1.04 (1.01-1.06)	
		2 097/			Incidence, breast cancer PR-	47.5 vs 15.4 g/day	1.13 (0.91-1.40) Ptrend:0.42	
						per 20 %	1.02 (0.99-1.06)	
Löf, 2007 BRE80144 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	974/ 44 569 13 years	Cancer registry	FFQ	Incidence, Invasive breast cancer	37.9 vs 12.9 g/day	1.12 (0.69-1.81) Ptrend:0.65	Age, age at first child birth, age at menarche, alcohol consumption, BMI, educational level, family history of cancer, non-alcohol energy, parity, total fat,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								use of oral contraception
						per 10 g/day	1.12 (0.84-1.49)	
Hunter, 1996 Canada, USA, the Netherlands, Sweden	The Pooling Project Pooled study of 7 cohorts*, Age: 28-90 years, W (*AHS, CNBSS, IWHS, NLCS, NYSC, NHS(a), NHS(b), SMC),	4 980/ 337 819	Self-reported and verified by medical records and/or record linkage with cancer registries	FFQ	Incidence, breast cancer	Q5 vs Q1	1.07 (0.95-1.20) Ptrend:0.41	Age at menarche, menopausal status, parity, age at birth of first child, BMI, height, education, history of benign breast disease, maternal history of breast cancer, history of breast cancer in a sister, OC use, fibre intake, alcohol intake, energy intake
						per 10 g/day	1.03 (0.95-1.11)	
	AHS	153/ 15 172				-	-	
	CNBSS	514/ 56 837				per 10 g/day	1.07 (0.85-1.35)	
	IWHS	723/ 34 406				per 10 g/day	1.26 (1.04-1.53)	
	NLCS	434/ 62 412				per 10 g/day	1.08 (0.87-1.35)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	NYSC	376/ 18 475				per 10 g/day	0.90 (0.69-1.19)	
	NHS(a)	1 094/ 89 046				per 10 g/day	0.95 (0.85-1.07)	
	NHS(b)	911/ 68 817				per 10 g/day	0.99 (0.84-1.17)	
	SMC	775/ 61 471				per 10 g/day	1.02 (0.87-1.19)	
Gaard, 1995 BRE17516 Norway	Norway National Health Screening Service, 1974, Prospective Cohort, Age: 35-49 years, W, Screening Program	248/ 24 897 10 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer,	≥28 vs ≤19.9 g/day	1.01 (0.75-1.57) Ptrend:0.74	Age , age-underlying cox models, BMI, energy Intake , height, menopausal status, smoking habits
Knekt, 1990 BRE04898 Finland	Mobile Clinic Health Examination Survey, 1973, Prospective Cohort, Age: 20-69 years, W, Screening Program	3 988 20 years	All histology	Dietary history questionnaire	Incidence, breast cancer,	≥55.4 vs ≤39.5 g/day	1.36 (0.50-3.73) Ptrend:0.31	Age, energy Intake
Jones, 1987 BRE04461 USA	NHANES I, Prospective Cohort,	86/ 5 485 10 years	Medical records + self-reported +death	24h recall	Incidence, breast cancer,	≥27 vs ≤12.9 g/day	0.29 (0.12-0.67)	Age, age at menarche, age at menopause,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Age: 25-74 years, W		certificate					BMI, educational level, family history, menopausal status

Table 189 Percentage of total energy from saturated fat and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Sieri, 2008 BRE80202 Europe	EPIC, Prospective Cohort, Age: 20-70 years, W	7 119/ 319 826 8.8 years	Cancer registry / database / pathology reports	FFQ	Incidence, breast cancer	18.2 vs 9.9 % energy/day	1.10 (1.01-1.19) Ptrend:0.068	Age, alcohol Intake, centre location, educational attainment, energy Intake, height, menopausal status, smoking status, weight
Farvid, 2014 BRE80577 USA	NHS II, Prospective Cohort, Age: 26-45 years, W	2 830/ 88 804 20 years	Self-report verified by medical record and pathology report	Semi-quantitative FFQ for premenopausal diet	Incidence, breast cancer	14.2 vs 8.3 %	1.11 (0.99-1.25) Ptrend:0.04	Age, age at menarche, age at menopause, alcohol Intake, BMI, calendar year, energy, energy from protein, family history of breast cancer In first degree relatives, height, history of

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								benign breast disease, hormone use, menopausal status, oc use, parity and age at first birth, race, smoking status and dose
Gago-Dominguez, 2003 BRE17518 China	SCHS, Prospective Cohort, Age: 45-74 years, W	314/ 63 257 5.3 years	Partially histological - over 80%	FFQ	Incidence, breast cancer,	≥10.73 vs ≤7.18 % energy	0.92 (0.67-1.26) Ptrend:0.59	Age , alcohol, educational level, ethnicity, family history, menstrual characteristics , parity/pregnancies
Smith-Warner, 2001b Canada, USA, the Netherlands, Sweden	The Pooling Project, Pooled study of 8 cohorts*, Age: 28-90 years, W (*AHS, CNBSS, IWHS, NHS(a), NHS(b), NLCS, NYSC, NYUWHS, SMC),	7 329/ 351 821	Self-reported and verified by medical records and/or record linkage with cancer registries	FFQ	Incidence, breast cancer	Q4 vs Q1	1.01 (0.89-1.16) Ptrend:0.85	Percent of energy from protein, percent of energy from alcohol, age at menarche, parity, age at birth of first child, menopausal status at diagnosis, MHT use, OC use, history of benign breast disease, family history of breast cancer, smoking status, education, BMI, BMI-menopausal status at diagnosis interaction, height, fibre intake, energy intake, monounsaturated

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								fat, polyunsaturated fat
						per 5% of energy	1.09 (1.00-1.19)	
	AHS	160/ 15 172				per 5% of energy	1.66 (0.77-3.55)	
	CNBSS	419/ 56 837				per 5% of energy	1.24 (0.87-1.75)	
	IWHS	1 130/ 34 406				per 5% of energy	1.19 (0.96-1.46)	
	NHS(a)	1 020/ 89 046				per 5% of energy	0.88 (0.73-1.06)	
	NHS(b)	1 638/ 68 817				per 5% of energy	1.04 (0.88-1.22)	
	NLCS	887/ 62 412				per 5% of energy	1.25 (1.02-1.53)	
	NYSC	367/ 18 475				per 5% of energy	0.84 (0.40-1.77)	
	NYUWHS	385/ 14 006				per 5% of energy	1.04 (0.82-1.32)	
	SMC	1 323/ 61 467				per 5% of energy	1.13 (0.94-1.35)	

Table 190 Saturated fat intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Key, 2011 UK	UK Dietary Cohort Consortium Pooled study of 4 cohorts* Mean age: 56.4 ±9.7 years among cases, W (*EPIC-Norfolk; EPIC-Oxford; UKWCS; Whitehall II study)	657 cases/ 1 911 controls EPIC-Norfolk: 353 cases/1 252 controls EPIC-Oxford: 194 cases/ 194 cases UKWCS: 42 cases/202 controls Whitehall II study: 68 cases/263 controls	Record linkage with National Statistics and cancer registries	Food diary and FFQ	Incidence, breast cancer	Food diaries ≥37.2 vs ≤14.1 g/day	0.86 (0.57-1.30) Ptrend:0.224	Age, alcohol consumption, parity, menopausal status, current hormone replacement therapy use, physical activity, height, weight, and energy intake	Superseded by Sieri, 2014, BRE80546
						per 9.6 g/day	0.92 (0.80-1.06)		
						FFQ ≥43.0 vs ≤13.7 g/day	0.67 (0.44-1.02) Ptrend: 0.606		(Results from FFQ was included in stratified analysis)
						per 12.5 g/day	0.96 (0.82-1.12)		
Martin, 2011 BRE80323 Canada	CDBCPT, Nested Case Control, Age: 47 years	220/ 440 controls 10	Pathology	Food records	Incidence, Invasive breast cancer	18 vs 11 g/day	1.14 (0.84-1.55)	Age, age at first child birth, age at menarche, family history of breast cancer, HRT use, menopausal status, number	Excluded, exposure was post-randomised diet

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								of childbirths, parity, randomisation, smoking	
		167/ 334 controls			Incidence, breast cancer ER+	18 vs 11 g/day	1.24 (0.88-1.75)		
		42/ 84 controls			Incidence, breast cancer ER-	18 vs 11 g/day	0.39 (0.13-1.14)		
Trichopoulou, 2010 BRE80320 Greece	EPIC-Greece, Prospective Cohort, Age: 20-68 years	240/ 14 807 9.8 years	Medical records and pathology reports	FFQ	Incidence, breast cancer	per 11 g/day	1.02 (0.84-1.23)	Age, age at first child birth, age at menarche, age at menopause, BMI, educational level, energy Intake, height, HRT use, menopausal status, metabolic equivalents, parity, smoking	Superseded by Sieri, 2014, BRE80546
Michels, 2006c BRE80633 USA	NHS I and II, Nested Case Control, W	582/ 1569 controls 17 years	Self report verified by medical record	Semi-quantitative FFQ on preschool (age 3-5 years) diet, completed by mother of participants	Incidence, Invasive breast cancer	35.4 vs 10.7 g	1.24 (0.87-1.78)	Age, age at first child, age at menarche, BMI, energy Intake, family history of breast cancer, parity	Excluded, childhood diet
						per 1 SD	1.05 (0.95-1.16)		
Sieri, 2008 BRE80202 Europe	EPIC, Prospective Cohort,	7 119/ 319 826 8.8 years	Cancer registry / database / pathology	FFQ	Incidence, breast cancer	45 vs 16.2 g/day	1.13 (1.00-1.27) Ptrend:0.038	Age, alcohol Intake, centre location,	Superseded by Sieri, 2014, BRE80546

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 20-70 years, W		reports					educational attainment, energy Intake, height, menopausal status, smoking status, weight	
Bingham, 2003 BRE14387 UK	EPIC-UK, Nested Case Control, Age: 45-74 years, W	13 070 7 years	Partially histological - over 80%	7-day record + questionnaire	Incidence, Invasive breast cancer,	34.31 vs 10.87 g/day	1.98 (1.05-3.72) Ptrend:0.005	Body weight, height, HRT use, menopausal status, parity/pregnancies, univariate partition	Superseded by Sieri, 2014, BRE80546
						45.93 vs 12.93 g/day	1.35 (0.69-2.61) Ptrend:0.229		
Frazier, 2003 BRE02941 USA	NHS, Nested Case Control, Age: 40-65 years, W, Registered nurses	121 700 10 years	All histology	FFQ	Incidence, breast cancer	48.4 vs 14.5 g/day	0.98 Ptrend:0.82	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, family history, height, HRT use, menopausal status, nutrients, parity/pregnancies	Excluded, adolescence intake
Horn-Ross, 2002 BRE15412 USA	CTS, Prospective Cohort, Age: 21-103 years,	111 383 2 years	Partially histological - over 80%	FFQ	Incidence, Invasive breast cancer,	≤25 vs ≤11 g/day	0.80 (0.60-1.20) Ptrend:0.2	Age , age at first child, age at menarche, BMI, energy Intake , ethnicity, family	Excluded, no exposure levels

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	W, Registered teachers							history, menopausal status, physical activity	
Thiebaut, 2001 BRE12244 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W, Registered teachers	65 879 3.4 years	Not specified	FFQ-semi-quantitative	Incidence, breast cancer,	4° quartile vs 1° quartiles g/day	1.22 (0.91-1.63)	Age , age at menarche, age at menopause, alcohol, benign breast disease, BMI, educational level, energy Intake , family history, marital status	Superseded by Sieri, 2014, BRE80546
Wolk, 1998 BRE13548 Sweden	SMC, Prospective Cohort, Age: 40-76 years, W, Screening Program	61 147 4.2 years	All histology	FFQ	Incidence, Invasive breast cancer,	≥21.71 vs ≤16.29 g/day	1.20 (0.89-1.63) Ptrend:.31	Age , age at first child, alcohol, BMI, educational level, energy Intake , family history, nutrients, parity/pregnancies, residual (willet)	Superseded by the Pooling Project (Hunter, 1996)
						per 10 g/day	1.26 (0.92-1.74)		
Toniolo, 1994 BRE12398 USA	NYUWHS, Nested Case Control, Age: 35-65 years, W	735 7 years	Medical records	FFQ-semi-quantitative	Incidence, Invasive breast cancer,	50 vs 11 g/day	1.47 (0.88-2.46) Ptrend:0.09		Excluded, number of cases and non-cases per category no available

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Giovannucci, 1993a BRE03262 USA	NHS, Nested Case Control, Age: 30-55 years, W, Registered nurses	392/ 786 controls 2 years	Medical records + death certificate	FFQ-semi-quantitative	Incidence, breast cancer,	Q 5 vs Q 1	0.90 (0.61-1.34) Ptrend:0.47	Age , residual (willet)	Superseded by the Pooling Project (Hunter, 1996)
						per 45 g/day	1.11 (0.65-1.90)		
Willett, 1992 BRE13438 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	1 439/ 89 494 8 years	Medical records + self-reported	FFQ-semi-quantitative	Incidence, breast cancer,	≥34 vs ≤21.9 g/day	0.86 (0.73-1.02) Ptrend:0.22	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, energy Intake , family history, menopausal status, nutrients, other design Issue, parity/pregnancies	Superseded by the Pooling Project (Hunter, 1996)
Howe, 1991 BRE17622 canada	CNBSS, Nested Case Control, Age: 40-59 years, W, Screening Program	519/ 1182 controls 5 years	All histology	Dietary history questionnaire	Incidence, breast cancer,	Q 4 vs Q 1	1.08 (0.73-1.59) Ptrend:.10	Age , energy Intake , recruitment center, time of recruitment	Superseded by the Pooling Project (Hunter, 1996)
Willett, 1987b BRE13442 USA	NHS, Prospective Cohort, Age: 34-59	601/ 89 538 4 years	Medical records + self-reported	FFQ-semi-quantitative	Incidence, breast cancer,	Q 5 vs Q 1	0.84 (0.66-1.08) Ptrend:0.06	Age , age at first child, alcohol, benign breast disease, body	Superseded by the Pooling Project (Hunter, 1996)

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	years, W, Registered nurses							weight, family history, menopausal status, smoking habits	

Table 191 Percentage of total energy from saturated fat and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Boeke, 2014a BRE80585 USA	NHS I and II, Prospective Cohort, Age: 25-55 years, W	9 979/ 182 671 30 years	Medical records, pathology reports, next of kin, death certificate, ndi	Semi-quantitative FFQ	Incidence, breast cancer	Q 5 vs Q 1	0.95 (0.86-1.05) Ptrend:0.29	Age, age at menarche, age at menopause, alcohol Intake, BMI at age 18 years, breastfeeding, calendar year, cohort, energy from fat sources, family history of breast cancer, height, history of benign breast disease, menopausal status, oral contraceptive use, parity and age at first birth, physical activity, postmenopausal hormone use, protein, total energy Intake, weight change	Superseded by the Pooling Project (Smith-Warner, 2001b)
		1 529/			Mortality, breast cancer	Q 5 vs Q 1	0.98 (0.75-1.26) Ptrend:0.96		
Key, 2011 UK	UK Dietary Cohort Consortium,	657 cases 1911 controls	Record linkage with National Statistics and	Food diary and FFQ	Incidence, breast cancer	Food diaries ≥16.5 vs ≤8.5 % of energy	0.81 (0.60-1.10) Ptrend:0.343	Age, alcohol consumption, parity,	Superseded by Sieri, 2008, BRE80202

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	Pooled study of 4 cohorts* Mean age: 56.4 ±9.7 years among cases, W (EPIC-Norfolk; EPIC-Oxford; UKWCS; Whitehall II study),	EPIC-Norfolk: 353 cases/1 252 controls EPIC-Oxford: 194 cases/ 194 cases UKWCS: 42 cases/202 controls Whitehall II study: 68 cases/263 controls	cancer registries					menopausal status, current hormone replacement therapy use, physical activity, height, weight, and energy intake	
						Per 1 SD (3.2% of energy)	0.95 (0.87-1.05)		
						FFQ ≥16.4 vs ≤7.9 % of energy	0.81 (0.60-1.09) Ptrend:0.434		(Results from FFQ was included in stratified analysis)
						Per 1 SD (3.4% of energy)	0.96 (0.87-1.06)		
Bingham, 2003 BRE14387 UK	EPIC-UK, Nested Case Control, Age: 45-74 years, W	13 070 7 years	Partially histological - over 80%	7-day record + questionnaire	Incidence, Invasive breast cancer,	Q 5 vs Q 1	1.17 (0.65-2.11) Ptrend:0.232	Body weight, density, height, HRT use, menopausal status, parity/pregnancies	Superseded by Sieri, 2008, BRE80202
Wakai, 2005 BRE24482 Japan	JACC, Prospective Cohort, Age: 40-79 years,	129/ 26 291 7.6 days	Partially histological - over 80%	FFQ	Incidence, breast cancer,	≥7.45 vs ≤5.24	0.68 (0.40-1.15) Ptrend:0.066	Age , age at first child, age at menarche, age at menopause, alcohol, BMI,	Excluded – low percentage of energy from saturated fat

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	W, Previous study							educational level, energy Intake , family history, height, HRT use, other energy Index, other nutritional factors, other physical activity Index, parity/pregnancies, recruitment center, smoking habits	
Thiebaut, 2001 BRE12244 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W, Registered teachers	65 879 3.4 years	Not specified	FFQ-semi-quantitative	Incidence, breast cancer,	Q4 vs Q1	1.06 (0.87-1.29)	Age , age at menarche, age at menopause, alcohol, benign breast disease, BMI, density, educational level, family history, marital status	Superseded by Sieri, 2008, BRE80202
Holmes, 1999 BRE04008 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	121 700 14 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, Invasive breast cancer,	per 5 % of total energy/day	0.94 (0.88-1.01)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, energy Intake , family history, height,	Superseded by the Pooling Project (Smith-Warner, 2001b)

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								HRT use, menopausal status, nutrients	

Figure 258 RR estimates of breast cancer by levels of saturated fat intake and percentage of total energy from saturated fat

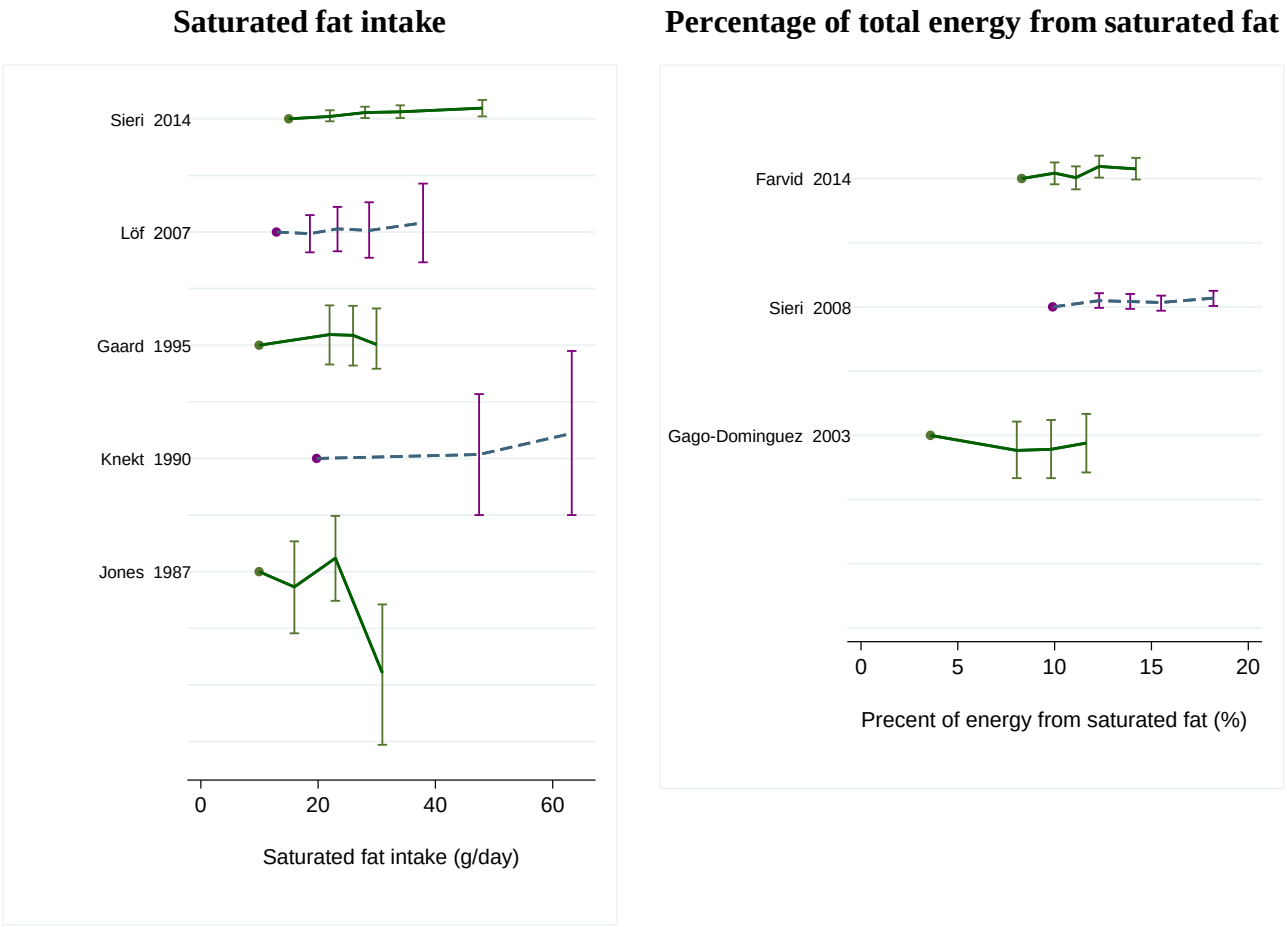


Figure 259 RR (95% CI) of breast cancer for the highest compared with the lowest saturated fat intake and percentage of total energy from saturated fat

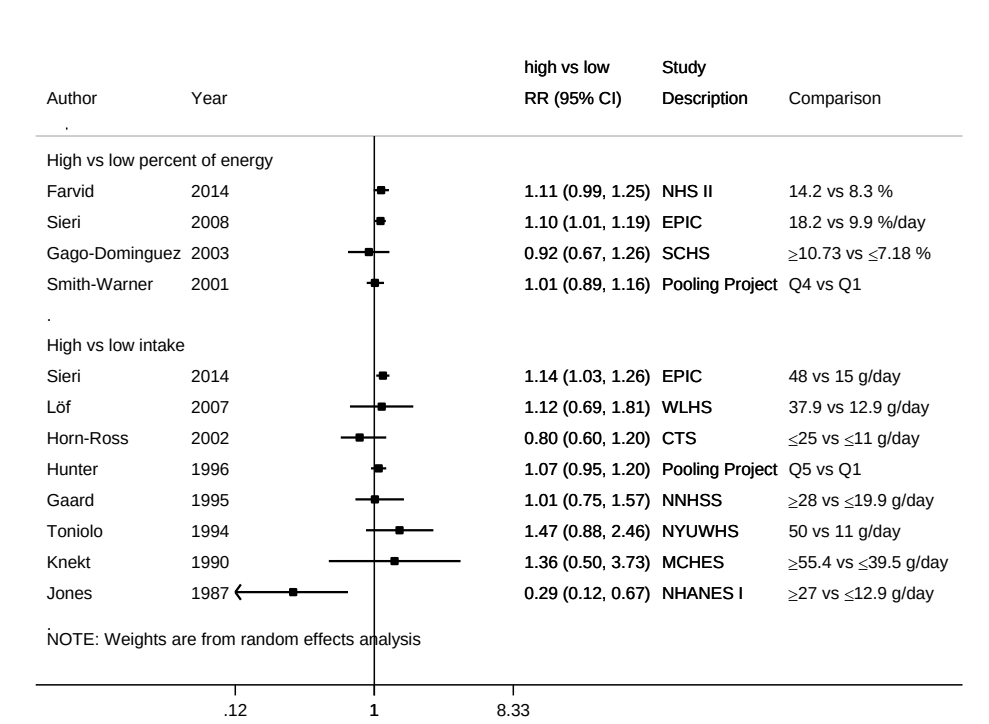


Figure 260 Relative risk of breast cancer for 10 g/day of saturated fat intake and 5% of total energy from saturated fat

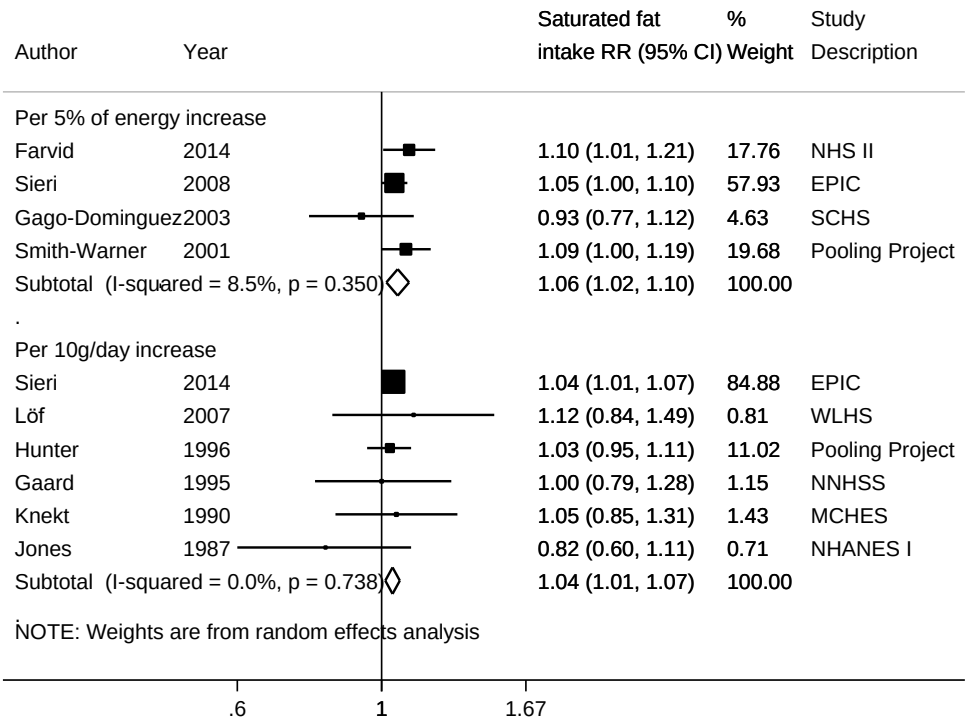
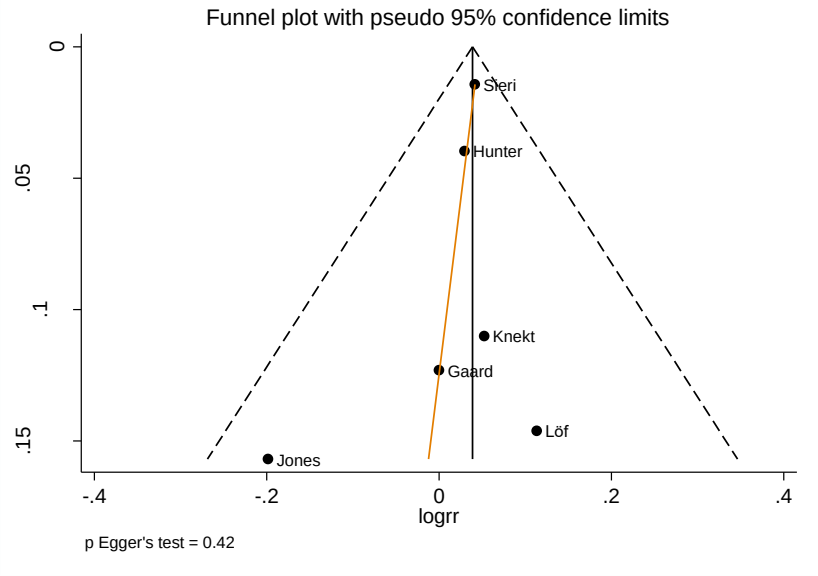
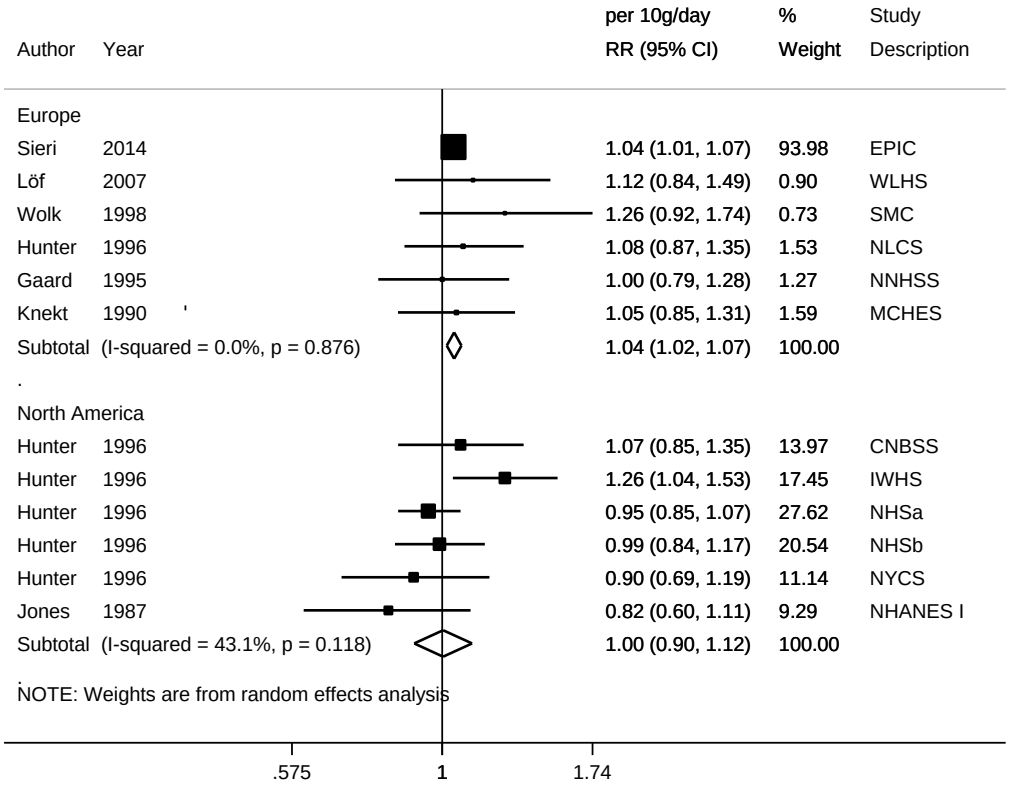


Figure 261 Funnel plot of studies included in the dose response meta-analysis of saturated fat intake and breast cancer



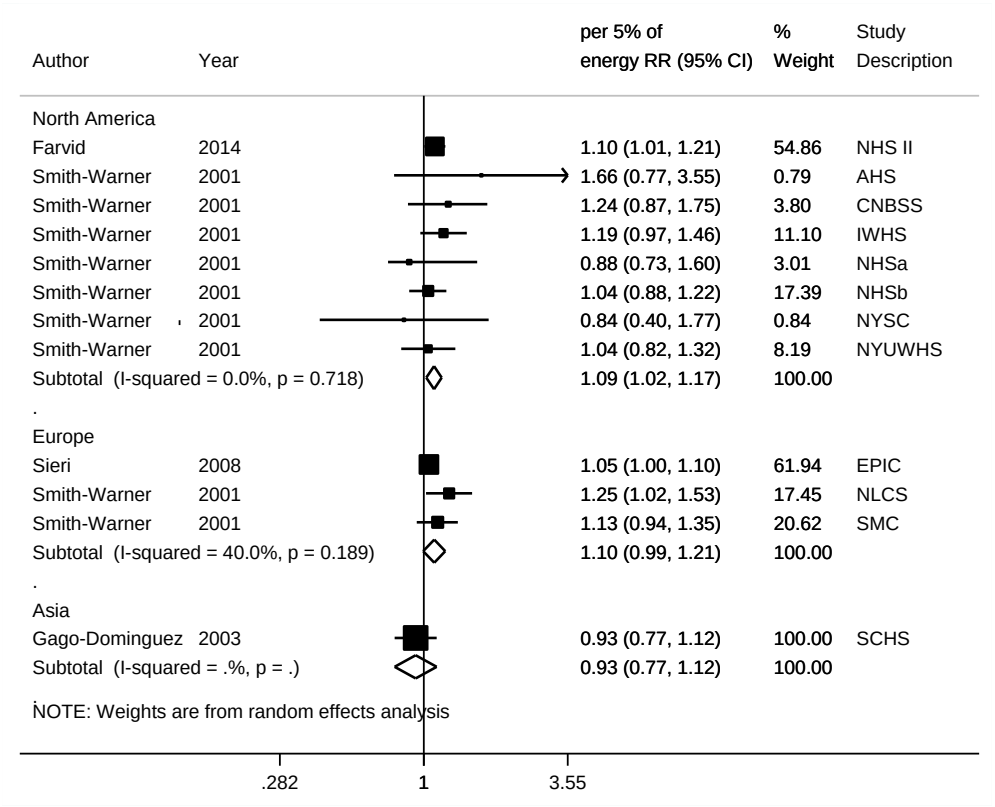
Note: Funnel plot of studies on percentage of total energy from saturated fat was not produced because of insufficient data.

Figure 262 Relative risk of breast cancer for 10 g/day of saturated fat intake, by geographic location



Note: Results from the individual studies in the Pooling Project and the study (Wolk, 1998) that was previously superseded by the Pooling Project were used in the strata.

Figure 263 Relative risk of breast cancer for 5% of total energy from saturated fat, by geographic location



Note: Results from the individual studies in the Pooling Project were used in the strata.

Figure 264 Relative risk of breast cancer for 10 g/day of saturated fat intake, by exposure assessment methods

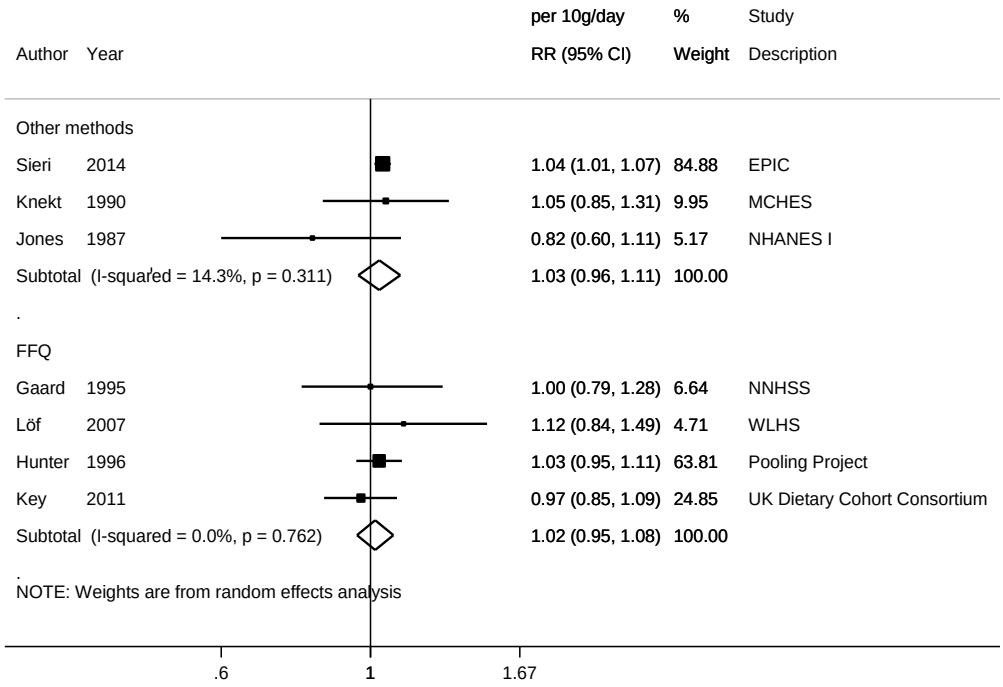
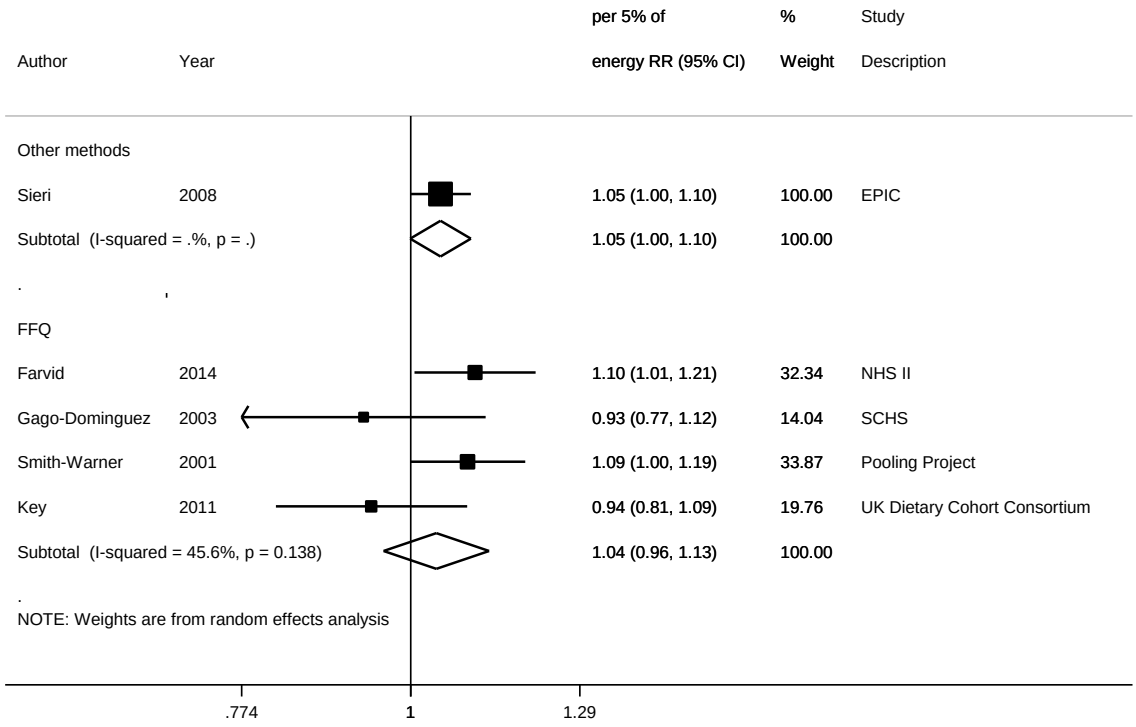


Figure 265 Relative risk of breast cancer for 5% of total energy from saturated fat, by exposure assessment methods



Premenopausal breast cancer

Summary

Main results:

Two out of four studies (six publications) on saturated fat intake and all six studies (four publications) on percentage of total energy from saturated fat identified could be included in the dose-response meta-analyses respectively.

Premenopausal breast cancer risk was non-significantly inversely associated with saturated fat intake (summary RR per 10 g/day=0.95, 95% CI=0.79-1.15, I^2=0%, P=0.40) and non-significantly positively associated with percentage of energy from saturated fat (summary RR per 5%=1.07, 95% CI=0.96-1.19, I^2=0%, P=0.73).

For the two excluded studies, one (NHS II - Linos, 2010; Frazier, 2004) investigated adolescent intake and the other (NHS – Willett, 1992; Willett, 1987b) did not have sufficient data to be included the analysis. For the highest versus the lowest saturated fat intake, a non-significant inverse association was observed.

Study quality:

Studies were either from North America or Europe. Saturated fat intake was assessed by a FFQ in all studies. Case ascertainment was through cancer registries or confirmed through medical records. Studies were adjusted for age, BMI, alcohol intake, and reproductive factors, apart from Trichopoulous, 2010 that was not adjusted for alcohol intake.

Table 192 Saturated fat intake and percentage of total energy from saturated fat and premenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	4 (6 publications) on saturated fat intake 9 (4 publications) on percentage of energy from saturated fat[1]
Studies included in forest plot of highest compared with lowest exposure	2 on saturated fat intake 1 on percentage of energy from saturated fat
Studies included in linear dose-response meta-analysis	2 on saturated fat intake 6[1] on percentage of energy from saturated fat
Studies included in non-linear dose-response meta-analysis	Not enough studies

[1]Included the Pooling Project (Smith-Warner, 2001b, five cohorts in the analysis of premenopausal women).

Table 193 Saturated fat intake and percentage of total energy from saturated fat and premenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR		**CUP**	
Increment unit used	**Per 10g/day**	**Per 5%/day**	**Per 10g/day**	**Per 5%/day**
Studies (n)	-	-	2	6[1]
Cases	-	-	545	>1511
RR (95%CI)	-		0.95 (0.79-1.15)	1.07 (0.96-1.19)
Heterogeneity (I^2, p-value)	-	-	0%, 0.40	0%, 0.73
P value Egger test	-	-	-	-

[1]Included the Pooling Project (Smith-Warner, 2001b, five cohorts in the analysis of premenopausal women).

Table 194 Saturated fat intake and premenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Turner, 2011	4 studies (2 cohorts, 2 case-control studies)	>4 025 premenopausal breast cancer	Germany, USA	Incidence, premenoapausal breast cancer	Highest vs lowest saturated fat intake (4 studies)	0.96 (0.87-1.05) Ptrend: >0.05	-

*All cohort studies identified were included in the present review.

Table 195 Saturated fat intake and premenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Trichopoulou, 2010 BRE80320 Greece	EPIC-Greece, Prospective Cohort, Age: 20-68 years	14 807 9.8 years	Medical records and pathology reports	FFQ	Incidence, breast cancer, premenopausal	per 11 g/day	0.99 (0.78-1.25)	Age, age at first child birth, age at menarche, BMI, educational level, energy Intake, height, metabolic equivalents, parity, smoking
Löf, 2007 BRE80144 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	432/ 44 569 13 years	Cancer registry	FFQ	Incidence, Invasive breast cancer, age < 50 yrs	37.9 vs 12.9 g/day	0.93 (0.56-1.88) Ptrend:0.86	Age, age at first child birth, age at menarche, alcohol consumption, BMI, educational level, family history of cancer, non-alcohol energy, parity, total

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								fat, use of oral contraception
						per 10 g/day	0.81 (0.53-1.23)	

Table 196 Percentage of total energy from saturated fat and premenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Farvid, 2014 BRE80577 USA	NHS II, Prospective Cohort, Age: 26-45 years, W	1 511/ 88 804 20 years	Self-report verified by medical record and pathology report	Semi-quantitative FFQ, premenopausal diet	Incidence, premenopausal breast cancer	14.2 vs 8.3 %	1.10 (0.93-1.29) Ptrend:0.4	Age, age at menarche, alcohol Intake, BMI, calendar year, energy, energy from protein, family history of breast cancer In first degree relatives, height, history of benign breast disease, OC use, parity and age at first birth, race, smoking status and dose
Smith-Warner, 2001b Canada, USA, the Netherlands, Sweden	The Pooling Project, Pooled study of 5 cohorts, Age: 28-90 years, W (*AHS, CNBSS, , NHS(a), NHS(b), , ,	-	Self-reported and verified by medical records and/or record linkage with cancer registries	FFQ	Incidence, premenopausal breast cancer	per 5% of energy	1.10 (0.91-1.35)	Percent of energy from protein, percent of energy from alcohol, age at menarche, parity, age at birth of first child, OC use, history of benign breast disease, family history of breast cancer, smoking status, education, BMI,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	NYUWHS, SMC)							height, fibre intake, energy intake, monounsaturated fat, polyunsaturated fat

Table 197 Saturated fat intake and premenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

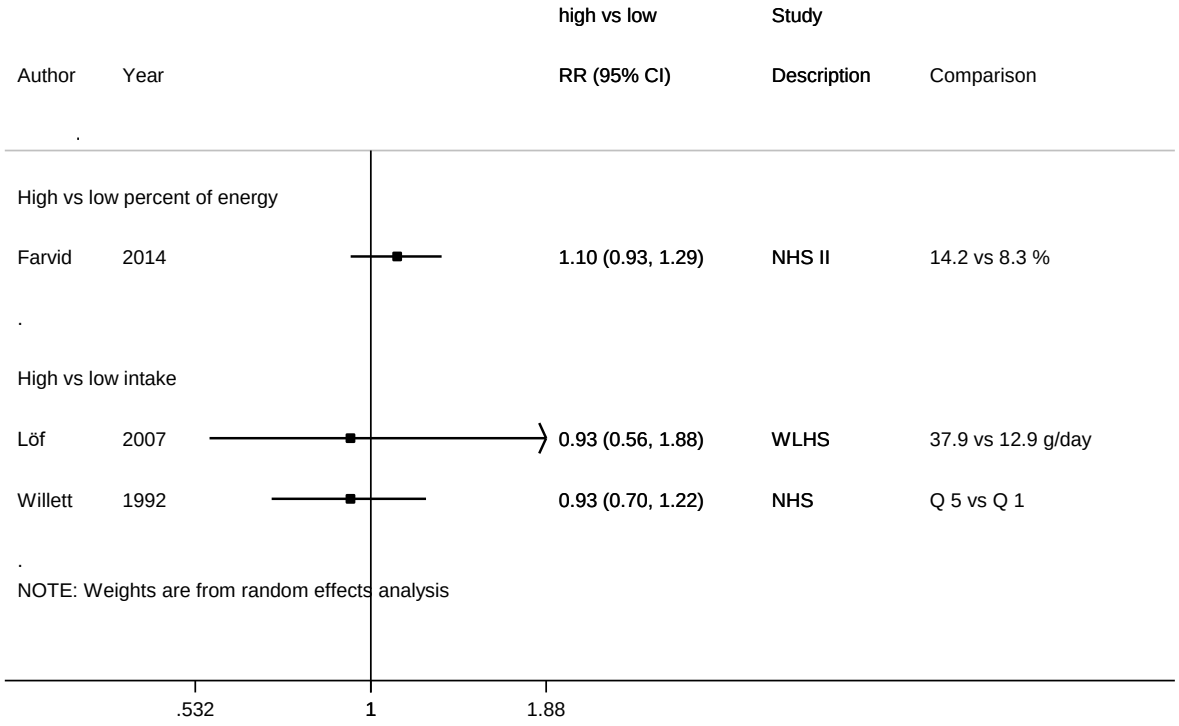
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Linos, 2010 BRE80298 USA	NHS II, Prospective Cohort, Age: 34-53 years, W, Premenopausal	455/ 39 268 7.8 years	Follow up questionnaires, medical records	Semi-quantitative FFQ, for adolescent diet	Incidence, Invasive breast cancer	58.9 vs 39.6 g/day	1.17 (0.84-1.62) Ptrend:0.29	Age, age at first child birth, age at menarche, alcohol consumption, benign breast disease, BMI, energy Intake, family history of cancer, menopausal status, oc use, parity, weight gain	Excluded, adolescent diet
Frazier, 2004 BRE02942 USA	NHS II, Historical Cohort, Age: 34-51 years, W, Registered	361/ 47 355 9 years	All histology	FFQ, for adolescent diet	Incidence, breast cancer, premenopausal	58.9 vs 39.7 g/day	0.93 (0.67-1.29) Ptrend:0.79	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, energy Intake , family	Excluded, adolescent diet

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	nurses							history, menopausal status, oc use, other anthropometric Index, other design Issue, parity/pregnancies	
Willett, 1992 BRE13438 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	527/ 89 494 8 years	Medical records + self-reported	FFQ-semi-quantitative	Incidence, breast cancer, premenopausal	Q 5 vs Q 1	0.93 (0.70-1.22) Ptrend:0.92	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, energy Intake , family history, nutrients, other design Issue, parity/pregnancies	Missing cases and person-years per category
Willett, 1987b BRE13442 USA	NHS, Prospective Cohort, Age: 34-59 years, W, Registered nurses	89 538 4 years	Medical records + self-reported	FFQ-semi-quantitative	Incidence, breast cancer, premenopausal	Q 5 vs Q 1	0.83 Ptrend:0.70	Age , age at first child, alcohol, benign breast disease, body weight, energy Intake , family history, menopausal status, smoking habits	Missing 95% CIs

Table 198 Percentage of total energy from saturated fat and premenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Cho, 2003a BRE17370 USA	NHS II, Prospective Cohort, Age: 25-42 years, W, Premenopausal	714/ 90 655 8 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, Invasive breast cancer, premenopausal	14 vs 8 %/day	1.17 (0.91-1.50) Ptrend:.02	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, family history, height, menopausal status, multivariate partition, OC use, parity/pregnancies, smoking habits	Superseded by Farvid, 2014, BRE80577
Holmes, 1999 BRE04008 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	121 700 14 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, Invasive breast cancer, premenopausal	per 5 % of total energy/day	0.98 (0.87-1.11)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, energy Intake , family history, height, HRT use, menopausal status, nutrients	Superseded by the Pooling Project (Smith-Warner, 2001b)

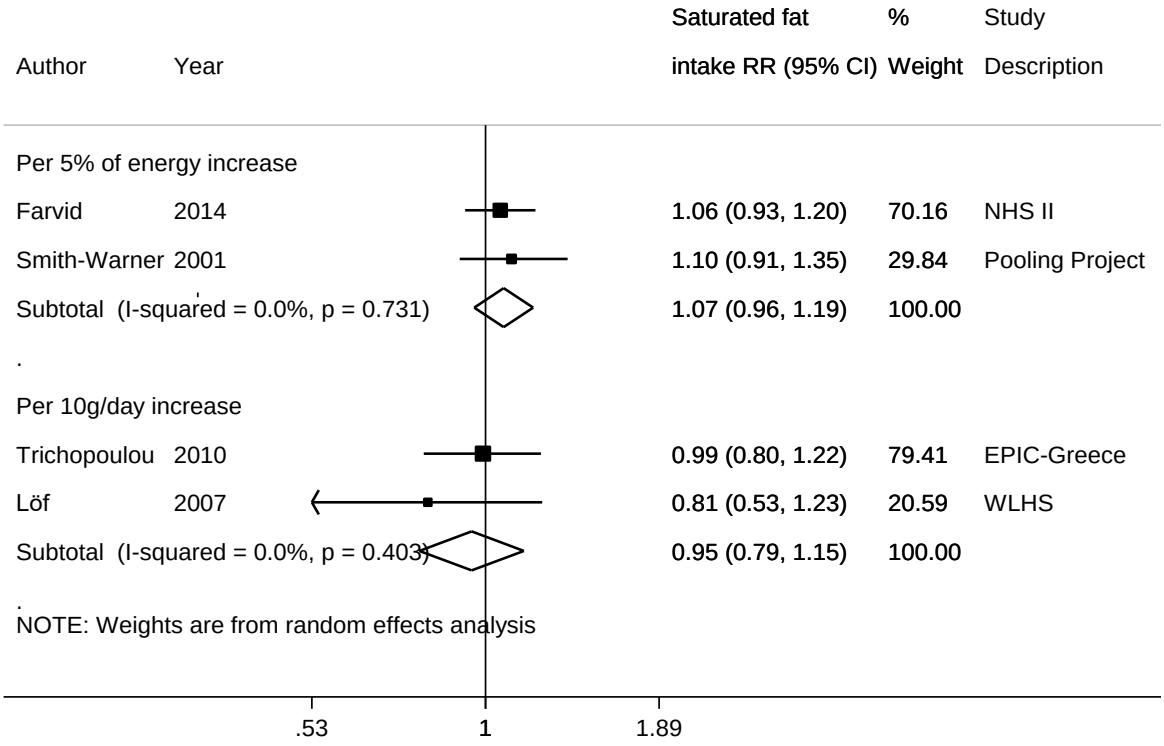
Figure 266 RR (95% CI) of premenopausal breast cancer for the highest compared with the lowest saturated fat intake and percentage of total energy from saturated fat



Note: The graphs of RR estimates of premenopausal breast cancer by levels of saturated fat was not produced as the number of studies with categorical results was limited.

RR estimates were 1.15, 0.96, 1.11, and 1.10 (all non-significant) for increasing quintile categories (median 10.0, 11.2, 12.3, 14.2 vs 8.3% of energy) in Farvid, 2014 and 0.93, 0.90, 0.88, 0.93 (all non-significant) for increasing quintile categories (median 18.6, 23.3, 28.7, 37.9 vs 12.9 g/day) in Lof, 2007a.

Figure 267 Relative risk of premenopausal breast cancer for 10 g/day of saturated fat intake and 5% of total energy from saturated fat



Postmenopausal breast cancer

Summary

Main results:

Eleven out of 15 studies (16 publications) on saturated fat intake and 16 out of 17 studies (nine publications) on percentage of total energy from saturated fat identified could be included in the dose-response meta-analyses respectively.

Non-significant positive associations (summary RR per 10 g/day=1.07 95% CI=0.95-1.20; summary RR per 5%=1.01, 95% CI=0.93-1.10 were observed for postmenopausal breast cancer risk, with high heterogeneity between studies (I^2=51%, P=0.05; I^2=64%, P=0.02, respectively)

There was no evidence of significant publication or small studies bias (P for Egger's test=0.76 and 0.52, respectively).

Four studies (Sieri, 2008; Byrne, 2002; Sieri, 2002, Barrett-Connor, 1993) on saturated fat intake and one (Velie, 2000) on percentage of energy from saturated fat did not have sufficient data to be included in the analyses. Non-significant inverse (Byrne, 2002) or positive associations (Sieri, 2008 by MHT use; Sieri, 2002; Velie, 2000) were reported for the highest versus the lowest intake or percentage of energy comparison. Barrett-Connor, 1993 reported a significant higher saturated fat intake among the cases compared with the non-cases.

Three studies reported results by breast cancer hormone receptor status, of which two with the highest compared with the lowest results were presented in the forest plot. Kim, 2006 reported similar non-significant inverse associations for all hormone receptor-defined breast cancers (RRs per 5% of energy ranged from 0.89-0.95). Kushi, 1995 reported non-significant associations that were positive with ER+PR+ (RR for the highest vs the lowest intake=1.18, 95% CI=0.91-1.53) and ER+PR- (RR=1.58, 95% CI=0.89-2.81) breast cancers and inverse with ER-PR+ (0.91, 95% CI=0.23-3.63) and ER-PR- (RR=0.74, 95% CI=0.39-1.41) breast cancers. Park, 2012 observed non-significant inverse associations with ER+PR+ (RR for the highest vs the lowest % of energy=0.83, 95% CI=0.71-0.99) and ER-PR- (RR=0.92, 95% CI=0.69-1.22) breast cancers and non-significant positive association with ER+PR- (RR=1.15, 95% CI=0.79-1.67) breast cancer. Sensitivity analyses:

Summary RR per 10 g/day increase of saturated fat intake ranged from 1.04 (95% CI=0.93-1.17) when Lof, 2007a was omitted to 1.11 (95% CI=1.01-1.23) when Key, 2011 was omitted in influence analysis. The study of Freedman, 2006 (WHI-DM, non-intervention group) included only women with ≥32% calories from fat. The summary RR per 10g/day was 1.05 (95% CI=0.92-1.21, when this study was excluded. For the analysis of percentage of total energy from saturated fat, summary RR remained non-significant when studies were omitted in turn in influence analysis.

A significant positive association with saturated fat intake was observed in three North American studies (summary RR per 10g/day=1.17, 95% CI=1.03-1.32, I^2=0%, P=0.98). Non-significant inverse or positive associations were observed in other subgroup analysis by geographic location, confounder adjustment, and methods of exposure assessment.

Non-linear dose-response meta-analysis:

There was evidence of non-linear relationship between saturated fat intake and postmenopausal breast cancer risk (P for non-linearity=0.01). The curve showed an increase risk with an increase of saturated fat intake, which flattened slightly after 30 g/day of where data were sparse and mainly came from one study (Wirfalt, 2002).

Study quality:

Most studies were from North America or Europe. One study was from Japan (Wakai, 2005). The MEC study was a cohort of multiple ethnicities. The WHI-DM trial (Freedman, 2006) included women with ≥32% calories from fat. The summary RR did not change materially when this study was omitted in influence analysis.

Saturated fat intake was assessed by a self-administered FFQ in most studies. Wirfalt, 2002 used a 7-day menu book combined with a questionnaire that was administered by interviewers. Subgroup analysis by exposure assessment methods showed non-significant associations. The UK Dietary Cohort Consortium (Key, 2011) and the WHI-DM trial (Freedman, 2006) compared the estimates from the food diaries with the estimates from the FFQs but no significant associations were observed in either method.

Case ascertainment was through cancer registries or confirmed through medical records. All studies were adjusted for age, BMI, alcohol intake, and reproductive factors, apart from Trichopoulou, 2010 that was not adjusted for alcohol intake.

Table 199 Saturated fat intake and percentage of total energy from saturated fat and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	15 (16 publications) on saturated fat intake[1] 17 (9 publications) on percentage energy from saturated fat[2]
Studies included in forest plot of highest compared with lowest exposure	9 on saturated fat intake 5 on percentage energy from saturated fat
Studies included in linear dose-response meta-analysis	11[1] on saturated fat intake 16[2] on percentage energy from saturated fat
Studies included in non-linear dose-response meta-analysis	6 on saturated fat intake Not enough studies on percentage energy from saturated fat

Note: Include cohort, case-cohort, and nested case-control designs.

[1] Included the UK Cohort Consortium (Key, 2011, four cohorts).

[2]Included the Pooling Project (Smith-Warner, 2001b, eight cohorts) and the UK Cohort Consortium (Key, 2011, four cohorts).

Table 200 Saturated fat intake and percentage of total energy from saturated fat and postmenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR		CUP	
Increment unit used	**Per 10g/day**	**Per 5%/day**	**Per 10g/day**	**Per 5%/day**
Studies (n)	4	-	11[1]	16[2]
Cases	1 148	-	3 463	>8 666
RR (95%CI)	1.12 (1.01-1.24)	-	1.07 (0.95-1.20)	1.01 (0.93-1.10)
Heterogeneity (I^2, p-value)	28.0%	-	51%, 0.05	65%, 0.02
P value Egger test	-	-	1.00	0.52
Subgroup analysis in the CUP				
Increment unit used	**Per 10g/day**	**Per 10g/day**	**Per 5% of energy**	**Per 5% of energy**
Geographic location	**Europe**	**North America**	**Europe**	**North America**
Studies (n)	8	3	1	4
Cases				
RR (95%CI)	1.01 (0.83-1.21)	1.17 (1.03-1.32)	0.78 (0.61-1.00)	1.02 (0.94-1.11)
Heterogeneity (I^2, p-value)	66%, 0.02	0%, 0.98	-	72%, 0.01
Adjustment for age, BMI, alcohol intake, reproductive factors	**Adjusted**	**Not adjusted**	**Adjusted**	**Not adjusted**
Studies (n)	10	1	16	-
Cases			>8 666	-
RR (95%CI)	1.07 (0.94-1.22)	1.03 (0.76-1.39)	1.01 (0.93-1.10)	-
Heterogeneity (I^2, p-value)	58%, 0.03	-	65%, 0.02	-
Adjustment for age, BMI, alcohol intake, and reproductive factors	**FFQ**	**Dietary history/food diaries**	**FFQ**	**Food diaries**
Studies (n)	10	6	16	1
Cases				

RR (95%CI)	1.08 (0.97-1.20)	0.92 (0.72-1.18)	1.02 (0.95-1.10)	0.78 (0.61-1.00)
Heterogeneity (I^2, p-value)	35%, 0.17	69%, 0.04	57%, 0.04	-

[1]Included the UK Cohort Consortium (Key, 2011, four cohorts).

[2]Included the Pooling Project (Smith-Warner, 2001b, eight cohorts) and the UK Cohort Consortium (Key, 2011, four cohorts).

Table 201 Saturated fat intake and postmenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Turner, 2011	15 studies (12 cohorts, 3 case-control studies)	>13 460 postmenopausal breast cancer	Germany, Italy, The Netherlands, Singapore, Sweden, USA	Incidence, postmenoapausal breast cancer	Highest vs lowest saturated fat intake (13 studies)	1.00 (0.93-1.09) Ptrend: >0.05	-
					Cohort studies (n=11)	(0.93-1.09) Ptrend: >0.05	-

*All cohort studies identified were included in the present review.

Table 202 Saturated fat intake and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Sczaniecka, 2012 BRE80434 USA	VITAL, Prospective Cohort, Age: 50-76 years, W, Postmenopausal	772/ 30 252 6 years	Seer registry	Semi-quantitative FFQ	Incidence, breast cancer	≥24 vs ≤9.9 g/day	1.47 (1.00-2.15) Ptrend:0.09	Age, age at first child birth, age at menarche, age at menopause, alcohol, BMI, breast biopsies, educational level, energy, estrogen replacement therapy, exercise, family history of breast cancer, fruits, height, history of hysterectomy, mammography, nsaid use, race, vegetable, years of combined hormone therapy

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Key, 2011 UK	UK Dietary Cohort Consortium, Pooled study of 4 cohorts* Mean age: 56.4 ±9.7 years among cases, W (*EPIC-Norfolk; EPIC-Oxford; UKWCS; Whitehall II study)	657 cases/ 1 911 controls EPIC-Norfolk: 353 cases/1 252 controls EPIC-Oxford: 194 cases/ 194 cases UKWCS: 42 cases/202 controls Whitehall II study: 68 cases/263 controls	Record linkage with National Statistics and cancer registries	Food diary and FFQ	Incidence, breast cancer	Food diaries: per 9.6 g/day	0.81 (0.64-1.02)	Age, alcohol consumption, parity, menopausal status, current hormone replacement therapy use, physical activity, height, weight, and energy intake
						FFQ: per 12.5 g/day	0.84 (0.66-1.07)	
Trichopoulou, 2010 BRE80320 Greece	EPIC-Greece, Prospective Cohort, Age: 20-68 years	14 807 9.8 years	Medical records and pathology reports	FFQ	Incidence, breast cancer, postmenopausal	per 11 gday	1.03 (0.74-1.43)	Age, age at first child birth, age at menarche, age at menopause, BMI, educational level, energy Intake, height, HRT use, menopausal status, metabolic equivalents, parity, smoking
Löf, 2007 BRE80144 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	542/ 44 569 13 years	Cancer registry	FFQ	Incidence, Invasive breast cancer, age >= 50 yrs	37.6 vs 12.9 g/day	1.29 (0.66-2.50) Ptrend:0.44	Age, age at first child birth, age at menarche, alcohol consumption, BMI, educational level, family history of cancer, non-alcohol energy, parity, total fat, use of oral contraception
						per 10 g/day	1.45 (0.99-2.12)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Freedman, 2006 BRE80628 USA	WHI-DM trial, Nested Case Control, Age: 50-79 years, W, Postmenopausal	603/ 1206 controls 6.92 years	Medical records and pathology reports	4-day food records	Incidence, Invasive breast cancer	31.8 vs 11.2 g/day	1.51 (0.94-2.43) Ptrend:0.20	Age at entry, breast biopsies, clinic, energy Intake, family history, HRT use, length of follow-up
				FFQ	Incidence, Invasive breast cancer	42.5 vs 13.7 g/day	1.00 (0.49-2.02) Ptrend:0.95	
Wirfalt, 2002 BRE13504 Sweden	MDCS, Nested Case Control, Age: 50- years, W, Postmenopausal	237/ 673 controls 8 years	Partially histological - over 80%	7-day record + questionnaire	Incidence, breast cancer, postmenopausal	53 vs 28 g/day	0.61 (0.31-1.22) Ptrend:0.081	Age at first child, alcohol, BMI, educational level, energy Intake , height, HRT use, past food habit change, waist circumference, n-6 fatty acids, n-3 fatty acids, monounsaturated fatty acids
Van den Brandt, 1993 BRE16919 Netherlands	NLCS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	437/ 1 598 3.3 years	All histology	FFQ-semi-quantitative	Incidence, Invasive breast cancer,	≥1 vs ≥-1 g/day	1.39 (0.94-2.06) Ptrend:0.049	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, educational level, family history, OC use, parity/pregnancies, residual (willet), smoking habits
Kushi L H, 1992 BRE05141 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	459/ 34 388 4 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	29.3 vs 18.8 g/day	1.07 (0.68-1.68) Ptrend:0.53	Age , age at first child, age at menarche, age at menopause, age-underlying cox models, alcohol, benign breast disease, BMI, BMI, energy Intake , family history, WHR

Table 203 Percentage of total energy from saturated fat and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Park, 2012 BRE80399 Hawaii	MEC, Prospective Cohort, Age: 45-75 years, Postmenopausal	3 885/ 85 089 12.4 years	Cancer registry	FFQ	Incidence, breast cancer	≥10.9 vs ≤6.4 % energy	0.93 (0.83-1.04) Ptrend:0.19	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, educational level, energy Intake, ethnicity, family history of breast cancer, HRT use, number of childbirths, smoking status, time, type of menopause
		1 764/			Incidence, breast cancer ER+/PR+	≥10.9 vs ≤6.4 % energy	0.83 (0.71-0.99) Ptrend:0.03	
		350/			Incidence, breast cancer ER+/PR-	≥10.9 vs ≤6.4 % energy	1.15 (0.79-1.67) Ptrend:0.36	
		499/			Incidence, breast cancer ER-/PR-	≥10.9 vs ≤6.4 % energy	0.92 (0.69-1.22) Ptrend:0.56	
Farvid, 2014 BRE80577 USA	NHS II, Prospective Cohort, Age: 26-45 years, W	918/ 88 804 20 years	Self report verified by medical record and pathology report	Semi-quantitative FFQ	Incidence, postmenopausal breast cancer, postmenopause	14.2 vs 8.2 %	1.03 (0.83-1.27) Ptrend:0.38	Age, age at menarche, age at menopause, alcohol Intake, BMI, calendar year, energy, energy from protein, family history of breast cancer In first degree relatives, height, history of benign breast disease, hormone use, oc use, parity and age at first birth, race, smoking status and dose
Key, 2011 UK	UK Dietary Cohort Consortium (EPIC-Norfolk; EPIC-Oxford; UKWCS;	657 cases/ 1 911 controls EPIC-Norfolk: 353 cases/1 252 controls	Record linkage with National Statistics and cancer registries	Food diary and FFQ	Incidence, breast cancer	Food diaries: per 3.2% of energy	0.85 (0.73-1.00)	Age, alcohol consumption, parity, menopausal status, current hormone replacement therapy use, physical activity, height, weight, and energy intake

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Whitehall II study), Pooled analysis Mean age: 56.4 ±9.7 years among cases, W	EPIC-Oxford: 194 cases/ 194 cases UKWCS: 42 cases/202 controls Whitehall II study: 68 cases/263 controls						
						FFQ: Per 3.4% of energy	0.90 (0.78-1.05)	
Thiébaut, 2007 BRE80012 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, Postmenopausal	3 501/ 188 736 4.4 years	Cancer registry	24h recall + FFQ	Incidence, Invasive breast cancer,	13.2 vs 5.8 %energy	1.18 (1.06-1.31) Ptrend:0.004	Age at first child birth, age at menopause, alcohol energy, BMI, menopausal hormone use, non-alcohol energy, parity, smoking habits
		3 529/				per 20 %	1.13 (1.05-1.22)	
Wakai, 2005 BRE24482 Japan	JACC, Prospective Cohort, Age: 40-79 years, W, Previous study	76/ 26 291 7.6 days	Partially histological - over 80%	FFQ	Incidence, breast cancer, postmenopausal	≥7.34 vs ≤5.19	0.64 (0.34-1.22) Ptrend:0.09	Age , age at first child, age at menarche, age at menopause, alcohol, BMI, educational level, energy Intake , family history, height, HRT use, other energy Index, other nutritional factors, other physical activity Index, parity/pregnancies, recruitment center, smoking habits
Smith-Warner, 2001b Canada, USA, the Netherlands, Sweden	The Pooling Project (AHS, CNBSS, IWHS, NHSa, NHSb, NLCS, NYSC,	-	Self-reported and verified by medical records and/or record linkage with	FFQ	Incidence, postmenopausal breast cancer	per 5% of energy	1.07 (0.93-1.24)	Percent of energy from protein, percent of energy from alcohol, age at menarche, parity, age at birth of first child, MHT use, OC use, history of benign breast

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	NYUWHS, SMC), Pooled analysis, Age: 28-90 years, W		cancer registries					disease, family history of breast cancer, smoking status, education, BMI, height, fibre intake, energy intake, monounsaturated fat, polyunsaturated fat

Table 204 Saturated fat intake and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Sieri, 2008 BRE80202 Europe	EPIC, Prospective Cohort, Age: 20-70 years, W	1 553/ 319 826 8.8 years	Cancer registry / database / pathology reports	FFQ	Incidence, breast cancer, HRT - no	45 vs 16.2 g/day	1.21 (0.99-1.48) Ptrend:0.044	Age, alcohol Intake, centre location, educational attainment, energy Intake, height, menopausal status, smoking status, weight	Excluded, cases and person-years per category by MHT use not available
		1 909/			HRT - yes	45 vs 16.2 g/day	1.01 (0.83-1.23) Ptrend:0.698		
Byrne, 2002 BRE01315 USA	NHS, Prospective Cohort, Age: 57 years, W, Postmenopausal	1 071/ 44 697 14 years	All histology	FFQ-semi-quantitative	Incidence, Invasive breast cancer, postmenopausal	Q 5 vs Q 1	0.88 (0.70-1.12) Ptrend:0.05	Age , age at first child, age at menopause, age at menopause, alcohol, BMI, density, family	Excluded, no exposure levels

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								history, height, nutrients, nutrients, parity/pregnancies	
Sieri, 2002 BRE20941 Italy	ORDET, Nested Case Control, Age: 41-70 years, W, Postmenopausal	56/ 214 controls 5.5 years	Cancer registry + death certificate	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	22.2-43.9 vs ≤18.3 g/day	1.12 (0.31-4.04) Ptrend:0.761	Birth cohort, educational level, nutrients, parity/pregnancies, residual (willet)	Excluded, cases and person-years per category not available
Voorrips, 2002 BRE13011 Netherlands	NLCS, Case Cohort, Age: 55-69 years, W, Postmenopausal	783/ 62 573 6.3 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer,	38 vs 22 g/day	1.40 (0.97-2.03) Ptrend:0.11	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, educational level, energy Intake , family history, oc use, parity/pregnancies, residual (willet), smoking habits	Superseded by Van den Brandt, 1993 BRE16919 (included in highest vs lowest plot)
Kushi, 1995 BRE05142 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	329/ 34 388 6 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer ER+/PR+,	≥25.4 vs ≤21.5 g/day	1.18 (0.91-1.53) Ptrend:0.20	Age , energy Intake	Excluded, results on specific breast cancer type, not enough studies to analyse

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		75/			Incidence, breast cancer ER+/PR-,	≥25.4 vs ≤21.5 g/day	1.58 (0.89-2.81) Ptrend:0.11		
		14/			Incidence, breast cancer ER-/PR+,	≥25.4 vs ≤21.5 g/day	0.91 (0.23-3.63) Ptrend:0.98		
		61/			Incidence, breast cancer ER-/PR-,	≥25.4 vs ≤21.5 g/day	0.74 (0.39-1.41) Ptrend:0.38		
Barrett-Connor, 1993 BRE00581 USA	Rancho Bernardo, 1972, Prospective Cohort, Age: 40-79 years, W	15/ 590 15 years	Medical records + death certificate	24h recall	Incidence, breast cancer, postmenopausal	(mean exposure)			Excluded, mean exposure comparison only
Willett, 1992 BRE13438 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	774/ 89 494 8 years	Medical records + self-reported	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	Q 5 vs Q 1	0.91 (0.73-1.14) Ptrend:0.45	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, energy Intake , family history, nutrients, other design Issue, parity/pregnancies	Excluded, cases and person-years per category not available
Willett, 1987b BRE13442 USA	NHS, Prospective Cohort, Age: 34-59 years, W, Registered nurses	89 538 4 years	Medical records + self-reported	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	Q 5 vs Q 1	0.96 Ptrend:0.52	Age , age at first child, alcohol, benign breast disease, body weight, energy Intake , family history, menopausal	Excluded, missing 95% CIs

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								status, smoking habits	

Table 205 Percentage of total energy from saturated fat and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Kim, 2006 BRE80115 USA	NHS, Prospective Cohort, W, Postmenopausal	3 537/ 121 701 20 years	Medical records	FFQ	Incidence, Invasive breast cancer,	per 5 %	0.93 (0.87-1.00)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, energy Intake , family history, height, HRT use, other design Issue, parity/pregnancies	Superseded by the Pooling Project (Smith-Warner, 2001b)
		1 653/			Incidence, breast cancer ER+/PR+,	per 5 %	0.94 (0.85-1.04)		
		477/			Incidence, breast cancer ER+/PR-,	per 5 %	0.95 (0.79-1.14)		
		517/			Incidence, breast cancer ER-/PR-,	per 5 %	0.93 (0.78-1.11)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		83/				per 5 %	0.89 (0.57-1.41)		
Velie, 2000 BRE12851 USA	BCDDP, 1973, Prospective Cohort, W, Screening Program	996/ 40 022 5.3 years	Medical records + self-reported	FFQ	Incidence, breast cancer, postmenopausal	Q 5 vs Q 1	1.12 (0.87-1.45) Ptrend:.67	Age at first child, age at menarche, alcohol, benign breast disease, BMI, educational level, energy Intake , family history, height, parity/pregnancies	Excluded, no exposure levels
Holmes, 1999 BRE04008 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	121 700 14 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, Invasive breast cancer, postmenopausal	per 5 % of total energy/day	0.93 (0.85-1.02)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, energy Intake , family history, height, HRT use, menopausal status, nutrients	Superseded by the Pooling Project (Smith-Warner, 2001b)

Figure 268 RR estimates of postmenopausal breast cancer by levels of saturated fat intake and percentage of total energy from saturated fat

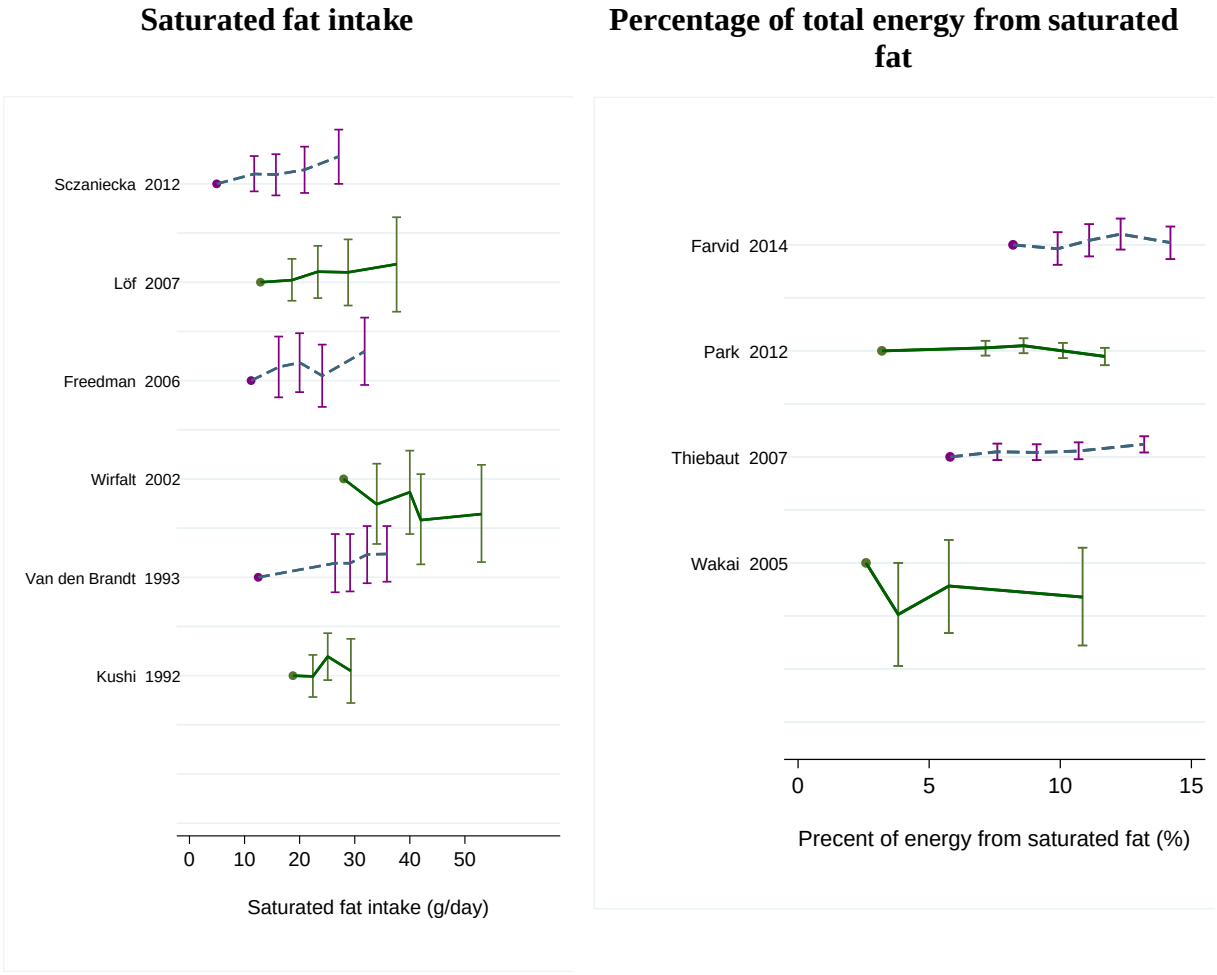


Figure 269 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest saturated fat intake and percentage of total energy from saturated fat

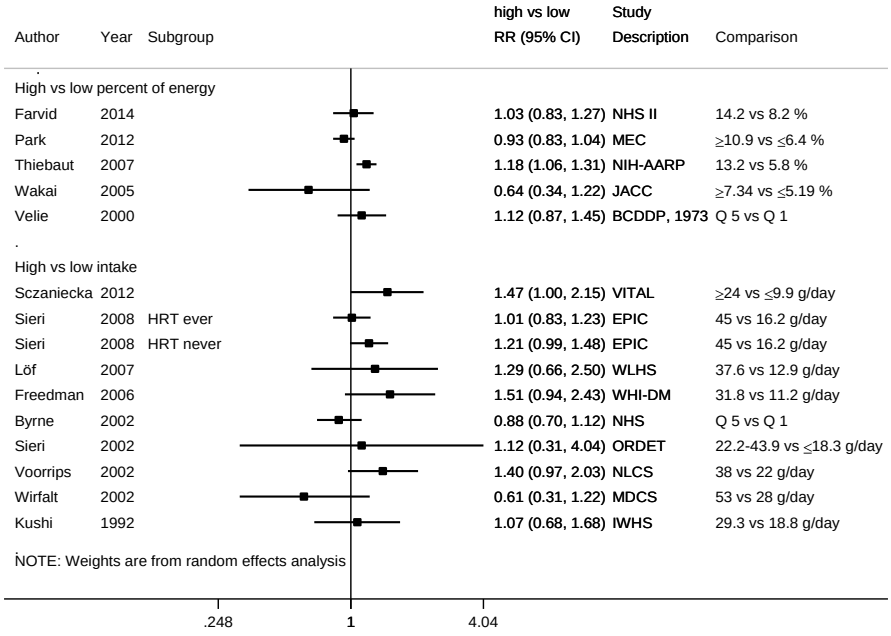


Figure 270 Relative risk of postmenopausal breast cancer for 10 g/day of saturated fat intake and 5% of total energy from saturated fat

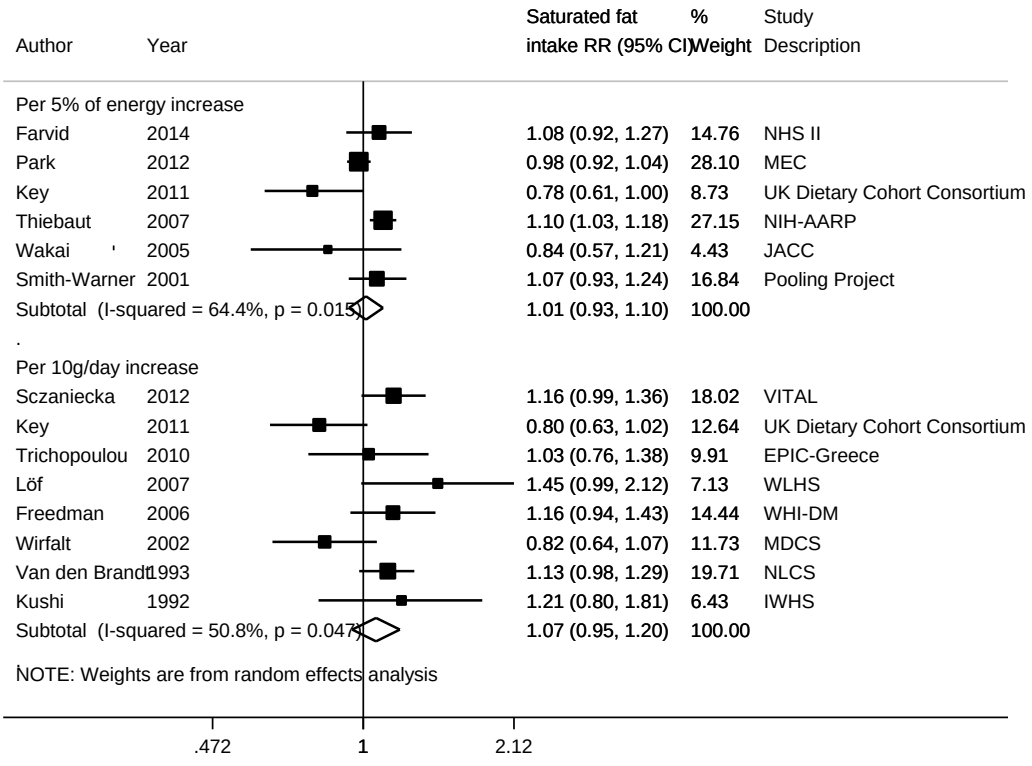


Figure 271 Funnel plot of studies included in the dose response meta-analysis of saturated fat intake and postmenopausal breast cancer

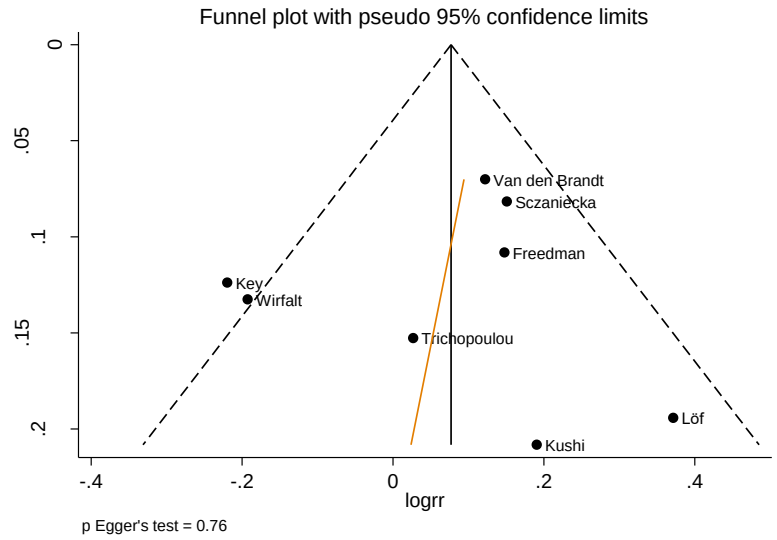


Figure 272 Funnel plot of studies included in the dose response meta-analysis of percentage of total energy from saturated fat and postmenopausal breast cancer

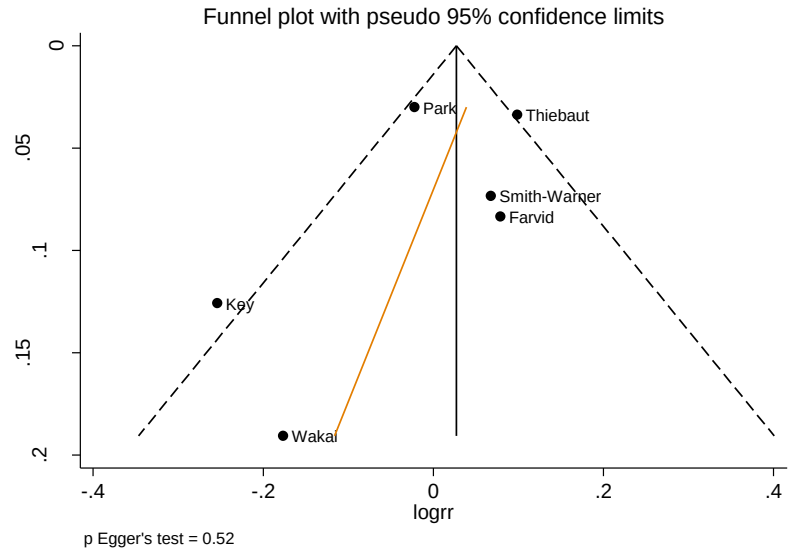


Figure 273 Relative risk of postmenopausal breast cancer for 10 g/day of saturated fat intake, by geographic location

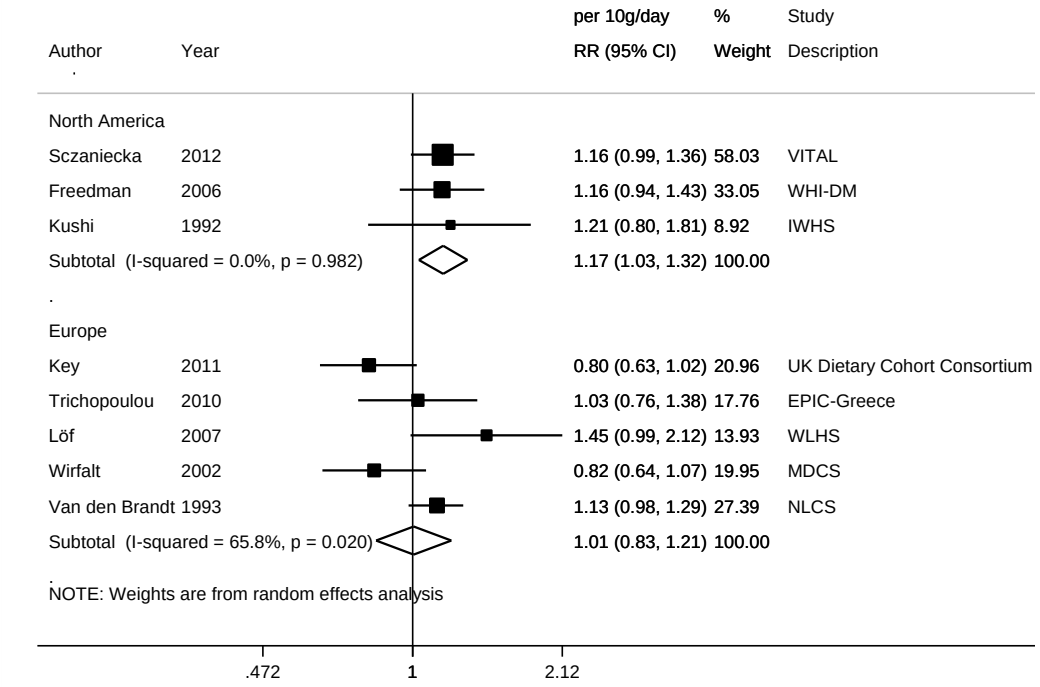


Figure 274 Relative risk of postmenopausal breast cancer for 5% of energy from saturated fat intake, by geographic location

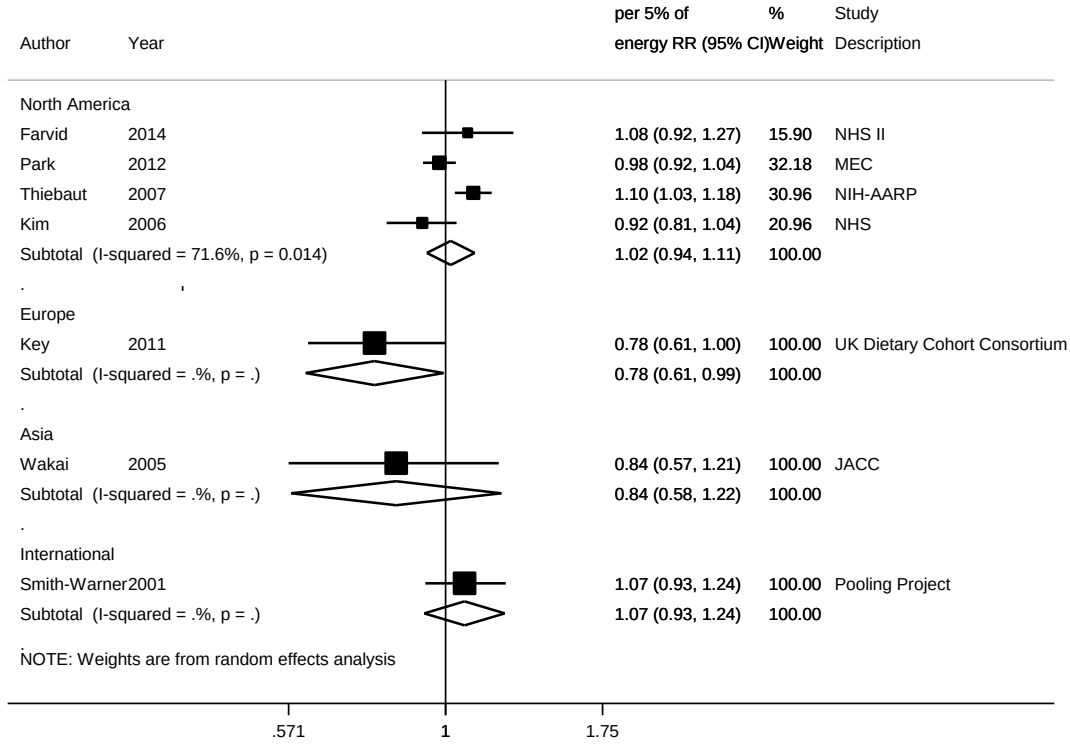


Figure 275 Relative risk of postmenopausal breast cancer for 10 g/day of saturated fat intake, by exposure assessment methods

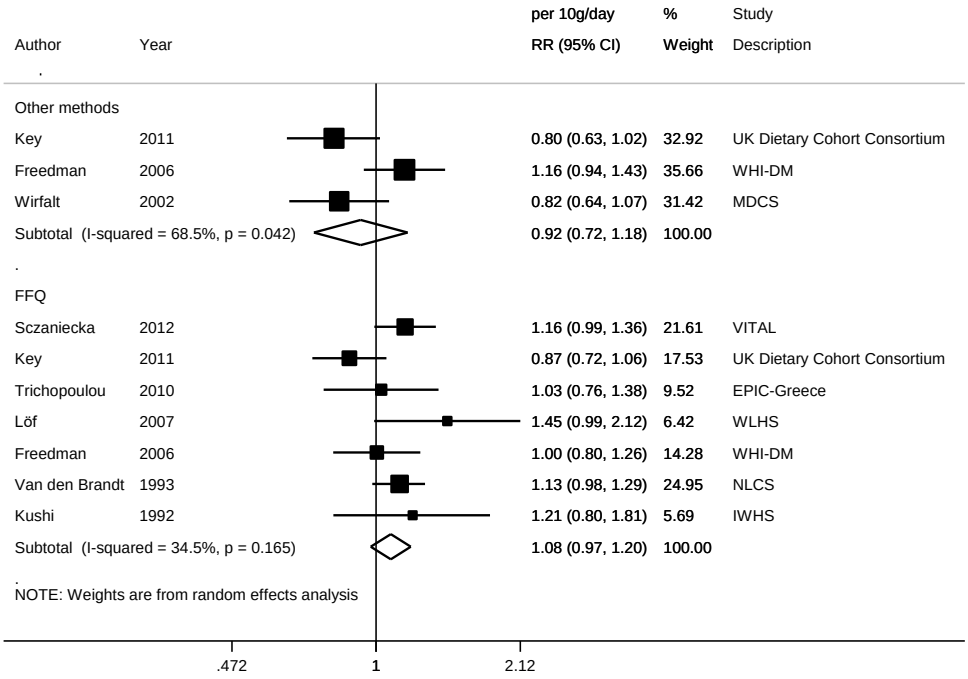


Figure 276 Relative risk of postmenopausal breast cancer for 5% of energy from saturated fat intake, by exposure assessment methods

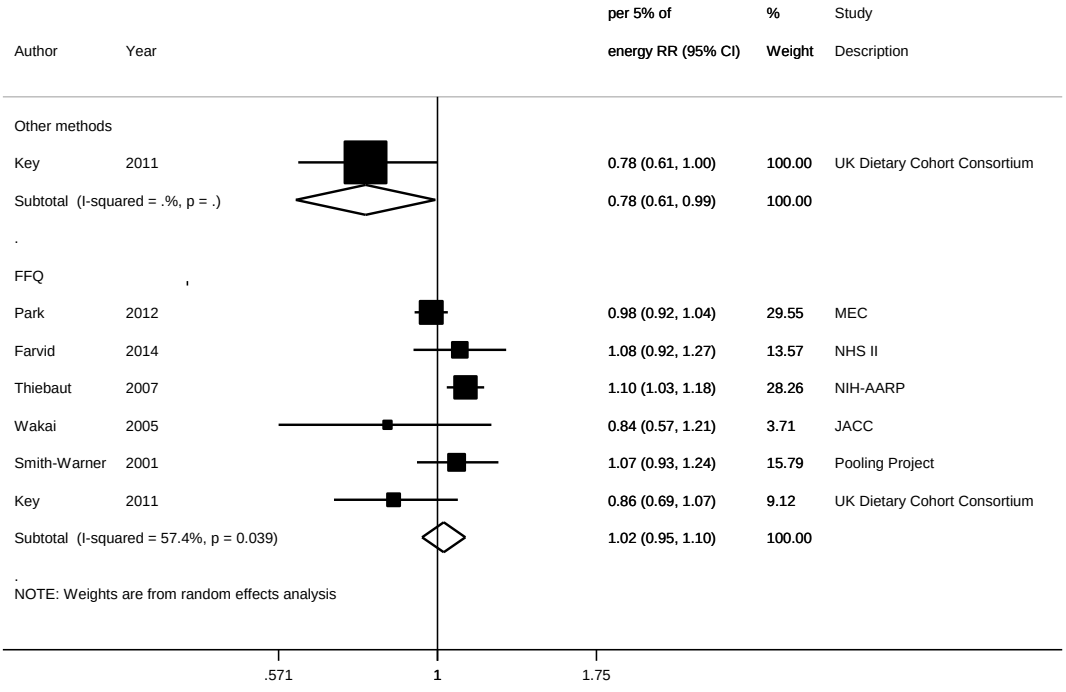


Figure 277 Non-linear dose-response meta-analysis of saturated fat intake and postmenopausal breast cancer

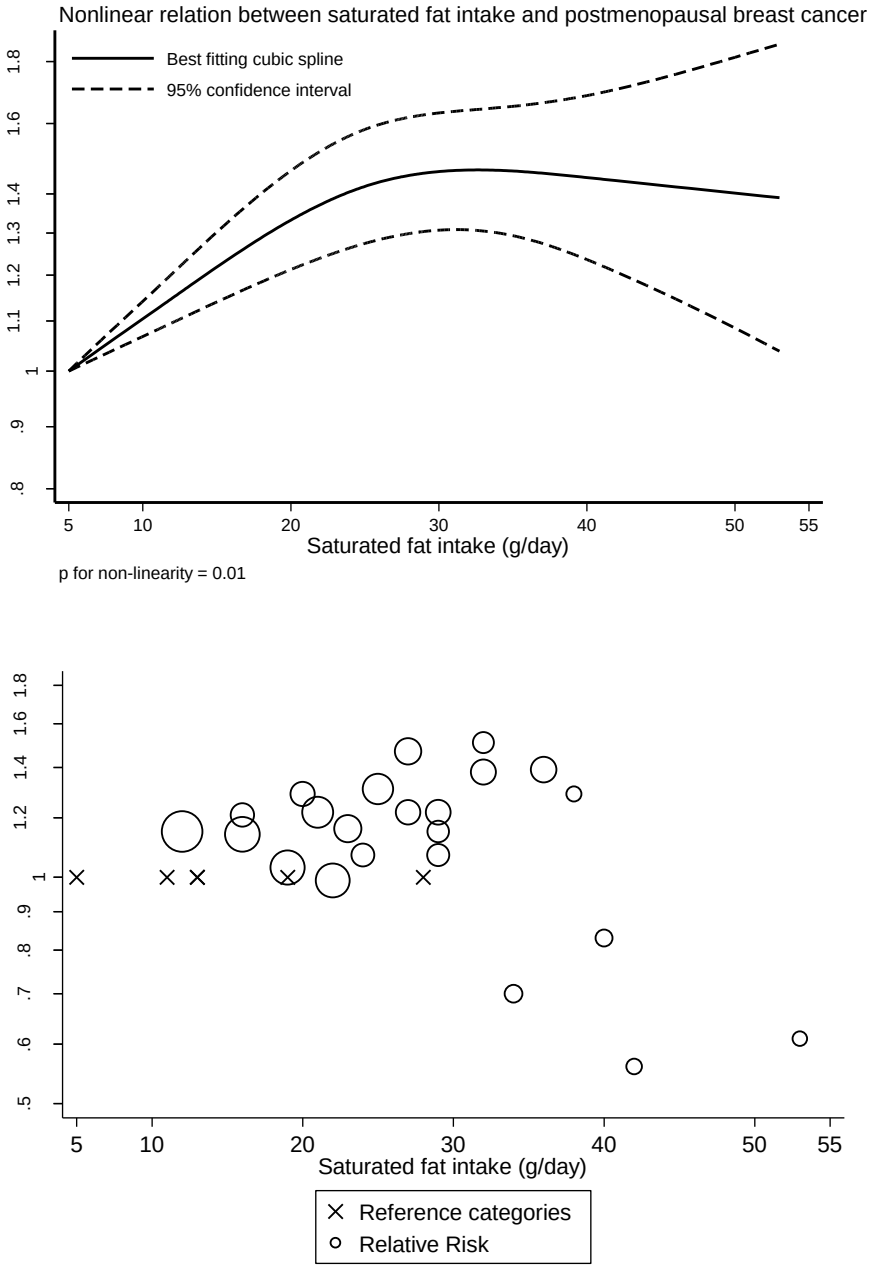
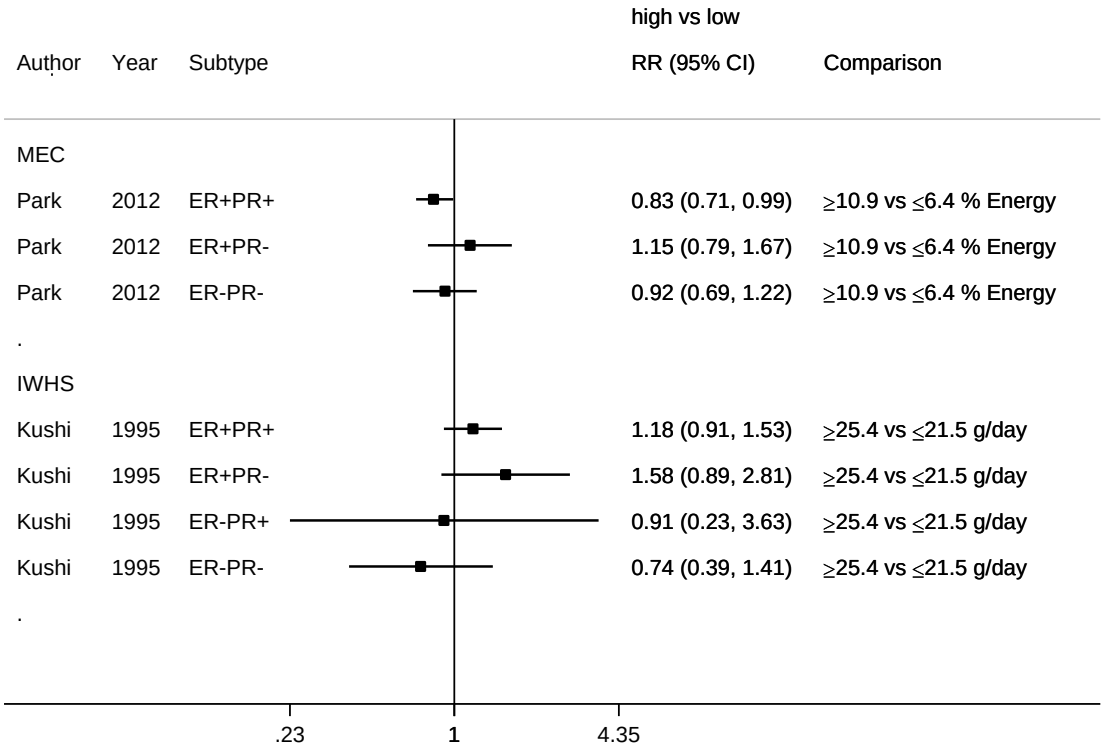


Table 206 Relative risk of postmenopausal breast cancer and saturated fat intake estimated using non-linear models

Saturated fat intake (g/day)	RR (95%CI)
5.0	1.00
13.0	1.17 (1.11-1.24)
20.0	1.33 (1.21-1.46)
32.0	1.47 (1.31-1.64)

Figure 278 RR (95% CI) of hormone receptor defined postmenopausal breast cancer for the highest compared with the lowest percentage of energy from saturated fat



5.2.3 Monounsaturated fatty acids

7.1.0.1 Energy from monounsaturated fatty acids

Cohort studies

Overall summary

Studies that measured monounsaturated fatty acids as an absolute intake (g/day) or as a relative intake expressed as a percentage of the total energy intake (% of energy) was considered together to facilitate a comprehensive review.

Thirty-seven publications from 30 studies that examined monounsaturated fatty acids intake and/or percentage of energy from fat were identified. Three pooled analyses, two from the Pooling Project (Smith-Warner, 2001b, eight cohorts; Hunter, 1996, seven cohorts) and one from the UK Dietary Cohort Consortium (Key, 2011, four cohorts) were identified.

Dose-response meta-analyses were conducted to examine the associations of monounsaturated fatty acids intake (per 10 g/day and per 5% of energy) with risk of breast cancer and of premenopausal and postmenopausal breast cancer.

Notes on method:

As in the Pooling Project, results from the model that was mutually adjusted for other type of fat were selected if the studies presented such results. Models adjusted for total energy intake were selected, which represents an increase in monounsaturated fat intake while keeping the total energy intake constant. If studies provided results both from the food diaries and the FFQs, results from the food diaries were used.

Table 207 Summary of results of the dose-response meta-analysis in the 2016 CUP SLR

	Breast cancer	**Premenopausal breast cancer**	**Postmenopausal breast cancer**
Monounsaturated fatty acids intake Increment unit used	Per 10 g/day	Per 10 g/day	Per 10 g/day
Studies (n)	12[1]	2	11[3]
Cases	16 404	545	3 463
RR (95%CI)	1.03 (0.93-1.15)	1.00 (0.87-1.16)	1.00 (0.84-1.20)
Heterogeneity (I^2, p-value)	62%, 0.02	0%, 0.47	73%, 0.001
P value Egger test	0.77	-	0.70
Percentage of energy from monounsaturated fatty acids			
Increment unit used	Per 5% of energy	Per 5% of energy	Per 5% of energy
Studies (n)	12[2]	6[2]	16[2,3]
Cases	17 721	>1 511	>8 666
RR (95%CI)	1.02 (0.95-1.09)	1.02 (0.86-1.21)	1.01 (0.92-1.10)
Heterogeneity (I^2, p-value)	45%, 0.12	28% 0.24	64%, 0.02
P value Egger test	0.70	-	0.50

[1]Included the Pooling Project (Hunter, 1996, seven cohorts).

[2]Included the Pooling Project (Smith-Warner, 2001b, eight cohorts, five in the analysis of premenopausal breast cancer).

[3]Included the UK Cohort Consortium (Key, 2011, four cohorts).

Breast cancer (any)

Summary

Main results:

Twelve out of 19 studies (16 publications) on monounsaturated fatty acids intake and 12 out of 17 studies (9 publications) on percentage of energy from monounsaturated fatty acids could be included in the dose-response meta-analyses, respectively.

There were no significant associations observed for breast cancer overall, and in the subgroups. The summary RRs were 1.03 (95% CI=0.93-1.15) per 10g/day intake of monounsaturated fatty acids and 1.02 (95% CI=0.95-1.09) per 5% of energy from monounsaturated fatty acids. There was evidence of high heterogeneity between studies (I^2= 62%, P=0.02; I^2= 45%, P=0.12, respectively).

There was no evidence of significant publication or small studies bias (P for Egger's test=0.77 and 0.70, respectively).

Seven and five studies were excluded from the analysis of monounsaturated fatty acids intake and percentage of energy from monounsaturated fatty acids, respectively. In six studies (Key, 2011, four cohorts; Trichopoulou, 2010; Thiebaut, 2001) and five studies (Key, 2011, four cohorts; Thiebaut, 2001), the study populations overlapped with other studies that were already included in the respective analysis. One further study on monounsaturated fatty acids intake (Martin, 2011) was excluded as diet was measured during the follow-up of a RCT.

One study (Sieri, 2014) reported similar non-significant associations by breast cancer subtypes.

Sensitivity analyses:

The summary RRs remained non-significant when studies were omitted in turn in influence analyses.

Non-linear dose-response meta-analysis:

There was no evidence of non-linear relationship between monounsaturated fatty acids intake and breast cancer risk (P for non-linearity=0.99) (graph not shown). There were not enough studies to conduct a non-linear dose-response meta-analysis of percentage of energy from monounsaturated fatty acids.

Study quality:

Most studies were from North America or Europe. One study was from Japan (Wakai, 2005) and one of Singaporean Chinese (Gago-Dominguez, 2003). Most studies used FFQs to assessed fat intake. Other studies used dietary questionnaires (Knekt, 1990) or a 24-hour recall (Jones, 1987). EPIC (Sieri, 2014; Sieri, 2008) used different methods (FFQs, dietary questionnaires).

There is some suggestion that measurement errors may attenuate the association. EPIC (Sieri, 2014) observed a significant positive association when calibrated (dietary questionnaires against 24-hour dietary recalls) monounsaturated fatty acids data was used (RR per 20%

increase of calibrated fat intake = 1.06, 95% CI=1.02-1.11 vs. RR for non-calibrated fat intake=1.02, 95% CI=1.00-1.04) (Sieri, 2014) and the same strengthening of association was observed for percentage of energy from monounsaturated fatty acids (RR per 20% increase =1.05, 95% CI=1.00-1.10 vs. RR=1.02, 95% CI= 0.99-1.04, respectively) (Sieri, 2008), although the RRs in the Pooling Project when corrected for measurement error was 1.01 (95% CI=0.80-1.28) per 10 g/day increase of intake and 1.01 (95% CI=0.86-1.19) per 5% of energy (Smith-Warner, 2001b); the consortium of four cohorts based in the UK (Key, 2011, UKDCC) observed non-significant associations using data from FFQs or food diaries; and on average, studies that used FFQs or other methods found similar non-significant results in the present review.

Case ascertainment was through cancer registries or confirmed through medical records. All studies were adjusted for age, BMI, alcohol intake, and reproductive factors, apart from Gaard, 1995 that did not adjust for any reproductive factors, and Knekt, 1990 and Jones, 1987 that did not adjust for alcohol consumption.

Table 208 Monounsaturated fatty acids intake and percentage of energy from monounsaturated fatty acids and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	19 (16 publications) monounsaturated fatty acids intake 17 (9 publications) percentage of energy from monounsaturated fatty acids
Studies included in forest plot of highest compared with lowest exposure	12 (6 publications) monounsaturated fatty acids intake 12 (5 publications) percentage of energy from monounsaturated fatty acids
Studies included in linear dose-response meta-analysis	12 (6 publications) monounsaturated fatty acids intake 12 (5 publications) percentage of energy from monounsaturated fatty acids
Studies included in non-linear dose-response meta-analysis	7 (7 publications) monounsaturated fatty acids intake Not enough studies on percentage of energy from monounsaturated fatty acids

Note: Include cohort, and nested case-control designs

Table 209 Monounsaturated fatty acids intake and percentage of energy from monounsaturated fatty acids and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and 2016 CUP

	2005 SLR		**CUP**	
Increment unit used	**Per 10g/day**	**-**	**Per 10g/day**	**Per 5%**
Studies (n)	4	-	12	12

Cases	2 292	-	16 404	17 721
RR (95%CI)	1.00 (0.94-1.07)	-	1.03 (0.93-1.15)	1.02 (0.95-1.09)
Heterogeneity (I^2, p-value)	73%	-	62%, 0.02	45%, 0.12
P value Egger test	-	-	0.77	0.70

Stratified analyses in the CUP					
Increment unit used	**Per 10g/day**	**Per 10g/day**	**Per 5% of energy**	**Per 5% of energy**	**Per 5% of energy**
Geographic location	**Europe**	**North America**	**Europe**	**North America**	**Asia**
Studies (n)	6	5	3	7	2
Cases	12 547	3 704	9 329	7 949	443
RR (95%CI)	1.03 (0.87-1.23)	1.00 (0.92-1.09)	0.88 (0.70-1.10)	1.05 (0.98-1.13)	1.00 (0.82-1.22)
Heterogeneity (I^2, p-value)	68%, 0.01	41%, 0.14	72%, 0.03	0%, 0.44	0%, 0.34

Increment unit used	**Per 10g/day**	**Per 10g/day**	**Per 5% of energy**	**Per 5% of energy**
Adjustment for age, BMI, alcohol intake, reproductive factors	**Adjusted**	**Not adjusted**	**Adjusted**	**Not adjusted**
Studies (n)	9	3	12	-
Cases	16 016	388	17 721	-
RR (95%CI)	1.02 (0.99-1.06)	1.23 (0.79-1.92)	1.02 (0.95-1.09)	-
Heterogeneity (I^2, p-value)	0%, 0.50	82%, <0.01	45%, 0.12	-
Exposure assessment methods	**FFQs**	**Other methods**	**FFQs**	**Other methods**
Studies (n)	13	3	15	1
Cases	6 859	10 202	11 259	7 119
RR (95%CI)	1.05 (0.87-1.26)	1.02 (0.85-1.23)	1.00 (0.91-1.11)	1.02 (0.97-1.07)
Heterogeneity (I^2, p-value)	62%, 0.05	62%, 0.07	47%, 0.11	-

Table 210 Monounsaturated fatty acids intake and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Turner, 2011	29 studies (1 pooled study of prospective studies, 18 cohorts*, 10 case-control studies)	31 201 any breast cancer	China, France, Germany, Greece, Italy, the Netherlands, USA, Uruguay, Singapore, Sweden	Incidecne, any breast cancer	Highest vs lowest monounsaturated fat intake (23 studies)	1.00 (0.95-1.05)	-
					Cohort studies (n=16)	0.99 (0.93-1.05)	-
					Case-control studies (n=7)	1.03 (0.91-1.17)	-

* Saadatian-Elahi, 2004 on serum fatty acids and Byrne, 2002, Horn-Ross, 2002, Velie, 2000, and Toniolo, 1994 on oleic acid were not included in the present review. Other cohorts were included.

Table 211 Monounsaturated fatty acids intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Sieri, 2014 BRE80546 France, Italy, Spain, UK, Netherlands, Greece, Germany,	EPIC, Prospective Cohort, Age: 20-70 years, W	10 062/ 337 327 11.5 years	Cancer and mortality registries, health Insurance & pathology records, active follow up	FFQ, diet history, 7-day food diary	Incidence, breast cancer	46 vs 14 g/day	1.07 (0.96-1.20) Ptrend:0.06	Age, BMI, educational level, energy from alcohol, HRT use, menopausal status, non-	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Sweden, Denmark, Norway								alcohol energy, pregnancies, smoking status, study center	
						per 20 %	1.02 (1.00-1.04)		
		3 540/			Incidence, breast cancer ER+/PR+	46.4 vs 14.2 g/day	1.09 (0.91-1.30) Ptrend:0.17		
						per 20 %	1.02 (0.99-1.06)		
		1 072/			Incidence, breast cancer ER+/PR-	46.4 vs 14.2 g/day	1.16 (0.83-1.61) Ptrend:0.34		
						per 20 %	1.04 (0.98-1.10)		
		1 018/			Incidence, breast cancer ER-/PR-	46.4 vs 14.2 g/day	0.95 (0.68-1.34) Ptrend:0.44		
						per 20 %	0.97 (0.92-1.03)		
		3 155/			Incidence, breast cancer unknown ER/PR status	46.4 vs 14.2 g/day	1.06 (0.87-1.30) Ptrend:0.07		
						per 20 %	1.03 (0.99-1.06)		
		539/			Incidence, breast cancer HER-2 +	47.4 vs 14.7 g/day	1.11 (0.70-1.76) Ptrend:0.80		
						per 20 %	1.02 (0.94-1.10)		
		1 720/			Incidence, breast cancer HER-2 -	47.4 vs 14.7 g/day	1.07 (0.82-1.40) Ptrend:0.28		
						per 20 %	1.05 (1.01-1.09)		
		5 756/			Incidence, breast cancer HER-2 unknown	47.4 vs 14.7 g/day	0.98 (0.85-1.13) Ptrend:0.54		
						per 20 %	1.01 (0.99-1.04)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
		5 615/			Incidence, breast cancer ER+	46.4 vs 14.2 g/day	1.11 (0.96-1.28) Ptrend:0.03		
						per 20 %	1.02 (1.00-1.05)		
		1 395/			Incidence, breast cancer ER-	46.4 vs 14.2 g/day	0.99 (0.74-1.33) Ptrend:0.51		
						per 20 %	0.99 (0.94-1.04)		
		3 761/			Incidence, breast cancer PR+	46.4 vs 14.2 g/day	1.07 (0.90-1.28) Ptrend:0.24		
						per 20 %	1.02 (0.99-1.05)		
		2 097/			Incidence, breast cancer PR-	46.4 vs 14.2 g/day	1.04 (0.82-1.32) Ptrend:0.91		
						per 20 %	1.01 (0.97-1.04)		
Löf, 2007 BRE80144 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	974/ 44 569 13 years	Cancer registry	FFQ	Incidence, Invasive breast cancer	26.5 vs 10.4 g/day	0.88 (0.53-1.46) Ptrend:0.65	Age, age at first child birth, age at menarche, alcohol consumption, BMI, educational level, family history of cancer, non-alcohol energy, parity, total fat, use of oral contraception	
						per 10 g/day	0.82 (0.49-1.35)		
Hunter, 1996 Canada, USA, the Netherlands,	The Pooling Project Pooled study of	4 980/ 337 819	Self-reported and verified by medical records	FFQ	Incidence, breast cancer	Q5 vs Q1	1.01 (0.88-1.16) Ptrend:0.73	Age at menarche, menopausal	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Sweden	7 cohorts*, Age: 28-90 years, W (*AHS, CNBSS, IWHS, NLCS, NYSC, NHS(a), NHS(b), SMC),		and/or record linkage with cancer registries					status, parity, age at birth of first child, BMI, height, education, history of benign breast disease, maternal history of breast cancer, history of breast cancer in a sister, OC use, fibre intake, alcohol intake, energy intake	
						per 10 g/day	0.99 (0.90-1.08)		
	AHS	153/ 15 172				-	-		
	CNBSS	514/ 56 837				per 10 g/day	1.14 (0.85-1.53)		
	IWHS	723/ 34 406				per 10 g/day	1.21 (0.99-1.48)		
	NLCS	434/ 62 412				per 10 g/day	0.77 (0.60-1.01)		
	NYSC	376/ 18 475				per 10 g/day	1.03 (0.92-1.16)		
	NHS(a)	1 094/ 89 046				per 10 g/day	0.98 (0.89-1.09)		
	NHS(b)	911/ 68 817				per 10 g/day	0.89 (0.75-1.06)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	SMC	775/ 61 471				per 10 g/day	0.91 (0.73-1.14)		
Gaard, 1995 BRE17516 Norway	Norway National Health Screening Service, 1974, Prospective Cohort, Age: 35-49 years, W, Screening Program	248/ 24 897 10 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer	≥21 vs ≤15.9 g/day	1.72 (1.19-2.49) Ptrend:0.01	Age, BMI, energy Intake , height, menopausal status, smoking habits	
Knekt, 1990 BRE04898 Finland	Mobile Clinic Health Examination Survey, 1973, Prospective Cohort, Age: 20-69 years, W, Screening Program	3 988 20 years	All histology	Dietary history questionnaire	Incidence, breast cancer	≥31.1 vs ≤22.6 g/day	2.70 (0.99-7.37) Ptrend:0.05	Age , energy Intake	
Jones, 1987 BRE04461 USA	NHANES I, Prospective Cohort, Age: 25-74 years, W	86/ 5 485 10 years	Medical records + self-reported +death certificate	24h recall	Incidence, breast cancer	≥29 vs ≤13.9 g/day	0.59 (0.30-1.13)	Age, age at menarche, age at menopause, BMI, educational level, family history, menopausal status	

Table 212 Percentage of energy from monounsaturated fatty acids and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Farvid, 2014 BRE80577 USA	NHS II, Prospective Cohort, Age: 26-45 years, W	2 830/ 88 804 20 years	Self report verified by medical record and pathology report	Semi-quantitative FFQ	Incidence, breast cancer	15 vs 8.9 %	1.13 (1.00-1.27) Ptrend:0.03	Age, age at menarche, age at menopause, alcohol Intake, BMI, calendar year, energy, energy from protein, family history of breast cancer In first degree relatives, height, history of benign breast disease, hormone use, menopausal status, OC use, parity and age at first birth, race, smoking status and dose	
Sieri, 2008 BRE80202 Europe	EPIC, Prospective Cohort, Age: 20-70 years, W	7 119/ 319 826 8.8 years	Cancer registry / database / pathology reports	FFQ	Incidence, breast cancer	18.2 vs 9.5 % energy/day	1.05 (0.96-1.16) Ptrend:0.323	Age, alcohol Intake, centre location, educational attainment, energy Intake, height, menopausal status, smoking status, weight	
						per 20 %	1.02 (0.99-1.04)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Wakai, 2005 BRE24482 Japan	JACC, Prospective Cohort, Age: 40-79 years, W, Previous study	129/ 26 291 7.6 days	Partially histological - over 80%	FFQ	Incidence, breast cancer	≥7.55 vs ≤5.49	0.62 (0.36-1.09) Ptrend:0.19	Age , age at first child, age at menarche, age at menopause, alcohol, BMI, educational level, energy Intake , family history, height, HRT use, other energy Index, other nutritional factors, other physical activity Index, parity/pregnancies, recruitment center, smoking habits	
Gago-Dominguez, 2003 BRE17518 China	SCHS, Prospective Cohort, Age: 45-74 years, W	314/ 63 257 5.3 years	Partially histological - over 80%	FFQ	Incidence, breast cancer	≥10.00 vs ≤7.23 %	1.02 (0.73-1.43) Ptrend:0.90	Age , alcohol, educational level, ethnicity, family history, menstrual characteristics , parity/pregnancies	
Smith-Warner, 2001b Canada, USA, the Netherlands, Sweden	The Pooling Project, Pooled study of 8 cohorts*, Age: 28-90 years, W	7 329/ 351 821	Self-reported and verified by medical records and/or record linkage with cancer registries	FFQ	Incidence, breast cancer	Q4 vs Q1	0.97 (0.86-1.09) Ptrend:0.78	Percent of energy from protein, percent of energy from alcohol, age at menarche, parity, age at	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	(*AHS, CNBSS, IWHS, NHS(a), NHS(b), NLCS, NYSC, NYUWHS, SMC),							birth of first child, menopausal status at diagnosis, MHT use, OC use, history of benign breast disease, family history of breast cancer, smoking status, education, BMI, BMI-menopausal status at diagnosis interaction, height, fibre intake, energy intake, saturated fat, polyunsaturated fat	
						per 5% of energy	0.93 (0.84-1.03)		
	AHS	160/ 15 172				per 5% of energy	0.52 (0.15-1.77)		
	CNBSS	419/ 56 837				per 5% of energy	0.88 (0.55-1.41)		
	IWHS	1 130/ 34 406				per 5% of energy	1.02 (0.80-1.30)		
	NHS(a)	1 020/ 89 046				per 5% of	1.09 (0.91-1.31)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
						energy			
	NHS(b)	1 638/ 68 817				per 5% of energy	0.87 (0.71-1.06)		
	NLCS	887/ 62 412				per 5% of energy	0.82 (0.65-1.02)		
	NYSC	367/ 18 475				per 5% of energy	0.89 (0.44-1.81)		
	NYUWHS	385/ 14 006				per 5% of energy	1.05 (0.75-1.45)		
	SMC	1 323/ 61 467				per 5% of energy	0.69 (0.47-1.01)		

Table 213 Monounsaturated fatty acids intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Key, 2011 UK	UK Dietary Cohort Consortium Pooled study of 4 cohorts* Mean age: 56.4 ±9.7 years among cases, W (*EPIC-Norfolk;	657 cases/ 1 911 controls EPIC-Norfolk: 353 cases/1 252 controls EPIC-Oxford: 194 cases/ 194 cases UKWCS: 42 cases/202 controls	Record linkage with National Statistics and cancer registries	Food diary and FFQ	Incidence, breast cancer	Food diaries ≥32.7 vs ≤13.8 g/day	1.03 (0.65-1.62) Ptrend:0.697	Age, alcohol consumption, parity, menopausal status, current hormone replacement therapy use, physical activity, height, weight, and	Superseded by Sieri, 2014 (EPIC-Norfolk, EPIC-Oxford overlapped with Sieri, 2014, EPIC)

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	EPIC-Oxford; UKWCS; Whitehall II study)	Whitehall II study: 68 cases/263 controls						energy intake	
						per 7.5 g/day	1.59 (0.93-2.71)		
						FFQ ≥36.0 vs ≤12.7 g/day	0.91 (0.58-1.43) Ptrend: 0.725		
						per 9.9 g/day	1.20 (0.65-2.20)		(Included in stratified analysis)
Martin, 2011 BRE80323 Canada	CDBCPT, Nested Case Control, Age: 47 years	220/ 440 controls 10	Pathology	Food records	Incidence, Invasive breast cancer	20 vs 13 g/day	1.02 (0.75-1.39)	Age, age at first child birth, age at menarche, family history of breast cancer, HRT use, menopausal status, number of childbirths, parity, randomisation, smoking	Excluded, post-randomised diet
		167/ 334 controls			Incidence, breast cancer ER+	20 vs 13 g/day	1.26 (0.88-1.80)		
		42/ 84 controls			Incidence, breast cancer ER-	20 vs 13 g/day	0.20 (0.07-0.64)		
Trichopoulou, 2010 BRE80320 Greece	EPIC-Greece, Prospective Cohort, Age: 20-68 years	240/ 14 807 9.8 years	Medical records and pathology reports	FFQ	Incidence, breast cancer	per 17 g/day	0.90 (0.74-1.09)	Age, age at first child birth, age at menarche, age at menopause, BMI,	Study superseded by Sieri, 2014

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								educational level, energy Intake, height, HRT use, menopausal status, metabolic equivalents, parity, smoking	
Sieri, 2008 BRE80202 Europe	EPIC, Prospective Cohort, Age: 20-70 years, W	7 119/ 319 826 8.8 years	Cancer registry / database / pathology reports	FFQ	Incidence, breast cancer	44.1 vs 15.3 g/day	1.05 (0.92-1.20) Ptrend:0.254	Age, alcohol Intake, centre location, educational attainment, energy Intake, height, menopausal status, smoking status, weight	Superseded by Sieri, 2014
						per 20 %	1.02 (0.99-1.04)		
Frazier, 2003 BRE02941 USA	NHS, Nested Case Control, Age: 40-65 years, W, Registered nurses	121 700 10 years	All histology	FFQ	Incidence, breast cancer	39.8 vs 13.3 g/day	0.89 Ptrend:0.28	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, family history, height, HRT use, menopausal status, nutrients, parity/pregnancies	Excluded, adolescent diet
Thiebaut, 2001 BRE12244	E3N EPIC-France,	65 879	Not specified	FFQ-semi-quantitative	Incidence, breast cancer	Q4 vs Q1	1.22 (0.93-1.59)	Age , age at menarche, age at	Study superseded by

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
France	Prospective Cohort, Age: 40-65 years, W, Registered teachers	3.4 years						menopause, alcohol, benign breast disease, BMI, educational level, energy Intake , family history, marital status	Sieri, 2014
Wolk, 1998 BRE13548 Sweden	SMC, Prospective Cohort, Age: 40-76 years, W, Screening Program	61 147 4.2 years	All histology	FFQ	Incidence, Invasive breast cancer	≥18.41 vs ≤14.39 g/day	0.80 (0.52-1.21) Ptrend:.10	Age , age at first child, alcohol, BMI, educational level, energy Intake , family history, nutrients, parity/pregnancies, residual (willet)	Publication superseded by Hunter, 1996
						per 10 g/day	0.45 (0.22-0.95)		
Giovannucci, 1993a BRE03262 USA	NHS, Nested Case Control, Age: 30-55 years, W, Registered nurses	392/ 786 controls 2 years	Medical records + death certificate	FFQ-semi-quantitative	Incidence, breast cancer	Q5 vs Q1	1.04 (0.70-1.55) Ptrend:0.25	Age , residual (willet)	Publication superseded by Hunter, 1996
Willett, 1992 BRE13438 USA	NHS, Prospective Cohort, Age: 30-55	1 439/ 89 494 8 years	Medical records + self-reported	FFQ-semi-quantitative	Incidence, breast cancer	≥34 vs ≤22.9 g/day	0.92 (0.78-1.09) Ptrend:0.56	Age , age at first child, age at menarche, alcohol, benign	Publication superseded by Hunter, 1996

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	years, W, Registered nurses							breast disease, BMI, energy Intake , family history, menopausal status, nutrients, other design Issue, parity/pregnancies	
Howe, 1991 BRE17622 Canada	CNBSS, Nested Case Control, Age: 40-59 years, W, Screening Program	519/ 1182 controls 5 years	All histology	Dietary history questionnaire	Incidence, breast cancer	Q4 vs Q1	1.23 (0.81-1.89) Ptrend:.04	Age , energy Intake , recruitment center, time of recruitment	Publication superseded by Hunter, 1996

Table 214 Percentage of energy from monounsaturated fatty acids and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Boeke, 2014a BRE80585 USA	NHS I and II, Prospective Cohort, Age: 25-55 years, W	9 979/ 182 671 30 years	Medical records, pathology reports, next of kin, death certificate, ndi	Semi-quantitative FFQ	Incidence, breast cancer	Q5 vs Q1	1.00 (0.89-1.12) Ptrend:0.81	Age, age at menarche, age at menopause, alcohol Intake, BMI at age 18 years, breastfeeding, calendar year, cohort, energy	Superseded by Farvid, 2014 BRE80577

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								from fat sources, family history of breast cancer, height, history of benign breast disease, menopausal status, oral contraceptive use, parity and age at first birth, physical activity, postmenopausal hormone use, protein, total energy Intake, weight change	
		1 529/			Mortality, breast cancer	Q5 vs Q1	0.84 (0.64-1.12) Ptrend:0.31		
Key, 2011	UK Dietary Cohort Consortium Pooled study of 4 cohorts* Mean age: 56.4 ±9.7 years among cases, W (*EPIC-Norfolk; EPIC-Oxford; UKWCS; Whitehall II	657 cases/ 1 911 controls EPIC-Norfolk: 353 cases/1 252 controls EPIC-Oxford: 194 cases/ 194 cases UKWCS: 42 cases/202 controls Whitehall II study: 68 cases/263	Record linkage with National Statistics and cancer registries	Food diary and FFQ	Incidence, breast cancer	Food diaries ≥14.1 vs ≤8.6% of energy	1.06 (0.78-1.44) Ptrend:0.813	Age, alcohol consumption, parity, menopausal status, current hormone replacement therapy use, physical activity, height, weight, and energy intake	Superseded by Sieri, 2014 (EPIC-Norfolk, EPIC-Oxford overlapped with Sieri, 2014, EPIC)

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	study)	controls							
						per 2.2% of energy	1.48 (1.04-2.09)		
						FFQ ≥13.4 vs ≤7.5% of energy	0.91 (0.67-1.24) Ptrend: 0.705		
						per 2.3% of energy	1.18 (0.84-1.64)		(Included in stratified analysis)
Thiebaut, 2001 BRE12244 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W, Registered teachers	65 879 3.4 years	Not specified	FFQ-semi-quantitative	Incidence, breast cancer	Q4 vs Q1	1.11 (0.91-1.37)	Age , age at menarche, age at menopause, alcohol, benign breast disease, BMI, density, educational level, family history, marital status	Study superseded by Sieri, 2008
Holmes, 1999 BRE04008 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	1 956/ 121 700 14 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, Invasive breast cancer	per 5 % of total energy/day	1.03 (0.89-1.18)	Age, age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight at 18 years, energy Intake , family history, height,	Superseded by Smith-Warner, 2001b

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								HRT use, menopausal status, nutrients, other types of fat	

Figure 279 RR estimates of breast cancer by levels of monounsaturated fatty acids intake and percentage of energy from monounsaturated fatty acids

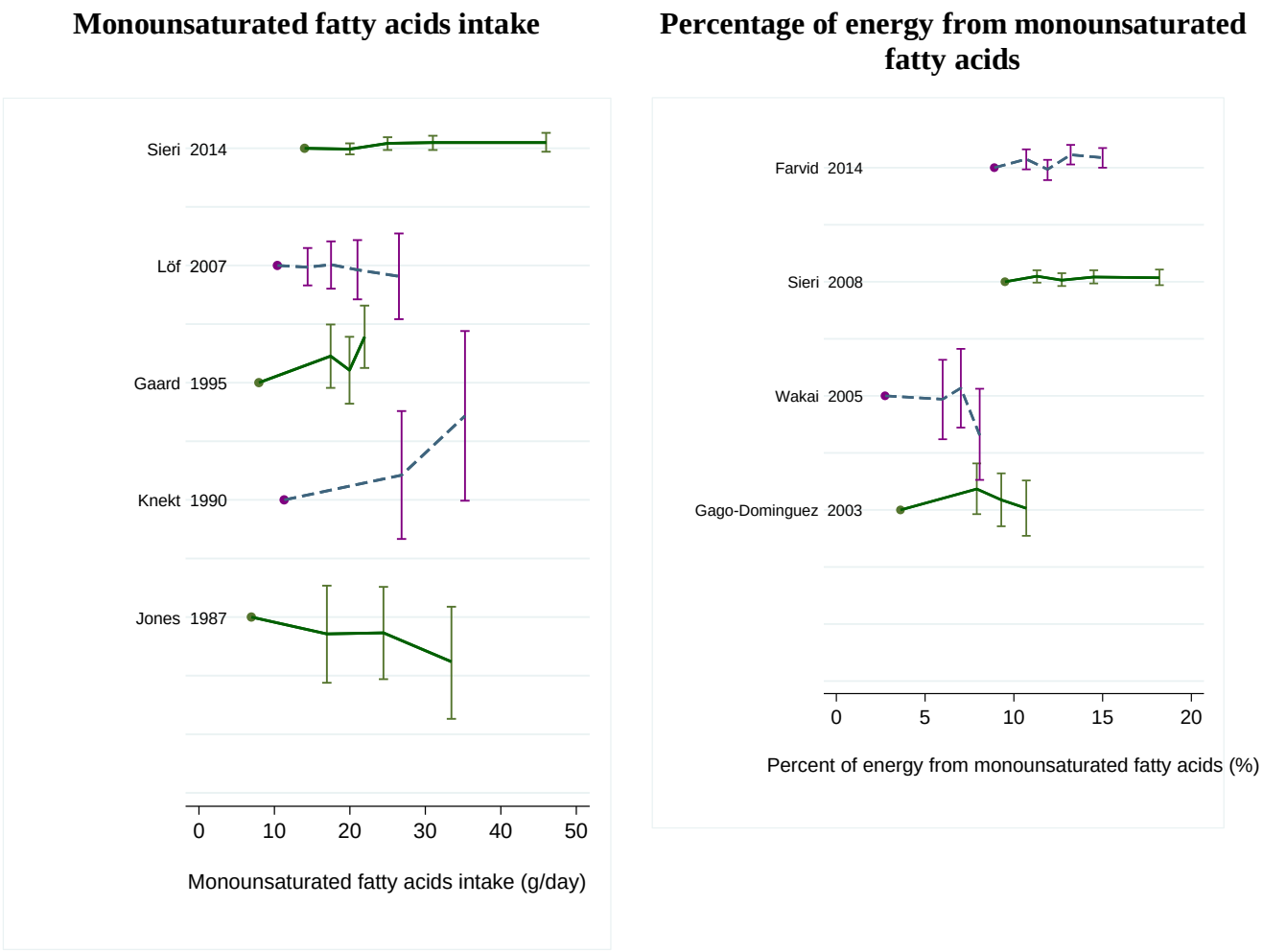


Figure 280 RR (95% CI) of breast cancer for the highest compared with the lowest monounsaturated fatty acids intake and percentage of energy from monounsaturated fatty acids

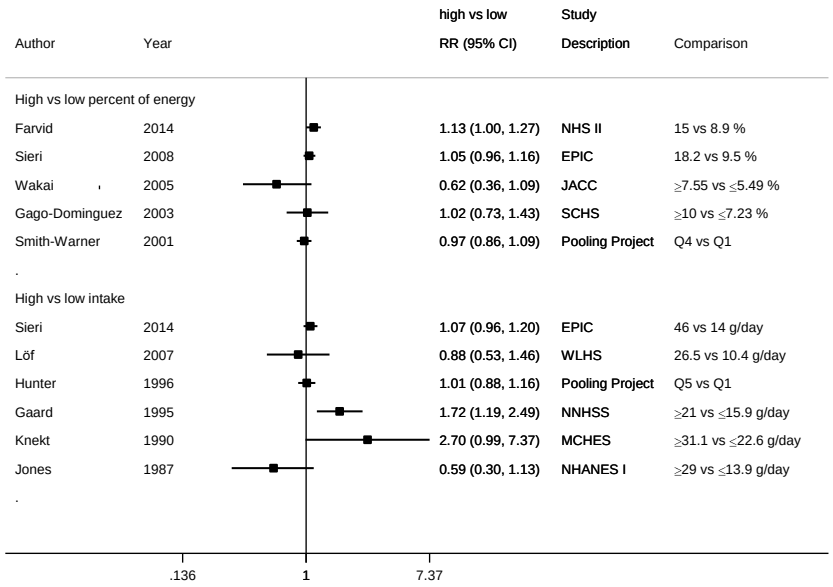


Figure 281 Relative risk of breast cancer for 10 g/day of monounsaturated fatty acids intake and 5% of energy from monounsaturated fatty acids

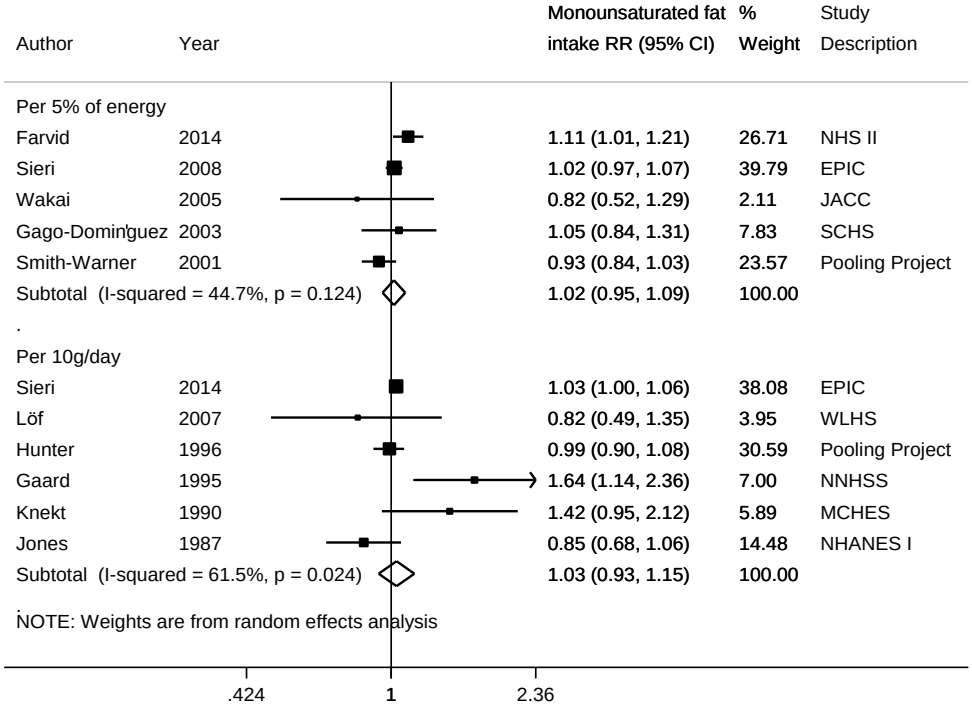


Figure 282 Funnel plot of studies included in the dose response meta-analysis of monounsaturated fatty acids intake and breast cancer

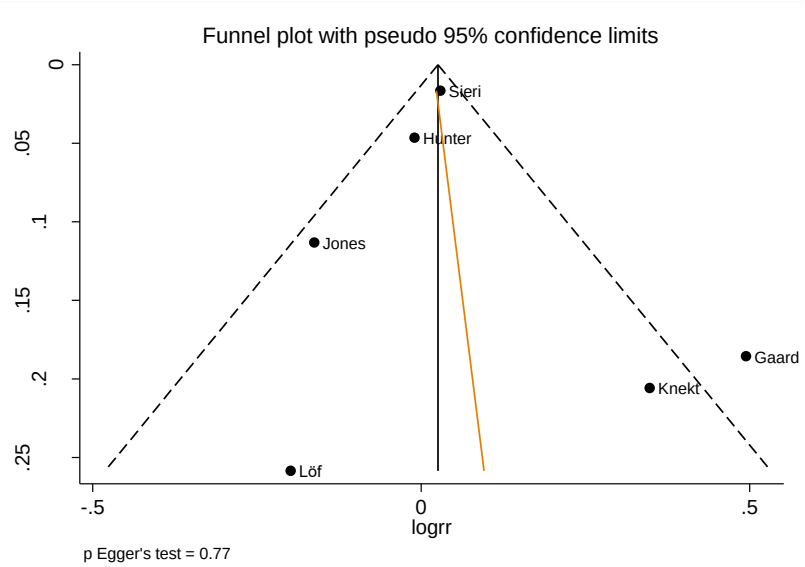


Figure 283 Funnel plot of studies included in the dose response meta-analysis of percentage of energy from monounsaturated fatty acids and breast cancer

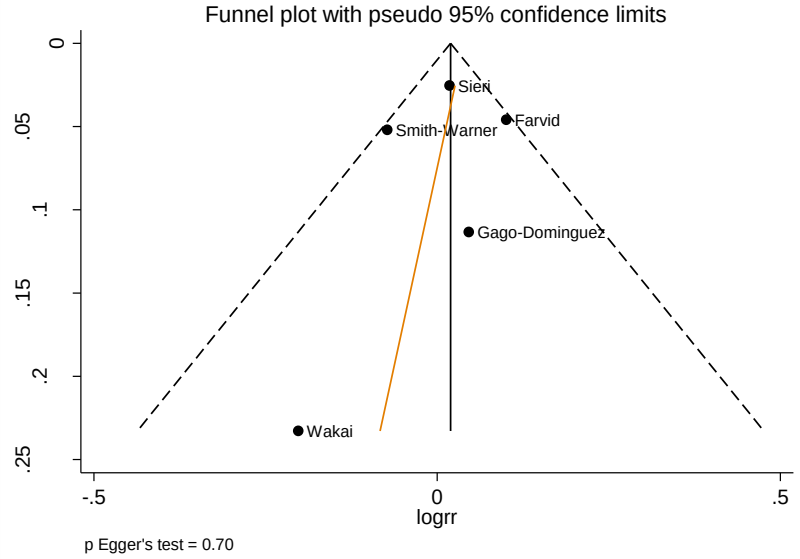
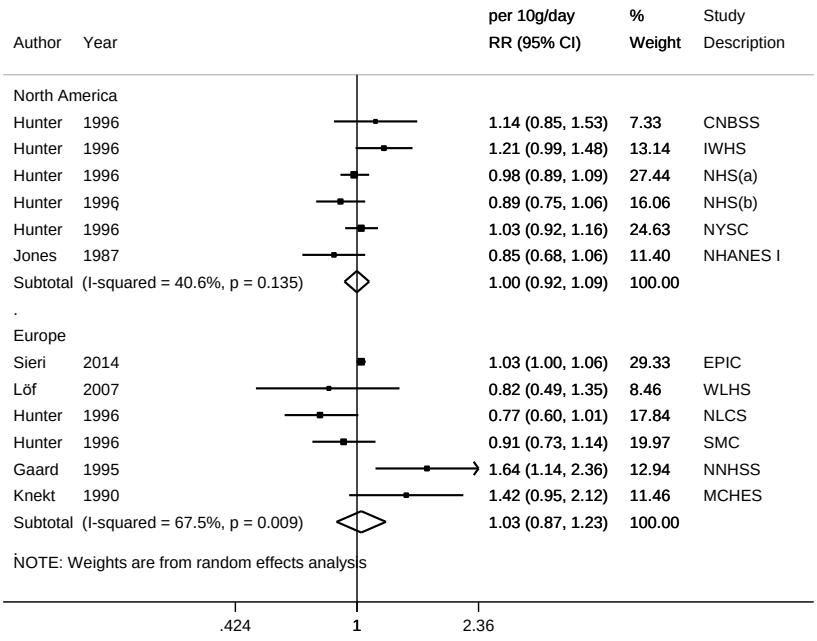
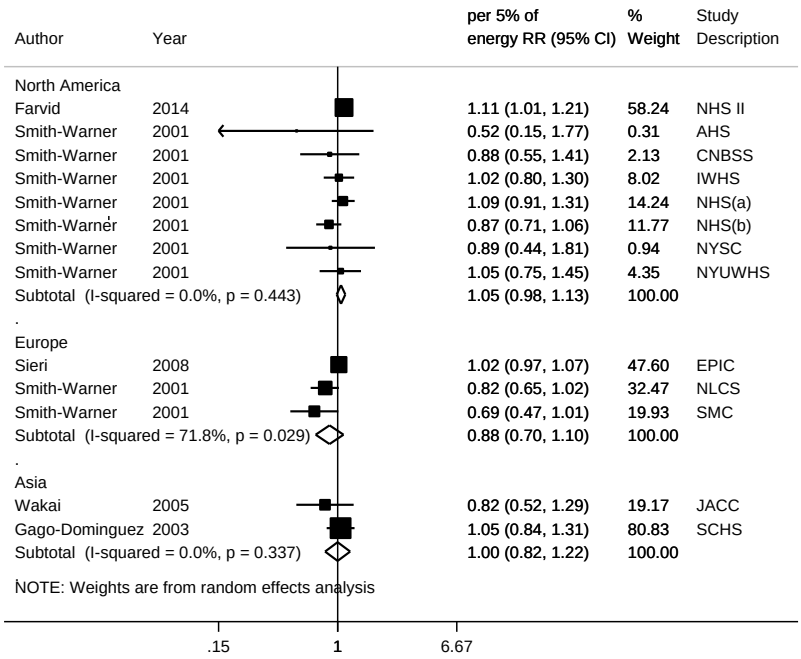


Figure 284 Relative risk of breast cancer for 10 g/day of monounsaturated fatty acids intake, by geographic location



Note: Results from the individual studies of the Pooling Project were used in the strata.

Figure 285 Relative risk of breast cancer for 5% of energy from monounsaturated fatty acids, by geographic location



Note: Results from the individual studies in the Pooling Project were used in the strata.

Figure 286 Relative risk of breast cancer for 10 g/day of monounsaturated fatty acids intake, by exposure assessment methods

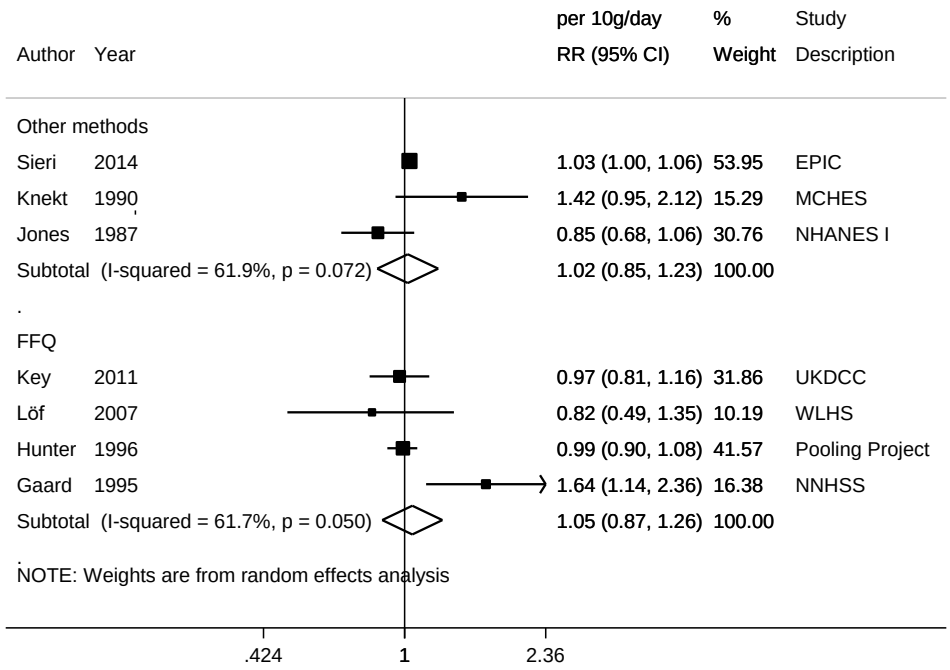
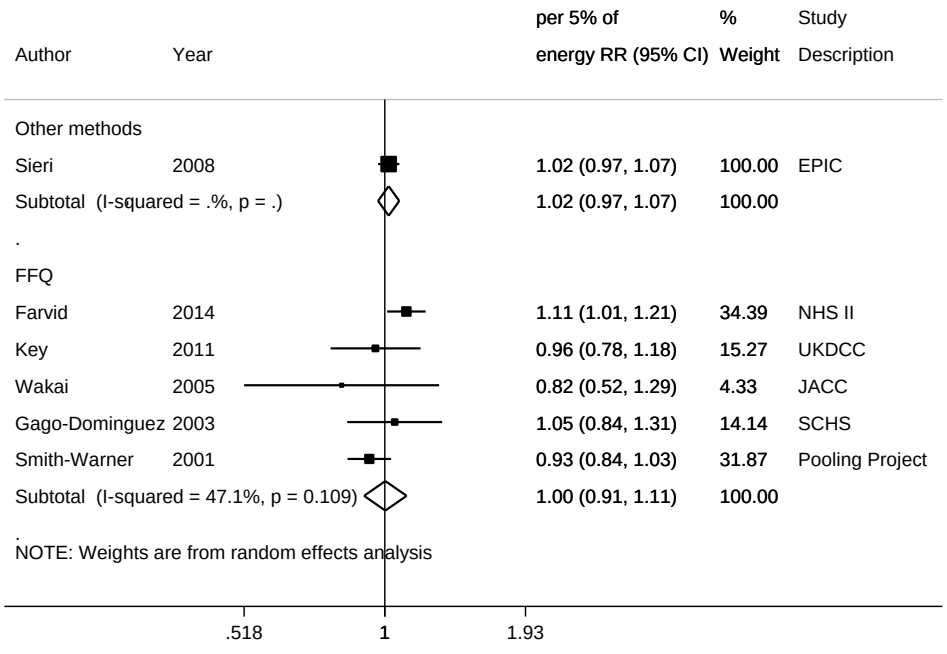


Figure 287 Relative risk of breast cancer for 5% of energy from monounsaturated fatty acids, by exposure assessment methods



Premenopausal breast cancer

Summary

Main results:

Two out of four studies (five publications) on monounsaturated fatty acids intake and all six studies (four publications) on percentage of energy from monounsaturated fatty acids identified could be included in the dose-response meta-analyses respectively.

There were no significant associations observed for premenopausal breast cancer. The summary RRs were 1.00 (95% CI=0.87-1.16; I^2=0%, P=0.47) per 10g/day intake of monounsaturated fatty acids and 1.02 (95% CI=0.86-1.21; I^2=28%, P=0.24) per 5% of energy from monounsaturated fatty acids.

One study (two publications) (Linos, 2010; Frazier, 2004) on adolescent monounsaturated fatty acids intake were excluded. The publication (Linos, 2010) that used prospective data observed a non-significant positive association and the other publication (Frazier, 2004) with retrospective data which could be affected by recall bias observed a non-significant inverse association. Another study (Willett, 1992) did not have sufficient data to be included in the analysis. A non-significant positive association was reported (Willett, 1992).

Stratified analysis and non-linear dose-response meta-analysis was not conducted due to limited number of studies.

Study quality:

Only North American and European studies reported results. All studies used FFQs to assess fat intake. Farvid, 2014 (NHS II) assessed premenopausal fat intake. Major confounding factors of breast cancer were adjusted for in the studies, apart from alcohol consumption in Trichopoulou, 2010.

Table 215 Monounsaturated fatty acids intake and percentage of energy from monounsaturated fatty acids and premenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	4 (5 publications) monounsaturated fatty acids intake 6 (4 publications) percentage of energy from monounsaturated fatty acids
Studies included in forest plot of highest compared with lowest exposure	Not enough studies
Studies included in linear dose-response meta-analysis	2 (2 publications) monounsaturated fatty acids intake 6 (2 publications) percentage of energy from monounsaturated fatty acids
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 216 Monounsaturated fatty acids intake and percentage of energy from monounsaturated fatty acids and premenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and 2016 CUP

	2005 SLR*		CUP	
Increment unit used	-	-	**Per 10g/day**	**Per 5%**
Studies (n)	-	-	2	6
Cases	-	-	545	>1 511
RR (95%CI)	-	-	1.00 (0.87-1.16)	1.02 (0.86-1.21)
Heterogeneity (I^2, p-value)	-	-	0%, 0.47	28%, 0.24
P value Egger test	-	-	-	-

*No meta-analysis was conducted in the 2005 and 2008 SLR

Table 217 Monounsaturated fatty acids intake and premenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Turner, 2011	6 studies (2 cohorts*, 2 case-control studies)	>4 025 premenopausal breast cancer	Germany, USA	Incidence, premenoapausal breast cancer	Highest vs lowest monounsaturated fat intake (3 studies)	0.96 (0.87-1.06)	-

*All cohort studies identified were included in the present review.

Table 218 Monounsaturated fatty acids intake and premenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Trichopoulou, 2010 BRE80320 Greece	EPIC-Greece, Prospective Cohort, Age: 20-68 years	14 807 9.8 years	Medical records and pathology reports	FFQ	Incidence, breast cancer, premenopausal	per 17 g/day	0.99 (0.77-1.26)	Age, age at first child birth, age at menarche, BMI, educational level, energy Intake, height, metabolic equivalents, parity	
Löf, 2007 BRE80144 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	432/ 44 569 13 years	Cancer registry	FFQ	Incidence, Invasive breast cancer, age < 50 yrs	26.5 vs 10.4 g/day	1.69 (0.81-3.51) Ptrend:0.2	Age, age at first child birth, age at menarche, alcohol consumption, BMI,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								educational level, family history of cancer, non-alcohol energy, parity, total fat, use of oral contraception	
						per 10 g/day	1.31 (0.63-2.73)		

Table 219 Percentage of energy from monounsaturated fatty acids and premenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Farvid, 2014 BRE80577 USA	NHS II, Prospective Cohort, Age: 26-45 years, W	1 511/ 88 804 20 years	Self report verified by medical record and pathology report	Semi-quantitative FFQ	Incidence, premenopausal breast cancer, premenopausal	15 vs 8.9 %	1.08 (0.91-1.27) Ptrend:0.29	Age, age at menarche, alcohol Intake, BMI, calendar year, energy, energy from protein, family history of breast cancer In first degree relatives, height, history of benign breast disease, OC use, parity and age at first birth, race,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								smoking status and dose	
Smith-Warner, 2001b Canada, USA, the Netherlands, Sweden	The Pooling Project, Pooled study of 5 cohorts, Age: 28-90 years, W (*AHS, CNBSS, , NHS(a), NHS(b), NYUWHS, SMC)	-	Self-reported and verified by medical records and/or record linkage with cancer registries	FFQ	Incidence, premenopausal breast cancer	per 5% of energy	0.87 (0.63-1.19)	Percent of energy from protein, percent of energy from alcohol, age at menarche, parity, age at birth of first child, OC use, history of benign breast disease, family history of breast cancer, smoking status, education, BMI, height, fibre intake, energy intake, saturated fat, polyunsaturated fat	

Table 220 Monounsaturated fatty acids intake and premenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Linos, 2010 BRE80298 USA	NHS II, Prospective Cohort, Age: 34-53 years, W, Premenopausal	455/ 39 268 7.8 years	Follow up questionnaires, medical records	Semi-quantitative FFQ for adolescent diet	Incidence, Invasive breast cancer, premenopausal	51.2 vs 37.7 g/day	1.16 (0.86-1.55) Ptrend:0.26	Age, age at first child birth, age at menarche, alcohol consumption, benign breast disease, BMI, energy Intake, family history of cancer, menopausal status, OC use, parity, weight gain	Excluded, adolescent diet
Frazier, 2004 BRE02942 USA	NHS II, Historical Cohort, Age: 34-51 years, W, Registered nurses	361/ 47 355 9 years	All histology	FFQ, for adolescent diet	Incidence, breast cancer, premenopausal	51.2 vs 37.7 g/day	0.86 (0.63-1.18) Ptrend:0.69	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, energy Intake , family history, menopausal status, OC use, other anthropometric Index, other design Issue, parity/pregnancies	Excluded, adolescent diet
Willett, 1992 BRE13438 USA	NHS, Prospective Cohort, Age: 30-55	527/ 89 494 8 years	Medical records + self-reported	FFQ-semi-quantitative	Incidence, breast cancer, premenopausal	Q5 vs Q1	1.03 (0.78-1.37) Ptrend:0.72	Age , age at first child, age at menarche, alcohol, benign	Excluded, missing cases and non-cases per category

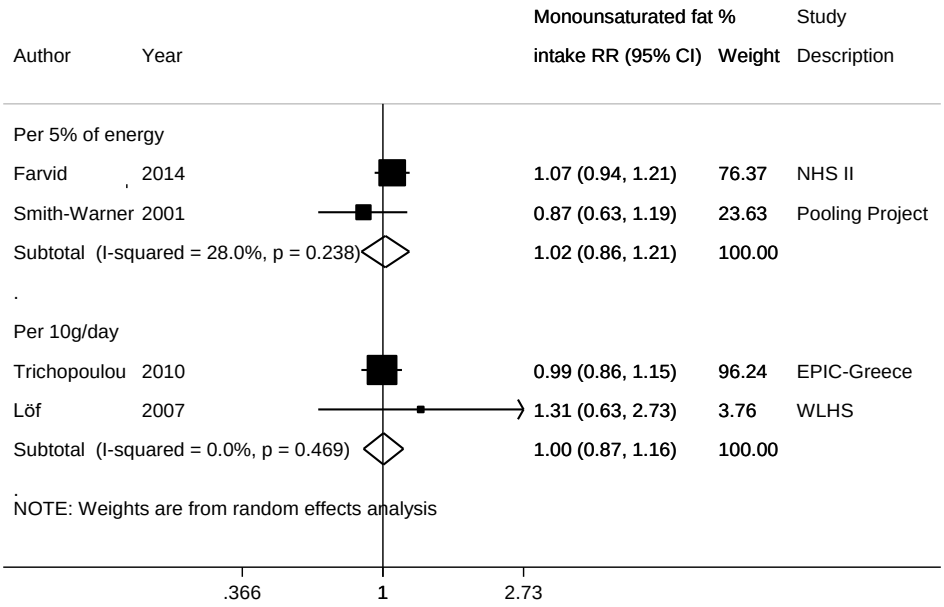
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	years, W, Registered nurses							breast disease, BMI, energy Intake , family history, nutrients, other design Issue, parity/pregnancies	

Table 221 Percentage of energy from monounsaturated fatty acids and premenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Cho, 2003a BRE17370 USA	NHS II, Prospective Cohort, Age: 25-42 years, W, Premenopausal	714/ 90 655 8 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, Invasive breast cancer, premenopausal	7 vs 4 %/day	1.06 (0.84-1.35) Ptrend:0.20	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, family history, height, menopausal status, multivariate partition, OC use, parity/pregnancies, smoking habits	Publication superseded by Farvid, 2014
Holmes, 1999	NHS,		Medical records	FFQ-semi-	Incidence,	per 5 % of total	0.99 (0.77-1.27)	Age , age at first	Publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
BRE04008 USA	Prospective Cohort, Age: 30-55 years, W, Registered nurses	121 700 14 years	+ self-reported +death certificate	quantitative	Invasive breast cancer, premenopausal	energy/day		child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight at 18 years, energy Intake , family history, height, HRT use, menopausal status, nutrients	superseded by Smith-Warner, 2001b

Figure 288 Relative risk of premenopausal breast cancer for 10 g/day of monounsaturated fatty acids intake and 5% of energy from monounsaturated fatty acids



Note: The graphs of RR estimates of premenopausal breast cancer by levels of monounsaturated fatty acids and the highest compared with the lowest forest plot were not produced as the number of studies with categorical results was limited.

RR estimates were 1.16 (95% CI=0.99-1.36), 0.97 (95% CI=0.82-1.15), 1.22 (95% CI=95% CI=1.04-1.43), and 1.08 (95% CI=0.91-1.27) for increasing quintile categories (median 10.6, 11.9, 13.1, and 15.0% vs 8.9% of energy) in Farvid, 2014 and 1.16 (95% CI=0.81-1.66), 1.35 (95% CI=0.88-2.06), 1.30 (95% CI=0.76-2.21), and 1.69 (95% CI=0.81-3.51) for increasing quintile categories (median 14.4, 17.5, 21.0, 26.5 g/day vs 10.4 g/day) in Lof, 2007a.

Postmenopausal breast cancer

Summary

Main results:

Eleven out of 15 studies (14 publications) on monounsaturated fatty acids intake and all 16 studies from eight publications on percentage of energy from monounsaturated fatty acids could be included in the dose-response meta-analyses respectively.

There were no significant associations observed for postmenopausal breast cancer. The summary RRs were 1.00 (95% CI=0.84-1.20) per 10g/day intake of monounsaturated fatty acids and 1.01 (95% CI=0.92-1.10) per 5% of energy from monounsaturated fatty acids. There was evidence of high heterogeneity between studies (I^2= 73%, P=0.001; I^2= 64%, P=0.02, respectively).

Subgroup analyses showed positive associations among North American studies and inverse associations among European studies. For monounsaturated fatty acids intake, the summary RRs per 10g/day were 1.22 (95% CI=1.08-1.37) and 0.87 (95% CI=0.72-1.06), respectively; for percentage of energy from monounsaturated fatty acids, the summary RRs per 5% of energy were 1.04 (95% CI=1.00-1.08) and 0.65 (95% CI=0.46-0.96), respectively.

There was no evidence of significant publication or small studies bias (P for Egger's test=0.76 for studies on monounsaturated fatty acids intake and 0.50 for studies on percentage of energy from monounsaturated fatty acids).

Four studies on monounsaturated fatty acids intake did not have sufficient data to be included in the analysis. Two studies observed non-significant positive associations, overall (Sieri, 2002) or among MHT non-users only (Sieri, 2008); and two studies reported non-significant inverse association, overall (Willett, 1992) or among MHT users only (Sieri, 2008). Barrett-Connor, 1993 reported that intake of monounsaturated fatty acids was significantly higher in the cases than in the non-cases (P=0.001).

Three studies reported results by breast cancer hormone receptor status. Non-significant associations were observed (Park, 2012; Kim, 2006; Kushi, 1995).

Sensitivity analyses:

Summary RRs for intake and percentage of energy from monounsaturated fatty acids remained non-significant in influence analyses.

Non-linear dose-response meta-analysis:

There was no evidence of non-linear relationship between monounsaturated fatty acids intake and postmenopausal breast cancer risk (P for non-linearity=0.29). There were not enough studies to conduct a non-linear dose-response meta-analysis of percentage of energy from monounsaturated fatty acids.

Study quality:

Most studies were from North America or Europe. One study was from Japan (Wakai, 2005). Park, 2012 was a cohort of multi-ethnicity. The study of Freedman, 2006 (WHI-DM, non-

intervention group) included only women with ≥32% calories from fat. Results in this study were adjusted for these selection criteria (Freedman, 2006). Key, 2011 included only MHT non-users. Summary RR remained non-significant when studies were omitted in turn in influence analysis.

Most studies used FFQs to assessed fat intake. Wirfalt, 2002 used a combination of 7-day food record and questionnaire. Key, 2011 (UKDCC) and Freedman, 2006 (WHI-DM, non-intervention arm) were able to use data from both sources (FFQs and food diaries or food records) in the analysis. Key, 2011 reported similar inverse associations that was only significant for percentage of energy from monounsaturated fatty acids assessed in food diaries. Freedman, 2006 found stronger association with data from food records than data from FFQs (RR for the highest versus the lowest intake=1.96, 95% CI=1.11-3.45, Ptrend=0.02 vs. RR=1.39, 95% CI=0.64-3.01, Ptrend=0.25).

Case ascertainment was through cancer registries or confirmed through medical records Major confounding factors of breast cancer were adjusted for in the studies, apart from alcohol consumption in Trichopoulou, 2010.

Table 222 Monounsaturated fatty acids intake and percentage of energy from monounsaturated fatty acids and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	15 (14 publications) monounsaturated fatty acids intake 16 (8 publications) percentage of energy from monounsaturated fatty acids
Studies included in forest plot of highest compared with lowest exposure	9 (9 publications) monounsaturated fatty acids intake 4 (4 publications) percentage of energy from monounsaturated fatty acids
Studies included in linear dose-response meta-analysis	11 (8 publications) monounsaturated fatty acids intake 16 (6 publications) percentage of energy from monounsaturated fatty acids
Studies included in non-linear dose-response meta-analysis	6 (6 publications) monounsaturated fatty acids intake Not enough studies on percentage of energy from monounsaturated fatty acids

Note: Include cohort, case-cohort, and nested case-control designs.

Table 223 Monounsaturated fatty acids intake and percentage of energy from monounsaturated fatty acids and postmenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and 2016 CUP

	2005 SLR		CUP	
Increment unit used	**Per 10g/day**	-	**Per 10g/day**	**Per 5%**
Studies (n)	4	-	11	16
Cases	1 148	-	3 463	>8 666
RR (95%CI)	1.10 (0.96-1.25)	-	1.00 (0.84-1.20)	1.01 (0.92-1.10)
Heterogeneity (I^2, p-value)	86%	-	73%, 0.001	64%, 0.02
P value Egger test	-	-	0.70	0.50

Stratified analyses in the CUP					
Increment unit used	**Per 10g/day**	**Per 10g/day**	**Per 5% of energy**	**Per 5% of energy**	**Per 5% of energy**
Geographic location	**Europe**	**North America**	**Europe**	**North America**	**Asia**
Studies (n)	5	3	4	4	1
Cases	1 629	1 834	286	11 841	76
RR (95%CI)	0.87 (0.72-1.06)	1.22 (1.08-1.37)	0.65 (0.46-0.96)	1.04 (1.00-1.08)	1.29 (0.67-2.49)
Heterogeneity (I^2, p-value)	53%, 0.08	0%, 0.64	-	10%, 0.34	-

Increment unit used	**Per 10g/day**	**Per 10g/day**	**Per 5% of energy**	**Per 5% of energy**
Adjustment for age, BMI, alcohol intake, reproductive factors	**Adjusted**	**Not adjusted**	**Adjusted**	**Not adjusted**
Studies (n)	10	1	16	-
Cases	3 336	127	>8 666	-
RR (95%CI)	1.03 (0.85-1.26)	0.86 (0.72-1.02)	1.01 (0.92-1.10)	-
Heterogeneity (I^2, p-value)	71%, <0.01	-	64%, 0.02	-
Exposure assessment methods	**FFQs**	**Other methods**	**FFQs**	**Other methods**
Studies (n)	10	6	16	4
Cases	3 226	1 126	>8 666	286

RR (95%CI)	0.96 (0.83-1.12)	1.12 (0.70-1.79)	1.02 (0.95-1.10)	0.65 (0.46-0.96)
Heterogeneity (I^2, p-value)	63%, 0.01	80%, 0.01	53%, 0.06	-

Table 224 Monounsaturated fatty acids intake and postmenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Turner, 2011	15 studies (12 cohorts*, 3 case-control studies)	>13 460 postmenopausal breast cancer	Germany, Italy, The Netherlands, Singapore, Sweden, USA	Incidence, postmenoapausal breast cancer	Highest vs lowest monounsaturated fatty acids intake (11 studies) Cohort studies (n=10)	1.02 (0.93-1.10) 1.01 (0.93-1.09)	- -

* Byrne, 2002 and Velie, 2000, on oleic acid were not included in the present review. Other cohorts were included.

Table 225 Monounsaturated fatty acids intake and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Sczaniecka, 2012 BRE80434 USA	VITAL, Prospective Cohort, Age: 50-76 years, W, Postmenopausal	772/ 30 252 6 years	Seer registry	Semi-quantitative FFQ	Incidence, breast cancer, postmenopausal	≥27.8 vs ≤12.1 g/day	1.61 (1.08-2.38) Ptrend:0.02	Age, age at first child birth, age at menarche, age at menopause, alcohol, BMI, breast biopsies, educational level, energy, estrogen replacement therapy, exercise, family	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								history of breast cancer, fruits, height, history of hysterectomy, mammography, NSAID use, race, vegetable, years of combined hormone therapy	
Key, 2011 UK	UK Dietary Cohort Consortium Pooled study of 4 cohorts* Mean age: 56.4 ±9.7 years among cases, W (*EPIC-Norfolk; EPIC-Oxford; UKWCS; Whitehall II study)	286 cases/ 699 controls	Record linkage with National Statistics and cancer registries	Food diary and FFQ	Incidence, breast cancer, postmenopausal, HRT non-users	Food diaries per 7.5 g/day	0.76 (0.58-1.01)	Age, alcohol consumption, parity, menopausal status, current hormone replacement therapy use, physical activity, height, weight, and energy intake	
						FFQ per 9.9 g/day	0.82 (0.62-1.09)		
Trichopoulou, 2010 BRE80320 Greece	EPIC-Greece, Prospective Cohort, Age: 20-68 years	14 807 9.8 years	Medical records and pathology reports	FFQ	Incidence, breast cancer, postmenopausal	per 17 g/day	0.77 (0.57-1.04)	Age, age at first child birth, age at menarche, age at menopause, BMI, educational level, energy	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								Intake, height, HRT use, menopausal status, metabolic equivalents, parity, smoking	
Löf, 2007 BRE80144 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	542/ 44 569 13 years	Cancer registry	FFQ	Incidence, Invasive breast cancer, age >= 50 yrs	26.4 vs 10.4 g/day	0.45 (0.25-0.99) Ptrend:0.01	Age, age at first child birth, age at menarche, alcohol consumption, BMI, educational level, family history of cancer, non-alcohol energy, parity, total fat, use of oral contraception	
						per 10 g/day	0.55 (0.28-1.09)		
Freedman, 2006 BRE80628 USA	Women's Health Initiative - Dietary Modification Trial, Nested Case Control, Age: 50-79 years, W, Postmenopausal	603/ 1206 controls 6.92 years	Medical records and pathology reports	4-day food record & FFQ	Incidence, Invasive breast cancer, postmenopausal	Food records 36.1 vs 14 g/day	1.96 (1.11-3.45) Ptrend:0.02	Age at entry, breast biopsies, clinic, energy Intake, family history, HRT use, length of follow-up	
						FFQ 44.3 vs 15.1 g/day	1.39 (0.64-3.01) Ptrend:0.25		
Wirfalt, 2002	MDCS,	237/	Partially	7-day record +	Incidence, breast	37 vs 23 g/day	2.00 (0.91-4.37)	Age at first	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
BRE13504 Sweden	Nested Case Control, Age: 50- years, W, Postmenopausal	673 controls 8 years	histological - over 80%	questionnaire	cancer, postmenopausal		Ptrend:0.015	child, alcohol, BMI, educational level, energy Intake , height, HRT use, past food habit change, waist circumference, n-6 fatty acids, n-3 fatty acids, saturated fatty acids	
van den Brandt, 1993 BRE16919 Netherlands	NLCS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	437/ 1 598 3.3 years	All histology	FFQ-semi-quantitative	Incidence, Invasive breast cancer, postmenopausal	≥31.2 vs ≤23.6 g/day	0.75 (0.50-1.12) Ptrend:0.13	Age, age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, educational level, family history, OC use, parity/pregnancies, residual (willet), smoking habits	(Not included in the highest vs the lowest forest plot, as publication of the same study Voorrips, 2002 was used)
Kushi L H, 1992 BRE05141 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	459/ 34 388 4 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	30.7 vs 20.3 g/day	1.09 (0.70-1.70) Ptrend:0.63	Age, age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, BMI at 18	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								years, energy Intake , family history, WHR	

Table 226 Percentage of energy from monounsaturated fatty acids and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Farvid, 2014 BRE80577 USA	NHS II, Prospective Cohort, Age: 26-45 years, W	918/ 88 804 20 years	Self report verified by medical record and pathology report	Semi-quantitative FFQ	Incidence, postmenopausal breast cancer	15.2 vs 8.9 %	1.12 (0.91-1.37) Ptrend:0.11	Age, age at menarche, age at menopause, alcohol Intake, BMI, calendar year, energy, energy from protein, family history of breast cancer In first degree relatives, height, history of benign breast disease, hormone use, OC use, parity and age at first birth, race, smoking status and dose	
Park, 2012	MEC,	3 885/	Cancer registry	FFQ	Incidence, breast	≥13.1 vs ≤8.3 %	1.01 (0.91-1.13)	Age, age at first	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
BRE80399 Hawaii	Prospective Cohort, Age: 45-75 years, Postmenopausal	85 089 12.4 years			cancer, postmenopausal	energy	Ptrend:0.83	child birth, age at menarche, age at menopause, alcohol consumption, BMI, educational level, energy Intake, ethnicity, family history of breast cancer, HRT use, number of childbirths, smoking status, time, type of menopause	
		1 764/			ER+/PR+	≥13.1 vs ≤8.3 % energy	0.98 (0.83-1.15) Ptrend:0.29		
		350/			ER+/PR-	≥13.1 vs ≤8.3 % energy	1.11 (0.76-1.62) Ptrend:0.27		
		499/			ER-/PR-	≥13.1 vs ≤8.3 % energy	1.08 (0.82-1.42) Ptrend:0.92		
Key, 2011 UK	UK Dietary Cohort Consortium Pooled study of 4 cohorts* Mean age: 56.4 ±9.7 years among cases, W	286 cases/ 699 controls	Record linkage with National Statistics and cancer registries	Food diary and FFQ	Incidence, breast cancer, postmenopausal, HRT non-users	Food diaries per 2.2% of energy	0.83 (0.71-0.98)	Age, alcohol consumption, parity, menopausal status, current hormone replacement therapy use, physical activity, height,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	(*EPIC-Norfolk; EPIC-Oxford; UKWCS; Whitehall II study)							weight, and energy intake	
						FFQ per 2.3% of energy	0.89 (0.76-1.05)		
Thiébaut, 2007 BRE80012 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, Postmenopausal	3 501/ 188 736 4.4 years	Cancer registry	24h recall + FFQ	Incidence, Invasive breast cancer, postmenopausal	15.2 vs 7.2 %energy	1.12 (1.00-1.24) Ptrend:0.028	Age at first child birth, age at menopause, alcohol energy, BMI, menopausal hormone use, non-alcohol energy, parity, smoking habits	
						per 100 %	1.12 (1.03-1.21)		
Wakai, 2005 BRE24482 Japan	JACC, Prospective Cohort, Age: 40-79 years, W, Previous study	76/ 26 291 7.6 days	Partially histological - over 80%	FFQ	Incidence, breast cancer, postmenopausal	≥7.48 vs ≤5.46	0.96 (0.45-2.05) Ptrend:0.82	Age , age at first child, age at menarche, age at menopause, alcohol, BMI, educational level, energy Intake , family history, height, HRT use, other energy Index, other nutritional factors, other physical activity	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								Index, parity/pregnancies, recruitment center, smoking habits	
Smith-Warner, 2001b Canada, USA, the Netherlands, Sweden	The Pooling Project, Pooled study of 8 cohorts*, Age: 28-90 years, W (*AHS, CNBSS, IWHS, NHS(a), NHS(b), NLCS, NYSC, NYUWHS, SMC)	-	Self-reported and verified by medical records and/or record linkage with cancer registries	FFQ	Incidence, postmenopausal breast cancer	per 5% of energy	0.81 (0.65-1.03)	Percent of energy from protein, percent of energy from alcohol, age at menarche, parity, age at birth of first child, OC use, history of benign breast disease, family history of breast cancer, smoking status, education, BMI, height, fibre intake, energy intake, saturated fat, polyunsaturated fat	

Table 227 Monounsaturated fatty acids intake and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Sieri, 2008 BRE80202 Europe	EPIC, Prospective Cohort, Age: 20-70 years, W	1 553/ 319 826 8.8 years	Cancer registry / database / pathology reports	FFQ	Incidence, breast cancer, HRT - no	44.1 vs 15.3 g/day	1.17 (0.94-1.46) Ptrend:0.239	Age, alcohol Intake, centre location, educational attainment, energy Intake, height, menopausal status, smoking status, weight	Excluded, missing cases and non-cases per categories in subgroups
		1 909/			HRT - yes	44.1 vs 15.3 g/day	0.90 (0.73-1.11) Ptrend:0.426		
Sieri, 2002 BRE20941 Italy	ORDET, Nested Case Control, Age: 41-70 years, W, Postmenopausal	56/ 214 controls 5.5 years	Cancer registry + death certificate	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	30-104.3 vs ≤23.5 g/day	2.96 (0.70-12.60) Ptrend:0.139	Birth cohort, educational level, nutrients, parity/pregnancies, residual (willet)	Excluded, missing cases and non-cases per categories
Voorrips, 2002 BRE13011 Netherlands	NLCS, Case Cohort, Age: 55-69 years, W, Postmenopausal	783/ 62 573 6.3 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer	27 vs 18 g/day	0.61 (0.38-0.96) Ptrend:.001	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, educational level, energy Intake , family history, OC use, parity/pregnanci	Superseded by van den Brandt, 1993 (Included in the highest vs the lowest forest plot)

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								es, residual (willet), smoking habits	
Kushi, 1995 BRE05142 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	329/ 34 388 6 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, postmenopausal breast cancer ER+/PR+	≥26.7 vs ≤22.6 g/day	1.27 (0.97-1.66) Ptrend:0.09	Age , energy Intake	Results by hormone receptor status not analysed
		75/			ER+/PR-	≥26.7 vs ≤22.6 g/day	0.89 (0.50-1.59) Ptrend:0.70		
		14/			ER-/PR+	≥26.7 vs ≤22.6 g/day	0.65 (0.18-2.31) Ptrend:0.51		
		61/			ER-/PR-	≥26.7 vs ≤22.6 g/day	0.80 (0.44-1.46) Ptrend:0.46		
Barrett-Connor, 1993 BRE00581 USA	Rancho Bernardo, 1972, Prospective Cohort, Age: 40-79 years, W	15/ 590 15 years	Medical records + death certificate	24h recall	Incidence, breast cancer, postmenopausal	(mean exposure)			Excluded, mean exposure values only
Willett, 1992 BRE13438 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	774/ 89 494 8 years	Medical records + self-reported	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	Q5 vs Q1	0.93 (0.74-1.17) Ptrend:0.77	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, energy Intake , family history, nutrients, other design Issue, parity/pregnanci	Excluded, missing cases and non-cases, and exposure levels per categories

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								es	

Table 228 Percentage of energy from monounsaturated fatty acids and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Kim, 2006 BRE80115 USA	NHS, Prospective Cohort, W, Postmenopausal	3 537/ 121 701 20 years	Medical records	FFQ	Incidence, Invasive breast cancer, postmenopausal	per 5 %	0.94 (0.88-1.01)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight at 18 years, energy Intake , family history, height, HRT use, other design Issue, parity/pregnancies, other fat types	Publication superseded by Smith-Warner, 2001b
		1 653/			ER+/PR+	per 5 %	0.95 (0.86-1.06)		
		517/			ER-/PR-	per 5 %	0.89 (0.75-1.06)		
		477/			ER+/PR-	per 5 %	0.98 (0.81-1.17)		
		83/			ER-/PR+	per 5 %	1.01 (0.65-1.58)		
Holmes, 1999	NHS,		Medical records	FFQ-semi-	Incidence,	per 5 % of total	0.91 (0.84-0.99)	Age , age at first	Publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
BRE04008 USA	Prospective Cohort, Age: 30-55 years, W, Registered nurses	121 700 14 years	+ self-reported +death certificate	quantitative	Invasive breast cancer, postmenopausal	energy/day		child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight at 18 years, energy Intake , family history, height, HRT use, menopausal status, nutrients	superseded by Smith-Warner, 2001b

Figure 289 RR estimates of postmenopausal breast cancer by levels of monounsaturated fatty acids intake and percentage of energy from monounsaturated fatty acids

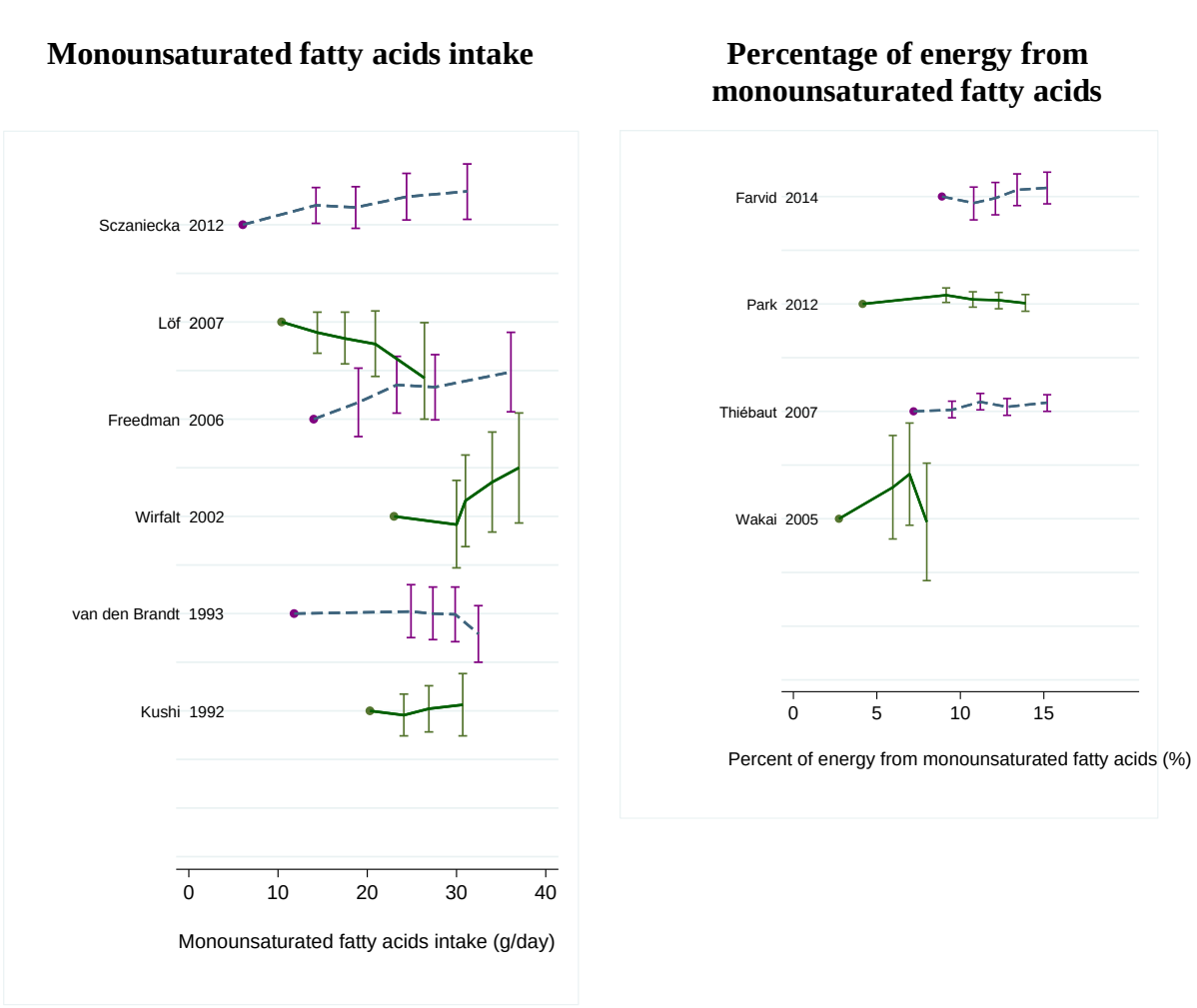


Figure 290 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest monounsaturated fatty acids intake and percentage of energy from monounsaturated fatty acids

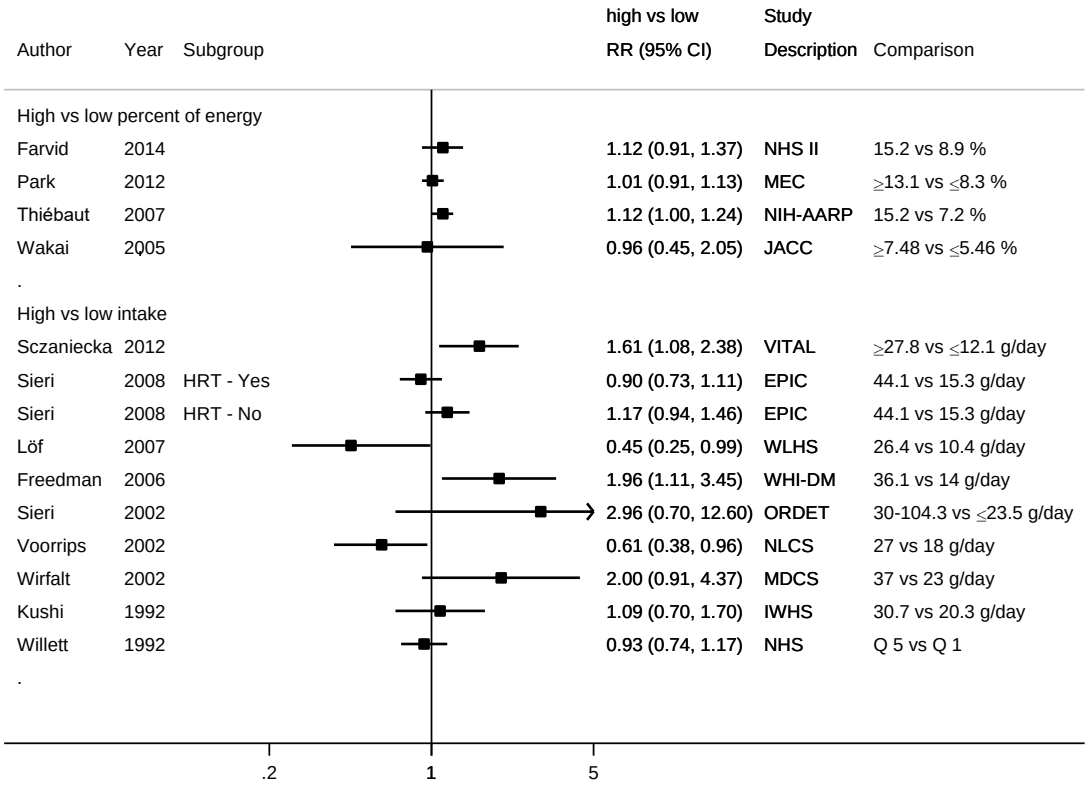


Figure 291 Relative risk of postmenopausal breast cancer for 10 g/day of monounsaturated fatty acids intake and 5% of energy from monounsaturated fatty acids

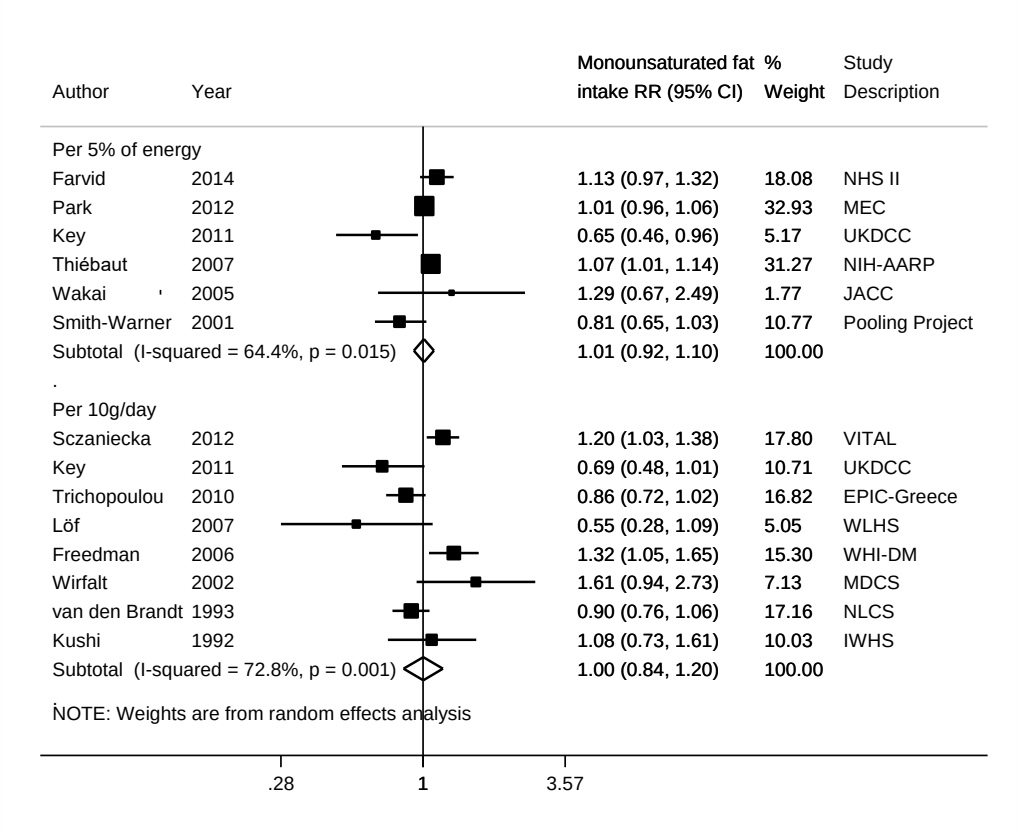


Figure 292 Funnel plot of studies included in the dose response meta-analysis of monounsaturated fatty acids intake and postmenopausal breast cancer

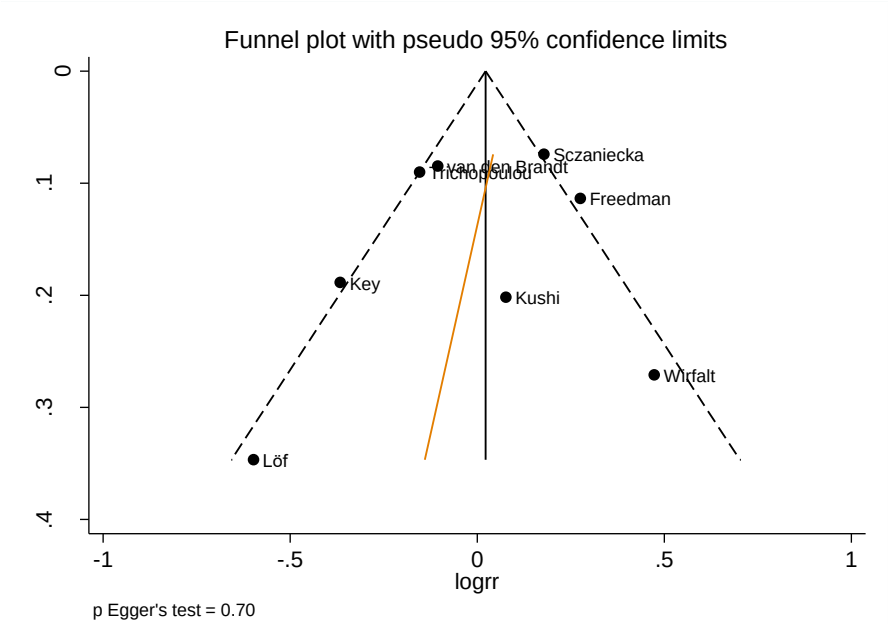


Figure 293 Funnel plot of studies included in the dose response meta-analysis of percentage of energy from monounsaturated fatty acids and postmenopausal breast cancer

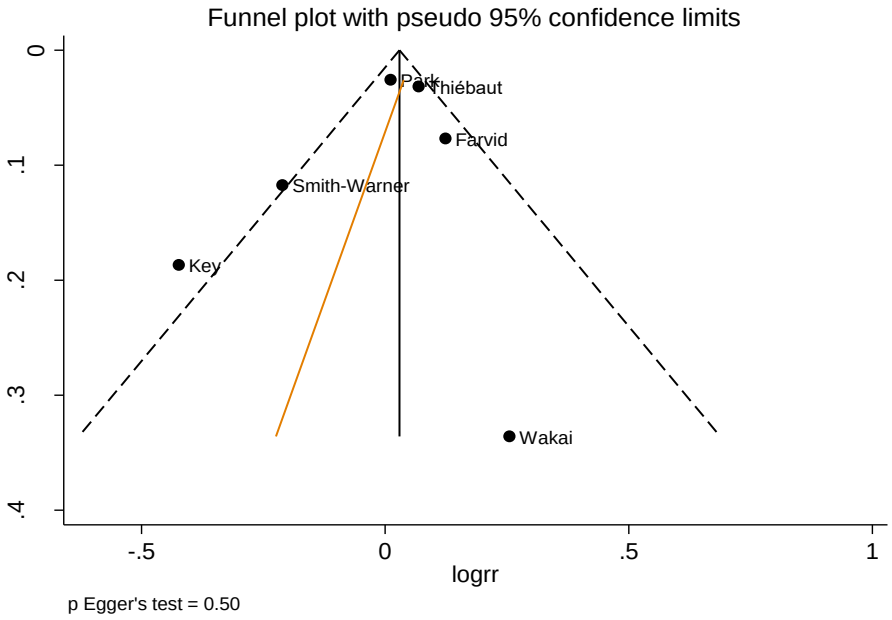


Figure 294 Relative risk of postmenopausal breast cancer for 10 g/day of monounsaturated fatty acids intake, by geographic location

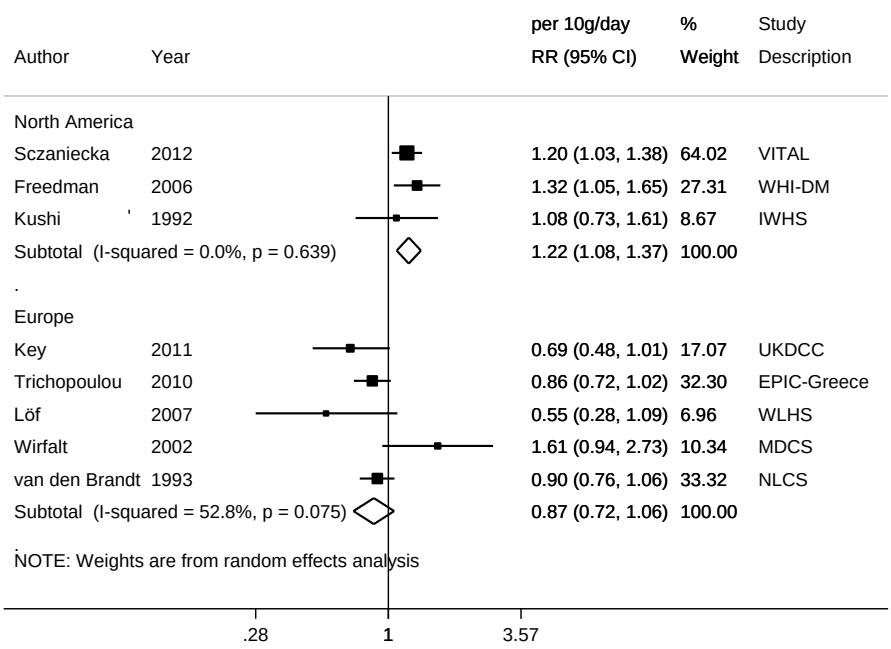


Figure 295 Relative risk of postmenopausal breast cancer for 5% of energy from monounsaturated fatty acids, by geographic location

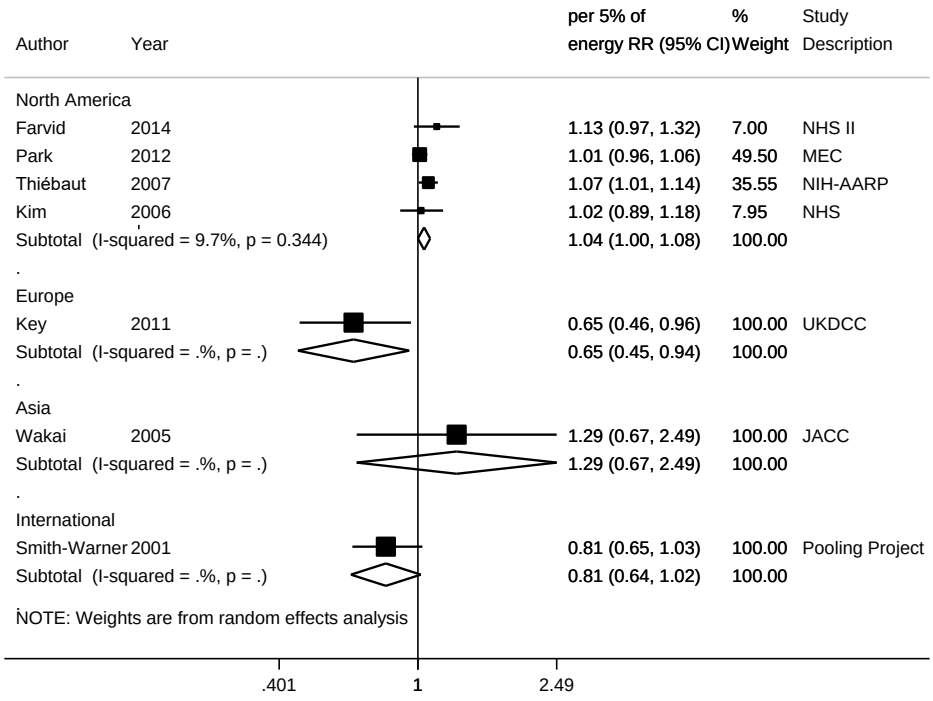


Figure 296 Relative risk of postmenopausal breast cancer for 10 g/day of monounsaturated fatty acids intake, by exposure assessment

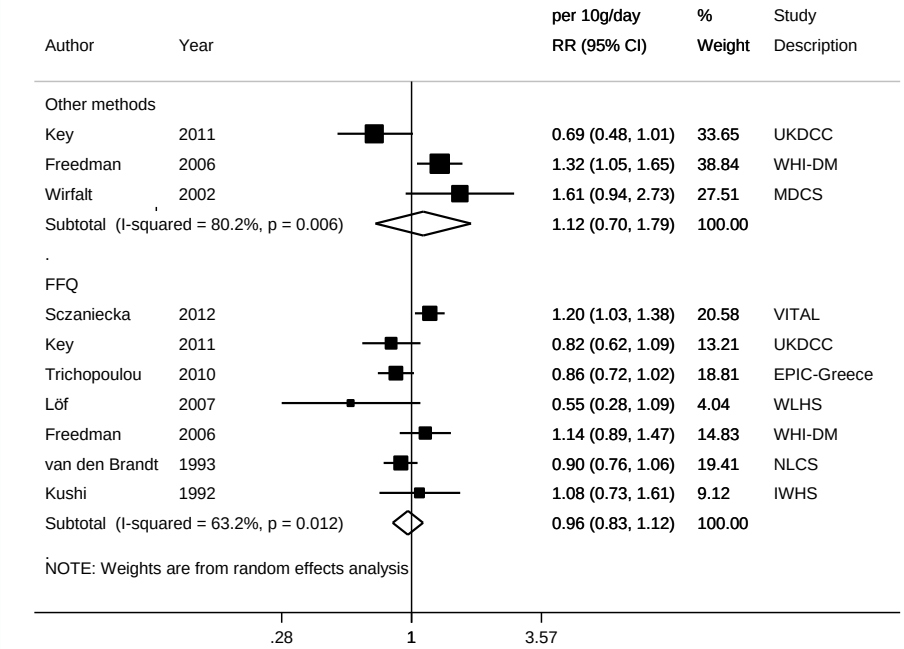
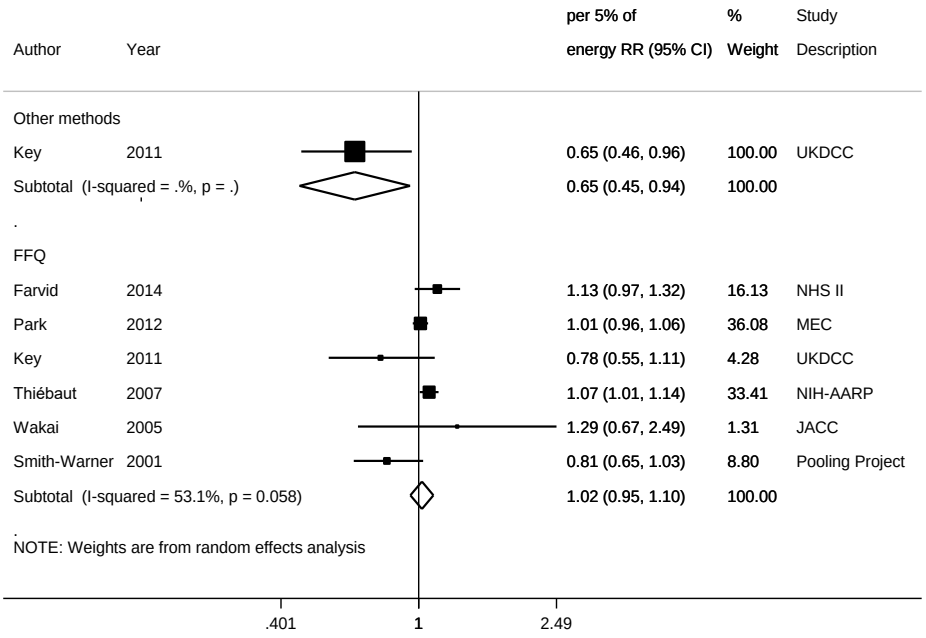


Figure 297 Relative risk of postmenopausal breast cancer for 5% of energy from monounsaturated fatty acids, by exposure assessment



5.2.4 Polyunsaturated fatty acids

7.1.0.1 Energy from polyunsaturated fatty acids

Cohort studies

Overall summary

Studies that measured polyunsaturated fatty acids as an absolute intake (g/day) or as a relative intake expressed as a percentage of the total energy intake (% of energy) was considered together to facilitate a comprehensive review.

Thirty-three publications from 28 studies that examined polyunsaturated fatty acids intake and/or percentage of energy from polyunsaturated fatty acids were identified. Three pooled analyses, two from the Pooling Project (Smith-Warner, 2001b, eight cohorts; Hunter, 1996, seven cohorts) and one from the UK Dietary Cohort Consortium (Key, 2011, four cohorts) were identified.

Dose-response meta-analyses were conducted to examine the associations of polyunsaturated fatty acids intake (per 5 g/day and per 5 % of energy) with risk of breast cancer and of premenopausal and postmenopausal breast cancer.

Notes on method:

As in the Pooling Project, results from the model that was mutually adjusted for other type of fat were selected if the studies presented such results. Models adjusted for total energy intake were selected, which represents an increase in polyunsaturated fat intake while keeping the total energy intake constant. If studies provided results both from the food diaries and the FFQs, results from the food diaries were used.

Table 229 Summary of results of the dose-response meta-analysis in the 2016 CUP SLR

	Breast cancer	**Premenopausal breast cancer**	**Postmenopausal breast cancer**
Polyunsaturated fatty acids intake Increment unit used	Per 5g/day	Per 5g/day	Per 5g/day
Studies (n)	11[1]	1	10[3]
Cases	16 156	432	3 336
RR (95%CI)	1.00 (0.98-1.02)	1.14 (0.89-1.57)	1.08 (0.94-1.24)
Heterogeneity (I^2, p-value)	0%, 0.68	-	76%, <0.001
P value Egger test	0.70	-	0.63
Percentage of energy from fat Increment unit used	Per 5% of energy	Per 5% of energy	Per 5% of energy
Studies (n)	12[2]	6[2]	16[2,3]

Cases	17 721	>1 511	>8 666
RR (95%CI)	1.00 (0.95-1.05)	1.06 (0.90-1.26)	1.05 (0.95-1.17)
Heterogeneity (I^2, p-value)	0%, 0.60	0%, 0.53	49%, 0.08
P value Egger test	0.45	-	0.66

[1]Included the Pooling Project (Hunter, 1996, seven cohorts).
[2]Included the Pooling Project (Smith-Warner, 2001b, eight cohorts, five in the analysis of premenopausal breast cancer).
[3]Included the UK Cohort Consortium (Key, 2011, four cohorts).

Breast cancer

Summary

Main results:

Eleven out of 17 studies (12 publications) on polyunsaturated fatty acids intake and 12 out of 17 studies (nine publications) on percentage of energy from polyunsaturated fatty acids could be included in the dose-response meta-analyses, respectively.

There were no significant associations observed for breast cancer overall, and in the subgroups. The summary RRs were 1.00 (95% CI=0.98-1.02) (I^2= 0%, P=0.68) per 5 g/day intake of polyunsaturated fatty acids and 1.00 (95% CI=0.95-1.05) (I^2= 0%, P=0.60) per 5% of energy from polyunsaturated fatty acids.

There was no evidence of significant publication or small studies bias (P for Egger's test=0.70 for studies on polyunsaturated fatty acids intake and 0.45 for studies on percentage of energy from polyunsaturated fatty acids).

Six and five studies were excluded from the analysis of polyunsaturated fatty acids intake and percentage of energy from polyunsaturated fatty acids, respectively. Study populations in five studies (Key, 2011, four cohorts; Thiebaut, 2001) overlapped with other studies that were already included in the meta-analyses. One further study (Martin, 2011) was excluded as polyunsaturated fatty acids intake was measured during the follow-up of a RCT.

One study (Sieri, 2014) reported results by breast cancer subtypes, which were of similar non-significant associations.

Sensitivity analyses:

The summary RRs remained non-significant when studies were omitted in turn in influence analyses. When Sieri, 2014 that contributed 71% weight in the analysis of polyunsaturated fatty acids intake was omitted, the summary RR was 1.01 (95% CI=0.97-1.05). When Sieri, 2008 (56% weight) was omitted in the analysis of percent of energy from polyunsaturated fatty acids, the summary RR was 1.03 (95% CI=0.95-1.12).

Non-linear dose-response meta-analysis:

There was no evidence of non-linear relationship between polyunsaturated fatty acids intake and breast cancer risk (P for non-linearity=0.11) (graph not shown). There were not enough

studies to conduct a non-linear dose-response meta-analysis of percentage of energy from polyunsaturated fatty acids.

Study quality:

Most studies were from North America or Europe. One study was from Japan (Wakai, 2005) and one of Singaporean Chinese (Gago-Dominguez, 2003). Most studies used FFQs to assessed fat intake. Other studies used dietary questionnaires (Knekt, 1990) or a 24-hour recall (Jones, 1987). EPIC (Sieri, 2014; Sieri, 2008) used different methods (FFQs, dietary questionnaires).

There is no suggestion that measurement errors attenuated the association. EPIC observed similar non-significant associations using calibrated or observed data. RRs per 20% increase of intake was 0.98 (95% CI=0.95-1.01) and 0.99 (95% CI=0.98-1.00), respectively (Sieri, 2014). The same was reported for percentage of energy from polyunsaturated fatty acids (RRs per 20% increase of energy=0.99, 95% CI=0.95-1.02; RR=0.99, 95% CI= 0.98-1.01, respectively) (Sieri, 2008). RRs in the Pooling Project when corrected for measurement error was 1.05 (95% CI=0.83-1.34) per 10 g/day increase of intake (Hunter, 1996) and 1.01 (95% CI=0.85-1.19) per 5% of energy (Smith-Warner, 2001b). The consortium of four cohorts based in the UK (Key, 2011, UKDCC) observed non-significant associations using data from FFQs or food diaries. On average, studies that used FFQs or other methods found similar non-significant results in the present review.

Case ascertainment was through cancer registries or confirmed through medical records. All studies were adjusted for age, BMI, alcohol intake, and reproductive factors, apart from Knekt, 1990 and Jones, 1987 that did not adjust for alcohol consumption.

Table 230 Polyunsaturated fatty acids intake and percentage of energy from polyunsaturated fatty acids and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	17 (12 publications) polyunsaturated fatty acids intake 17 (9 publications) percentage of energy from polyunsaturated fatty acids
Studies included in forest plot of highest compared with lowest exposure	11 (5 publications) polyunsaturated fatty acids intake 12 (5 publications) percentage of energy from polyunsaturated fatty acids
Studies included in linear dose-response meta-analysis	11 (5 publications) polyunsaturated fatty acids intake 12 (5 publications) percentage of energy from polyunsaturated fatty acids
Studies included in non-linear dose-response meta-analysis	5 (5 publications) polyunsaturated fatty acids intake Not enough studies on percentage of energy from polyunsaturated fatty acids

Note: Include cohort, and nested case-control designs

Table 231 Polyunsaturated fatty acids intake and percentage of energy from polyunsaturated fatty acids and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and 2016 CUP

	2005 SLR*		CUP	
Increment unit used	-	-	**Per 5 g/day**	**Per 5%**
Studies (n)	-	-	11	12
Cases	-	-	16 156	17 721
RR (95%CI)	-	-	1.00 (0.98-1.02)	1.00 (0.95-1.05)
Heterogeneity (I^2, p-value)	-	-	0%, 0.68	0%, 0.60
P value Egger test	-	-	0.70	0.45
Stratified analyses in the CUP				
Increment unit used	**Per 5 g/day**	**Per 5 g/day**	**Per 5% of energy**	**Per 5% of energy**	**Per 5% of energy**
Geographic location	**Europe**	**North America**	**Europe**	**North America**	**Asia**
Studies (n)	5	5	3	7	2
Cases	12 299	3 704	9 329	7 949	443
RR (95%CI)	0.99 (0.97-1.02)	1.03 (0.98-1.08)	1.01 (0.89-1.15)	1.02 (0.93-1.13)	1.13 (0.86-1.50)
Heterogeneity (I^2, p-value)	0%, 0.89	0%, 0.51	44%, 0.17	0%, 0.67	0%, 0.88
Increment unit used	**Per 5 g/day**	**Per 5 g/day**	**Per 5% of energy**	**Per 5% of energy**
Adjustment for age, BMI, alcohol intake, reproductive factors	**Adjusted**	**Not adjusted**	**Adjusted**	**Not adjusted**
Studies (n)	9	2	12	-
Cases	16 016	140	17 721	-
RR (95%CI)	1.00 (0.98-1.02)	0.94 (0.70-1.25)	1.00 (0.95-1.05)	-
Heterogeneity (I^2, p-value)	0%, 0.48	0%, 0.42	0%, 0.60	-
Exposure assessment methods	**FFQs**	**Other methods**	**FFQs**	**Other methods**
Studies (n)	12	3	15	1

Cases	6 611	10 202	11 259	7 119
RR (95%CI)	1.01 (0.97-1.05)	0.99 (0.97-1.02)	1.03 (0.95-1.11)	0.97 (0.90-1.04)
Heterogeneity (I^2, p-value)	0%, 0.56	0%, 0.67	0%, 0.73	-

*No meta-analysis was conducted in the 2005 and 2008 SLR

Table 232 Polyunsaturated fatty acids intake and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Turner, 2011	29 studies (1 pooled study of prospective studies, 18 cohorts*, 10 case-control studies)	31 201 any breast cancer	China, France, Germany, Greece, Italy, the Netherlands, USA, Uruguay, Singapore, Sweden	Incidecne, any breast cancer	Highest vs lowest polyunsaturated fat intake (20 studies)	1.07 (1.01-1.14)	-
					Cohort studies (n=13)	1.09 (1.00-1.18)	-
					Case-control studies (n=7)	1.04 (0.95-1.14)	-

* Saadatian-Elahi, 2004 on serum fatty acids, Bryne, 2002 on linoleic acid, and Fung, 2006 on polyunsaturated: saturated fat ratio score were not included in the present review. Other cohort studies were included.

Table 233 Polyunsaturated fatty acids intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Sieri, 2014 BRE80546 France, Italy, Spain, UK, Netherlands, Greece, Germany, Sweden, Denmark,	EPIC, Prospective Cohort, Age: 20-70 years, W	10 062/ 337 327 11.5 years	Cancer and mortality registries, health Insurance & pathology records, active follow up	FFQ, diet history, 7-day food diary	Incidence, breast cancer	22 vs 7 g/day	0.99 (0.91-1.08) Ptrend:0.57	Age, BMI, educational level, energy from alcohol, HRT use, menopausal status, non-alcohol energy, pregnancies,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Norway								smoking status, study center	
		3 540/			Incidence, breast cancer ER+/PR+	per 20 %	0.98 (0.96-1.00)		
						21.6 vs 6.6 g/day	0.98 (0.85-1.13) Ptrend:0.28		
		1 072/			Incidence, breast cancer ER+/PR-	per 20 %	0.97 (0.93-1.00)		
						21.6 vs 6.6 g/day	0.90 (0.69-1.16) Ptrend:0.45		
		1 018/			Incidence, breast cancer ER-/PR-	per 20 %	0.98 (0.94-1.02)		
						21.6 vs 6.6 g/day	0.91 (0.70-1.19) Ptrend:0.77		
		3 155/			Incidence, breast cancer unknown ER/PR status	per 20 %	1.00 (0.98-1.03)		
						21.6 vs 6.6 g/day	1.03 (0.89-1.20) Ptrend:0.68		
		539/			Incidence, breast cancer HER-2 +	per 20 %	1.01 (0.95-1.06)		
						22.1 vs 6.6 g/day	1.12 (0.77-1.62) Ptrend:0.33		
		1 720/			Incidence, breast cancer HER-2 -	per 20 %	0.98 (0.95-1.01)		
						22.1 vs 6.6 g/day	1.00 (0.81-1.23) Ptrend:0.98		
		5 756/			Incidence, breast cancer HER-2 unknown	per 20 %	0.99 (0.97-1.01)		
						22.1 vs 6.6 g/day	0.93 (0.84-1.04) Ptrend:0.13		
		10 062/			Incidence, breast cancer	per 20 %	0.99 (0.98-1.00)		
		5 615/			Incidence, breast	21.6 vs 6.6	0.94 (0.84-1.06)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
					cancer ER+	g/day	Ptrend:0.15		
						per 20 %	0.98 (0.96-1.00)		
		1 395/			Incidence, breast cancer ER-	21.6 vs 6.6 g/day	0.88 (0.70-1.10) Ptrend:0.58		
						per 20 %	0.97 (0.94-1.00)		
		3 761/			Incidence, breast cancer PR+	21.6 vs 6.6 g/day	0.97 (0.84-1.11) Ptrend:0.18		
						per 20 %	0.97 (0.94-1.00)		
		2 097/			Incidence, breast cancer PR-	21.6 vs 6.6 g/day	0.91 (0.75-1.09) Ptrend:0.72		
						per 20 %	0.97 (0.95-1.00)		
Löf, 2007 BRE80144 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	974/ 44 569 13 years	Cancer registry	FFQ	Incidence, Invasive breast cancer	11.2 vs 4.3 g/day	0.72 (0.52-1.00) Ptrend:0.08	Age, age at first child birth, age at menarche, alcohol consumption, BMI, educational level, family history of cancer, non-alcohol energy, parity, total fat, use of oral contraception	
						per 10 g/day	0.83 (0.54-1.27)		
Knekt, 1990 BRE04898 Finland	Mobile Clinic Health Examination Survey, 1973,	3 988 20 years	All histology	Dietary history questionnaire	Incidence, breast cancer	≥6.8 vs ≤4.5 g/day	1.23 (0.55-2.75) Ptrend:0.28	Age , energy Intake	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	Prospective Cohort, Age: 20-69 years, W, Screening Program								
Hunter, 1996 Canada, USA, the Netherlands, Sweden	The Pooling Project Pooled study of 7 cohorts*, Age: 28-90 years, W (*AHS, CNBSS, IWHS, NLCS, NYSC, NHS(a), NHS(b), SMC),	4 980/ 337 819	Self-reported and verified by medical records and/or record linkage with cancer registries	FFQ	Incidence, breast cancer	Q5 vs Q1	1.07 (0.97-1.17) Ptrend:0.32	Age at menarche, menopausal status, parity, age at birth of first child, BMI, height, education, history of benign breast disease, maternal history of breast cancer, history of breast cancer in a sister, OC use, fibre intake, alcohol intake, energy intake	
						per 10 g/day	1.03 (0.95-1.12)		
	AHS	153/ 15 172				-	-		
	CNBSS	514/ 56 837				per 10 g/day	1.38 (0.95-2.01)		
	IWHS	723/ 34 406				per 10 g/day	1.10 (0.84-1.45)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	NLCS	434/ 62 412				per 10 g/day	0.94 (0.77-1.14)		
	NYSC	376/ 18 475				per 10 g/day	1.09 (0.93-1.26)		
	NHS(a)	1 094/ 89 046				per 10 g/day	1.01 (0.81-1.27)		
	NHS(b)	911/ 68 817				per 10 g/day	0.93 (0.73-1.18)		
	SMC	775/ 61 471				per 10 g/day	0.98 (0.69-1.38)		
Jones, 1987 BRE04461 USA	NHANES I, Prospective Cohort, Age: 25-74 years, W	86/ 5 485 10 years	Medical records + self-reported +death certificate	24h recall	Incidence, breast cancer	≥9 vs ≤2.9 g/day	0.73 (0.39-1.36)	Age , age at menarche, age at menopause, BMI, educational level, family history, menopausal status	

Table 234 Percentage of energy from polyunsaturated fatty acids and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Farvid, 2014 BRE80577 USA	NHS II, Prospective Cohort, Age: 26-45	2 830/ 88 804 20 years	Self report verified by medical record and pathology	Semi-quantitative FFQ	Incidence, breast cancer	7.3 vs 4.1 %	0.95 (0.84-1.07) Ptrend:0.54	Age, age at menarche, age at menopause, alcohol Intake,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	years, W		report					BMI, calendar year, energy, energy from protein, family history of breast cancer In first degree relatives, height, history of benign breast disease, hormone use, menopausal status, OC use, parity and age at first birth, race, smoking status and dose	
Sieri, 2008 BRE80202 Europe	EPIC, Prospective Cohort, Age: 20-70 years, W	7 119/ 319 826 8.8 years	Cancer registry / database / pathology reports	FFQ	Incidence, breast cancer	9.4 vs 4 % energy/day	0.96 (0.88-1.04) Ptrend:0.390	Age, alcohol Intake, centre location, educational attainment, energy Intake, height, menopausal status, smoking status, weight	
						per 20 %	0.99 (0.98-1.01)		
Wakai, 2005 BRE24482 Japan	JACC, Prospective Cohort, Age: 40-79 years, W,	129/ 26 291 7.6 days	Partially histological - over 80%	FFQ	Incidence, breast cancer	≥6.03 vs ≤4.38	1.10 (0.63-1.90) Ptrend:0.83	Age , age at first child, age at menarche, age at menopause, alcohol, BMI, educational	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	Previous study							level, energy Intake , family history, height, HRT use, other energy Index, other nutritional factors, other physical activity Index, parity/pregnancies, recruitment center, smoking habits	
Gago-Dominguez, 2003 BRE17518 China	SCHS, Prospective Cohort, Age: 45-74 years, W	314/ 63 257 5.3 years	Partially histological - over 80%	FFQ	Incidence, breast cancer	≥6.27 vs ≥3.95 % energy	1.27 (0.92-1.74) Ptrend:0.46	Age , alcohol, educational level, ethnicity, family history, menstrual characteristics , parity/pregnancies	
Smith-Warner, 2001b Canada, USA, the Netherlands, Sweden	The Pooling Project, Pooled study of 8 cohorts*, Age: 28-90 years, W (*AHS, CNBSS, IWHS, NHS(a), NHS(b), NLCS, NYSC, NYUWHS,	7 329/ 351 821	Self-reported and verified by medical records and/or record linkage with cancer registries	FFQ	Incidence, breast cancer	Q4 vs Q1	1.04 (0.95-1.14) Ptrend:0.53	Percent of energy from protein, percent of energy from alcohol, age at menarche, parity, age at birth of first child, menopausal status at diagnosis, MHT use, OC use,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	SMC),							history of benign breast disease, family history of breast cancer, smoking status, education, BMI, BMI-menopausal status at diagnosis interaction, height, fibre intake, energy intake, monounsaturated fat, saturated fat	
						per 5% of energy	1.05 (0.96-1.16)		
	AHS	160/ 15 172				per 5% of energy	1.67 (0.74-3.74)		
	CNBSS	419/ 56 837				per 5% of energy	1.50 (0.92-2.45)		
	IWHS	1 130/ 34 406				per 5% of energy	1.02 (0.79-1.30)		
	NHS(a)	1 020/ 89 046				per 5% of energy	0.97 (0.75-1.26)		
	NHS(b)	1 638/ 68 817				per 5% of energy	1.04 (0.85-1.27)		
	NLCS	887/ 62 412				per 5% of energy	1.02 (0.87-1.19)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	NYSC	367/ 18 475				per 5% of energy	1.39 (0.58-3.35)		
	NYUWHS	385/ 14 006				per 5% of energy	1.02 (0.75-1.40)		
	SMC	1 323/ 61 467				per 5% of energy	1.58 (0.94-2.65)		

Table 235 Polyunsaturated fatty acids intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Key, 2011 UK	UK Dietary Cohort Consortium Pooled study of 4 cohorts* Mean age: 56.4 ±9.7 years among cases, W (*EPIC-Norfolk; EPIC-Oxford; UKWCS; Whitehall II study)	657 cases/ 1 911 controls EPIC-Norfolk: 353 cases/1 252 controls EPIC-Oxford: 194 cases/ 194 cases UKWCS: 42 cases/202 controls Whitehall II study: 68 cases/263 controls	Record linkage with National Statistics and cancer registries	Food diary and FFQ	Incidence, breast cancer	Food diaries ≥19.1 vs ≤7/3 g/day	0.77 (0.53-1.13) Ptrend:0.667	Age, alcohol consumption, parity, menopausal status, current hormone replacement therapy use, physical activity, height, weight, and energy intake	Superseded by Sieri, 2014, BRE80546 (EPIC-Norfolk and EPIC-Oxford overlapped with Sieri, 2014, EPIC)
						per 4.9 g/day	0.66 (0.42-1.03)		
						FFQ	0.91 (0.63-1.31)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
						≥22.8 vs ≤7.2 g/day	Ptrend: 0.603		
						per 6.5 g/day	1.06 (0.71-1.59)		(Included in stratified analysis)
Martin, 2011 BRE80323 Canada	CDBCPT, Nested Case Control, Age: 47 years	220/ 440 controls 10	Pathology	Food records	Incidence, Invasive breast cancer	10 vs 7 g/day	1.03 (0.84-1.28)	Age, age at first child birth, age at menarche, family history of breast cancer, HRT use, menopausal status, number of childbirths, parity, randomisation, smoking	Excluded, post-randomised diet
		167/ 334 controls			Incidence, breast cancer ER+	10 vs 7 g/day	1.21 (0.96-1.54)		
		42/ 84 controls			Incidence, breast cancer ER-	10 vs 7 g/day	0.26 (0.11-0.63)		
Sieri, 2008 BRE80202 Europe	EPIC, Prospective Cohort, Age: 20-70 years, W	7 119/ 319 826 8.8 years	Cancer registry / database / pathology reports	FFQ	Incidence, breast cancer	21.3 vs 7.2 g/day	0.97 (0.88-1.07) Ptrend:0.372	Age, alcohol Intake, centre location, educational attainment, energy Intake, height, menopausal status, smoking status, weight	Superseded by Sieri, 2014
						per 20 %	0.99 (0.98-1.01)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
						per 20 %	0.99 (0.95-1.03)		
Thiebaut, 2001 BRE12244 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W, Registered teachers	65 879 3.4 years	Not specified	FFQ-semi-quantitative	Incidence, breast cancer	Q4 vs Q1	1.14 (0.91-1.42)	Age , age at menarche, age at menopause, alcohol, benign breast disease, BMI, educational level, energy Intake , family history, marital status	Study superseded by Sieri, 2014
Wolk, 1998 BRE13548 Sweden	SMC, Prospective Cohort, Age: 40-76 years, W, Screening Program	61 147 4.2 years	All histology	FFQ	Incidence, Invasive breast cancer	≥7.71 vs ≤5.29 g/day	1.18 (0.85-1.64) Ptrend:.20	Age , age at first child, alcohol, BMI, educational level, energy Intake , family history, nutrients, parity/pregnancies, residual (willet)	Publication superseded by Hunter, 1996
						per 5 g/day	1.69 (1.02-2.78)		
Giovannucci, 1993a BRE03262 USA	NHS, Nested Case Control, Age: 30-55 years, W, Registered nurses	392/ 786 controls 2 years	Medical records + death certificate	FFQ-semi-quantitative	Incidence, breast cancer	Q5 vs Q1	0.83 (0.57-1.21) Ptrend:0.43	Age , residual (willet)	Publication superseded by Hunter, 1996
Howe, 1991	CNBSS,	519/	All histology	Dietary history	Incidence, breast	Q4 vs Q1	1.30 (0.93-1.82)	Age , energy	Publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
BRE17622 canada	Nested Case Control, Age: 40-59 years, W, Screening Program	1182 controls 5 years		questionnaire	cancer		Ptrend:.13	Intake , recruitment center, time of recruitment	superseded by Hunter, 1996

Table 236 Percentage of energy from polyunsaturated fatty acids and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

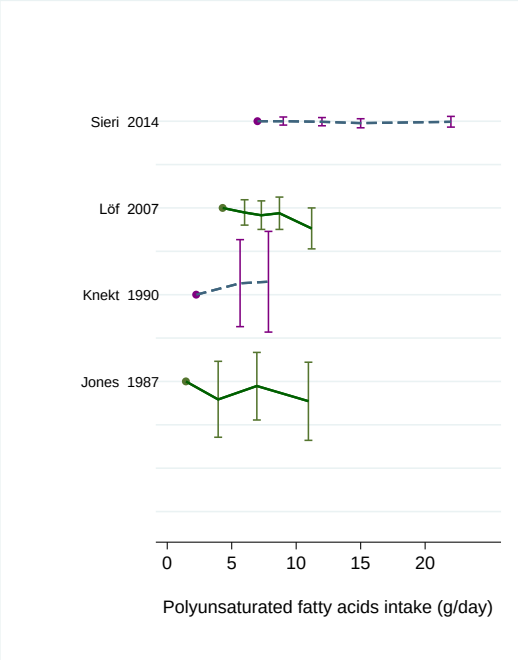
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Boeke, 2014a BRE80585 USA	NHS I and II, Prospective Cohort, Age: 25-55 years, W	9 979/ 182 671 30 years	Medical records, pathology reports, next of kin, death certificate, ndi	Semi-quantitative FFQ	Incidence, breast cancer	Q5 vs Q1	0.94 (0.87-1.02) Ptrend:0.16	Age, age at menarche, age at menopause, alcohol Intake, BMI at age 18 years, breastfeeding, calendar year, cohort, energy from fat sources, family history of breast cancer, height, history of benign breast disease, menopausal status, oral contraceptive	Superseded by Farvid, 2014 and Smith-Warner, 2001b

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								use, parity and age at first birth, physical activity, postmenopausal hormone use, protein, total energy Intake, weight change	
		1 529/			Mortality, breast cancer	Q5 vs Q1	1.11 (0.92-1.35) Ptrend:0.28		
Key, 2011 UK	UK Dietary Cohort Consortium Pooled study of 4 cohorts* Mean age: 56.4 ±9.7 years among cases, W (*EPIC-Norfolk; EPIC-Oxford; UKWCS; Whitehall II study)	657 cases/ 1 911 controls EPIC-Norfolk: 353 cases/1 252 controls EPIC-Oxford: 194 cases/ 194 cases UKWCS: 42 cases/202 controls Whitehall II study: 68 cases/263 controls	Record linkage with National Statistics and cancer registries	Food diary and FFQ	Incidence, breast cancer	Food diaries ≥8.6 vs ≤4.3 % of energy	0.97 (0.71-1.31) Ptrend:0.565	Age, alcohol consumption, parity, menopausal status, current hormone replacement therapy use, physical activity, height, weight, and energy intake	Superseded by Sieri, 2008 (EPIC-Norfolk and EPIC-Oxford overlapped with Sieri, 2008, EPIC)
						per 1.8 % of energy	0.77 (0.54-1.10)		
						FFQ ≥9.1 vs ≤4.0 % of energy	0.94 (0.71-1.26) Ptrend: 0.546		
						per 2.1% of energy	1.09 (0.82-1.46)		(Included in stratified

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
									analysis)
Thiebaut, 2001 BRE12244 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W, Registered teachers	65 879 3.4 years	Not specified	FFQ-semi-quantitative	Incidence, breast cancer	Q4 vs Q1	1.13 (0.92-1.37)	Age , age at menarche, age at menopause, alcohol, benign breast disease, BMI, density, educational level, family history, marital status	Study superseded by Sieri, 2008
Holmes, 1999 BRE04008 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	121 700 14 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, Invasive breast cancer	per 5 % of total energy/day	0.97 (0.81-1.16)	Age, age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight at 18 years, energy Intake , family history, height, HRT use, menopausal status, multivariate partition, nutrients	Superseded by Smith-Warner, 2001b

Figure 298 RR estimates of breast cancer by levels of polyunsaturated fatty acids intake and percentage of energy from polyunsaturated fatty acids

Polyunsaturated fatty acids intake



Percentage of energy from polyunsaturated fatty acids

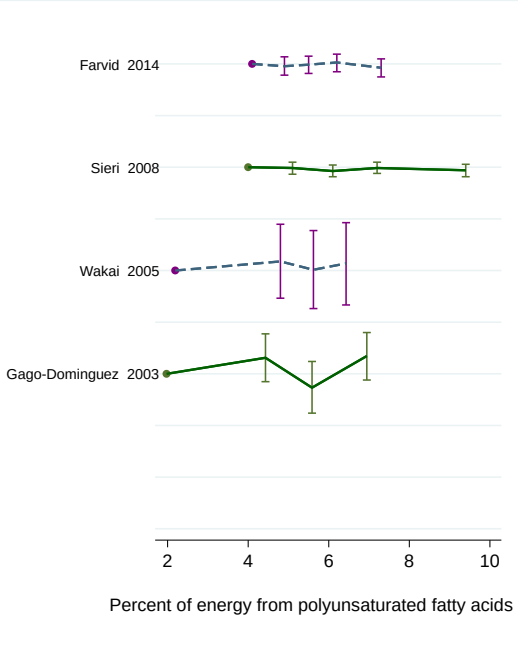


Figure 299 RR (95% CI) of breast cancer for the highest compared with the lowest polyunsaturated fatty acids intake and percentage of energy from polyunsaturated fatty acids

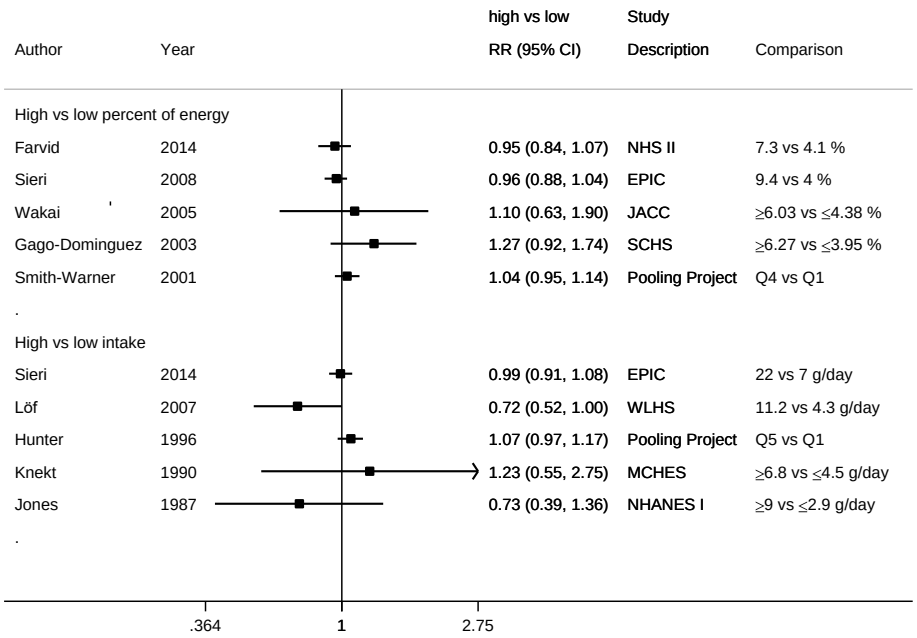


Figure 300 Relative risk of breast cancer for 5 g/day of polyunsaturated fatty acids intake and 5% of energy from polyunsaturated fatty acids

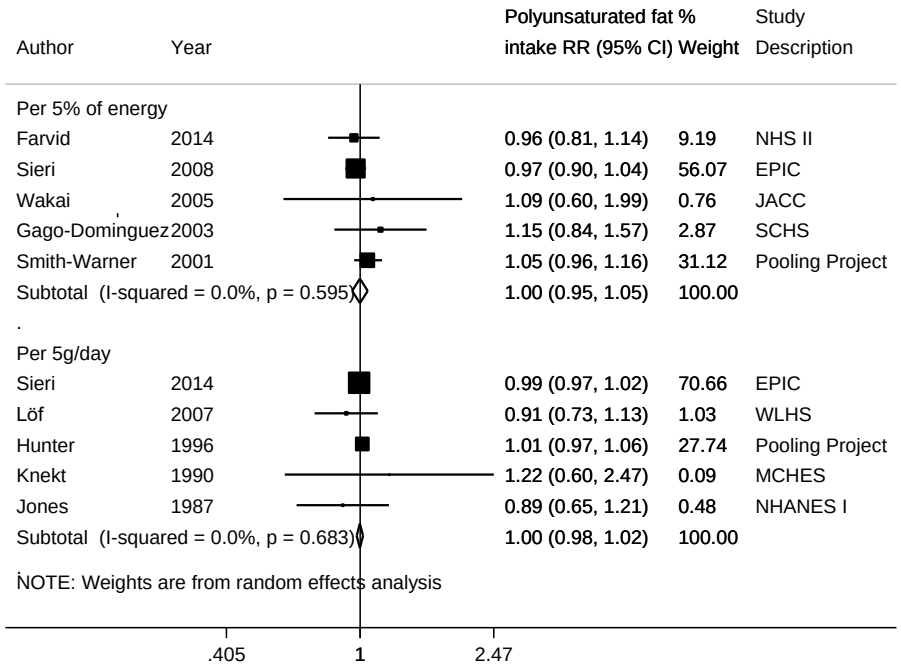


Figure 301 Funnel plot of studies included in the dose response meta-analysis of polyunsaturated fatty acids intake and breast cancer

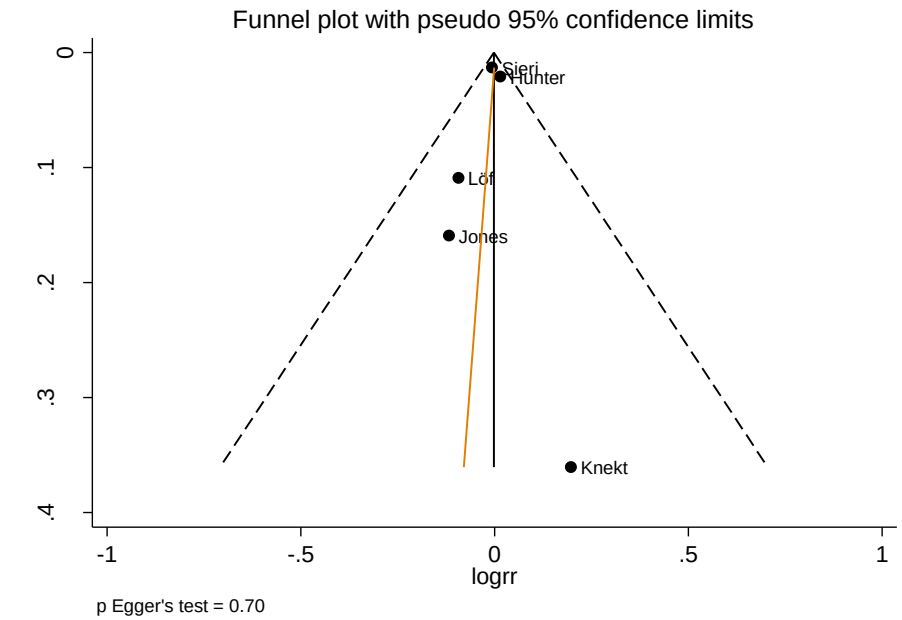


Figure 302 Funnel plot of studies included in the dose response meta-analysis of percentage of energy from polyunsaturated fatty acids and breast cancer

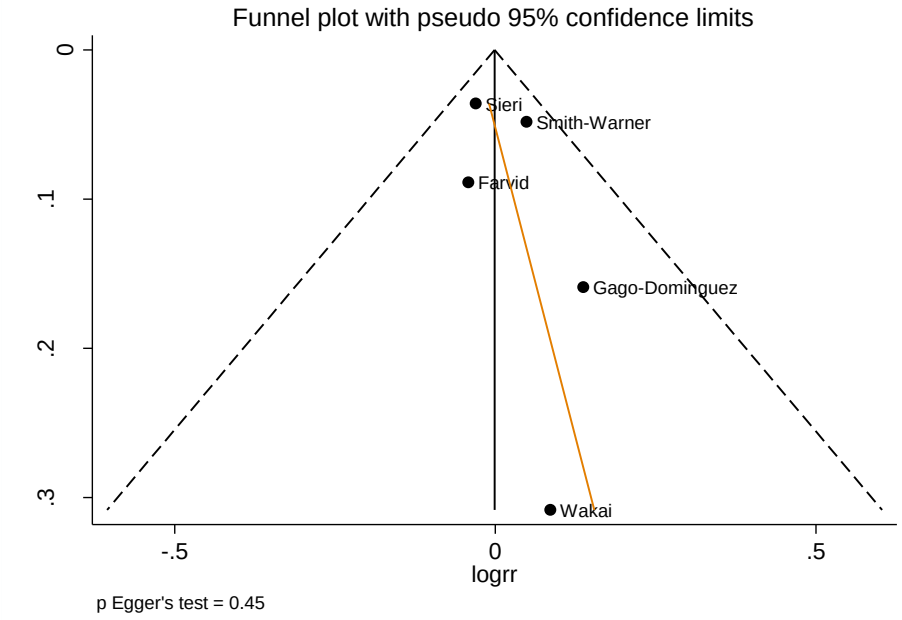
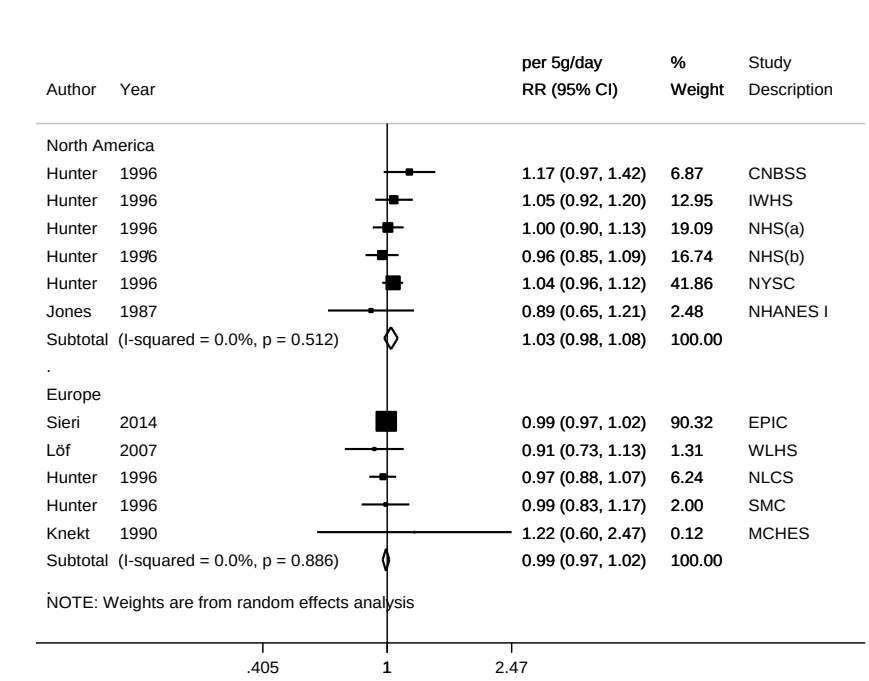
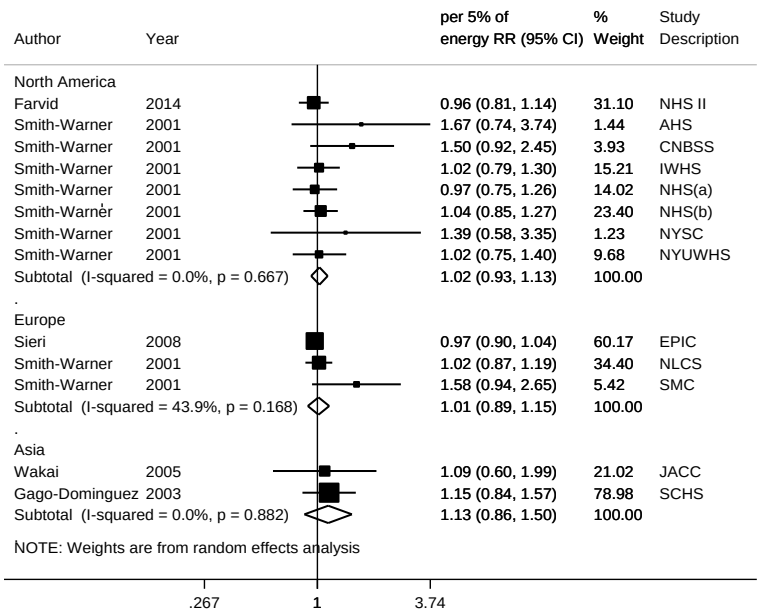


Figure 303 Relative risk of breast cancer for 5 g/day of polyunsaturated fatty acids intake, by geographic location



Note: Results from the individual studies in the Pooling Project (Hunter, 1996) were used in the strata.

Figure 304 Relative risk of breast cancer for 5% of energy from polyunsaturated fatty acids, by geographic location



Note: Results from the individual studies in the Pooling Project (Smith-Warner, 2001b) were used in the strata.

Figure 305 Relative risk of breast cancer for 5 g/day of polyunsaturated fatty acids intake, by exposure assessment methods

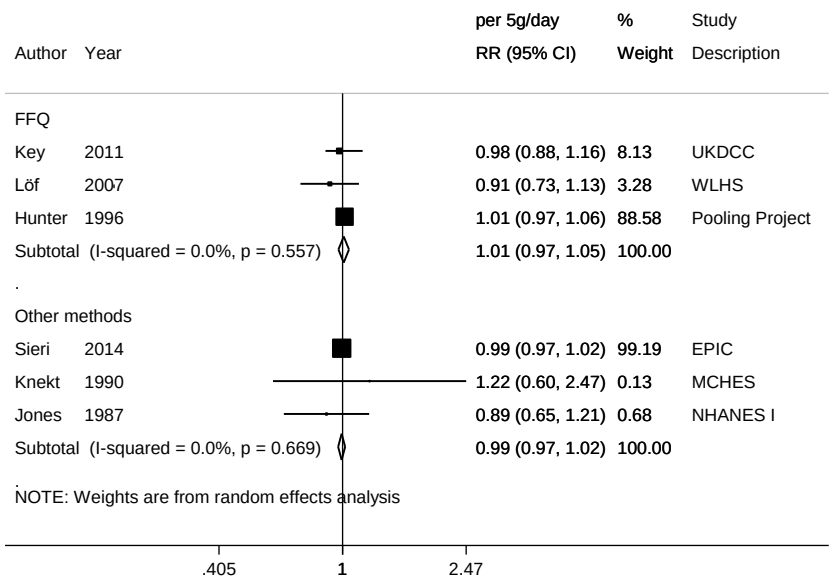
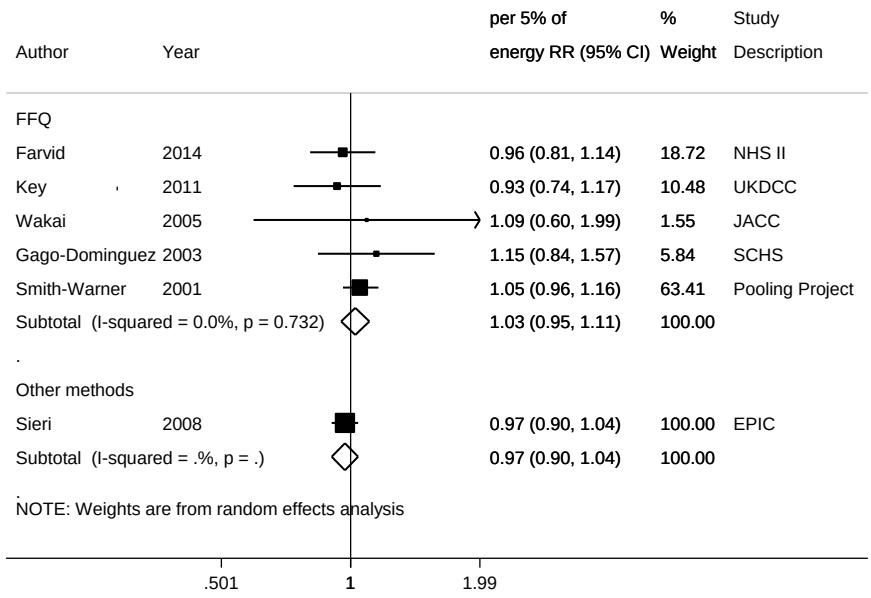


Figure 306 Relative risk of breast cancer for 5% of energy from polyunsaturated fatty acids, by exposure assessment methods



Premenopausal breast cancer

Summary

Main results:

Two studies (three publications) on polyunsaturated fatty acids intake and six studies (four publications) on percentage of energy from polyunsaturated fatty acids were identified. One and six studies could be included in the dose-response meta-analyses, respectively.

No significant associations were observed for premenopausal breast cancer (summary RR per 5% of energy=1.06. 95% CI=0.90-1.26) (I^2=0%, 0.53). The only study reported on polyunsaturated fatty intake observed a RR of 1.14 (95% CI=0.89-1.57) per 5g/day increase of intake.

One study (two publications) on adolescent polyunsaturated fatty acids intake (Linos, 2010; Frazier, 2004) were excluded. The publication (Linos, 2010) that used prospective data observed a non-significant positive association and the other publication (Frazier, 2004) with retrospective data which could be affected by recall bias observed a non-significant inverse association.

Stratified analysis and non-linear dose-response meta-analysis was not conducted due to limited number of studies.

Study quality:

Only North American and European studies reported results. All studies used FFQs to assess fat intake. Farvid, 2014 (NHS II) assessed premenopausal fat intake. Major confounding factors of breast cancer were adjusted for in the studies.

Table 237 Polyunsaturated fatty acids intake and percentage of energy from polyunsaturated fatty acids and premenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	2 (3 publications) polyunsaturated fatty acids intake 6 (4 publications) percentage of energy from polyunsaturated fatty acids
Studies included in forest plot of highest compared with lowest exposure	Not enough studies
Studies included in linear dose-response meta-analysis	1 (1 publication) polyunsaturated fatty acids intake 6 (2 publications) percentage of energy from polyunsaturated fatty acids
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 238 Polyunsaturated fatty acids intake and percentage of energy from polyunsaturated fatty acids and premenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and 2016 CUP

	2005 SLR[1]		CUP	
Increment unit used	-	-	**Per 5 g/day**	**Per 5%**
Studies (n)	-	-	1	6[2]
Cases	-	-	432	>1 511
RR (95%CI)	-	-	1.14 (0.89-1.57)	1.06 (0.90-1.26)
Heterogeneity (I^2, p-value)	-	-	-	0%, 0.53
P value Egger test	-	-	-	-

[1]No meta-analysis was conducted in the 2005 and 2008 SLR
[2] Included five cohort studies with data on premenopausal women from the Pooling Project (Smith-Warner, 2001b).

Table 239 Polyunsaturated fatty acids intake and premenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Turner, 2011	6 studies (2 cohorts*, 2 case-control studies)	>4 025 premenopausal breast cancer	Germany, USA	Incidence, premenoapausal breast cancer	Highest vs lowest polyunsaturated fat intake (3 studies)	0.94 (0.81-1.10)	-

*All cohort studies identified were included in the present review.

Table 240 Polyunsaturated fatty acids intake and premenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Löf, 2007 BRE80144 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	432/ 44 569 13 years	Cancer registry	FFQ	Incidence, Invasive breast cancer, age < 50 yrs	11.2 vs 4.3 g/day	1.06 (0.64-1.75) Ptrend:0.71	Age, age at first child birth, age at menarche, alcohol consumption, BMI, educational level, family history of cancer, non-alcohol energy, parity, total fat, use of oral contraception	
						Per 10g/day	1.31 (0.79-2.46)		

Table 241 Percentage of energy from polyunsaturated fatty acids and premenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Farvid, 2014 BRE80577 USA	NHS II, Prospective Cohort, Age: 26-45 years, W	1 511/ 88 804 20 years	Self report verified by medical record and pathology report	Semi-quantitative FFQ	Incidence, premenopausal breast cancer, premenopausal	7.3 vs 4.1 %	0.98 (0.83-1.15) Ptrend:0.99	Age, age at menarche, alcohol Intake, BMI, calendar year, energy, energy from protein, family history of breast cancer In first degree relatives, height, history of benign breast disease, OC use, parity and age at first birth, race, smoking status and dose	
Smith-Warner, 2001b Canada, USA, the Netherlands, Sweden	The Pooling Project, Pooled study of 5 cohorts, Age: 28-90 years, W (*AHS, CNBSS, , NHS(a), NHS(b), NYUWHS, SMC)	-	Self-reported and verified by medical records and/or record linkage with cancer registries	FFQ	Incidence, premenopausal breast cancer	per 5% of energy	1.12 (0.88-1.41)	Percent of energy from protein, percent of energy from alcohol, age at menarche, parity, age at birth of first child, OC use, history of benign breast disease, family history of breast cancer, smoking status,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								education, BMI, height, fibre intake, energy intake, monounsaturated fat, saturated fat	

Table 242 Polyunsaturated fatty acids intake and premenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Linos, 2010 BRE80298 USA	NHS II, Prospective Cohort, Age: 34-53 years, W, Premenopausal	455/ 39 268 7.8 years	Follow up questionnaires, medical records	Semi-quantitative FFQ	Incidence, Invasive breast cancer	25.5 vs 15.4 g/day	1.29 (0.96-1.73) Ptrend:0.07	Age, age at first child birth, age at menarche, alcohol consumption, benign breast disease, BMI, energy Intake, family history of cancer, menopausal status, OC use, parity, weight gain	Excluded, adolescent diet
Frazier, 2004 BRE02942 USA	NHS II, Historical Cohort,	361/ 47 355 9 years	All histology	FFQ	Incidence, breast cancer, premenopausal	25.5 vs 15.4 g/day	0.86 (0.61-1.20) Ptrend:0.11	Age , age at first child, age at menarche,	Excluded, adolescent diet

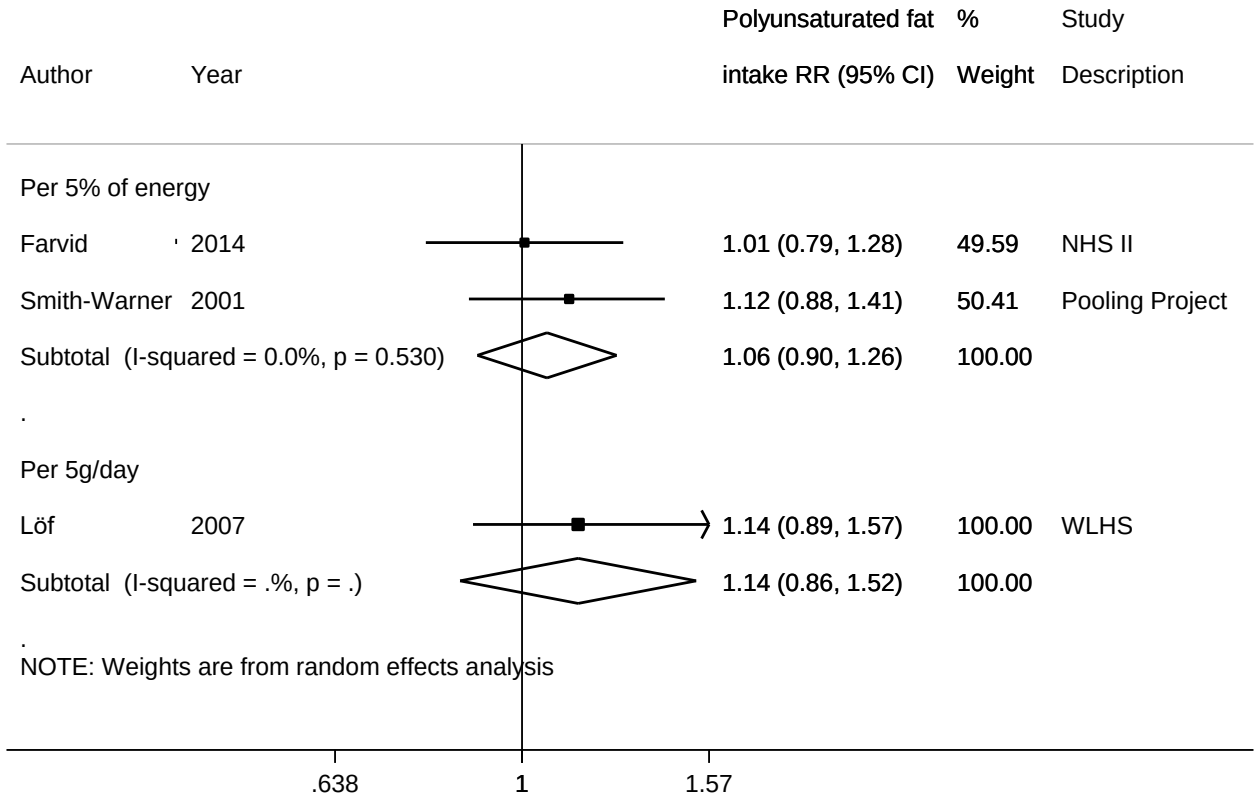
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 34-51 years, W, Registered nurses							alcohol, benign breast disease, BMI, energy Intake , family history, menopausal status, OC use, other anthropometric Index, other design Issue, parity/pregnancies	

Table 243 Percentage of energy from polyunsaturated fatty acids and premenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Cho, 2003a BRE17370 USA	NHS II, Prospective Cohort, Age: 25-42 years, W, Premenopausal	714/ 90 655 8 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, Invasive breast cancer, premenopausal	7 vs 4 %/day	1.06 (0.84-1.35) Ptrend:.20	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, family history, height, menopausal status, multivariate partition, OC use,	Superseded by Farvid, 2014

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								parity/pregnancies, smoking habits	
Holmes, 1999 BRE04008 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	121 700 14 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, Invasive breast cancer, premenopausal	per 5 % of total energy/day	0.99 (0.77-1.27)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, energy Intake , family history, height, HRT use, menopausal status, nutrients	Superseded by Smith-Warner, 2001b

Figure 307 Relative risk of premenopausal breast cancer for 5 g/day of polyunsaturated fatty acids intake and 5% of energy from polyunsaturated fatty acids



Note: The graphs of RR estimates of premenopausal breast cancer by levels of polyunsaturated fatty acids and the highest compared with the lowest forest plot were not produced as the number of studies with categorical results was limited.

RR estimates were 0.94, 0.99, 1.00, and 0.98 (95% CI=0.83-1.15) (all non-significant) for increasing quintile categories (median 4.9, 5.5, 6.1, and 7.3% vs 4.1% of energy) in Farvid, 2014 and 0.99, 1.16, 1.20, and 1.06 (95% CI=0.64-1.75) (all non-significant) for increasing quintile categories (median 6, 7.3, 8.7, and 11.2 g/day vs 4.3 g/day) in Lof, 2007a.

Postmenopausal breast cancer

Summary

Main results:

Ten out of 13 studies (12 publications) on polyunsaturated fatty acids intake and all 16 studies (eight publications) on percentage of energy from polyunsaturated fatty acids could be included in the dose-response meta-analyses, respectively.

No significant associations were observed for postmenopausal breast cancer overall, and in most subgroup analyses (For each 5 g/day increase of polyunsaturated fatty acids intake, summary RR=1.08, 95% CI=0.94-1.24; for each increase of 5% of energy, summary RR=1.05, 95% CI=0.95-1.17). High and moderate heterogeneity were observed between studies (76%, P<0.001; 49%, P=0.08, respectively).

There was no evidence of significant publication or small studies bias (P for Egger's test=0.63 for studies on polyunsaturated fatty acids intake and 0.66 for studies on percentage of energy from polyunsaturated fatty acids).

Three studies on polyunsaturated fatty acids intake were excluded because of insufficient data. For the highest versus the lowest intake, non-significant associations, that was positive overall (Sieri, 2002) and inverse among MHT users and non-users (Sieri, 2008) were reported. Barrett-Connor, 1993 reported that intake of polyunsaturated fatty acids was significantly higher in the cases than in the non-cases (P=0.001).

The Pooling Project (Smith-Warner, 2001b) observed a significant interaction between percent energy from polyunsaturated fat and MHT use in relation to postmenopausal breast cancer (P for interaction=0.01). Significant positive association was observed in current MHT users (RR per 5% energy=1.60, 95% CI=1.25-2.06) but not never (RR=1.01, 95% CI=0.89-1.15) or past users (RR=1.03, 95% CI=0.80-1.34).

Three studies reported results by breast cancer hormone receptor status. Non-significant inverse associations were observed (Park, 2012; Kim, 2006; Kushi, 1995)

Sensitivity analyses:

Summary RRs remained non-significant when studies were omitted in turn in influence analyses. Summary RR per 5 g/day increase of intake ranged from 1.03 (95% CI=0.91-1.16) when Wirfalt, 2002 was omitted to 1.12 (95% CI=0.98-1.29) when Lof, 2007a was omitted. Summary RR per 5% of energy ranged from 1.03 (95% CI=0.93-1.14) when Smith-Warner, 2001b was omitted to 1.08 (95% CI=0.90-1.29) when Park, 2012 was omitted.

Non-linear dose-response meta-analysis:

There was no evidence of non-linear relationship between polyunsaturated fatty acids intake and postmenopausal breast cancer risk (P for non-linearity=0.99) (graph not shown). There were not enough studies to conduct a non-linear dose-response meta-analysis of percentage of energy from polyunsaturated fatty acids.

Study quality:

Most studies were from North America or Europe. One study was from Japan (Wakai, 2005). Park, 2012 was a cohort of multi-ethnicity. The study of Freedman, 2006 (WHI-DM, non-intervention group) included only women with ≥32% calories from fat. Results in this study were adjusted for these selection criteria (Freedman, 2006). Key, 2011 included only MHT non-users. Summary RR remained non-significant when studies were omitted in turn in influence analysis.

Most studies used FFQs to assessed fat intake. Wirfalt, 2002 used a combination of 7-day food record and questionnaire. Key, 2011 (UKDCC) and Freedman, 2006 (WHI-DM, non-intervention arm) were able to use data from both sources (FFQs and food diaries or food records) in the analysis. Key, 2011 reported non-significant inverse associations. Freedman, 2006 found stronger association with data from food records than data from FFQs (RR for the highest versus the lowest intake=1.74, 95% CI=1.06-2.84, Ptrend=0.01 vs. RR=1.02, 95% CI=0.57-1.83, Ptrend=0.79).

Case ascertainment was through cancer registries or confirmed through medical records Major confounding factors of breast cancer were adjusted for in the studies.

Table 244 Polyunsaturated fatty acids intake and percentage of energy from polyunsaturated fatty acids and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	13 (12 publications) polyunsaturated fatty acids intake 16 (8 publications) percentage of energy from polyunsaturated fatty acids
Studies included in forest plot of highest compared with lowest exposure	8 (8 publications) polyunsaturated fatty acids intake 4 (4 publications) percentage of energy from polyunsaturated fatty acids
Studies included in linear dose-response meta-analysis	10 (7 publications) polyunsaturated fatty acids intake 16 (6 publications) percentage of energy from polyunsaturated fatty acids
Studies included in non-linear dose-response meta-analysis	6 (6 publications) polyunsaturated fatty acids intake Not enough studies on percentage of energy from polyunsaturated fatty acids

Note: Include cohort, case-cohort, and nested case-control designs.

Table 245 Polyunsaturated fatty acids intake and percentage of energy from polyunsaturated fatty acids and postmenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and 2016 CUP

	2005 SLR		CUP	
Increment unit used	**Per 5 g/day**	**Per 5%**	**Per 5 g/day**	**Per 5%**
Studies (n)	3	-	10	16
Cases	711	-	3 336	>8 666
RR (95%CI)	1.56 (1.33-1.84)	-	1.08 (0.94-1.24)	1.05 (0.95-1.17)
Heterogeneity (I^2, p-value)	30%	-	76%, <0.001	49%, 0.08
P value Egger test	-	-	0.63	0.66

Stratified analyses in the CUP					
Increment unit used	**Per 5 g/day**	**Per 5 g/day**	**Per 5% of energy**	**Per 5% of energy**	**Per 5% of energy**
Geographic location[1]	**Europe**	**North America**	**Europe**	**North America**	**Asia**
Studies (n)	7	3	4	4	1
Cases	1 502	1 834	286	11 841	76
RR (95%CI)	1.02 (0.79-1.30)	1.15 (0.99-1.34)	0.72 (0.47-1.12)	1.03 (0.98-1.09)	2.23 (0.96-5.17)
Heterogeneity (I^2, p-value)	84%, <0.001	59%, 0.09	-	0%, 0.44	-

Increment unit used	**Per 5 g/day**	**Per 5 g/day**	**Per 5% of energy**	**Per 5% of energy**
Adjustment for age, BMI, alcohol intake, reproductive factors	**Adjusted**	**Not adjusted**	**Adjusted**	**Not adjusted**
Studies (n)	10	-	16	-
Cases	3 336	-	>8 666	-
RR (95%CI)	1.08 (0.94-1.24)	-	1.05 (0.95-1.17)	-
Heterogeneity (I^2, p-value)	76%, <0.001	-	49%, 0.08	-
Exposure assessment methods	**FFQs**	**Other methods**	**FFQs**	**Other methods**
Studies (n)	9	6	16	4
Cases	3 099	1 126	>8 666	286

RR (95%CI)	1.01 (0.94-1.09)	1.18 (0.87-1.62)	1.06 (0.97-1.15)	0.72 (0.47-1.12)
Heterogeneity (I^2, p-value)	32%, 0.20	86%, 0.001	34%, 0.18	-

[1]Results from the individual studies in the Pooling Project were not provided (Smith-Warner, 2001b). The study combined data from European and North American studies (RR per 5% of energy=1.28, 95% CI=0.96-1.69)

Table 246 Polyunsaturated fatty acids intake and postmenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Turner, 2011	15 studies (12 cohorts, 3 case-control studies)	>13 460 postmenopausal breast cancer	Germany, Italy, The Netherlands, Singapore, Sweden, USA	Incidence, postmenoapausal breast cancer	Highest vs lowest polyunsaturated fatty acids intake (10 studies) Cohort studies (n=9)	1.22 (1.08-1.38) 1.23 (1.09-1.39)	- -

*Bryne, 2002 on linoleic acid, and Fung, 2006 on polyunsaturated: saturated fat ratio score were not included in the present review. Other cohorts were included.

Table 247 Polyunsaturated fatty acids intake and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Sczaniecka, 2012 BRE80434 USA	VITAL, Prospective Cohort, Age: 50-76 years, W, Postmenopausal	772/ 30 252 6 years	Seer registry	Semi-quantitative FFQ	Incidence, breast cancer	≥16.6 vs ≤7.1 g/day	1.07 (0.76-1.52) Ptrend:0.62	Age, age at first child birth, age at menarche, age at menopause, alcohol, BMI, breast biopsies, educational level, energy, estrogen replacement therapy, exercise, family history of breast	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								cancer, fruits, height, history of hysterectomy, mammography, NSAID use, race, vegetable, years of combined hormone therapy	
Key, 2011 UK	UK Dietary Cohort Consortium Pooled study of 4 cohorts* Mean age: 56.4 ±9.7 years among cases, W (*EPIC-Norfolk; EPIC-Oxford; UKWCS; Whitehall II study)	286 cases/ 699 controls	Record linkage with National Statistics and cancer registries	Food diary and FFQ	Incidence, breast cancer, postmenopausal, HRT non-users	Food diaries per 4.9 g/day	0.87 (0.71-1.07)	Age, alcohol consumption, parity, menopausal status, current hormone replacement therapy use, physical activity, height, weight, and energy intake	
						FFQ per 6.5 g/day	0.98 (0.81-1.19)		
Löf, 2007 BRE80144 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	542/ 44 569 13 years	Cancer registry	FFQ	Incidence, Invasive breast cancer, age >= 50 yrs	11.2 vs 4.3 g/day	0.54 (0.35-0.85) Ptrend:0.08	Age, age at first child birth, age at menarche, alcohol consumption, BMI, educational level, family	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								history of cancer, non-alcohol energy, parity, total fat, use of oral contraception	
						Per 10 g/day	0.58 (0.32-1.05)		
Freedman, 2006 BRE80628 USA	Women's Health Initiative - Dietary Modification Trial, Nested Case Control, Age: 50-79 years, W, Postmenopausal	603/ 1206 controls 6.92 years	Medical records and pathology reports	4-day food record & FFQ	Incidence, Invasive breast cancer	Food records 20.8 vs 7.2 g/day	1.74 (1.06-2.84) Ptrend:0.01	Age at entry, breast biopsies, clinic, energy Intake, family history, HRT use, length of follow-up	
						FFQ 25.8 vs 8.1 g/day	1.02 (0.57-1.83) Ptrend:0.79		
Wirfalt, 2002 BRE13504 Sweden	MDCS, Nested Case Control, Age: 50- years, W, Postmenopausal	237/ 673 controls 8 years	Partially histological - over 80%	7-day record + questionnaire	Incidence, breast cancer, postmenopausal	19 vs 9.3 g/day	3.02 (1.75-5.21) Ptrend:0.0007	Age at first child, alcohol, BMI, educational level, energy Intake , height, HRT use, nutritional factors , waist circumference	
van den Brandt, 1993 BRE16919 Netherlands	NLCS, Prospective Cohort, Age: 55-69 years,	437/ 1 598 3.3 years	All histology	FFQ-semi-quantitative	Incidence, Invasive breast cancer	≥20.2 vs ≤10.1 g/day	0.95 (0.64-1.40) Ptrend:0.85	Age , age at first child, age at menarche, age at menopause, alcohol, benign	(Not included in the highest vs the lowest forest plot as another publication of

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	W, Postmenopausal							breast disease, BMI, educational level, family history, OC use, parity/pregnancies, residual (willet), smoking habits	the same study Voorrips, 2002 was used)
Kushi L H, 1992 BRE05141 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	459/ 34 388 4 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	15.8 vs 9.2 g/day	1.49 (1.01-2.20) Ptrend:0.05	Age, age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, BMI at 18 years, energy Intake , family history, WHR	

Table 248 Percentage of energy from polyunsaturated fatty acids and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Farvid, 2014 BRE80577 USA	NHS II, Prospective Cohort, Age: 26-45 years, W	918/ 88 804 20 years	Self report verified by medical record and pathology report	Semi-quantitative FFQ	Incidence, postmenopausal breast cancer, postmenopausal	7.5 vs 4.1 %	0.96 (0.78-1.19) Ptrend:0.88	Age, age at menarche, age at menopause, alcohol Intake, BMI, calendar year, energy, energy from protein, family	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								history of breast cancer In first degree relatives, height, history of benign breast disease, hormone use, OC use, parity and age at first birth, race, smoking status and dose	
Park, 2012 BRE80399 Hawaii	MEC, Prospective Cohort, Age: 45-75 years, Postmenopausal	3 885/ 85 089 12.4 years	Cancer registry	FFQ	Incidence, breast cancer, postmenopausal	≥9 vs ≤5.8 % energy	0.97 (0.88-1.08) Ptrend:0.91	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, educational level, energy Intake, ethnicity, family history of breast cancer, HRT use, number of childbirths, smoking status, time, type of menopause	
Key, 2011 UK	UK Dietary Cohort Consortium Pooled study of	286 cases/ 699 controls	Record linkage with National Statistics and cancer registries	Food diary and FFQ	Incidence, breast cancer, postmenopausal, HRT non-users	Food diaries per 1.8% of energy	0.89 (0.76-1.04)	Age, alcohol consumption, parity, menopausal	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	4 cohorts* Mean age: 56.4 ±9.7 years among cases, W (*EPIC-Norfolk; EPIC-Oxford; UKWCS; Whitehall II study)							status, current hormone replacement therapy use, physical activity, height, weight, and energy intake	
						FFQ per 2.1% of energy	0.96 (0.83-1.11)		
Thiébaut, 2007 BRE80012 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, Postmenopausal	3 501/ 188 736 4.4 years	Cancer registry	24h recall + FFQ	Incidence, Invasive breast cancer	10.3 vs 4.5 %energy	1.12 (1.01-1.25) Ptrend:0.04	Age at first child birth, age at menopause, alcohol energy, BMI, menopausal hormone use, non-alcohol energy, parity, smoking habits	
						per 100 %	1.10 (1.01-1.20)		
		83/			Incidence, breast cancer ER-/PR+	per 5 %	0.62 (0.18-2.10)		
Wakai, 2005 BRE24482 Japan	JACC, Prospective Cohort, Age: 40-79 years, W,	76/ 26 291 7.6 days	Partially histological - over 80%	FFQ	Incidence, breast cancer, postmenopausal	≥6.06 vs ≤4.4	1.98 (0.94-4.18) Ptrend:0.071	Age , age at first child, age at menarche, age at menopause, alcohol, BMI, educational	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	Previous study							level, energy Intake , family history, height, HRT use, other energy Index, other nutritional factors, other physical activity Index, parity/pregnancies, recruitment center, smoking habits	
Smith-Warner, 2001b Canada, USA, the Netherlands, Sweden	The Pooling Project, Pooled study of 8 cohorts*, Age: 28-90 years, W (*AHS, CNBSS, IWHS, NHS(a), NHS(b), NLCS, NYSC, NYUWHS, SMC)	-	Self-reported and verified by medical records and/or record linkage with cancer registries	FFQ	Incidence, postmenopausal breast cancer	per 5% of energy	1.28 (0.96-1.69)	Percent of energy from protein, percent of energy from alcohol, age at menarche, parity, age at birth of first child, OC use, history of benign breast disease, family history of breast cancer, smoking status, education, BMI, height, fibre intake, energy intake, monounsaturated fat, saturated fat	

Table 249 Polyunsaturated fatty acids intake and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reaons for exclusion
Sieri, 2008 BRE80202 Europe	EPIC, Prospective Cohort, Age: 20-70 years, W	1 553/ 319 826 8.8 years	Cancer registry / database / pathology reports	FFQ	Incidence, breast cancer, HRT - no	21.3 vs 7.2 g/day	0.95 (0.79-1.15) Ptrend:0.298	Age, alcohol Intake, centre location, educational attainment, energy Intake, height, menopausal status, smoking status, weight	Excluded, missing cases and non-cases per category in subgroups
						per 20 %	0.99 (0.96-1.01)		
		1 909/			HRT - yes	21.3 vs 7.2 g/day	0.97 (0.82-1.16) Ptrend:0.460		
						per 20 %	0.99 (0.97-1.02)		
Sieri, 2002 BRE20941 Italy	ORDET, Nested Case Control, Age: 41-70 years, W, Postmenopausal	56/ 214 controls 5.5 years	Cancer registry + death certificate	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	7.7-18 vs ≤6.3 g/day	2.03 (0.68-6.03) Ptrend:0.202	Birth cohort, educational level, nutrients, parity/pregnancies, residual (willet)	Excluded, missing cases and non-cases per category
Voorrips, 2002 BRE13011 Netherlands	NLCS, Case Cohort, Age: 55-69 years, W, Postmenopausal	783/ 62 573 6.3 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	24 vs 8 g/day	0.88 (0.65-1.21) Ptrend:0.39	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI,	Superseded by van den Brandt, 1993 (Included in the highest vs the lowest forest

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reaons for exclusion
								educational level, energy Intake , family history, OC use, parity/pregnancies, residual (willet), smoking habits	plot)
Kushi, 1995 BRE05142 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	329/ 34 388 6 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, postmenopausal breast cancer ER+/PR+	≥13.1 vs ≤10.6 g/day	0.93 (0.71-1.22) Ptrend:0.58	Age , energy Intake	Results by hormone receptor status, not analysed
		75/			ER+/PR-	≥13.1 vs ≤10.6 g/day	0.90 (0.52-1.54) Ptrend:0.70		
		14/			ER-/PR+	≥13.1 vs ≤10.6 g/day	0.50 (0.12-1.99) Ptrend:0.32		
		61/			ER-/PR-	≥13.1 vs ≤10.6 g/day	1.32 (0.73-2.40) Ptrend:0.32		
Barrett-Connor, 1993 BRE00581 USA	Rancho Bernardo, 1972, Prospective Cohort, Age: 40-79 years, W	15/ 590 15 years	Medical records + death certificate	24h recall	Incidence, breast cancer, postmenopausal	(mean exposure)			Excluded, mean exposure values only

Table 250 Percentage of energy from polyunsaturated fatty acids and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Kim, 2006 BRE80115 USA	NHS, Prospective Cohort, W, Postmenopausal	3 537/ 121 701 20 years	Medical records	FFQ	Incidence, Invasive breast cancer	per 5 %	0.95 (0.79-1.14)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, energy Intake , family history, height, HRT use, other design Issue, parity/pregnancies, other fat types	Superseded by Smith -Warner, 2001
		1 653/			Incidence, breast cancer ER+/PR+	per 5 %	0.96 (0.73-1.26)		
		517/			Incidence, breast cancer ER-/PR-	per 5 %	0.96 (0.59-1.55)		
		477/			Incidence, breast cancer ER+/PR-	per 5 %	1.07 (0.66-1.74)		
		83/			Incidence, breast cancer ER-/PR+	per 5 %	0.62 (0.18-2.10)		
Holmes, 1999 BRE04008 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered	121 700 14 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, Invasive breast cancer, postmenopausal	per 5 % of total energy/day	0.88 (0.74-1.04)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body	Superseded by Smith -Warner, 2001

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	nurses							weight, energy Intake , family history, height, HRT use, menopausal status, nutrients	

Figure 308 RR estimates of postmenopausal breast cancer by levels of polyunsaturated fatty acids intake and percentage of energy from polyunsaturated fatty acids

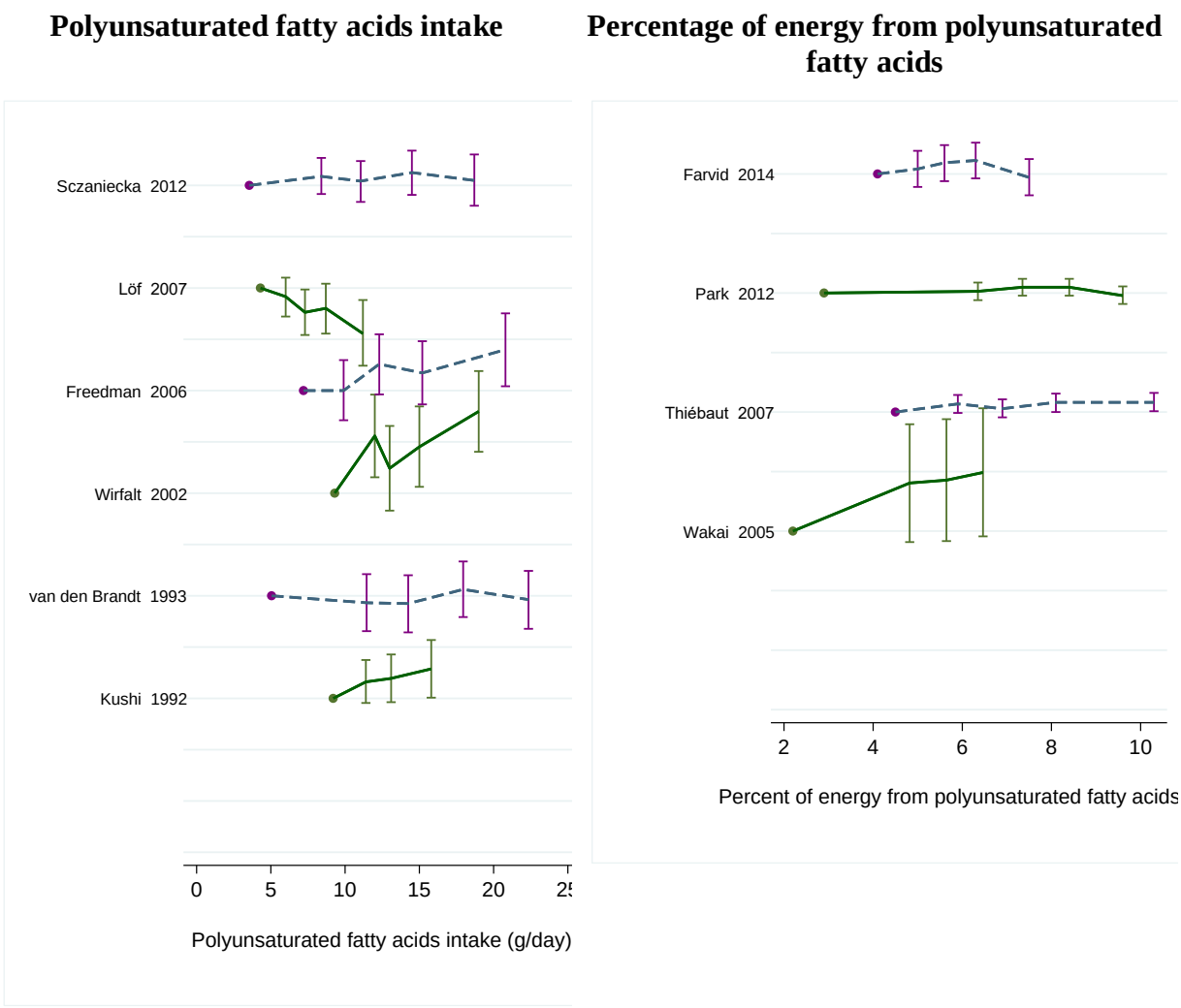


Figure 309 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest polyunsaturated fatty acids intake and percentage of energy from polyunsaturated fatty acids

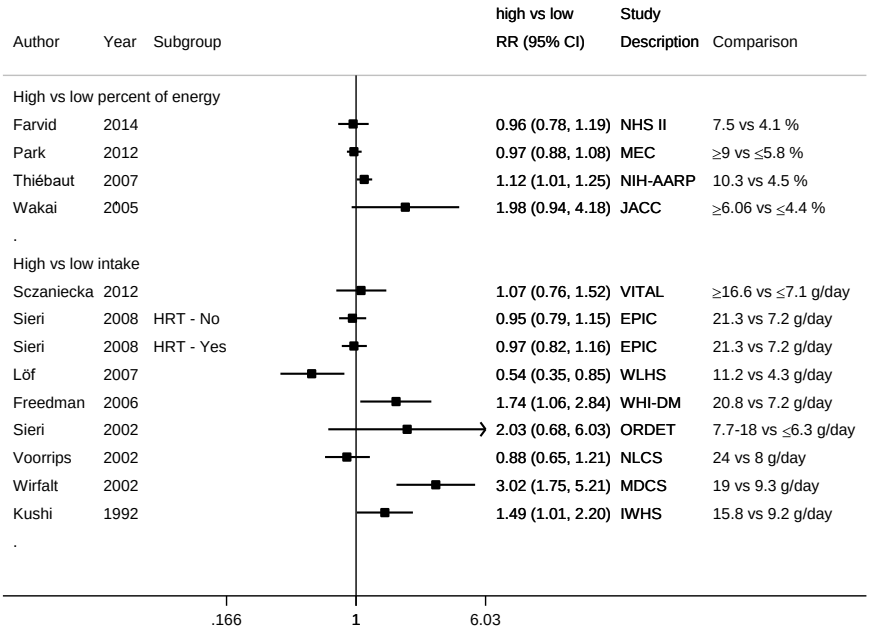


Figure 310 Relative risk of postmenopausal breast cancer for 5 g/day of polyunsaturated fatty acids intake and 5% of energy from polyunsaturated fatty acids

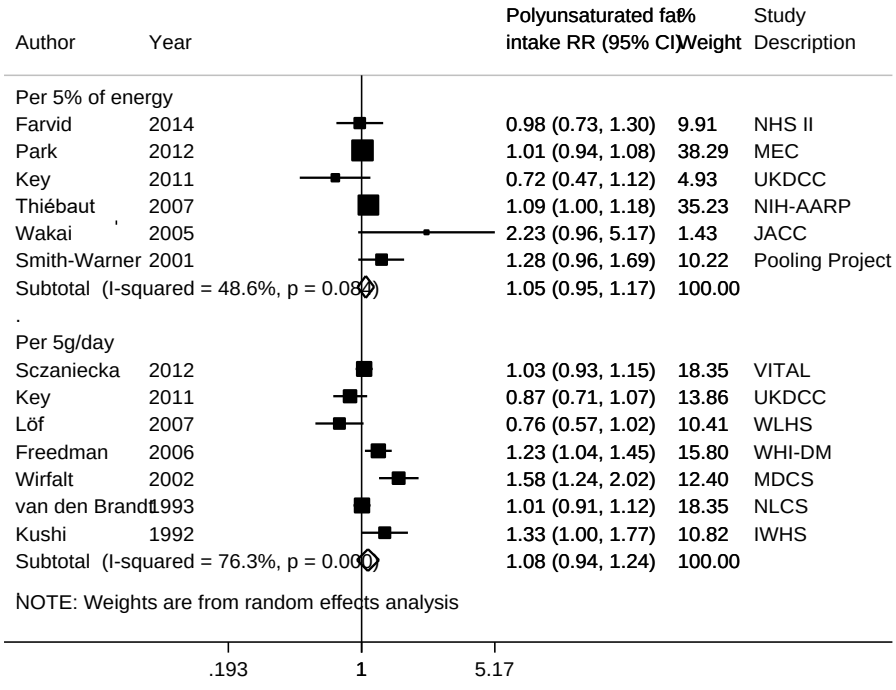


Figure 311 Funnel plot of studies included in the dose response meta-analysis of polyunsaturated fatty acids intake and postmenopausal breast cancer

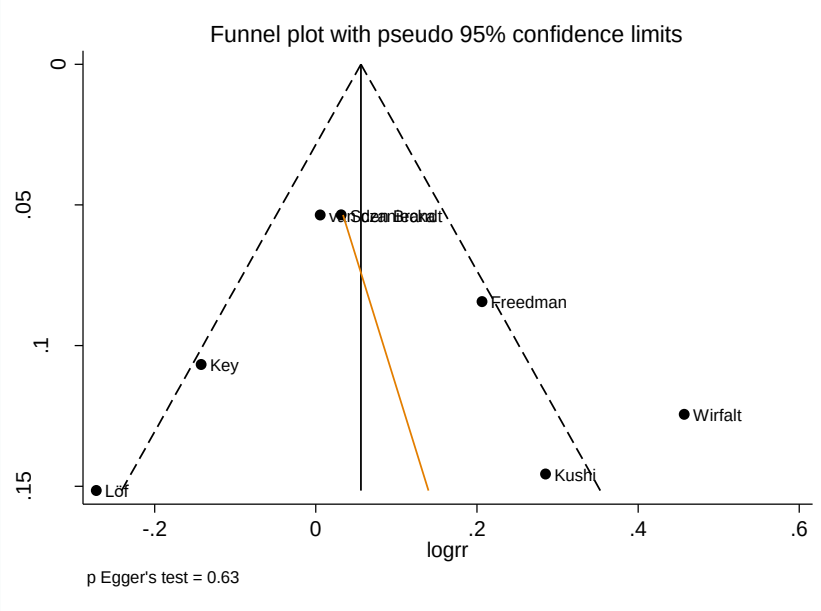


Figure 312 Funnel plot of studies included in the dose response meta-analysis of percentage of energy from polyunsaturated fatty acids and postmenopausal breast cancer

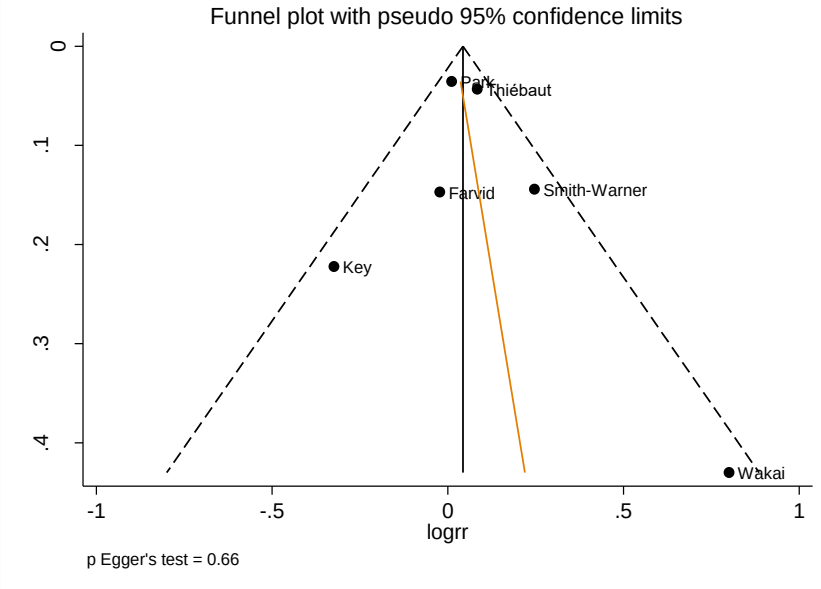


Figure 313 Relative risk of postmenopausal breast cancer for 5 g/day of polyunsaturated fatty acids intake, by geographic location

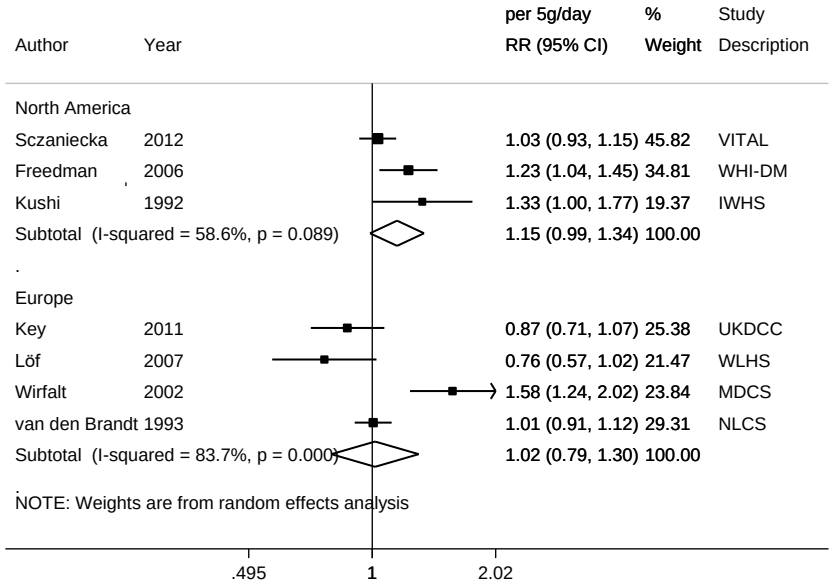


Figure 314 Relative risk of postmenopausal breast cancer for 5% of energy from polyunsaturated fatty acids, by geographic location

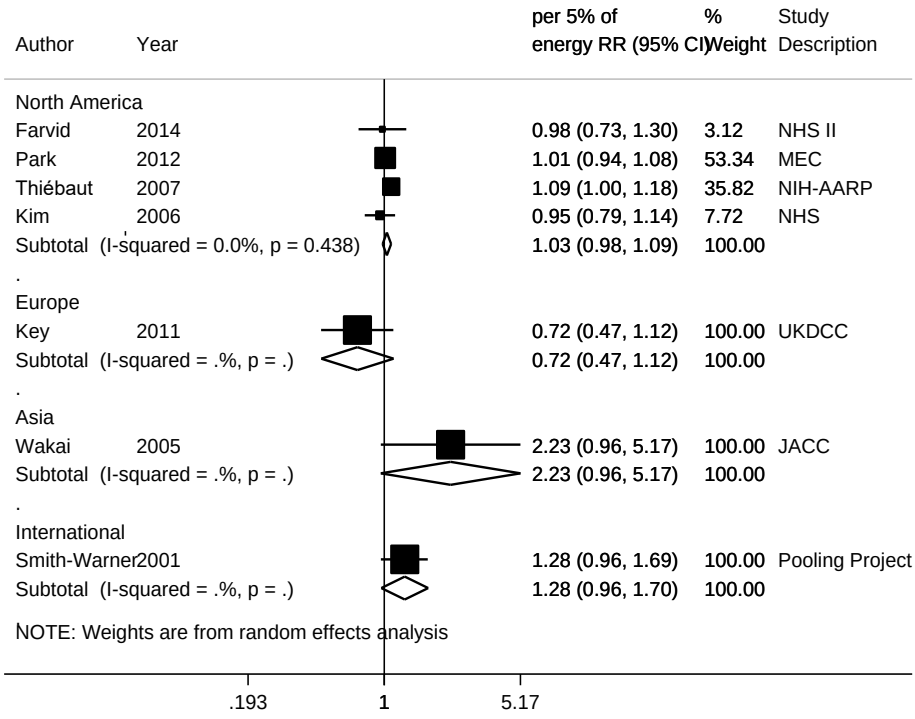


Figure 315 Relative risk of postmenopausal breast cancer for 5 g/day of polyunsaturated fatty acids intake, by exposure assessment

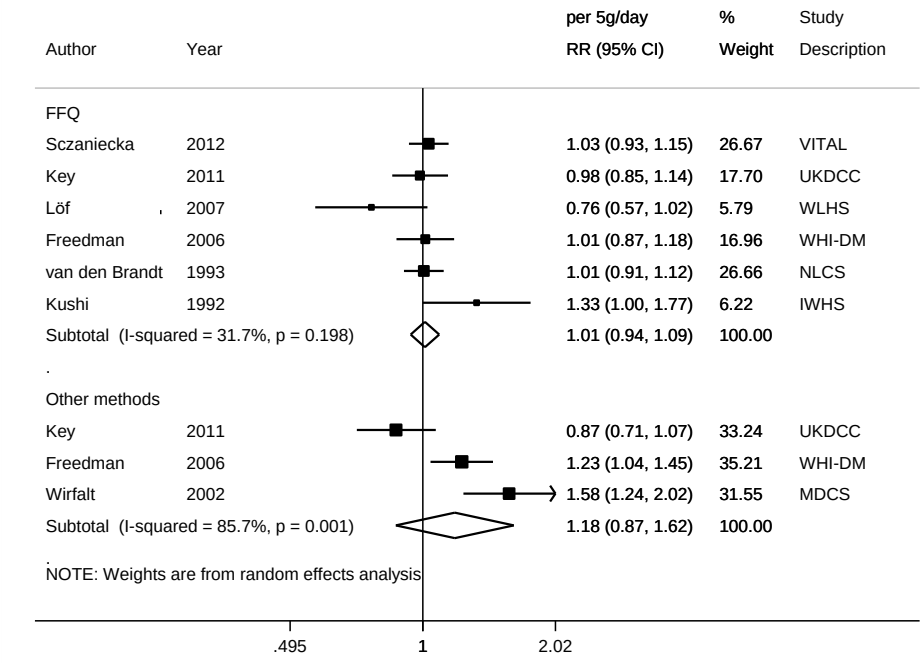
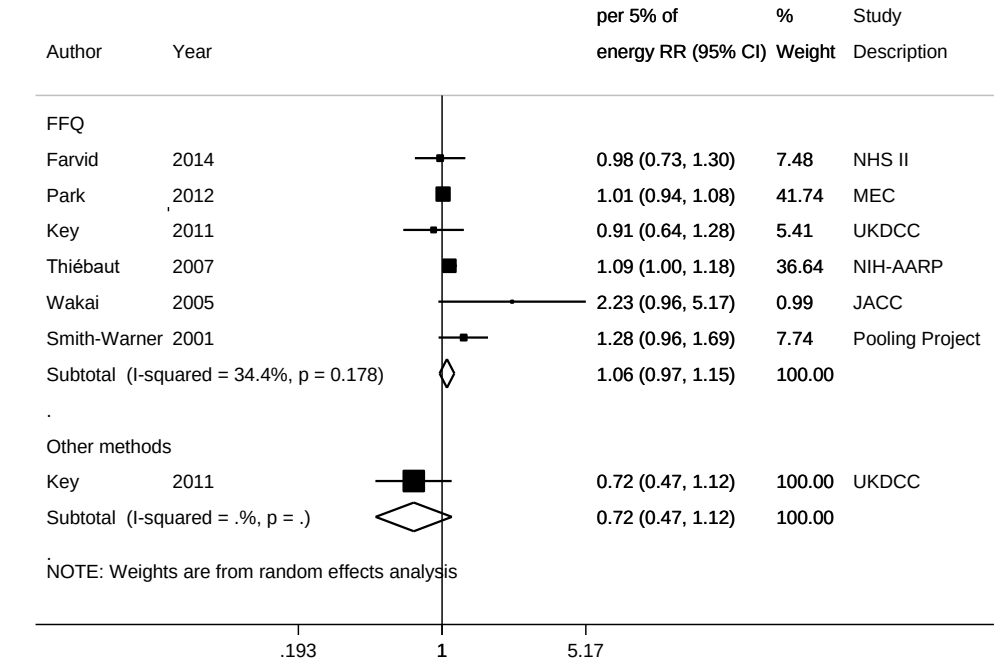


Figure 316 Relative risk of postmenopausal breast cancer for 5% of energy from polyunsaturated fatty acids, by exposure assessment



5.4.1 Total alcohol (as ethanol)

Overall summary

120 publications from 62 studies were identified, including one pooled study on breast cancer (any) incidence (Keogh, 2012 (4 cohorts), table 130) and two pooled studies on postmenopausal breast cancer (Hvidtfeldt, 2015 (2 cohorts); Schonfeld, 2011 (4 cohorts), table 139). Dose-response meta-analyses were conducted to examine the association of alcohol (as ethanol) with risk of breast cancer, and with premenopausal and postmenopausal breast cancer.

The working group is aware of a publication by the Pooling Project of Prospective Studies on Diet and Cancer after the end of the search for this review (Jung, 2015). The study included 20 prospective studies. The Pooling Project publication is more recent than most of the individual publications of its participating cohorts. Therefore, the CUP analyses of the individually published studies is complemented with analyses including the overall result of the Pooling Project and the studies identified in the CUP not overlapping with those in the Pooling Project.

Alcohol intake in early age and breast cancer risk:

Three studies reported results on alcohol intake in early ages and breast cancer risk (Liu, 2013; Tjønneland, 2007; Horn-Ross, 2004). Inconsistent results were observed. In the NHS II study, alcohol intake between menarche and first pregnancy was associated with increased breast cancer risk (RR per 10g/day = 1.13; 95% CI: 1.03-1.24) (Liu, 2013). In the EPIC study, alcohol intake in one's twenties and thirties was not associated with invasive breast cancer diagnosed between age 35-75 years (RRs per 10g/day= 0.99; 95% CI: 0.94-1.05 and 1.01, 95% CI: 0.95-1.08, respectively) (Tjønneland, 2007). In the CTS study, alcohol intake at age 18-22 years and breast cancer risk later on in life was inversely associated in pre/perimenopausal women and positively associated in postmenopausal women (RRs for the highest vs the lowest intake=0.62, 95% CI: 0.34-1.13 and 1.07; 95% CI: 0.72-1.58, respectively) (Horn-Ross, 2004).

Table 251 Summary of results of the dose-response meta-analysis in the CUP SLR

	Breast cancer (any)	**Premenopausal breast cancer**	**Postmenopausal breast cancer**
Increment unit used	10 g/day	10 g/day	10 g/day
Studies identified in the CUP search excluding Pooling Project			
Studies (n)	23	10	22
Cases	98 046	4 227	35 221
RR (95%CI)	1.07 (1.05-1.09)	1.05 (1.02-1.08)	1.09 (1.07-1.12)
Heterogeneity (I^2, p-value)	74%, <0.001	0%, 0.79	71%, <0.001

P value Egger test	0.14	0.07	0.04
Pooling Project of Cohort Studies*			
Studies (n)	20	15	20
Cases	36 183	3730	25 411
RR (95%CI)	1.08 (1.07-1.09)	1.03 (0.99–1.08)	1.09 (1.07-1.11)
Heterogeneity (I^2, p-value)	0.47	p-value test for interaction=0.04	
Pooling Project and not overlapping studies identified in the CUP			
Studies (n)	35	18	29
Cases	117 399	4 426	33 415
RR (95%CI)	1.07 (1.05-1.10)	1.03 (0.99-1.07)	1.11 (1.06-1.16)
Heterogeneity (I^2, p-value)	81.9%, <0.0001	19%, 0.30	81%, <0.001

Note: Jung 2015; analyses restricted to women drinking <55g/day

Breast cancer (any)

Summary

Main results:

Twenty three studies (98 046 cases) (23 publications) were included in the dose-response meta-analysis. Alcohol intake was positively significantly associated with breast cancer risk (RR for 10 g/day increase=1.07; 95% CI=1.05-1.09). High heterogeneity was observed. There was no evidence of publication or small study bias.

The publication of the NHS II (Liu, 2013) was excluded from the analysis because it reported on alcohol intake between menarche and first full-term pregnancy. In this study, alcohol intake between menarche and first full-term pregnancy was marginally significantly positively associated with breast cancer risk before menopause, significantly positively associated with risk of ER+/PR+ tumours, and non-significantly inversely associated with ER+/PR- and ER-PR- tumours.

Five studies could only be used in the highest versus lowest analysis but not in dose-response meta-analysis. Three studies reported non-significant positive associations (Hoyer, 1998, Redaniel, 2012, Wen, 2009) and two studies (Lubinski, 2012, Gibson, 2010) reported non-significant inverse associations. Hoyer, 1992 reported non-significant unadjusted inverse association and was excluded.

Three studies on breast cancer mortality were excluded: Ozasa, 2007 reported a relative risk estimate with only one case in the third intake category (RR 3.44 (95%CI: 0.47-25.1); and

two studies (Lin, 2013 and Shen, 2013) that compared only two levels of alcohol intake reported non-significant inverse associations.

Breast cancer risk and alcohol intake by hormone receptor status:

Three studies investigated the association of alcohol intake and breast cancer risk by tumour hormone receptor status: the Pooling Project of Cohort Studies on Diet and Cancer (Jung, 2015), EPIC (Romieu, 2015) and the cohort from the Kaiser Permanente Medical Care Programme (KPMCP) (Li, 2009).

In the Pooling Project (Jung, 2015), alcohol consumption was significantly positively associated with risk of both ER^+ and ER^- breast cancers (7829 cases ER^+ and 1836 ER^-), and the associations were similar for PR^+ and PR^- cancers.

In EPIC (Romieu, 2015), similar dose-response associations were observed for ER^+ and ER^- cancers. In categorical analysis, the positive association was not statistically significant for ER^-PR^+ breast cancer, for which the number of cases was low (3553 cases ER^+PR^+; 1133 cases ER^+PR^-; 217 cases ER^-PR^+, 1050 ER^-PR^-).

In the KPMCP study, the positive association was restricted to ER^+ cancers (1019 cases). Alcohol intake was not related to ER^- cancers (218 cases). The positive association was significant for PR^+ cancers (808 cases) and non-significant for PR^- cancers.

The results are shown in the Table of study characteristics and in a figure in this section.

Influence and stratified analyses:

In influence analysis including the Pooling Project and no overlapping studies, the summary relative risk changed from 1.06 (95% CI, 1.03-1.08) when Allen, 2009 was excluded to 1.08 (1.05-1.10) when Romieu, 2015 was excluded.

In analysis stratified by geographic area including the studies identified in the CUP, a stronger association was observed in Asian studies that were mainly driven by an outlier study with low number of cases among drinkers in the analysis (Lin, 2005). The Pooling Project reported similar estimates studies from North American studies and from other continents (one study from Japan, one from Australia and four studies from Europe), and the positive association of alcohol with breast cancer risk was not modified by total folate intake, multivitamin use, family history of breast cancer and smoking status (Jung, 2015). Separate analyses in the Pooling Project for North American studies containing cases diagnosed before mandatory folate fortification in in the USA were similar to the main results (Jung, 2015).

Nonlinear dose-response meta-analysis:

There was no significant evidence of non-linear relationship (p=0.12). The dose-response is mainly driven by observations for intakes below 50 g/day. The number of observations at higher intake levels was lower (see Figure).

A Danish study reported a threshold at 27 drinks/week of intake (Mørch, 2007). In a British study, no further risk increase was reported above more than 7 units/day (Hippisley-Cox, 2015). In EPIC (Romieu, 2015), the test for nonlinearity was compatible with a linear trend (35 g/day that was the 99 percentile of intake) and in the Pooling Project (Jung, 2015) no

further risk increment was observed above 55 g/day but less than 1% of women reported intakes above that level.

Study quality:

All studies reported assessment of alcohol intake by questionnaire. Case ascertainment was through cancer registries or when active follow-up, diagnosis were confirmed through medical records. Most studies have large number of cases, but some smaller studies tended to report extreme associations, as expected. One study in Norway (Bjerkass, 2013) categorised the intake in less than weekly, weekly and more than weekly and the approximations to g/day by the review team may be biased – exclusion of this study does not modify the summary estimate of the meta-analysis. The estimates in Asian studies are based in relatively low range of intake and the number of alcohol drinkers' cases was low. Among large studies, only one study each did not adjust for parity (Allen, 2009) and BMI (Mørch, 2007) and both reported stronger associations than other large studies. On the other hand, only drinkers were included in the dose-response analysis in the MWS (Allen, 2009) and the Danish study (Mørch, 2007) was a study in nurses that had alcohol intake higher than the general female population. The top category of intake was more than 27 drinks/week.

Former/past drinkers were excluded from the reference category (0 g/day) in eight studies (Bassett, 2013, Kawai, 2011, Suzuki, 2010, Li, 2009, Brinton, 2008, Lin, 2005, Goodman, 1997, Holmberg, 1995), included in two studies (Romieu, 2015, Rohan, 2000a) and unspecified in all remaining studies. The reference category included intakes of ≥0 g/day in three studies (Bjerkaas, 2013, Petri, 2004, Wu 1999). Risk estimates from Allen, 2009 and Mørch, 2007 used in the dose-response meta-analysis were in alcohol drinkers only.

Table 252 Alcohol (as ethanol) and breast cancer risk. Number of studies in the CUP SLR

	Number	
	Incidence	Mortality
Studies identified	51 (64 publications)	9 (10 publications)
Studies included in forest plot of highest compared with lowest exposure	28 (27 publications)	9 (9 publications)
Studies included in linear dose-response meta-analysis	23 (22 publications)	6 (6 publications)
Studies included in non-linear dose-response meta-analysis	18 (18 publications)	Not enough studies

Table 253 Alcohol (as ethanol) and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**	**Pooling Project and CUP**
Increment unit used	10 g/day	10 g/day	10 g/day
Studies (n)	9	23	33
Cases	NA	98 046	117 399
RR (95%CI)	1.10 (1.06-1.14)	1.07 (1.05-1.09)	1.07 (1.05-1.10)
Heterogeneity (I^2, p-value)	82%	74%, <0.001	83.6 %, <0.0001
Stratified analyses in CUP			
Geographic area	**Asia**	**Europe**	**North America**
Studies (n)	4	7	11
RR (95%CI)	1.13 (0.89-1.43)	1.08 (1.04-1.11)	1.07 (1.05-1.10)
Heterogeneity (I^2, p-value)	64%, 0.04	88%, <0.001	48%, 0.04
	Australia		
Studies (n)	1		
RR (95%CI)	1.01 (0.95-1.07)		
Adjustment for age, BMI and reproductive factors	**Adjusted**	**Not adjusted**	
Studies (n)	16	7	
RR (95%CI)	1.07 (1.04-1.10)	1.09 (1.05-1.12)	
Heterogeneity (I^2, p-value)	72%, <0.001	80%, <0.001	
Breast cancer mortality			
Studies (n)	6		
Cases	2 557		
RR (95%CI)	1.05 (0.99-1.10)		
Heterogeneity (I^2, p-value)	76%, 0.001		
	0.36		

Table 254 Alcohol intake and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend
Meta-analysis							
Bagnardi, 2015	42 cohort studies 37 cohort studies 43 cohort and 75 case-control studies	117 317 cases in drinking categories, 48 433 cases in reference category	Europe, North America, Asia	Breast cancer (female)	Light drinkers vs nondrinkers Moderate drinkers vs nondrinkers Light drinkers vs nondrinkers Moderate drinkers vs nondrinkers Heavy drinkers vs nondrinkers	1.06 (1.03-1.10) 1.22 (1.17-1.27) 1.04 (1.01-1.07) 1.23 (1.19-1.28) 1.61 (1.33-1.94)	41% 31% 63% 54% 10%

Table 255 Alcohol intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Jung, 2015 North America, Europe, Asia, Australia	20 cohorts:	36 183, 6 to 18 years maximum follow-up	Variable in each cohort	Questionnaires	Incidence	≥30 g/day vs non-drinkers	1.32 (1.23-1.41)	Age, energy intake, ethnicity, education, BMI, height, physical activity, smoking status, age at menarche, menopausal status and HRT, parity and age at first birth, oral contraceptive use, family history of breast cancer, personal history of benign breast disease	None
						10 g/day increase	1.08 (1.07-1.09)		
		21 202			ER+	≥30 g/day vs non-drinkers	1.35 (1.23-1.48)		
		4 984			ER-		1.28 (1.10-1.49)		
		17 294			PR+		1.36 (1.21-1.54)		
		7 716			PR-		1.30 (1.16-1.46)		
		16 422			ER+PR+		1.36 (1.21-1.54)		
	19 cohorts: CARET excluded	3 556			ER+PR-		1.46 (1.23-1.73)		
	19 cohorts: JPHC I excluded	3 982			ER-PR-		1.25 (1.06-1.48)		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
	12 cohorts: CARET, CLUE II, CNBSS, JPHC I, NLCS, Prospective Study on Hormones, Diet and Breast Cancer (Italy), PLCO, WHS excluded	612			ER-PR+		1.36 (0.98-1.90)		
USA	CARET*	367/							
USA	BCDDP	1 305/							
USA	CTS	2 696/							
USA	CNBSS	1 240/							
USA	CPS II	2 999/							
USA	CLUE II	288/							
USA	IWHS*	1 849/							
Japan	JPHC I	289/							
Australia	MCCS	799/							
USA	MEC	3308/							
Europe	NLCS*	2013/							
USA	NYUWHS	919 /							

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
USA	NIH-AARP*	5 972/							
USA	NHS (a)	1 122/							
USA	NHS (b)	4 467/							
USA	NHS II	1 331/							
Europe	Prospective Study on Hormones, Diet and Breast Cancer (Italy)	283/							
USA	PLCO*	1 090/							
Europe	SMC	2 605/							
USA	WHS	1 177/							
Europe	SWLHCS	1 072/							
Hippisley-Cox, 2015 BRE80584 England	QRDS, Prospective cohort, age: 25-84 years, W	41 315/ 2 495 899 15 years	Cancer registry/death certificates/ medical records	Medical records	Incidence	>9 vs 0 units/day	1.25 (0.92-1.71)	Age, benign breast disease, BMI, cancer diagnosis, ethnicity, family history of breast cancer, HRT use, oral contraceptive use, presence of other disease, Townsend social and material deprivation score	Units/day converted to ethanol g/day (7.9g ethanol per unit, UK standard), cases and mid-points per categories
Romieu, 2015 BRE80588 France, Italy,	EPIC, Prospective cohort,	11 576/ 334 850 11 years	Cancer registries, health insurance	Questionnaire	Incidence	Per 10 g/day	1.04 (1.03-1.06)	Age, age at first child birth, age at first menses, age at	For non-linear analysis
					Incidence	>30 vs 0.1-5	1.25 (1.17-1.35)		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Spain, UK, Netherlands, Greece, Germany, Sweden, Denmark, Norway	age: 35-70 years, W		records, pathology rec & active follow up			g/day	ptrend: <0.001	menopause, educational level, height, hormone replacement therapy, menopausal status, non-alcoholic energy intake, oral contraceptive use, physical activity, smoking status, study centre, weight	reference category changed using Hamling's method
		3 653/			ER+/PR+	>30 vs 0.1-5 g/day Per 10 g/day	1.3 (1.15-1.48) ptrend: 0.001 1.04 (0.99-1.09)		
		1 133/			ER+/PR-	>30 vs 0.1-5 g/day Per 10 g/day	1.13 (0.88-1.43) ptrend: 0.41 1.04 (1.01-1.06)		
		217/			ER-/PR+	>30 vs 0.1-5 g/day Per 10 g/day	1.03 (0.57-1.86) ptrend: 0.26 1.05 (0.95-1.17)		
		1 050/			ER-/PR-	>30 vs 0.1-5 g/day Per 10 g/day	1.28 (1.01-1.61) ptrend: 0.06 1.05 (1.0-1.1)		
		1 764/			HER-2 -	>30 vs 0.1-5 g/day Per 10 g/day	1.41 (1.17-1.68) ptrend: 0.007 1.05 (1.02-1.09)		
		570/			HER-2 +	>30 vs 0.1-5 g/day Per 10 g/day	0.97 (0.68-1.39) ptrend: 0.83 0.98 (0.92-1.06)		
		226/			Incidence, ER-/PR-/HER2-	>30 vs 0.1-5 g/day Per 10 g/day	1.97 (1.23-3.16) ptrend: 0.03 1.12 (1.03-1.23)		
Bassett, 2013 BRE80473 Australia	MCCS, Prospective cohort, age: 27-80 years, W	936/ 20 756 16.3 years	Cancer registry and national health database	FFQ	Incidence	≥40 g/day vs abstainers Per 10 g/day	1.15 (0.78-1.69) ptrend: 0.80 1.01 (0.95-1.07)	Age at menarche, BMI, breastfeeding, educational level, energy intake, ethnicity, HRT use, menopausal status, OC use, parity, physical activity, smoking status	For non-linear analysis, person-years per category and mid-points of exposure categories

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
		690/			Incidence, ER+/PR+	≥40 g/day vs abstainers Per 10 g/day	1.36 (0.89-2.07) ptrend: 0.25 1.04 (0.97-1.12)		
		179/			Incidence, ER-/PR-	≥40 g/day vs abstainers Per 10 g/day	0.61 (0.19-1.93) ptrend: 0.37 0.93 (0.8-1.09)		
Bjerkaas, 2013 BRE80485 Norway	NNHSSS, Prospective cohort, Mean (SD) age: 44 (9) years, W	1 759/ 302 865 14 years	Cancer registry		Incidence	>weekly vs <weekly	1.26 (1.1-1.44)	Age, age at first child birth, age at study entry, BMI, educational level, number of children	"Weekly" converted to g ethanol/day, mid-points of exposure categories
Couto, 2013 BRE80454 Sweden	SWLHCS, Prospective cohort, age: 30-49 years, W	1 278/ 16 years	Cancer registry	FFQ	Incidence	Per 5 g/day	1.082 (0.98-1.188)	Age at first child birth, number of childbirths, age at menarche, benign breast disease, energy intake, height, smoking, intake of beverages, cereal, fish, fruits, vegetables, dairy products, legumes, meat, potatoes, eggs, sweet products, ratio unsaturated/saturated fat, educational level	RR rescaled for an increment of 10g/day
McCarty,	PLCO,	927/	Health	FFQ	Incidence	3 vs 0	2. (1.11-3.61)	Age, age at first	Servings

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
2012 BRE80404 USA	Nested case control, age: 55-74 years, W		surveys/cancer registry/death registry			servings/day		child birth, age at menarche, age at menopause, benign breast disease, ethnicity, family history of breast cancer, parity, race, year	converted to ethanol g/day using 12.5 g ethanol per serving, mid-points of exposure categories
Breslow, 2011 BRE80392 USA	NHIS, Prospective cohort, W	205/ 184 764	National centre for health statistics & national death index	Questionnaire	Mortality, drinkers	≥3 vs <1 drink/day	0.72 (0.45-1.16) ptrend: 0.13	BMI, educational level, marital status, race/ethnicity, region, smoking status	Drinks converted to g ethanol using 12.5g/ethanol per drink, mid-points of exposure categories
Chen, 2011 BRE80397 USA	NHS I, Prospective cohort, age: 30-55 years, W	6 194/ 2.4 years	Questionnaire, medical records or pathology reports, death certificate, physician, family member	Semi-quantitative FFQ	Incidence	≥30 vs 0 g/day Per 10 g	1.5 (1.34-1.67) ptrend: 0.001 1.09 (1.07-1.11)	Age, age at first child birth, age at menarche, age at menopause, benign breast disease, BMI, breastfeeding, family history of cancer, HRT use, parity, smoking, year	(nothing estimated for the main analysis)
		5 874/			Incidence	≥30 vs 0 g/day	1.46 (1.27-1.67)		
		791/			Incidence, lobular	≥30 vs 0 g/day	2.02 (1.41-2.88)		
		3 847/			Incidence, ER+/PR+	≥30 vs 0 g/day	1.58 (1.34-1.86) ptrend: 0.001		
		1 033/			Incidence, ER-/PR-	≥30 vs 0 g/day	1.24 (0.87-1.76) ptrend: 0.23		
		1 013/			Incidence, ER+/PR-	≥30 vs 0 g/day	1.35 (0.96-1.89) ptrend: 0.04		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
		177/			Incidence, ER-/PR+	≥30 vs 0 g/day	2.45 (1.24-4.86) ptrend: 0.02		
Kawai, 2011 BRE80305 Japan	MCS, Prospective cohort, age: 40-64 years, W	233/ 12.8 years	Cancer registry	FFQ	Incidence	≥15.0 g/day vs never	0.87 (0.4-1.91) ptrend: 0.85	Age, age at menarche, age at menopause, BMI, educational level, energy-adjusted folate intake, energy-adjusted intake of fat, family history of breast cancer, occupation, parity, smoking, use of HRT, walking time	
		23/			Incidence, HRT ever,	Current vs never	0.66 (0.22-1.97)		
		188/			Incidence, HRT never,	Current vs never	1.1 (0.79-1.54)		
		22/			Incidence, HRT ever,	≥15.0 vs never g/day	1.67 (0.17-16.73)		
		182/			Incidence, HRT never,	≥15.0 vs never g/day	0.98 (0.42-2.32)		
Kim, 2010 BRE80423 Korea	KNHIC, Prospective cohort, age: 49 years, W	72/ 1 341 393 5 years	National death certificate	Questionnaire	Mortality	≥15 g/day vs non-drinker	1.33 (0.46-3.86) ptrend: 0.68	>=3 times/week regular exercise, age, BMI, current smoking status, diastolic blood pressure, fasting blood sugar, residential (urban/rural), systolic blood pressure, total cholesterol	Soju equivalents converted to ethanol g/day, mid-points of exposure categories, cases and person-years per category
Suzuki, 2010 BRE80275 Japan	JPHC, Prospective cohort,	572/ 13.8 years	Cancer registry	FFQ	Incidence	Per 10 g/day	1.06 (1.01-1.13)	Age, area of residence, BMI, height, hormone	(nothing estimated for the main
		572/			Incidence	>150 g/week	1.76 (1.16-2.67)		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
	age: 40-69 years, W					vs never-drinkers	ptrend: 0.035	use, leisure time physical activity, smoking habits age at menarche, age at first-birth, parity , use of exogenous female hormones, energy-adjusted intake of isoflavones	analysis)
		176/			Incidence, ER+	>150 g/week vs never-drinkers	1.58 (0.72-3.48) ptrend: 0.16		
		113/			Incidence, ER+/PR+	>150 g/week vs never-drinkers	2.09 (0.88-4.97) ptrend: 0.27		
		56/			Incidence, ER+/PR-	>150 g/week vs never-drinkers	1.51 (0.7-3.27) ptrend: 0.41		
		99/			Incidence, ER-	>150 g/week vs never-drinkers	1.03 (0.5-2.13) ptrend: 0.26		
		77/			Incidence, ER-/PR-	>150 g/week vs never-drinkers	1.09 (0.48-2.46) ptrend: 0.43		
		182/			Incidence, folate intake <351 mg/day	Per 10 g/day	1.08 (1.02-1.16)		
		230/			Incidence, folate intake ≥351 mg/day	Per 10 g/day	1.01 (0.9-1.14)		
Allen, 2009 BRE80227 UK	MWS, Prospective cohort, age: 55 years, W	21 971/ 1 280 296 7.2 years	National health records	Questionnaire (general)	Incidence	Per 10 g/day	1.12 (1.09-1.14)	Age, area of residence, BMI, HRT use, OCP use, physical activity, smoking habits,	For the non-linear analysis floating CIs converted to
		28 380/			Incidence	≥15 vs ≤2 drinks/week	1.29 (1.23-1.36) ptrend: <0.001		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
					Incidence, HRT - no	Per 10 g/day	1.11 (1.08-1.14)	socio-economic status	conventional excluding non-drinkers/never/former drinkers first category and using second as a reference; intake in drinks/week converted to ethanol g/day using 10g ethanol/drink
					Incidence, HRT - yes	Per 10 g/day	1.12 (1.08-1.15)		
Li, 2009 BRE80285 USA	KPMCP, Prospective cohort, age: 41 years, W	2 829/ 70 033 16 years	SEER Registry	Questionnaire	Incidence	Per 1 drink/day	1.04 (1.008-1.079)	Age, BMI, breast diseases, educational level, ethnicity, family history, marital status, parity, smoking habits	RR rescaled for an increment of 10g/day, intake in drinks/day converted to g ethanol using 12.5g, mid-points of exposure categories for the non-linear analysis
		2 794/			Incidence	≥3 drinks/day vs never drinkers	1.4 (1.1-1.7)		
		288/			Mortality, Hispanic	>3 drinks/day vs never drinkers	1.2 (0.6-2.3)		
		1 019/			Incidence, ER+ Hispanic,	≥3 drinks/day vs never drinkers	1.7 (1.2-2.3)		
		268/			Incidence, ER-, Hispanic	≥3 drinks/day vs never	0.8 (0.3-1.8)		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
						drinkers			
		808/			Incidence, PR+, Hispanic	≥3 drinks/day vs never drinkers	1.6 (1.1-2.3)		
		446/			Incidence, PR-, Hispanic	≥3 drinks/day vs never drinkers	1.2 (0.7-2.1)		
		782/			Incidence, ER+/PR+, Hispanic	≥3 drinks/day vs never drinkers	1.7 (1.2-2.5)		
		236/			Incidence, ER-/PR-, Hispanic	≥3 drinks/day vs never drinkers	0.7 (0.3-1.8)		
		207/			Incidence, ER+/PR-, Hispanic	≥3 drinks/day vs never drinkers	1.7 (0.9-3.4)		
		26/			Incidence, ER-/PR+, Hispanic	≥3 drinks/day vs never drinkers	0.7 (0.1-6.5)		
Setiawan, 2009 BRE80272 USA	MEC, Prospective cohort, age: 45-75 years, W	1 672/ 84 427 10.4 years	SEER registry	Self-administered questionnaire	Incidence, ER+/PR+	≥2.0 vs 0 drinks/day	1.4 (1.14-1.72) ptrend: 0.001	Age, age at first child birth, age at menarche, BMI, ethnicity, family history of cancer, HRT use, menopausal status, parity, study centre, year of recruitment	Dose-response meta-analysis by these subtypes was not conducted
		303/			Incidence, ER+/PR-	≥2.0 vs 0 drinks/day	1.42 (0.85-2.36) ptrend: 0.22		
		491/			Incidence, ER-/PR-	≥2.0 vs 0 drinks/day	1.71 (1.19-2.46) ptrend: 0.006		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Brinton, 2008 BRE80203 USA	NIH-AARP, Prospective cohort, age: 50-71 years, W	3 657/ 126 638 6 years	Cancer registry	FFQ	Incidence	≥3 drinks/day vs never	1.3 (1.08-1.57)	Age, age at first child birth, breast biopsies, family history of cancer, mammography, menopausal status, race	Intake in drinks/day converted to ethanol g/day using 12.5g ethanol per drink, mid-points of exposure categories
Mørch, 2007 BRE80004 Denmark	DNCS, Prospective cohort, age: 44-93 years, W	365/ 17 647 7.6 years	Cancer registry	Questionnaire	Incidence	Per 1 drink/week	1.117 (1.057-1.18)	Age, age at first child, age at menarche, family history, self-reported benign breast disease	RR for an increment of drink/week rescaled to g ethanol/day
		457/			Incidence	>27 vs 1-3 drinks/week	1.62 (1.04-2.52)		
Zhang, 2007 BRE20023 USA	WHS, Prospective cohort, age: 55 years,	1 484/ 10 years	Medical notes	FFQ + questionnaire	Incidence and in situ tumours	Per 10 g/day	1.07 (1.01-1.14)	Age, age at first child, age at menarche, age at menopause, benign breast disease, BMI, energy intake, family history, hormonal variables, menopausal status, parity/pregnancies, physical activity, randomized treatment assignment, supplements	(nothing estimated in the main analysis)
						≥30g/day vs none	1.32 (0.96-1.82) ptrend: 0.02		
		1 190/			Incidence, invasive	Per 10 g/day	1.09 (1.02-1.16)		
						≥30g/day vs none	1.43 (1.02-2.02) ptrend: 0.01		
		804/			Incidence, ER+/PR+	Per 10 g/day	1.11 (1.03-1.2)		
						≥30g/day vs none	1.39 (0.9-2.15) ptrend: 0.02		
		125/			Incidence, ER+/PR-	Per 10 g/day	1. (0.81-1.24)		
						≥30g/day vs none	0.69 (0.17-2.88) ptrend: 0.97		
		167/			Incidence, ER-/PR-	Per 10 g/day	0.99 (0.82-1.2)		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
						≥30g/day vs none	1.15 (0.41-3.19) ptrend: 0.79		
Lin, 2005 BRE23154 Japan	JACC, Prospective cohort, age: 40-79 years, W	132/ 35 844 7.6 years	Cancer registry systems	Questionnaire	Incidence	>15 g/day vs non-drinkers	2.93 (1.55-5.54) ptrend: 0.01	Age, age at first child, age at menarche, age at menopause, BMI, family history, HRT use, parity/ pregnancies, physical activity, place of residence	Mid-points of exposure categories
Petri, 2004 BRE16325 Denmark	CCPPS, Prospective cohort, age: 20-91 years, W	473/		Questionnaire	Incidence	>27 vs 1-6 drinks/week	1.19 (0.58-2.41)	Age, HRT use, other design issue, parity/ pregnancies	Reference category changed using Hamling's method, intake in drinks/week converted to ethanol g/day, mid points of intake categories.
Horn-Ross, 2002 BRE15412 USA	CTS, Prospective cohort, age: 21-103 years, W	681/ 111 383 2 years	CCR and SEER records	FFQ	Incidence	≥20 g/day vs non-drinkers	1.5 (1.2-2.0) ptrend: 0.01	Age, age at first child, age at menarche, BMI, energy intake, ethnicity, family history, menopausal status, physical activity	Person years per category, mid-points of exposure categories
		187/			Incidence, family history - no,	Daily vs never	0.9 (0.42-1.9) ptrend: 0.97		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Feigelson, 2001 BRE19514 USA, Puerto Rico	CPS II, Prospective cohort, W	1 419/ 14 years	Medical Records	Questionnaire	Mortality	≥3 drinks/day vs none	1.20 (1.00-1.50) ptrend: 0.08	Age, age at first child, age at menarche, age at menopause, BMI, educational level, ethnicity, family history, food, height, HRT use, other specified factor, physical activity, smoking habits, supplements	Intake in drinks converted to g ethanol using 12.5g/ethanol per drink, mid-points of exposure categories
Jain, 2000 BRE17653 Canada	CNBSS, Prospective cohort, age: 40-59 years, W	223/ 10.3 years	National Mortality Database	FFQ-quantitative	Mortality	Per 10 g/day	1.012 (1.005-1.019)	Age, age at menarche, BMI, educational level, energy intake, family history, mammography, menopausal status, OC use, other specified factor, parity/pregnancies, recruitment centre, smoking habits	(nothing estimated for the main analysis)
		223/			Mortality	>20 vs 0 g/day	1.063 (1.029-1.098) ptrend: 0.0001		
		110/			Mortality, family history - no	Per 10 g/day	1.015 (1.001–1.002)		
		64/			Mortality, family history - yes	Per 10 g/day	1.002 (0.984-1.016)		
		54/			Mortality, lean	Per 10 g/day	1.013 (0.998-1.028)		
		60/			Mortality,	Per 10 g/day	1.025 (1.009-		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
					overweight		1.041)		
Rohan, 2000a BRE16489 Canada	CNBSS, Case cohort, age: 40-59 years, W	1 336/ 10 years	National Mortality Database and to the Canadian Cancer Database	FFQ-quantitative	Incidence	>50 vs 0 g/day	1.7 (0.97-2.98) ptrend: 0.35	Age, age at menarche, energy intake, family history, menopausal status, other design issue, other specified factor, parity/pregnancies, recruitment centre, RR remained similar after adjustment for Quetelet's index	Nothing estimated in the main analysis
		263/			Incidence, lean	Per 10 g/day	1. (0.9-1.1)		
		262/			Incidence, overweight	Per 10 g/day	1.13 (0.92-1.42)		
Wu, 1999 BRE13618 USA	CLUE I, Nested case control, age: 18-90 years, W	133/ 12 450 21 years	Washington County Registry.	Questionnaire	Incidence	≥4 vs <1 drink/week	1.5 (0.62-3.65)	Only variables related to exposure and disease (p<0.10) were considered: family history of breast cancer, bilateral ovariectomy, age at menarche, age at menopause, age at first birth, number of pregnancies, months of breast feeding, oral contraceptive use, hormone replacement therapy, education and marital status, BMI, and regular	Intake in drinks/week converted to g ethanol/day using 12.5g ethanol per drink, mid-points of exposure categories
Wu, 1999 BRE63618 USA	CLUE II, Nested case control, age: 18-90 years, W	110/ 14 625 6 years					1.83 (0.74-4.54)		Intake in drinks/week converted to g ethanol/day using 12.5g ethanol per drink, mid-points of exposure

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								physical exercise	categories
Zhang, 1999b BRE13965 USA	FHS, Prospective cohort, age: 12-62 years, W	287/ 5 048 34.3 years	Self-report at examination + surveillance of admission at the only local hospital.	Interview	Incidence	≥15 g/day vs non-drinker	0.7 (0.5-1.1)	Age at first child, age at menarche, age at menopause, age-underlying cox models, BMI, educational level, height, HRT use, parity/pregnancies, physical activity, smoking habits	Mid-points of exposure categories
Goodman, 1997 BRE03352 Japan	LSS, Prospective cohort, W	127/ 22 200 8.31 years	Medical Records and death certificates	Questionnaire	Incidence	≥55 ml/week vs never drinkers	0.68 (0.32-1.46) ptrend: 0.27	Age, other age indicator, other specified factor, place of residence	Ethanol intake in ml/week converted to g/day (x 0.789)
Byrne, 1996 BRE05719 USA	NHANESI/ NHEFS, Prospective cohort, age: 25-74 years, W	52/ 6 156 3.9 years	Hospital records and death certificates	FFQ	Incidence	>7 vs 0 drinks/week	1.4 (0.6-3.2)	Age	Intake in drinks/week converted to g ethanol/day using 12.5g ethanol per drink, mid-points of exposure categories
Fuchs, 1995 BRE15082 USA	NHS I, Prospective cohort, age: 34-59 years, W	350/ 85 709 12 years	National death indexes, report from family members and postal authorities	FFQ-semi-quantitative	Mortality	≥30 vs 0 g/day	1.67 (1.1-2.53)	Age, BMI, diseases (not breast), diseases (not breast), diseases (not breast), HRT use, leisure time physical activity,	Mid-points of exposure categories

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								menopausal status, nutrients, nutrients, OC use, other specified factor, smoking habits	

*Studies in postmenopausal women only.

Table 256 Alcohol intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Fagherazzi, 2015 BRE80543 France	E3N EPIC-France, Prospective cohort, age: 40-65 years, W	2 812/ 16 years	Questionnaire and death certificate	Validated FFQ	Incidence	≥2 drinks/day vs non-alcohol-consumer	1.19 (1.04-1.36)	Age, age at first child, age at menarche, age at menopause, BMI, breastfeeding, educational level, family history of breast cancer, history of benign breast disease, mammography, menopausal women and	Excluded, EPIC component study, Romieu, 2015 used instead

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								use of MHT, parity, physical activity, use of HRT, use of oral contraceptives, use of progestagens in premenopause	
Klatsky, 2015 BRE80587 USA	KPMCP, Prospective cohort, W	3 639/ 69 153 17.8 years	Cancer registry	Questionnaire	Incidence	≥3 vs 0 drinks/day	1.3 (1.1-1.5)	Age, BMI, educational level, marital status, race/ethnicity, smoking	Excluded, no data, used in the HvL only and Li, 2009 used in dose-response analysis
Makarem, 2015 BRE80589 USA	FHS - Offspring Cohort, Prospective cohort, W	124/ 1 602 11.5 years	Death certificate and medical records	Semi-quantitative FFQ	Incidence	Per 1 points	0.51 (0.29-0.89)	Age, smoking status	Excluded, adherence to WCRF/AICR guideline on alcohol Zhang 1999 included
Catsburg, 2014a BRE80536 Canada	CNBSS, Prospective cohort, age: 40-59 years,	/ 48 840 16.6 years	Cancer registry	FFQ	Incidence	Adhered vs not adhered	0.9 (0.8-1.0)	Age, age at first child birth, age at menarche, BMI, energy,	Excluded, met ACS/WCRF guideline on alcohol intake Rohan 2000

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	W							family history of breast cancer, history of breast disease, HRT use, OC use, menopausal status, parity, physical activity, red and processed meat, sodium, study center, vegetable and fruit intake, whole grains	included
Klatsky, 2014 BRE80576 USA	KPMCP, Prospective cohort, W	3 200/ 70 906 18.2 years	Cancer registry	Questionnaire	Incidence	≥3 vs ≤0 drinks/day	1.35 (1.1-1.65)	Age, BMI, cigarette smoking, educational level, ethnicity, marital status	Superseded by Klatsky, 2015
Land, 2014 BRE80566 USA	NSABP, Prospective cohort, age: 54 years, W	395/ 13 388 7 years	Follow-up visits	Questionnaire	Incidence	≥1.1 vs ≤0 drinks/day		Age, BMI, diabetes, estrogen use, gail model risk, leisure time physical	Excluded, no risk estimate (p=0.49 for difference between >1 vs 0-1 drink/day)

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								activity, menstrual status, race, smoking duration, smoking intensity, smoking status, treatment allocation	
Lin, 2013 BRE80465 USA	NHANES III, Prospective cohort, W	26/ 2 730 12.4 years	Cancer registry	FFQ and 24 hour recall	Mortality	Use vs no use	0.81 (0.17-3.89) ptrend: 0.79	Age, BMI, calories intake, race/ethnicity, smoking status, urinary cadmium, zinc	Excluded, only two levels of exposure, used in the HvL analysis
Link, 2013 BRE80489 USA	CTS, 1995, Prospective cohort, age: 50 years, W	4 140/ 91 779 14.1 years	Cancer registry	FFQ	Incidence	≥20 vs none	1.24 (1.11-1.38)	Age, age at menarche, BMI, energy intake, family history of breast cancer, height, history of benign breast disease, HRT use, menopausal	Excluded, only two levels of exposure, Horn-ross, 2002 used instead
		4 140/			Incidence	≥20 vs none	1.24 (1.11-1.38)		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								status, parity and age at first birth, physical activity, race/ethnicity, socioeconomic status	
Liu, 2013 BRE80495 USA	NHS II, Prospective cohort, age: 25-44 years, W	1 609/ 91 005 20 years	Self report verified by medical record	FFQ Cumulative average alcohol intake between menarche and first full-term pregnancy	Incidence	≥15 vs ≤0 g/day Per 10 g/day	1.34 (1.0-1.8) ptrend: 0.051 1.11 (1.0-1.23)	Age, age first child birth, age menarche, BMI, body size, duration breastfeeding, family history breast cancer, menopausal status, parity, HRT use	Excluded, alcohol intake between menarche and first full-term pregnancy
		1 135/		Cumulative average alcohol intake after first full-term pregnancy	Incidence	≥15 vs ≤0 g/day Per 10 g/day	1.21 (0.84-1.76) ptrend: 0.20 1.09 (0.96-1.23)		
Shen, 2013 BRE80499	CECS, Prospective	143/ 66 820	Hospital records and	Questionnaire	Mortality	<1 time/week vs	0.87 (0.45-1.67)	Age, BMI, educational	Excluded, only two

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
China	cohort, W	10.5 years	death register			never		level, exercise, health status, housing, monthly expenditure, smoking status	levels of exposure, used in the HvL analysis
Keogh, 2012 Pooled analysis		656/ 1905	Cancer registries	FFQs and 4- or 7-day diet diaries	Incidence, breast cancer risk	Per 10g/day	1.10 (1.02-1.19)	Age, parity, height, weight, MHT use, physical activity, total energy intake, folate intake, menopausal status, smoking, education level	Excluded, EPIC-Norfolk and EPIC-Oxford are superseded by EPIC and UKWCS and Whitehall II would only add 109 additional cases
	EPIC-Norfolk	353/1605					1.12 (1.01-1.24)		
	EPIC-Oxford	194/388					1.15 (0.95-1.38)		
	UKWCS	41/237					0.77 (0.46-1.30)		
	Whitehall II	68/331					1.05 (0.86-1.28)		
Lubinski, 2012 BRE80390	HBCCS, Prospective cohort, age: 25-65 years Subjects with BRCA1 mutation	130/ 1 477 4.3 years	Pathology	Questionnaire	Incidence	Yes vs no	0.92 (0.6-1.39) ptrend: 0.67	Age, contraception, family history of breast cancer, HRT use, oophorectomy /hysterectomy, smoking, Tamoxifen therapy	Excluded, only two levels of exposure, used in the HvL only

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Redaniel, 2012 BRE80428 UK	UKGPR, Prospective cohort, W	1 528/ 52 657	Medical record		Incidence	Current vs never	1.2 (0.91-1.59)	Age, period, region	Excluded, only two levels of exposure, used in the HvL only
Tamimi, 2012 USA	NHS I, Prospective Cohort, Age: 30-55 years, W, Registered nurses	1267/121 700	Self-report verified by medical records, death certificates	Questionnaire	Incidence, breast cancer luminal A	15+ vs none	1.30 (1.00-1.60) Ptrend:0.04	Age at menopause, family history of breast cancer, personal history of benign beast disease, BMI at age 18, weight change since age 18, age at menarche, parity or age at first birth, alcohol, menopausal status or PMH use, smoking	Dose-response meta-analysis by these cancer subtypes was not conducted
		321/			luminal B		(0.70-1.50)		
		113/			HER-2		1.40 (0.70-2.80)		
		226/			basal-like		0.80 (0.50-1.40)		
		95/			unclassified		0.80 (0.40-1.60)		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Schütze, 2011 BRE80372 France, Italy, Spain, UK, Netherlands, Greece, Germany, Sweden, Denmark	EPIC, Prospective cohort, age: 37-70 years, W	5 259/ 363 988 8.8 years	Self-report (provided evidence of treatment), medical records and pathology reports, national death index	Dietary questionnaire	Incidence	Per 12 g/day	1.05 (1.02-1.07)	Age at menarche, BMI, breastfeeding, contraception, educational level, nonalcohol energy intake, intakes of fish, fruits and vegetables, fibre, meat, HRT use, physical activity menopausal status, smoking	Superseded by Romieu, 2015
		256/			Incidence	Former vs never consumers	1.03 (0.88-1.2)		
Benzon Larsen s, 2010 BRE80302 Denmark	DCH, Nested case control, age: 50-64 years, W	809/ 1 618 13 years	Cancer registry	FFQ	Incidence	>30 g/day vs abstain	1.15 (0.6-2.24)	Age, age at first child birth, BMI, duration of HRT use, educational level, HRT use, menopausal status, NSAID	Excluded, EPIC component study, Romieu, 2015 used instead

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								use, parity	
Gibson, 2010 BRE80237 Philippines	CBET Manila, Nested case control, age: 48 years, W	123/ 1 101	Cancer registry	Questionnaire (general)	Incidence	Drinker vs non drinker	0.5 (0.2-1.5)	Age, age at first child birth, area of residence, date of enrolment, educational level, parity	Two categories
Trichopoulou, 2010 BRE80320 Greece	EPIC-Greece, Prospective cohort, age: 20-68 years,	240/ 9.8 years	Medical records and pathology reports	FFQ	Incidence	Per 5 g/day	0.99 (0.89-1.1)	Age, age at first child birth, age at menarche, age at menopause, BMI, educational level, energy intake, height, HRT use, menopausal status, metabolic equivalents, parity	Excluded, EPIC component study, Romieu, 2015 used instead
Key, 2009 BRE80560 UK	EPIC-Oxford, Prospective cohort, age: 20-89 years, W	734/ 40 476 12 years	National cancer registers	FFQ	Incidence	≥16 vs 1-7 g/day	1.2 (0.96-1.52)	Age-underlying cox models, method of recruitment, smoking	Excluded, EPIC component study, Romieu, 2015 used instead

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Pezzotti, 2009 BRE80348 USA	NHS II, Nested case control, W	1 242/ 32 826	Self-reported verified by medical record	FFQ	Incidence, a10398 carriers	Non-drinkers vs drinkers	0.96 (0.83-1.12)	Age, benign breast disease, blood draw visit, BMI, family history of breast cancer, fasting condition, menopausal status	Excluded, two categories
		319/			Incidence, g10398 carriers	Non-drinkers vs drinkers	1.52 (1.1-2.08)		
Pezzotti, 2009 BRE80349 USA	WHS, Nested case control, W	529/ 28 263	Self-reported verified by medical record	FFQ	Incidence, a10398 carriers	Non-drinkers vs drinkers	1.22 (0.95-1.57)	Age, benign breast disease, family history of breast cancer	Excluded, two categories
		148/			Incidence, g10398 carriers	Non-drinkers vs drinkers	0.96 (0.6-1.53)		
Wen, 2009 BRE80209 China	SWHS, Prospective cohort, age: 40-70 years, W	616/ 73 328 7.35 years	Cancer registry	Quantitative FFQ	Incidence	Ever drank alcohol vs never	1.15 (0.63-2.1)	Age, age at first child birth, age at menarche, age at menopause, anthropometry, benign breast disease, educational level, energy intake, family	Excluded, only two levels of exposure, used in the HvL only

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								history of cancer, HRT use, physical activity, smoking status	
Kabat, 2008 BRE80194 Canada	CNBSS, Prospective cohort, age: 40-59 years, W	2 491/ 49 654 16.4 years	Cancer registry	FFQ	Incidence	≥30 g/day vs nondrinker	1.17 (0.98-1.39) ptrend: 0.06	Age, age at menarche, BMI, breast biopsies, educational level, energy intake, family history of cancer, hormone use, menopausal status, OC use, pack-years of smoking, parity	Excluded: no cases or person years per category, Rohan, 2000a used instead
Ozasa, 2007 BRE80443 Japan	JACC, Prospective cohort, W	79/			Mortality	<54 ml/day vs rare/none	1.62 (0.9-2.91)	Age, area of study	Excluded, only 1 case in the third category (RR 3.44 (95% CI:0.47-25.1), used in the HvL analysis only

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Tjønneland, 2007 BRE80013 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective cohort, age: 35-70 years, W	4 291/ 274 688 6.4 years	Population cancer registries and other procedures	FFQ + recall	Incidence	>19 vs >0-1.5 g/day	1.13 (1.01-1.25)	Age at menarche, body weight, educational level, height, HRT use, menopausal status, OC use, parity/pregnancies, smoking habits (and supplements in folate analysis)	Superseded by Romieu, 2015
		711/			Folate intake <=200mcg/ day	Per 10 g/day	1.01 (0.96-1.07)		
		876/			Folate intake >200-<=300 mcg/day	Per 10 g/day	1.05 (1.01-1.11)		
		944/			Folate intake >300-<=400 mcg/day	Per 10 g/day	1.04 (1.0-1.09)		
		957/			Folate intake >400mcg/day	Per 10 g/day	1.02 (0.97-1.06)		
Limited to Denmark, Germany, France, Spain, Italy, and Greece						Intake in twenties per 10 g/day	0.99 (0.94-1.05)	Additionally adjusted for recent alcohol intake, mutually adjusted within the age groups	
						Intake in thirties per 10g/day	1.01 (0.95-1.08)		
Visvanathan, 2007 BRE80020 USA	CLUE II, Nested case control, age: 57 years,	262/	Cancer Registry	FFQ + questionnaire	Incidence	Drinkers vs non-drinkers	1.4 (0.97-2.03)	Age, menopausal status	Excluded, only two levels of exposure, Wu,
		44/			Incidence,	Drinkers vs	1.84 (0.75-		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	W				ER-	non-drinkers	4.51)		1999 used instead
		176/			Incidence, ER+,	Drinkers vs nondrinkers	1.47 (0.93-2.31)		
Baglietto, 2005 BRE21669 Australia	MCCS, Prospective cohort, age: 7-75 years, W	537/ 17 447 13 years	Medical Records	Questionnaire	Incidence	≥40 g/day vs abstainer	1.41 (0.9-2.23) ptrend: 0.29	Energy intake, nutrients	Superseded by Bassett, 2013
					Incidence, folate intake 200 mcg/day	≥40 g/day vs abstainer	2. (1.14-3.49)		
					Incidence, folate intake 330 mcg/day	≥40 g/day vs abstainer	1.08 (0.6-1.93)		
					Incidence, folate intake 400 mcg/day	≥40 g/day vs abstainer	0.77 (0.33-1.8)		
Mørch, 2005 BRE23480 Denmark	DNCS, Prospective cohort, W	/ 17 647 10 years		Questionnaire	Incidence	≥27 vs 1-3 drinks/week	1.62 (1.04-2.56)		Superseded by Mørch, 2007
Dumeaux, 2004 BRE14906 Norway	NOWAC, Prospective cohort, age: 30-70 years,	1 082/ 86 948 11 years	National Cancer registry	FFQ	Incidence	≥10 g/day vs none	1.69 (1.32-2.15) ptrend: 0.0001	Age, age at first child, age at menarche, BMI, duration of OC use,	Excluded, EPIC component study, Romieu, 2015

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	W							family history, HRT use, mammography, menopausal status, parity/pregnancies	used instead
Kilkkinen, 2004 BRE17698 Finland	Helsinki and Oulu, 1982, Nested case control, age: 25-74 years, W	/ 15 497 15 years	Finnish Cancer registry	Questionnaire	Incidence	(mean exposure)		Age, place of residence	Excluded, no risk estimate, only mean intakes
Rissanen, 2003 BRE17954 Finland	FMCHES, Nested case control, age: 18-89 years, W	/ 10 years			Incidence	(mean exposure)			Excluded, no risk estimate, only mean intakes
Zhang, 2003 BRE13958 USA	NHS I, Nested case control, age: 43-69 years, W	/ 32 826 40 years	By mail	FFQ-semi-quantitative	Incidence	(mean exposure)			Superseded, by Chen, 2010
Colditz, 2000 BRE19251 USA	NHS I, Prospective cohort,	/ 58 520 14 years	Self-reported diagnosis checked by	Questionnaire	Incidence	1 drink/day vs never	1.07 (1.0-1.13)	Age at first child, age at menarche, age	Superseded by Chen, 2010

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	age: 30-55 years, W		medical records.					at menopause, alcohol, benign breast disease, body weight, family history, height, HRT use, other menstrual characteristics	
Hines, 2000 BRE15364 USA	NHS I, Nested case control, age: 30-55 years, W	455/ 32 826 8 years	By mail and follow-up questionnaire	FFQ-semi-quantitative	Incidence	≥10 g/day vs none	1.1 (0.7-1.6) ptrend: 0.94	Age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, duration of HRT use, family history, parity/pregnancies	Superseded by Chen, 2011
Key, 1999 BRE04758 Japan	LSS, Prospective cohort, W	427/ 34 759 24 years	Population-based cancer registries in Hiroshima and Nagasaki	Questionnaire	Incidence	Drinker vs non drinker	0.96 (0.74-1.23)	Age, calendar year, other factors, other factors, place of residence	Excluded, only two levels of exposure, Goodman, 1997 used

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
									instead
Hoyer, 1998 BRE15433 Denmark	CCHS, Nested case control, W	237/ 7 712 17 years	Danish cancer registry	Questionnaire	Incidence	Every day vs never/hardly ever	1.6 (0.82-3.11) ptrend: 0.16	Alcohol, body weight, educational level, height, income, marital status, menopausal status, parity/pregnancies, physical activity, smoking habits	Excluded, intake categories are not quantified, used in HvL only
Thun, 1997 BRE12310 USA	CPS II, Prospective cohort, age: 30-104 years, W	691/ 251 420 9 years	Personal inquiries and linkage if National Death Index	Questionnaire	Mortality	≥4 drinks/day vs none	1. (0.7-1.4) ptrend: 0.02	Age, age at first child, age at menarche, age at menopause, BMI, breast diseases, educational level, ethnicity, family history, HRT use, nutrients, OC use, other specified	Superseded by Feigelson, 2001

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								factor, smoking habits	
Holmberg, 1995 BRE15392 Sweden	SMC, Nested case control, age: 40-74 years, W	276/	Surveillance of pathology, computerized registers of cancer diagnoses at screening centres.	FFQ	Incidence	≥2 g/day vs never	1.6 (1.0-2.4)	Age at first child, BMI, educational level, family history, parity/pregnancies	Excluded, extremely low alcohol intake (≥2 g/day in the highest category resulting in wide CIs (RR for 10g/day increment was 6.82 (95%ci: 1.35-34.35)
Friedenreich, 1993 BRE17508 Canada	CNBSS, Nested case control, W	519/ 5.5 years		FFQ	Incidence	≥30 g/day vs nondrinkers	1.22 (0.78-1.9) ptrend: 0.88	Age, energy intake, family history, menopausal status, other specified factor, parity/pregnancies, smoking habits	Superseded by Kabat, 2008
Giovannucci, 1993b BRE17530 USA	NHS I, Nested case control, age: 30-55	616/ 95 000 3 years	Medical record + Pathology report	FFQ-semi-quantitative	Incidence	≥30 vs 0 g/day	1.55 (1.01-2.39)	Age, age at first child, benign breast disease, BMI,	Superseded by Chen, 2011

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	years, W							family history, menopausal status, parity/pregnancies	
Hoyer, 1992 BRE04086 Denmark	Glostrup Population Studies, Prospective cohort, age: 30-80 years, W	/ 5 207 26 years	Direct contact at home	Questionnaire	Incidence	≥9 vs 0 drinks/week	0.8 (0.3-2.0) ptrend: >0.20		Excluded, unadjusted RR, no cases or person-years per category
Schatzkin, 1989 BRE18013 USA	FHS, Prospective cohort, age: 31-64 years, W	143/ 2 636 26 years	Medical history, a physical examination, and a series of laboratory tests.	Interview	Incidence	≥5 g/day vs none	0.6 (0.4-1.0) ptrend: 0.03	Age, BMI, educational level, height, menopausal status, parity/pregnancies, smoking habits	Superseded by Zhang, 1999b
Hiatt, 1988a BRE03888 USA	KPMCP, Case cohort,	303/ 6 years	Hospital discharge records	FFQ	Incidence	≥6 drinks/day vs never drinker	3.3 (1.18-9.28)	Age, BMI, ethnicity, smoking habits	Superseded by Li, 2009
Schatzkin, 1987 BRE18010 USA	NHEFS, Prospective cohort, age: 25-74	88/ 10 years	Medical records + Death certificate	24h recall	Incidence	≥5 vs ≤0 g/day	2.0 (1.09-3.67)	Age, age at first child, age at menarche, BMI,	Superseded by Byrne, 1996

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	years, W							educational level, family history, menopausal status, nutrients, parity/pregnancies	
Willett, 1987a BRE13441 USA	NHS, Prospective cohort, age: 34-59 years, W	601/ 89 538 4 years	Pathology report + Self-reported	FFQ-semi-quantitative	Incidence	≥15 g/day vs none	1.6 (1.3-2.0)	Age, age at first child, age at menarche, family history, menopausal status, parity/pregnancies	Superseded by Chen, 2011

Figure 317 RR estimates of breast cancer by levels of alcohol (as ethanol) intake

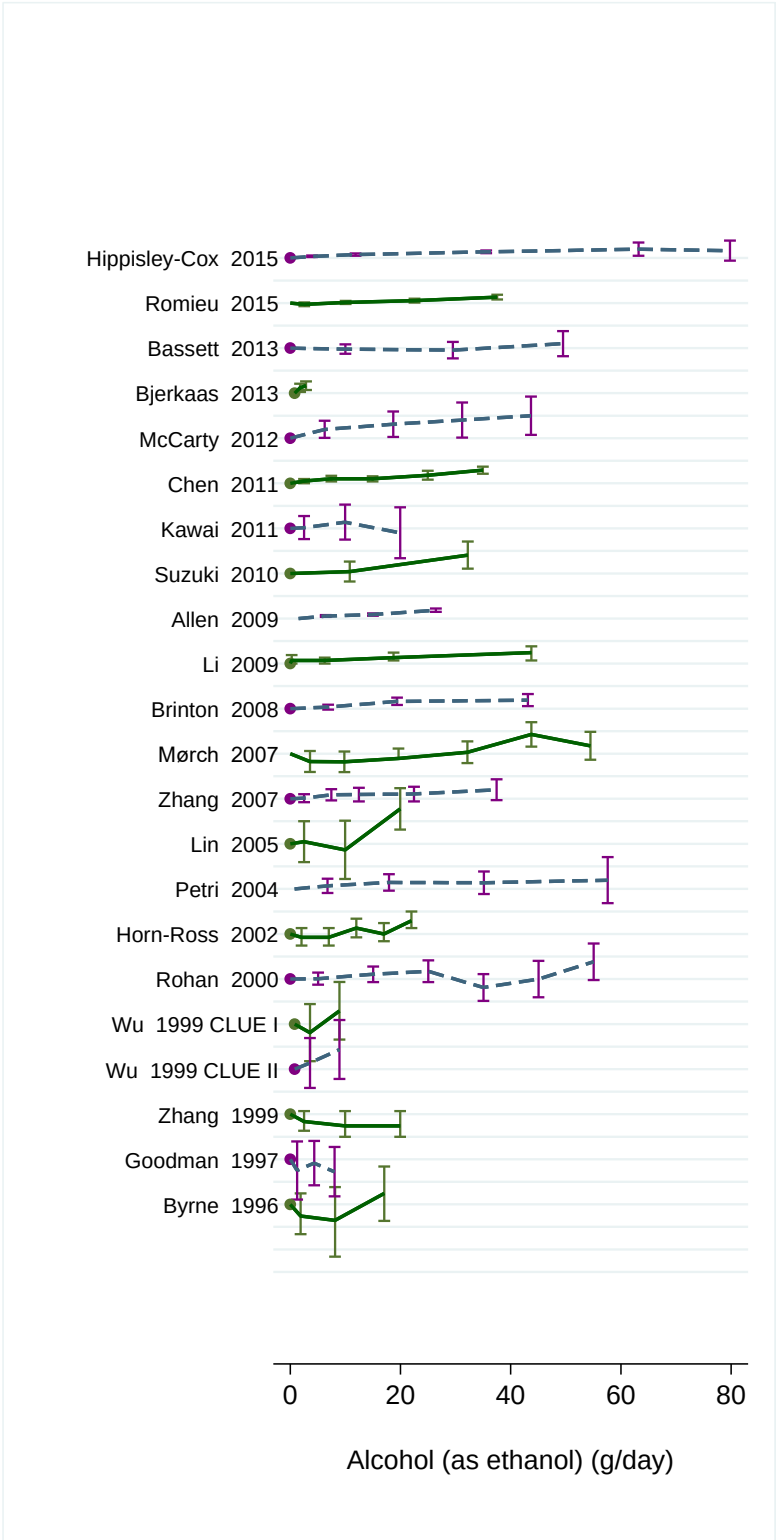
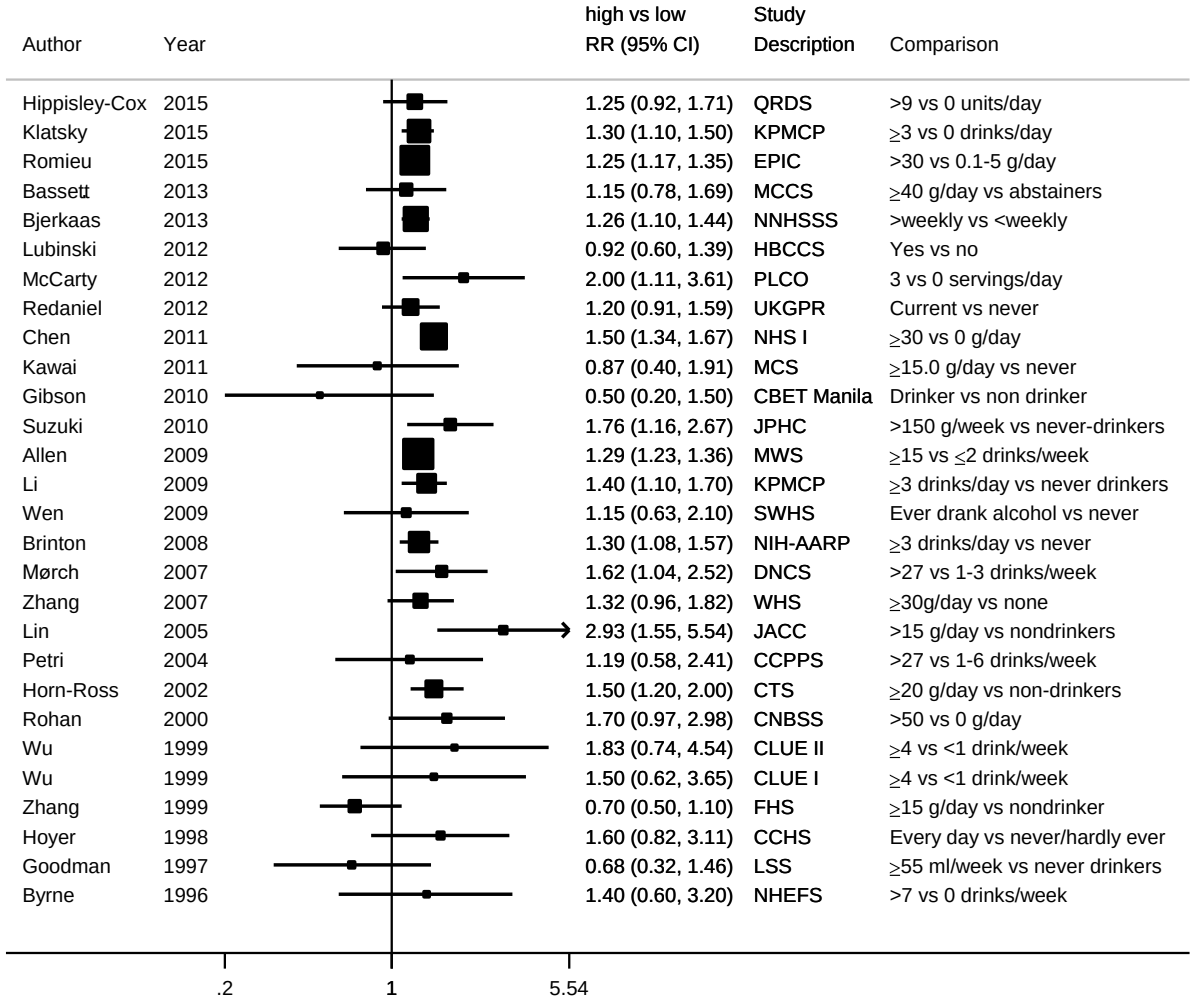


Figure 318 RR (95% CI) of breast cancer for the highest compared with the lowest level of alcohol as ethanol intake



Note: The Pooling Project (Jung, 2005) is not shown in the figure. The pooled multivariate relative risk for ≥30 g/day compared of non-drinkers was 1.32 (1.23-1.41).

Nine studies included in the Pooling Project that are not showed in the Figure:

Nurses' Health Study II (1331 cases, premenopausal), Prospective Study on Hormones, Diet and Breast Cancer (Italy) (283 cases), Beta-Carotene and Retinol Efficacy Trial (367 cases, postmenopausal), Breast Cancer Detection Demonstration Project Follow-up Study (1305 cases), Netherlands Cohort Study (2013 cases, postmenopausal), Cancer Prevention Study II Nutrition Cohort (2999 cases), New York University Women's Health Study (919 cases), Iowa Women's Health Study (1849 cases, postmenopausal), Women's Lifestyle and Health Study (Sweden) (1072 Cases)

The remaining 11 studies in the Pooling Project are in the figure.

Figure 319 Relative risk of breast cancer incidence for 10g/day increase of alcohol (as ethanol) intake. Studies identified in the CUP

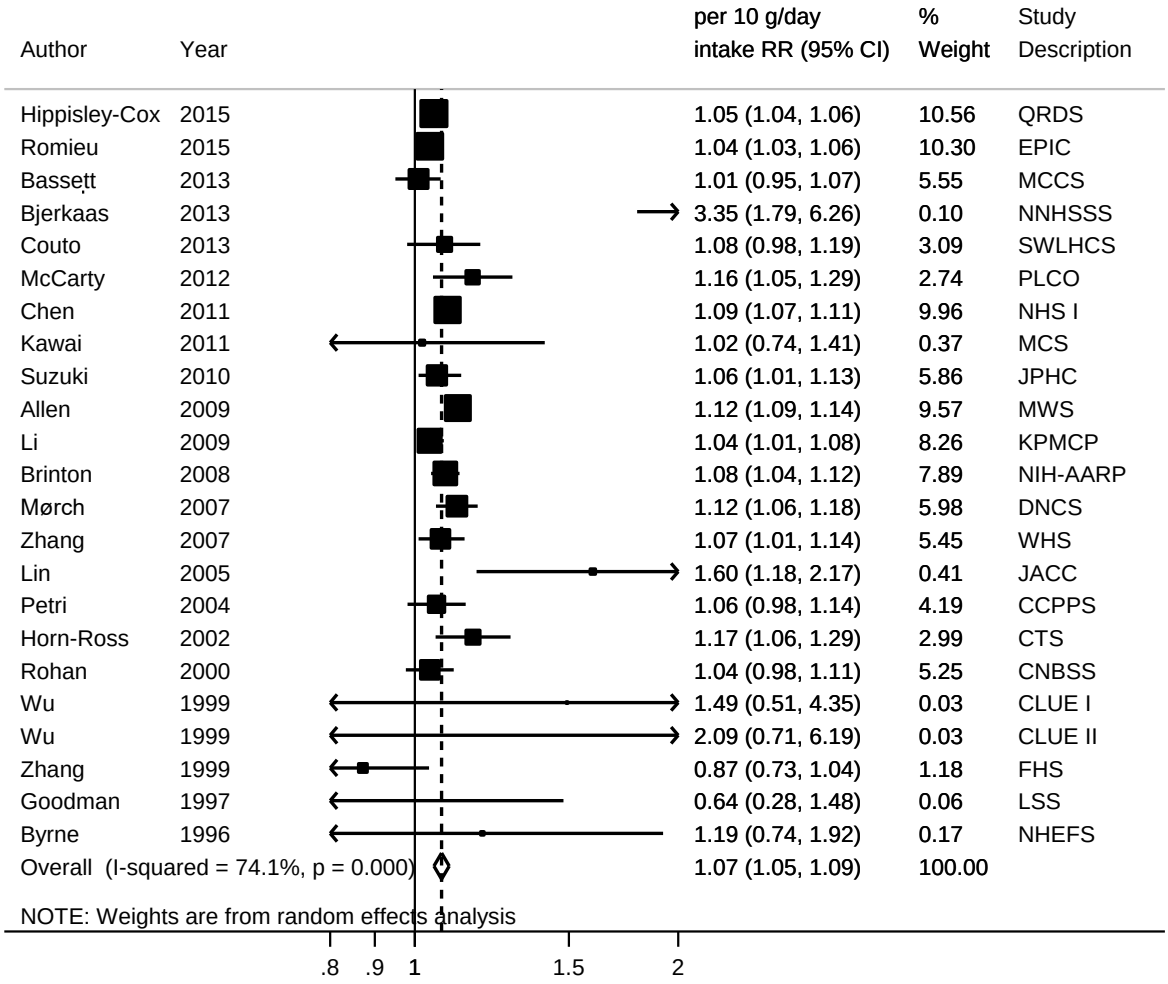
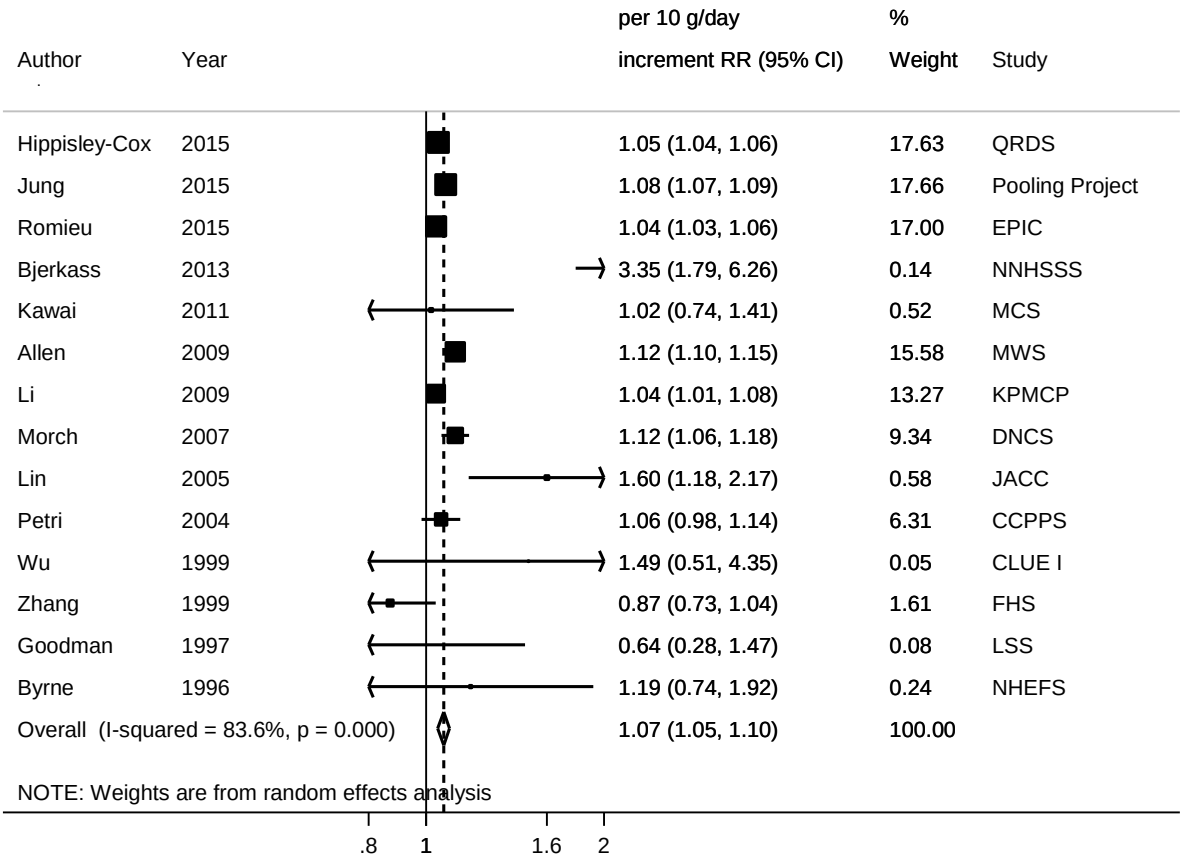


Figure 320 Relative risk of breast cancer incidence for 10g/day increase of alcohol (as ethanol) intake. Studies identified in the CUP and Pooling Project of Cohort Studies



Note: Five studies in the Pooling Project are only in postmenopausal women.

Figure 321 Relative risk of breast cancer and alcohol intake by hormone receptor status. Studies identified in the CUP and Pooling Project of Cohort Studies

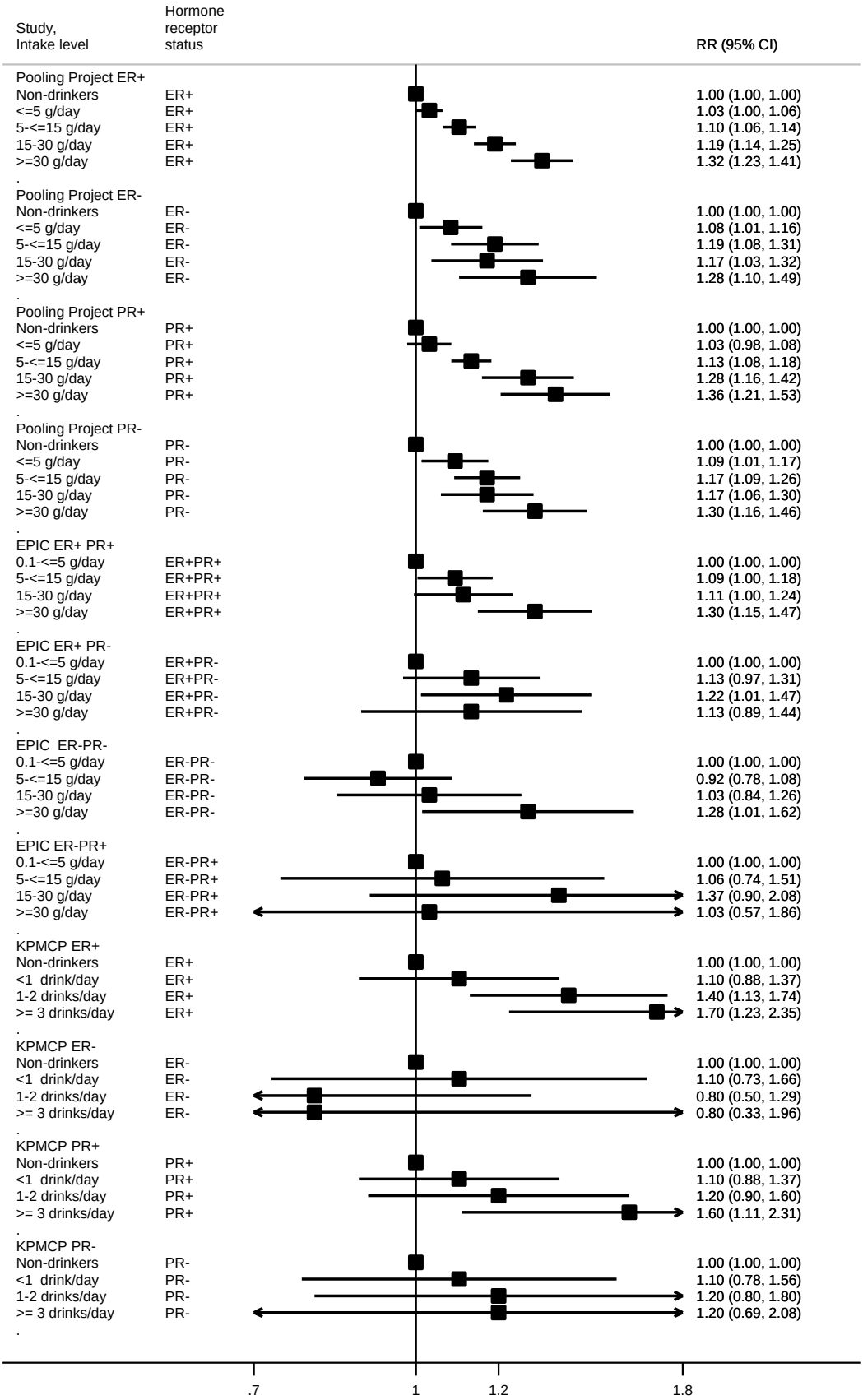


Figure 322 Funnel plot of studies identified in the CUP included in the dose response meta-analysis of alcohol and breast cancer

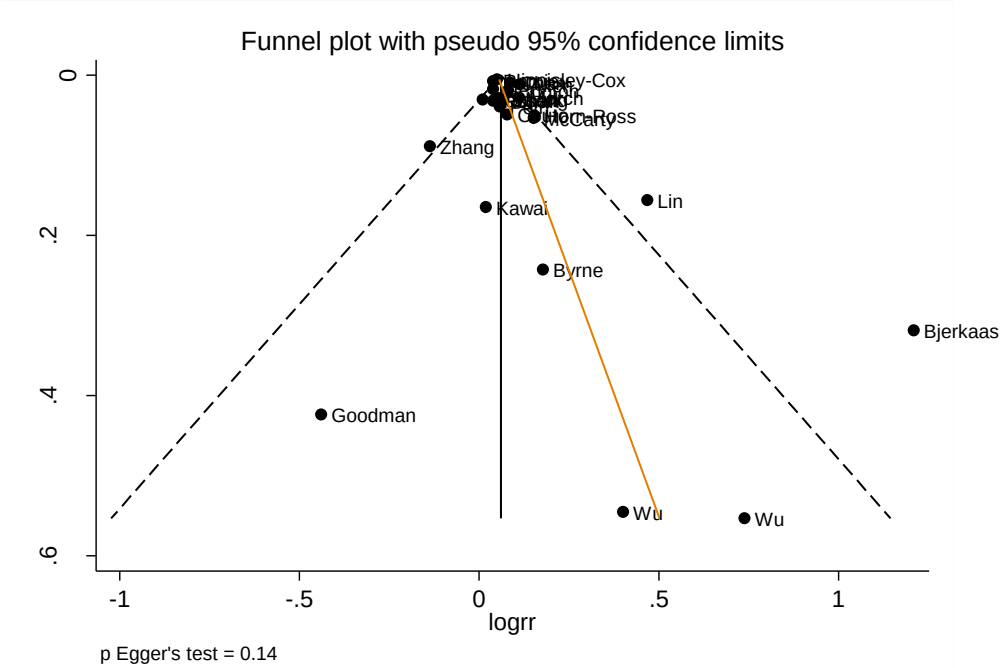
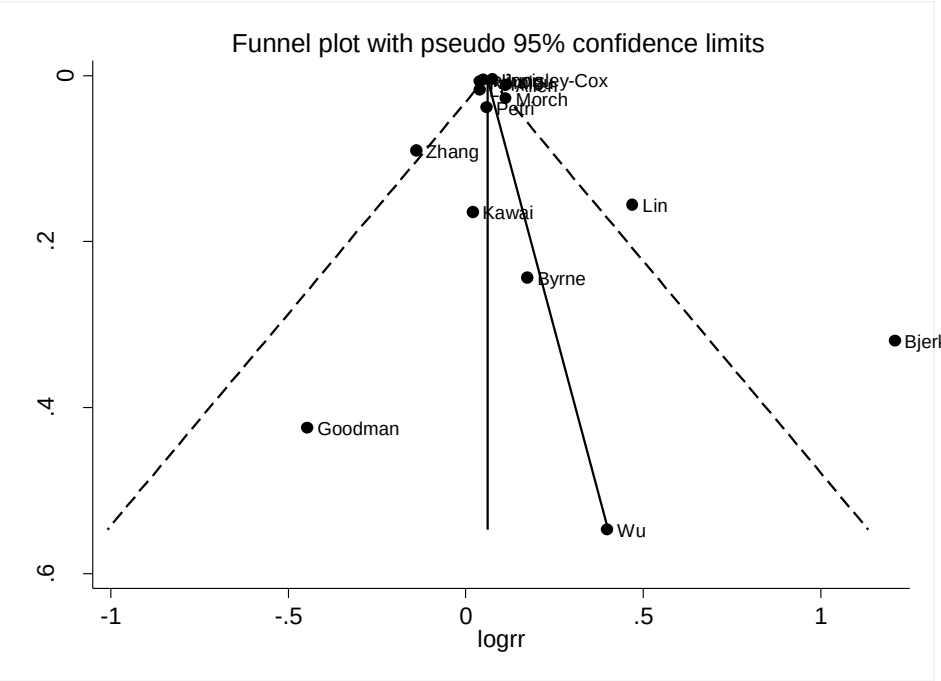


Figure 323 Funnel plot of Pooling Project and nonoverlapping studies identified in the CUP included in the dose response meta-analysis of alcohol and breast cancer



P Egger's test =0.478

Figure 324 Relative risk of breast cancer incidence for 10g/day increase of alcohol (as ethanol) intake, by geographic location

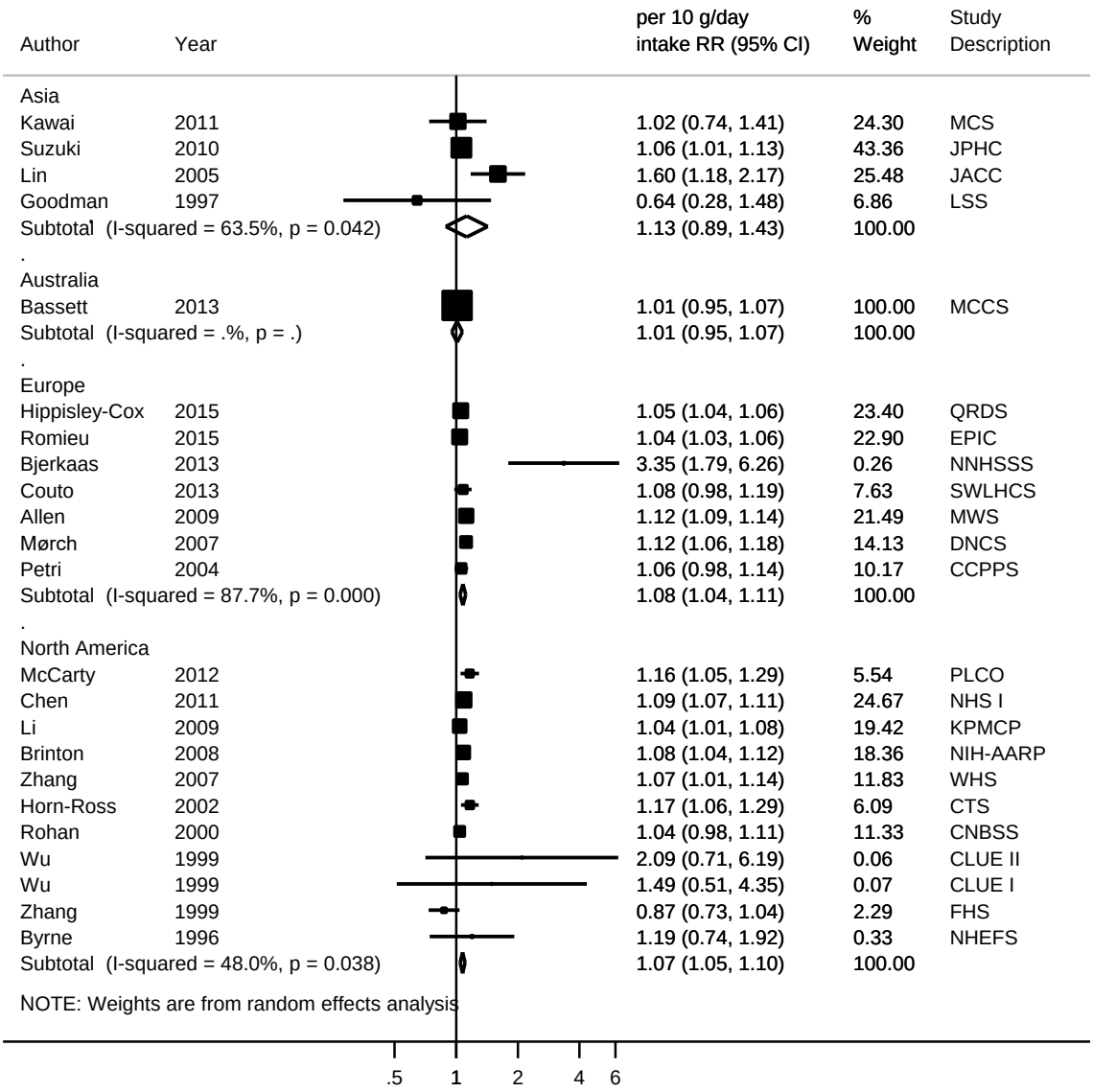


Figure 325 RR (95% CI) of breast cancer mortality for the highest compared with the lowest level of alcohol (as ethanol) intake

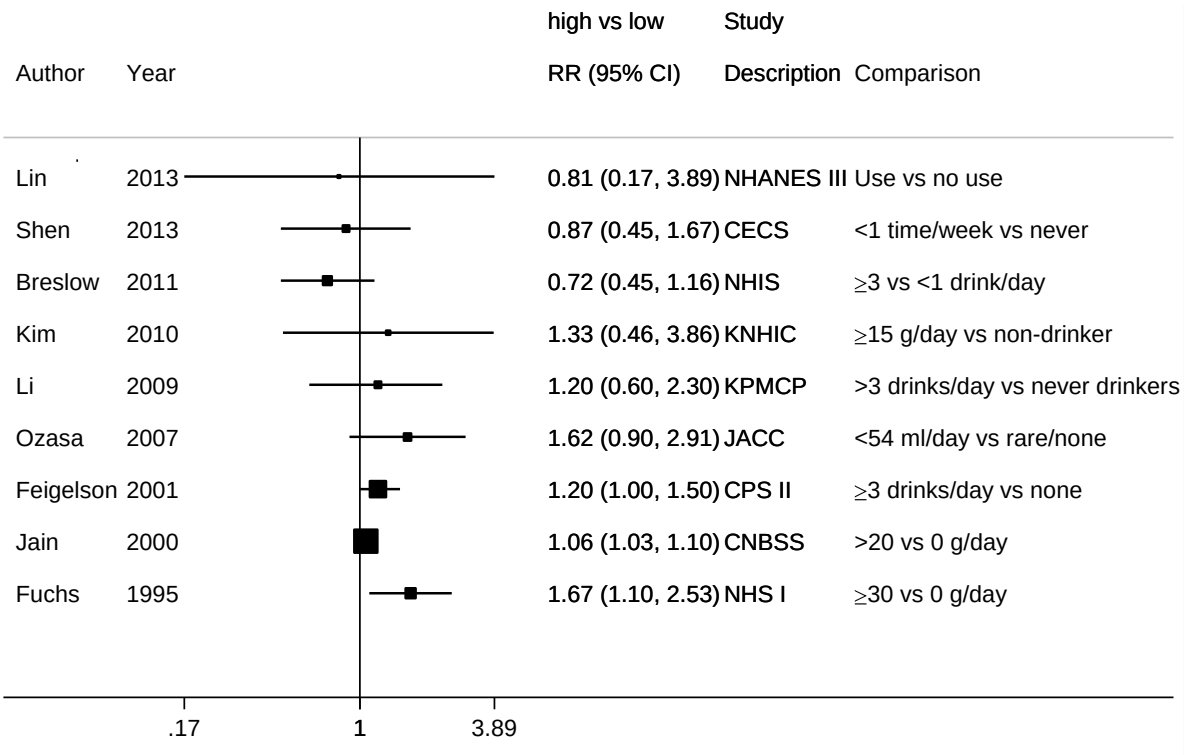


Figure 326 Relative risk of breast cancer mortality for 10g/day increase of alcohol (as ethanol) intake

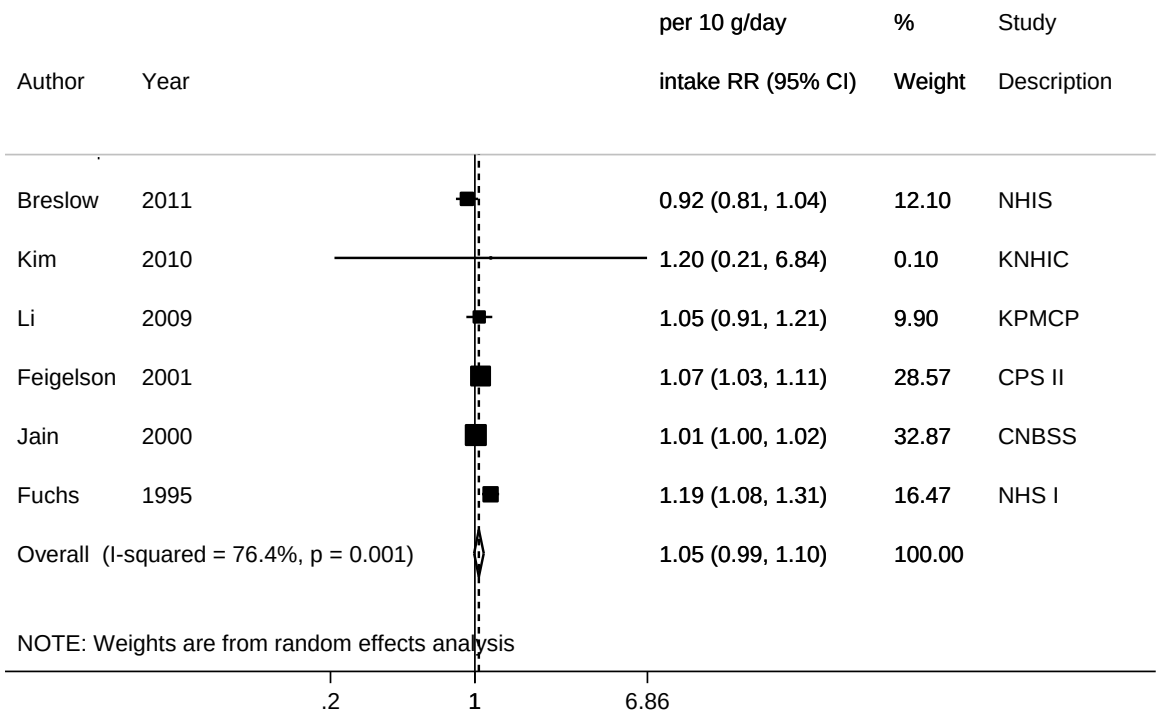
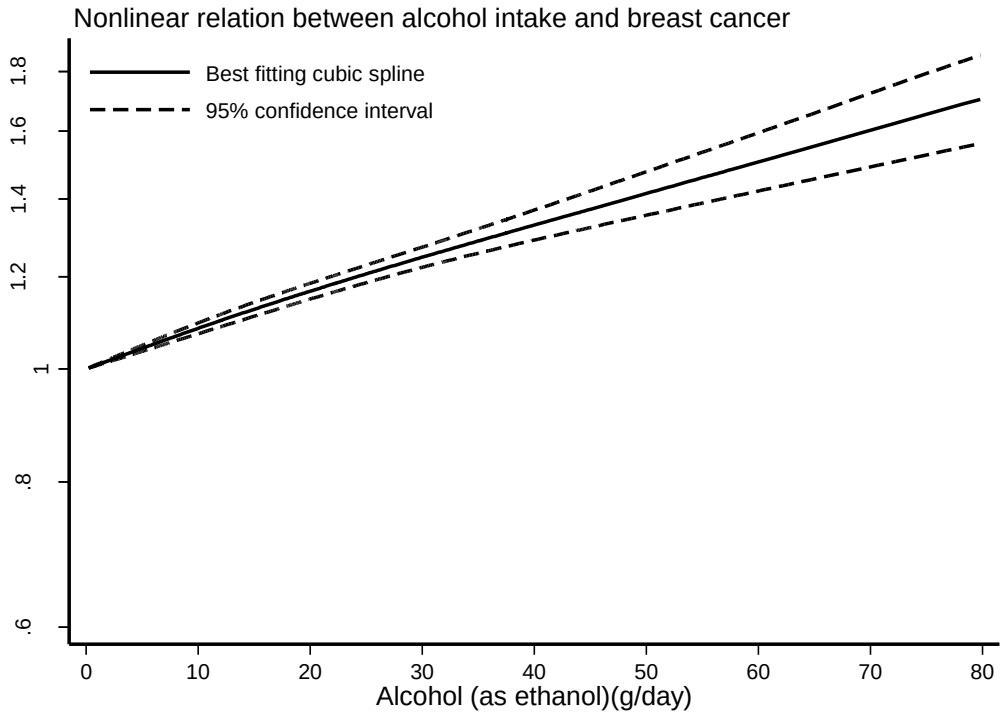


Figure 327 Nonlinear dose-response meta-analysis of alcohol (as ethanol) and breast cancer



P nonlinear= 0.12

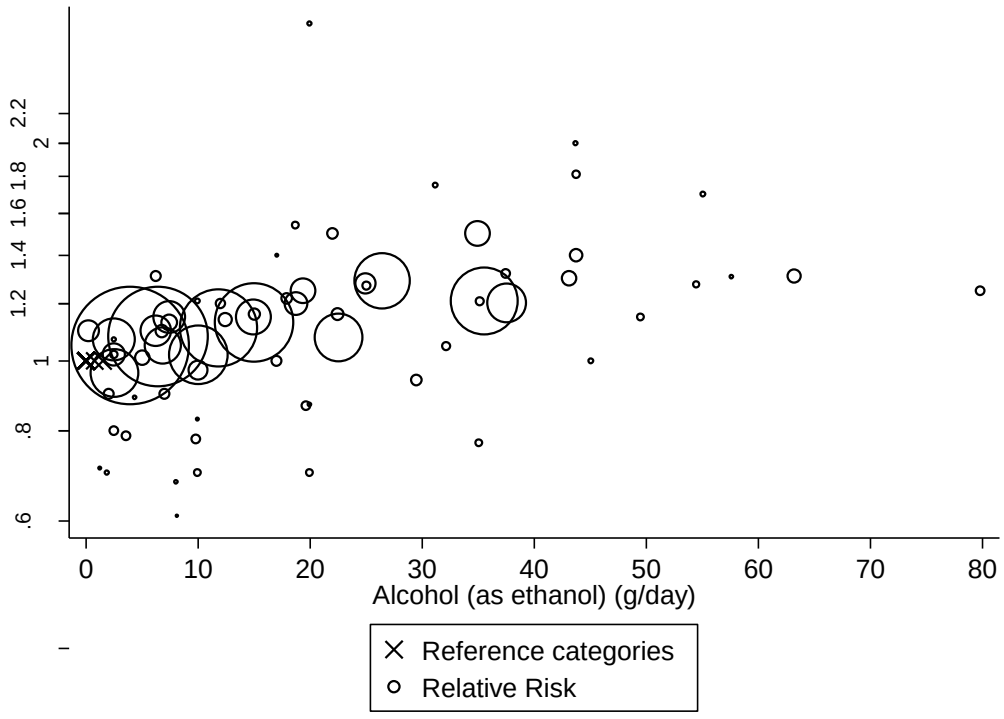


Table 257 Relative risk of breast cancer and alcohol (as ethanol) estimated using non-linear models

Alcohol (as ethanol) (g/day)	RR (95%CI)
0	1.00
2.5	1.02 (1.02-1.02)
5.1	1.04 (1.04-1.05)
10	1.08 (1.07-1.10)
15	1.13 (1.11-1.14)
22	1.18 (1.16-1.20)
31.2	1.26 (1.23-1.28)
43.8	1.36 (1.31-1.41)
55	1.46 (1.39-1.54)

Premenopausal breast cancer

Summary

Main results:

Ten studies (4 227 cases) (10 publications) were included in the dose-response meta-analysis. Alcohol intake was associated with a significantly higher risk of premenopausal breast cancer.

Three studies (Kawai, 2011, Visvanathan, 2007, Schatzkin, 1987) reported RRs for two levels of exposure and could only be used in the highest versus lowest analysis. Rissanen, 2003 reported only mean intakes and was excluded from the meta-analysis. Friedenreich, 1993 was superseded by Rohan, 2000a in the main analysis but used in the non-linear meta-analysis.

No heterogeneity was observed. There was no evidence of a significant publication or small study bias.

No meta-analyses were identified.

Breast cancer risk and alcohol intake by hormone receptor status:

One study (JPHC) investigated the association of alcohol intake and premenopausal breast cancer risk by tumour hormone receptor status (Suzuki, 2010). In this study, alcohol consumption was non-significantly positively associated with risk of ER^+ premenopausal breast cancer (63 cases).

In the Pooling project (Jung, 2015), alcohol consumption was nonsignificantly positively associated with risk of both ER^+ and ER^- premenopausal breast cancers (2 122 cases ER^+ and 843 ER^-).

Influence and stratified analyses:

In influence analysis including the Pooling project and no overlapping studies, the summary relative risk changed from 1.02 (95% CI, 0.98-1.05) when Petri, 2004 was excluded to 1.05 (0.98-1.13) when Fagherazzi, 2015 was excluded.

Study quality:

Reference category included intake of ≥0 g/day in one study (Petri, 2004). Continuous RR estimate reported in Rohan, 2000a study was restricted to drinkers only. Former/past drinkers were excluded from the reference category in Suzuki, 2010 study and unspecified in all remaining studies.

Table 258 Alcohol (as ethanol) intake and premenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	16 (17 publications)
Studies included in forest plot of highest compared with lowest exposure	9 (9 publications)
Studies included in linear dose-response meta-analysis	10 (10 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Note: Identified studies include two publications (one new cohort study) that reported on mortality and were excluded from the main analysis.

Table 259 Alcohol (as ethanol) intake and premenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR	**CUP**	**Pooling Project and CUP**
Increment unit used	10 g/day	10 g/day	10 g/day
Studies (n)	5	10	18
Cases	N/A	4 227	4 426
RR (95%CI)	1.09 (1.01-1.17)	1.05 (1.02-1.08)	1.03 (0.99-1.07)
Heterogeneity (I^2, p-value)	67%	0%, 0.74	19%, 0.30
Stratified analyses in CUP SLR			
Geographic area	**Asia**	**Europe**	**North America**

Studies (n)	1	4	5
RR (95%CI)	1.05 (0.97-1.13)	1.04 (0.98-1.11)	1.07 (1.02-1.12)
Heterogeneity (I^2, p-value)	-	26%, 0.26	0%, 0.98
Adjustment for age, BMI and reproductive factors	**Adjusted**	**Not adjusted**	
Studies (n)	9	1*	
RR (95%CI)	1.04 (1.01-1.08)	1.15 (1.01-1.31)	
Heterogeneity (I^2, p-value)	0%, 0.85	-	

*One study (Petri, 2004) was unadjusted for BMI.

Table 260 Alcohol intake and premenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Fagherazzi, 2015 BRE80543 France	E3N EPIC-France, Prospective cohort, age: 40-65 years, W	507/ 16 years	Questionnaire and death certificate	Validated FFQ	Incidence	≥2 drinks/day vs non-alcohol-consumer	0.95 (0.68-1.32)	Age, age at first child, age at menarche, age at menopause, BMI, breastfeeding, educational level, family history of breast cancer, history of benign breast disease, mammography, menopausal women and use of MHT, parity, physical activity, use of oral contraceptives, use of progestagens in premenopause	Intake in drinks converted to g/ethanol using 10g ethanol/drink, distribution of person-years by exposure categories, mid-points of exposure categories

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Jung, 2015 North America, Europe, Asia, Australia	15 cohorts: BCDDP CTS CNBSS CPS II CLUE II JPHC I MCCS MEC NYUWHS NHS (a) NHS (b) NHS II Prospective Study on Hormones, Diet and Breast Cancer (Italy) SMC WHS SWLHCS	3 730, 6 to 18 years maximum follow-up	Variable in each cohort	Questionnaires	Incidence	10 g/day increase	1.03 (0.99-1.08)	Age, energy intake, ethnicity, education, BMI, height, physical activity, smoking status, age at menarche, parity and age at first birth, oral contraceptive use, family history of breast cancer, personal history of benign breast disease	None 899

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Couto, 2013 BRE80454 Sweden	SWLHCS, Prospective cohort, age: 30-49 years, W	736/ 16 years	Cancer registry	FFQ	Incidence	Per 5 g/day	1.03 (0.98-1.09)	Age at first child birth, age at menarche, benign breast disease, beverage intake, cereal, dairy products consumption, educational level, egg, energy intake, fish, fruits intake, height, history of breast cancer, legumes, meat, number of childbirths, potatoes, ratio unsat/sat fat, smoking, sweet products, vegetable	RR rescaled for an increment of 10g/day
Chen, 2011 BRE80397 USA	NHS I, Prospective cohort, age: 30-55 years, W	946/	Questionnaire, medical report and National Death Index	Semi-Quantitative FFQ	Incidence	≥30 vs 0 g/day	1.3 (0.92-1.82)		Mid-points of exposure categories
Suzuki, 2010 BRE80275 Japan	JPHC, Prospective cohort,	194/ 13.8 years	Cancer registry	FFQ	Incidence	Per 10 g/day	1.05 (0.98-1.14)	Age, area of residence, BMI, height,	(nothing estimated for the main

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
	age: 40-69 years, W							leisure time physical activity, nutrients, smoking habits	analysis)
					Incidence,	>150 g/week vs never-drinkers	1.78 (1.09-2.9)		
		63/			Incidence, ER+	Per 10 g/day	1.06 (0.92-1.21)		
Trichopoulou, 2010 BRE80320 Greece	EPIC-Greece, Prospective cohort, age: 20-68 years,	113/ 9.8 years	Medical records and pathology reports	FFQ	Incidence	Per 5 g/day	0.98 (0.85-1.13)	Age, age at menarche, BMI, educational level, energy intake, height, metabolic equivalents, parity	RR rescaled for an increment of 10g/day
Zhang, 2007 BRE20023 USA	WHS, Prospective cohort, age: 55 years,	362/ 10 years	Medical notes	FFQ + questionnaire	Incidence	Per 10 g/day	1.08 (0.96-1.22)	Age, age at first child, age at menarche, benign breast disease, BMI, energy intake, family history, parity/pregnancies, physical activity, randomized treatment assignment,	(nothing estimated in the main analysis)

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								supplements	
Horn-Ross, 2004 BRE15413 USA	CTS, Prospective cohort, W	295/ 5 years	CCR and SEER records	FFQ	Incidence	≥20 g/day vs nondrinkers	1.21 (0.76-1.92)	Age, age at menarche, BMI, energy intake, ethnicity, family history, other reproductive index, physical activity	Mid-points of exposure categories
	>22 years at baseline						0.62 (0.34-1.13)		
Petri, 2004 BRE16325 Denmark	CCPPS, Prospective cohort, age: 20-91 years, W	76/	Danish Cancer Registry	Questionnaire	Incidence	>27 vs 1-6 drinks/week	3.49 (1.36-8.99)	Age, HRT use, other design issue, parity/pregnancies	Reference category changed using Hamling's method, intake in drinks/week converted to ethanol g/day, mid points of intake categories.
Feigelson, 2001 BRE19514 USA, Puerto Rico	CPS II, Prospective cohort, W	365/ 14 years	Medical Records	Questionnaire	Mortality	≥3 drinks/day vs none	1.1 (0.74-1.6) ptrend: 0.37	Age, age at first child, age at menarche, age at menopause, BMI, educational level, ethnicity,	Intake in drinks converted to g ethanol using 12.5g/ethanol per drink, mid-points of exposure categories

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								family history, food, height, HRT use, other specified factor, physical activity, smoking habits, supplements	
Jain, 2000 BRE17653 Canada	CNBSS, Prospective cohort, age: 40-59 years, W	76/ 10.3 years	National Mortality Database	FFQ-quantitative	Mortality	Per 10 g/day	1.018 (1.007-1.029)	Age, age at menarche, BMI, educational level, energy intake, family history, mammography, OC use, other specified factor, parity/pregnancies, recruitment center, smoking habits	(nothing estimated in the main analysis)
Rohan, 2000a BRE16489 Canada	CNBSS, Case cohort, age: 40-59 years, W	598/ 10 years	National Mortality Database and Canadian Cancer database	FFQ-quantitative	Incidence	Per 10 g/day	1.06 (0.97-1.15)	Age, age at menarche, energy intake, family history, other design issue, other specified factor,	(nothing estimated in the main analysis). Friedenreich, 1993 included in the figure of individual

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								parity/pregnancies, recruitment center, RR remained similar after adjustment for Quetelet's index	dose-response results.
Garland, 1999 BRE19618 USA	NHS II, Prospective cohort, age: 25-42 years, W	400/ 116 671 6 years	By family members, postal service and are detected by a search of the National Death Index	Questionnaire	Incidence	>20 g/day vs none	1.23 (0.68-2.21) ptrend: 0.85	Age, age at first child, age at menarche, benign breast disease, BMI, family history, menopausal status, parity/pregnancies	Mid-points of exposure categories

Table 261 Alcohol intake and premenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis.

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Kawai, 2011 BRE80305 Japan	MCS, Prospective cohort, age: 40-64 years, W	/ 12.8 years	Cancer registry	FFQ	Incidence	Current vs never drinkers	1.05 (0.7-1.56)	Age, age at menarche, age at menopause, BMI, educational level, energy-adjusted folate intake, energy-adjusted intake of fat, family history of breast cancer, occupation, parity, smoking, use of HRT, walking time	Excluded, only two levels of exposure, used in HvL analysis only
Visvanathan, 2007 BRE80020 USA	CLUE II, Nested case control, age: 57 years, W	41/	Pathology report + Cancer registry	FFQ + questionnaire	Incidence	Drinkers vs nondrinkers	2.69 (1.0-7.26)	Age, menopausal status	Excluded, only two levels of exposure, used in HvL analysis only
Rissanen, 2003 BRE17954 Finland	Mobile Clinic Health Examination Survey, 1973, Nested case control, age: 18-89 years,	/ 10 years	80% histology		Incidence	(mean exposure)			Excluded, no risk estimate, only mean intakes

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	W								
Friedenreich, 1993 BRE17508 Canada	CNBSS, Nested case control, W	235/ 5.5 years	All histology	FFQ	Incidence	≥30 g/day vs nondrinkers	1.88 (0.96-3.66) ptrend: 0.07	Age, energy intake, family history, parity/pregnancies, smoking habits	Superseded by Rohan, 2000a, used in non-linear analysis
Schatzkin, 1987 BRE18010 USA	NHEFS, Prospective cohort, age: 25-74 years, W	45/ 10 years	Medical records + Death certificate	24h recall	Incidence	Any drinking vs nondrinking	2.0 (1.0-3.8)	Age	Excluded, only two levels of exposure, used in HvL only

Figure 328 RR estimates of premenopausal breast cancer by levels of alcohol (as ethanol) intake

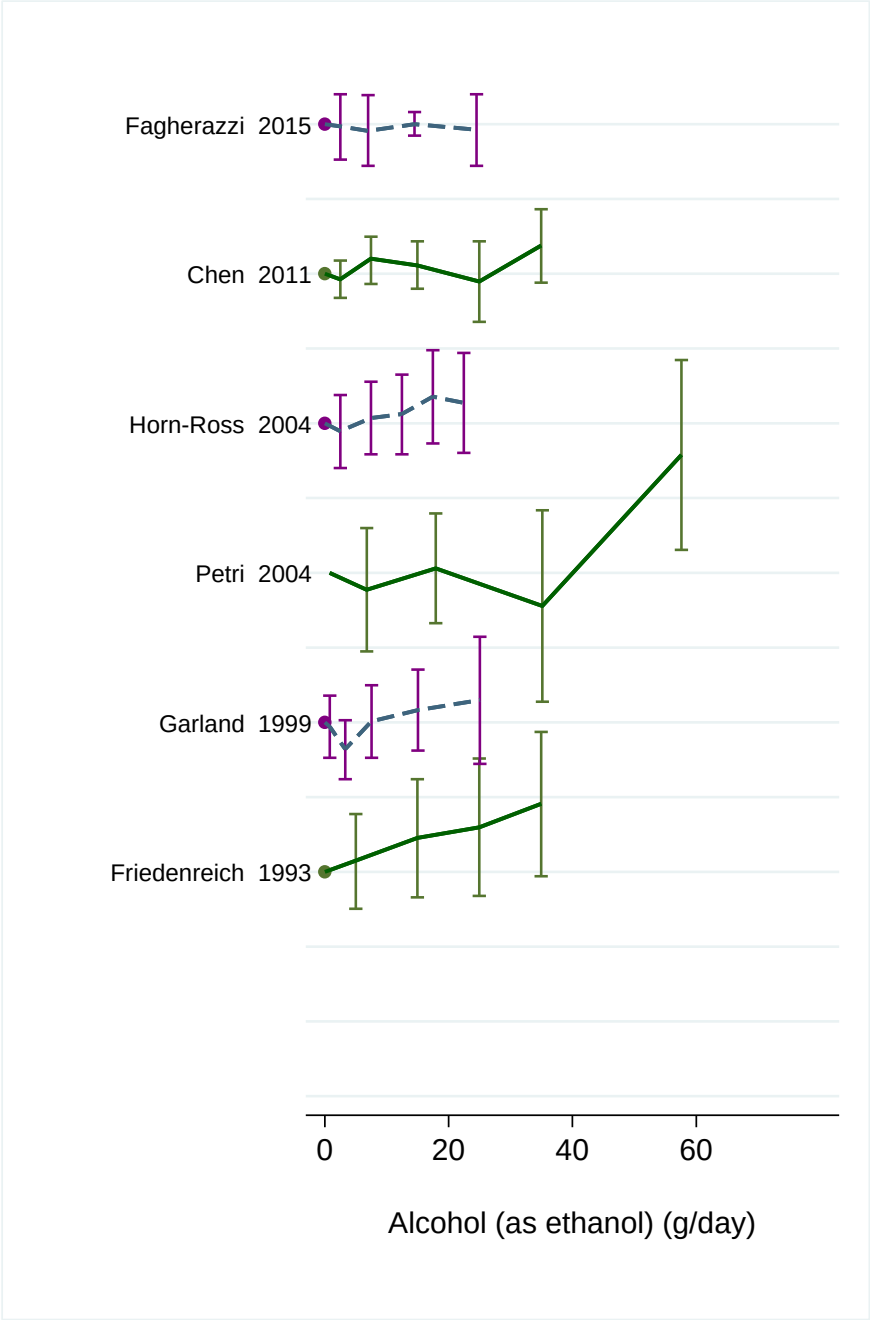


Figure 329 RR (95% CI) of premenopausal breast cancer for the highest compared with the lowest level of alcohol as ethanol intake

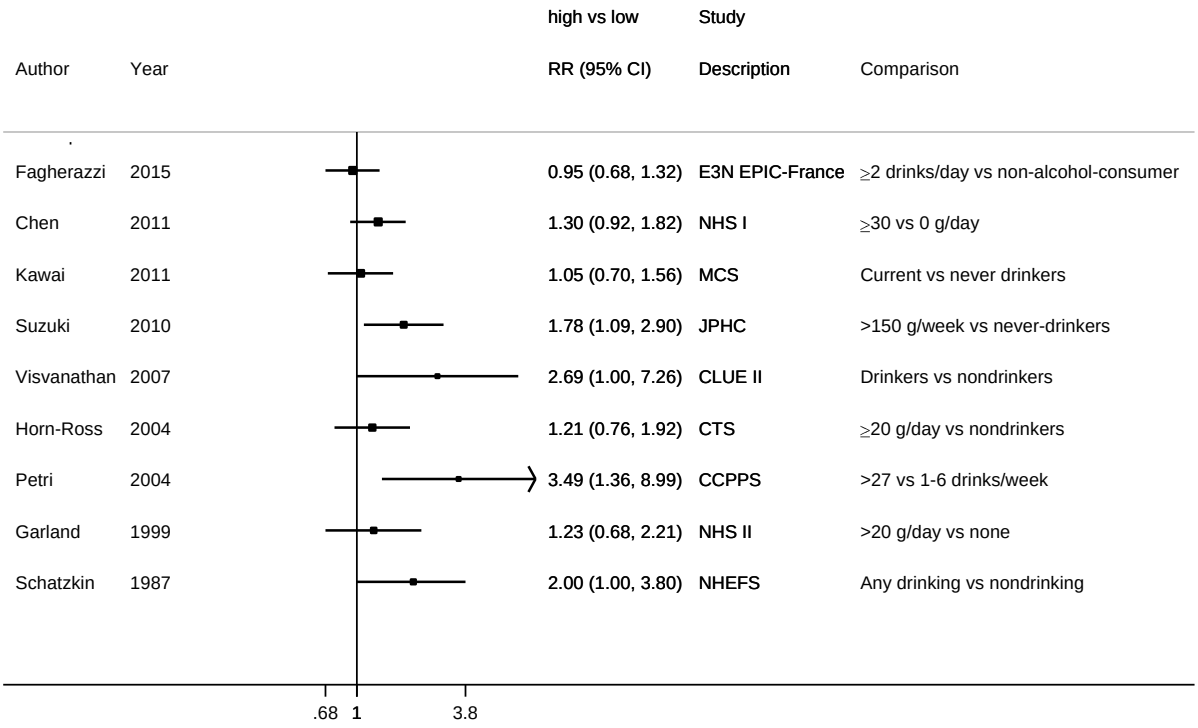


Figure 330 Relative risk of premenopausal breast cancer incidence for 10g/day increase of alcohol (as ethanol) intake

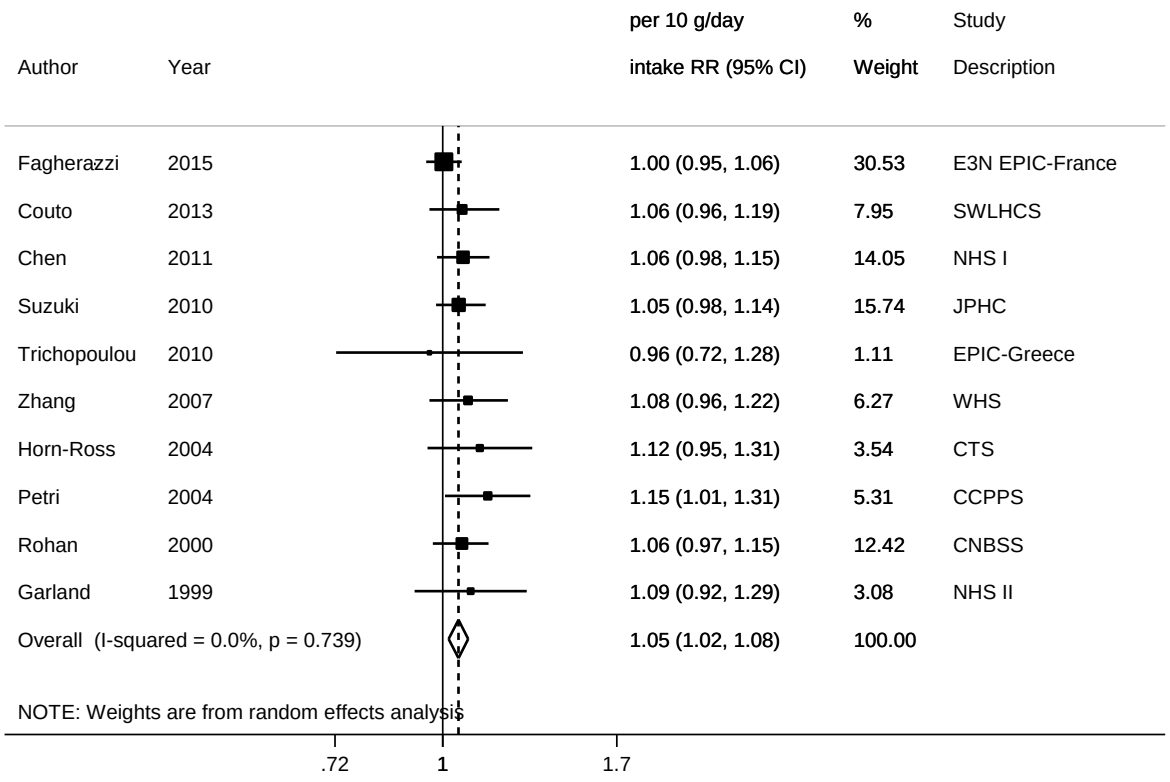


Figure 331 Relative risk of premenopausal breast cancer incidence for 10g/day increase of alcohol (as ethanol) intake. Studies identified in the CUP and Pooling Project of Cohort Studies

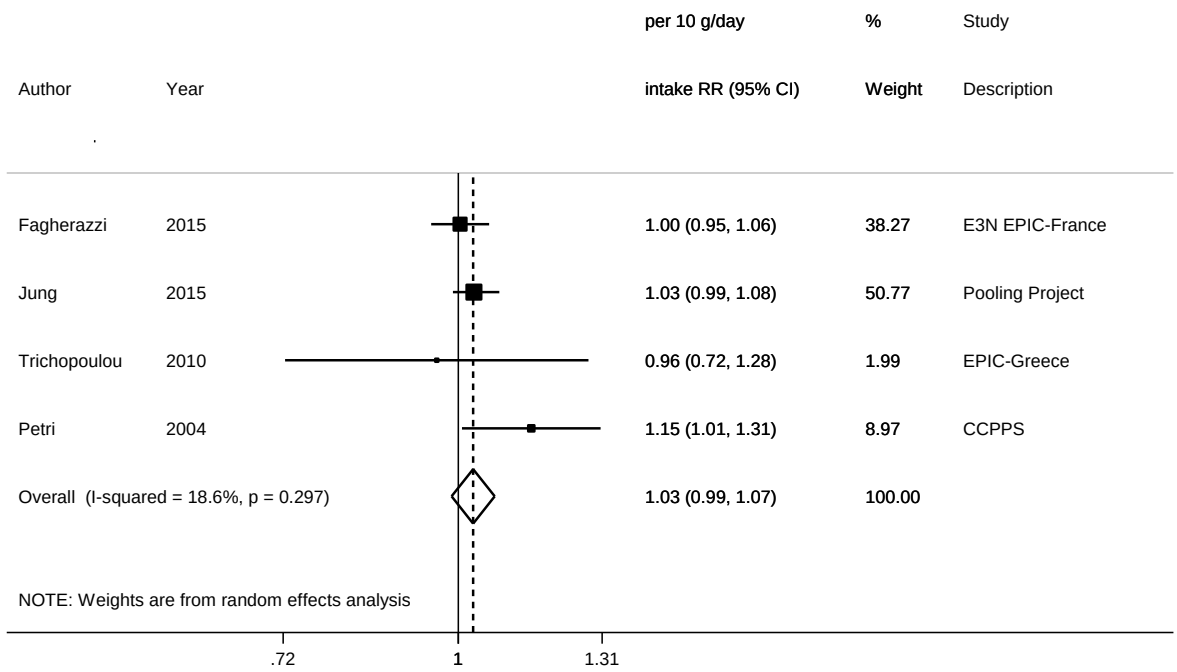


Figure 332 Funnel plot of studies included in the dose response meta-analysis of alcohol as ethanol and premenopausal breast cancer

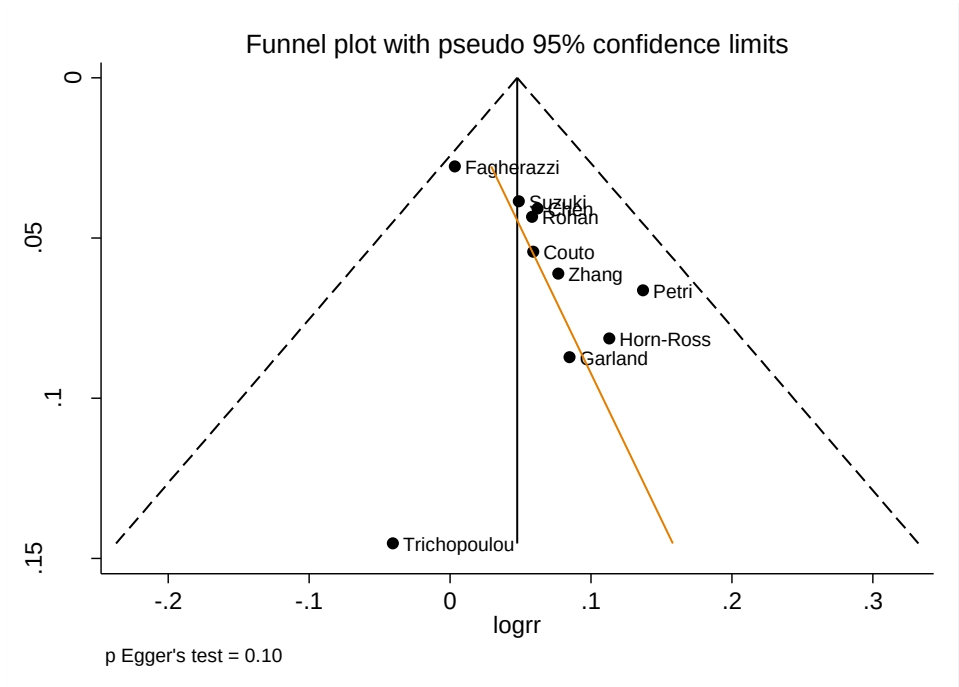
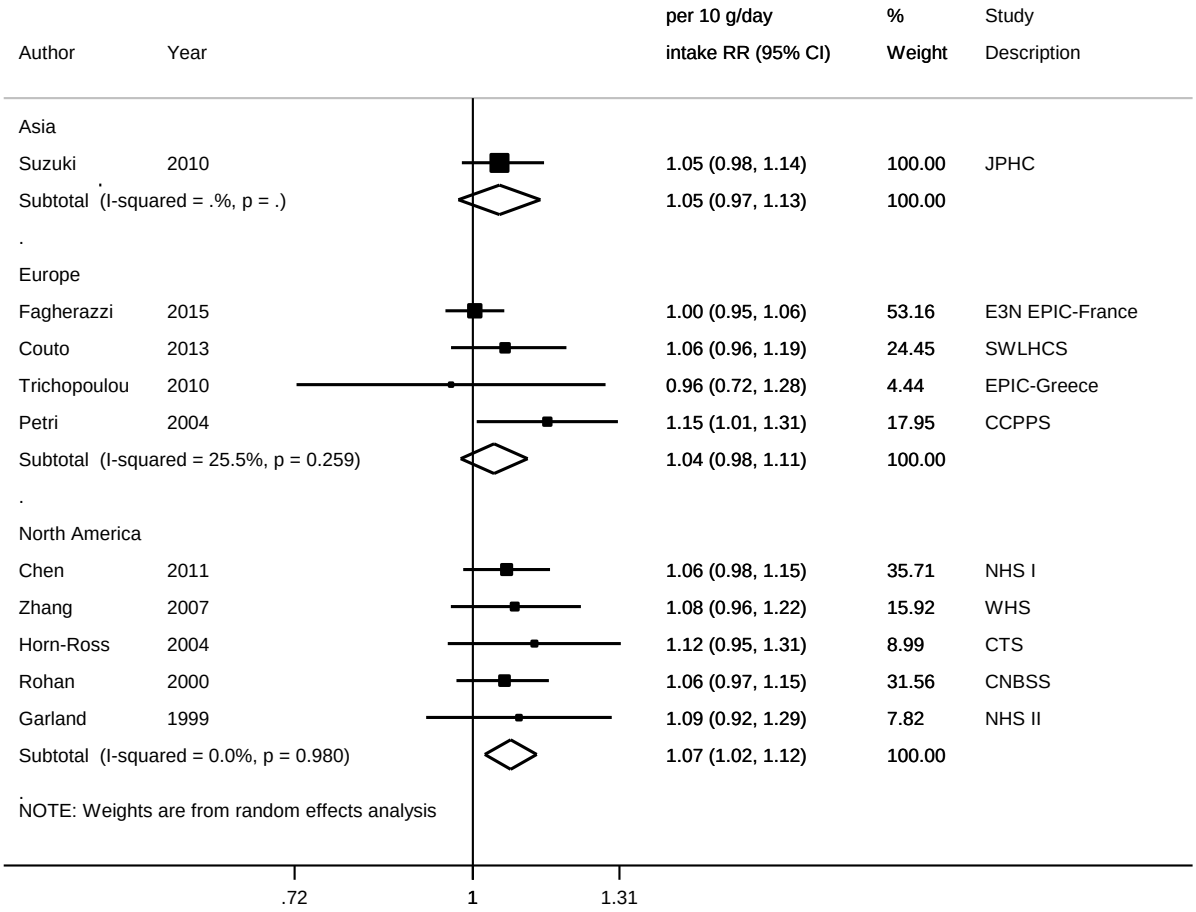


Figure 333 Relative risk of premenopausal breast cancer mortality for 10g/day increase of alcohol (as ethanol) intake, by geographic location



Postmenopausal breast cancer

Summary

Main results:

Twenty two studies (35 221 cases) (22 publications) were included in the dose-response meta-analysis. Alcohol intake was associated with a significantly higher risk of postmenopausal breast cancer.

Allen, 2009 reported stratified results by MHT use and was only included in the dose-response meta-analysis in MHT nonusers and current users of MHT. Chlebowski, 2007 by hormone receptor status (ER+, ER-) and could not be included in the main dose-response meta-analysis. Two studies (Rissanen, 2003, Pike, 2002) provided no measure of association, one study (Hiatt, 1988a) reported no cases or person-years per category and two publications that reported on cancer mortality (Feigelson, 2001, Jain, 2000) were excluded from the main meta-analysis. Three more studies (Kawai, 2011, Visvanathan, 2007, Schatzkin, 1987) examined only two categories of intake and were only used in the highest versus lowest analysis. All excluded studies reported positive associations that were statistically significant in one study (Hiatt, 1988a). Chlebowski, 2007 reported significantly positive association with postmenopausal ER+ breast cancer but not with ER-.

High heterogeneity was observed. There was evidence of a significant publication or small study bias.

Sensitivity and stratified analyses:

In influence analysis including the Pooling Project and no overlapping studies, the summary relative risk changed from 1.08 (95% CI, 1.04-1.13) when Sczaniecka, 2012 was excluded to 1.13 (1.07-1.20) when Fagherazzi, 2015 was excluded.

In stratified analysis, the association was similar comparing European and North American studies and only one study was conducted in Asia. Alcohol intake was positively associated with postmenopausal breast cancer for ER+ tumours but not statistically significant associated with ER-PR- tumours. Analysis stratified by menopausal hormone therapy use showed stronger of breast cancer and alcohol in women who were current users at baseline than in other subgroups.

Nonlinear dose-response meta-analysis:

There was no significant evidence of non-linear relationship (p=0.08). The dose-response is mainly driven by observations for intakes below 45 g/day. Only one data point was above that level (CCPPS) (see Figure).

Study quality:

Former/past drinkers were excluded from the reference category in four studies (Falk, 2014, Li, 2010, Suzuki, 2010, Sellers, 2004). Continuous RR estimate reported by Rohan, 2000a was restricted to drinkers only. All remaining studies did not specify if reference category included former/past drinkers. Reference category included intakes of ≥0 g/day in two studies (Sczaniecka, 2012, Petri, 2004).

Table 262 Alcohol (as ethanol) and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	41 (63 publications)
Studies included in forest plot of highest compared with lowest exposure	20 (20 publications)
Studies included in linear dose-response meta-analysis	22 (22 publications)
Studies included in non-linear dose-response meta-analysis	14 (14 publications)

Note: identified studies include two publications (no new cohort studies) that reported on mortality and were excluded from the main analysis.

Table 263 Alcohol (as ethanol) and postmenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2008 SLR and CUP SLR

	2008 SLR	CUP	Pooling Project and CUP
Increment unit used	10 g/day	10 g/day	10 g/day
Studies (n)	13	22	29
Cases	10 915	35 221	33 415
RR (95%CI)	1.08 (1.05-1.11)	1.09 (1.07-1.12)	1.11 (1.06-1.16)
Heterogeneity (I^2, p-value)	21%, 0.23	71%, <0.001	81%, <0.001
Stratified analyses in CUP SLR			
Geographic area	**Asia**	**Europe**	**North America**
Studies (n)	1	9	12
RR (95%CI)	1.01 (0.87-1.18)	1.08 (1.04-1.12)	1.11 (1.07-1.15)
Heterogeneity (I^2, p-value)	-	41%, 0.09	79%, <0.001
Adjustment for age, BMI and reproductive factors	**Adjusted**	**Not adjusted**	
Studies (n)	17	5	
RR (95%CI)	1.08 (1.05-1.10)	1.20 (1.07-1.35)	
Heterogeneity (I^2, p-value)	60%, 0.001	84%, <0.001	
Other analyses in CUP SLR			
	Ductal	**Lobular**	
Studies (n)	4	4	
Cases	12 053	2 254	
RR (95%CI)	1.09 (1.05-1.13)	1.15 (1.07-1.24)	
Heterogeneity (I^2, p-value)	50%, 0.11	46%, 0.14	
	-	-	
	ER+PR+	**ER+PR-**	**ER-PR-**
Studies (n)	6	5	6
RR (95%CI)	1.06 (1.03-1.09)	1.12 (1.01-1.24)	1.02 (0.98-1.06)
Heterogeneity (I^2, p-value)	61%, 0.03	76%, 0.002	10%, 0.35
	ER-PR+		
Studies (n)	1		

RR (95%CI)	0.90 (0.37-2.17)		
Heterogeneity (I^2, p-value)	-		
MHT use	**MHT current**	**MHT ever**	
Studies (n)	5	2	
RR (95%CI)	1.12 (1.09-1.16)	1.07 (0.98-1.18)	
Heterogeneity (I^2, p-value)	0%, 0.44	0%, 0.36	
	MHT former	**MHT never**	**MHT former/never**
Studies (n)	2	6	3
RR (95%CI)	1.07 (0.82-1.39)	1.04 (1.02-1.07)	1.12 (1.00-1.24)
Heterogeneity (I^2, p-value)	76%, 0.04	0%, 0.30	15.9%, 0.79

Table 264 Alcohol and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Fagherazzi, 2015 BRE80543 France	E3N EPIC-France, Prospective cohort, age: 40-65 years, W	2 305/ 16 years	Questionnaire and death certificate	Validated FFQ	Incidence	≥2 drinks/day vs non-alcohol-consumer	1.24 (1.07-1.44)	Age, age at first child, age at menarche, age at menopause, BMI, breastfeeding, educational level, family history of breast cancer, history of benign breast disease, mammography, menopausal women and use of MHT, parity, physical activity, use of HRT, use of oral contraceptives, use of progestagens in premenopausal	Intake in drinks converted to g/ethanol using 10g ethanol/drink, distribution of person-years by exposure categories, mid-points of exposure categories
		1 366/			Incidence, ER+PR+	≥2 drinks/day vs non-alcohol-consumer	1.32 (1.08-1.6)		
		365/			Incidence, ER-PR-	≥2 drinks/day vs non-alcohol-consumer	1.24 (0.87-1.78)		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
		978/			Incidence, non MHT users,	≥2 drinks/day vs non-alcohol-consumer	1.52 (1.21-1.92)		
		1 327/			Incidence, current MHT users,	≥2 drinks/day vs non-alcohol-consumer	1.07 (0.88-1.3)		
Jung, 2015 North America, Europe, Asia, Australia	20 cohorts:	25 411, 6 to 18 years maximum follow-up	Variable in each cohort	Questionnaires	Incidence	10 g/day increase	1.09 (1.07-1.11)	Age, energy intake, ethnicity, education, BMI, height, physical activity, smoking status, age at menarche, HRT, parity and age at first birth, oral contraceptive use, family history of breast cancer, personal history of benign breast disease	None
USA	CARET*	367/							
USA	BCDDP								
USA	CTS								
USA	CNBSS								
USA	CPS II								
USA	CLUE II								
USA	IWHS*	1 849/							
Japan	JPHC I								

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Australia	MCCS								
USA	MEC								
Europe	NLCS*	2013/							
USA	NYUWHS								
USA	NIH-AARP*	5 972/							
USA	NHS (a)								
USA	NHS (b)								
USA	NHS II								
Europe	Prospective Study on Hormones, Diet and Breast Cancer (Italy)								
USA	PLCO*	1 090/							
Europe	SMC								
USA	WHS								
Europe	SWLHCS								
Hippisley-Cox, 2015 BRE80584 England	QRDS, Prospective cohort, age: 25-84 years, W	41 315/ 2 495 899 15 years	Cancer registry/death certificates/ medical records	Medical records	Incidence	>9 vs 0 units/day	1.25 (0.92-1.71)	Age, benign breast disease, BMI, cancer diagnosis, ethnicity, family history of breast cancer, HRT	Units/day converted to ethanol g/day (7.9g ethanol per unit, UK standard), cases and

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								use, oral contraceptive use, presence of other disease, Townsend social and material deprivation score	mid-points per categories
Brinton, 2014 BRE80579 USA	NIH-AARP, Prospective cohort, age: 50-71 years, W	7 384/ 190 872 9.3 years	Cancer registry	Semi-quantitative FFQ	Incidence	>35 g/day vs nondrinker	1.43 (1.27-1.61) ptrend: <0.0001	Age at menarche, alcohol intake, BMI, breast biopsies, educational level, family history of breast cancer in first degree relatives, marital status, menopausal age, menopausal status, parity and age at first birth, postmenopausal hormone use, race	Mid-points of exposure categories
Falk, 2014 BRE80544 USA	PLCO, Prospective cohort, age: 55-74 years, W	1 599/ 54 562 8.9 years	Self-report, cancer registries, death certificates, physician referrals, reports	Diet history method	Incidence	≥7 drinks/week vs never	1.35 (1.12-1.64)	Age, age at menarche, age at menopause, educational level, family history of breast	Intake in drinks converted to g/ethanol using 12.5g ethanol/drink

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
			from next of kin, medical and pathologic reports					cancer, BMI, height, menopausal hormone use, oral contraceptive use, race, reproductive history, smoking	, distribution of person-years by exposure categories, mid-points of exposure categories
		1 290/			Incidence, ER+	≥7 drinks/week vs never	1.48 (1.19-1.83)		
		216/			Incidence, ER-	≥7 drinks/week vs never	0.84 (0.49-1.44)		
		1 140/			Incidence, PR+	≥7 drinks/week vs never	1.64 (1.31-2.06)		
		354/			Incidence, PR-	≥7 drinks/week vs never	0.76 (0.5-1.16)		
		1 121/			Incidence, ER+/PR+	≥7 drinks/week vs never	1.63 (1.3-2.05)		
		157/			Incidence, ER+/PR-	≥7 drinks/week vs never	0.74 (0.39-1.42)		
		197/			Incidence, ER-/PR-	≥7 drinks/week vs never	0.78 (0.44-1.36)		
		1 220/			Incidence, ductal	≥7 drinks/week vs never	1.26 (1.0-1.58)		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
		195/			Incidence, lobular carcinoma	≥7 drinks/week vs never	1.42 (0.83-2.43)		
		88/			Incidence, mixed ductal/lobular	≥7 drinks/week vs never	2.51 (1.2-5.24)		
Park, 2014 BRE80494 USA	MEC, Prospective cohort, age: 60.9 years, W	3 885/ 85 089 12.4 years	SEER cancer registry for Hawaii & California & National Death Index	Quantitative FFQ	Incidence	Per 10 g/day	1.04 (1.02-1.06)	Age, age at first child birth, age at menarche, age at menopause, BMI, educational level, energy intake, ethnicity, family history of breast cancer, hormone replacement therapy, number of children, physical activity, smoking status, type of menopause	(nothing estimated for the main analysis), person years per category and mid-points of exposure categories for the non-linear analysis
		3 885/			Incidence	≥30 vs 0 g/day	1.53 (1.32-1.77) ptrend: <0.001		
		1 764/			Incidence,	≥30 vs 0 g/day	1.61 (1.3-2.0)		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
					ER+/PR+		ptrend: <0.001		
		350/			Incidence, ER+/PR-	≥30 vs 0 g/day	1.72 (1.06-2.79) ptrend: 0.054		
		499/			Incidence, ER-/PR-	≥30 vs 0 g/day	1.58 (1.04-2.38) ptrend: 0.025		
		1 764/			Incidence, ER+/PR+	Per 10 g/day	1.06 (1.03-1.08)		
		350/			Incidence, ER+/PR-	Per 10 g/day	1.06 (1.01-1.11)		
		499/			Incidence, ER-/PR-	Per 10 g/day	1.04 (0.99-1.09)		
Couto, 2013 BRE80454 Sweden	SWLHCS, Prospective cohort, age: 30-49 years, W	448/ 16 years	Cancer registry	FFQ	Incidence	Per 5 g/day	1.05 (0.98-1.13)	Age at first child birth, age at menarche, benign breast disease, beverage intake, cereal, dairy products consumption, educational level, egg, energy intake, fish, fruits intake, height, history of breast cancer, legumes, meat,	RRs rescaled for an increment of 10 g/day

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								number of childbirths, potatoes, ratio unsaturated/saturated fat, smoking, sweet products, vegetable	
Hartz, 2013 BRE80483 USA	WHI, Prospective cohort, age: 55-70 years, W	2 944/ 147 202 8 years	Self-reported/death certificate/ medical records	Questionnaire	Incidence	Per 1 serving/week	1.06 (1.03-1.09)	Age, family history of prostate cancer, history of cancer, history of polyp diagnosis, medication, number of cigarettes smoked, osteoporosis, psychological character, race, study, weight	RRs rescaled for an increment of 10 g/day, using 12.5g ethanol per serving
		2 944/			Incidence	>1 serving/week vs none	1.13 (1.05-1.2)		
Nyante, 2013 BRE80496 USA	NIH-AARP, Prospective cohort, age: 50-71 years, W	5 334/ 192 076 9.6 years	Cancer registry	FFQ	Incidence, ductal	>20 vs 0 g/day	1.26 (1.12-1.41) ptrend: <0.01	Age, age at first child birth, age at menarche, age at menopause, BMI, breast biopsies, educational	Mid-points of exposure categories

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								level, family history of breast cancer, HRT use, marital status, OC use, parity, race, type of menopause, vigorous activity	
		216/			Incidence, mucinous breast cancer	>20 vs 0 g/day	1.1 (0.62-1.94) ptrend: 0.84		
		132/			Incidence, tubular breast cancer	>20 vs 0 g/day	1.78 (0.86-3.68) ptrend: 0.08		
		836/			Incidence, lobular carcinoma	>20 vs 0 g/day	1.42 (1.07-1.89) ptrend: 0.03		
		639/			Incidence, ductal-lobular breast cancer	>20 vs 0 g/day	1.26 (0.9-1.77) ptrend: 0.07		
Sczaniecka, 2012 BRE80434 USA	VITAL, Prospective cohort, age: 50-76 years, W	772/ 30 252 6 years	Seer registry	Semi-quantitative FFQ	Incidence	≥10 vs 0-0.5 g/day	1.58 (1.31-1.89) ptrend: <0.0001	Age	Mid-points of exposure categories
Chen, 2011 BRE80397	NHS I, Prospective	6 374/	National Death Index, medical		Incidence, breast cancer	≥30 vs 0 g/day	1.54 (1.35-1.75)	Age, questionnaire	Mid-points of exposure

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
USA	cohort,		records					year, ages at menarche and menopause, family history of breast cancer in first-degree relative, benign breast disease, BMI, parity and age at first full-term birth, hormone therapy use, total duration of breastfeeding (months), and cigarette smoking	categories
Kotsopoulos, 2010 BRE80335 USA	NHS I, Prospective cohort, age: 30-55 years, W	4 193/ 107 759 26 years	Self-report (provided evidence of treatment), medical records and pathology reports, National Death Index	Semi-quantitative FFQ	Incidence, ductal	≥15 vs 0 g/day	1.31 (1.19-1.45)	Age, age at first child birth, age at menarche, age at menopause, alcohol intake, benign breast disease, BMI, BMI at age 18 years, family history of breast cancer, menopausal age, menopausal type, parity, postmenopausal	Mid-points of exposure categories, person years per category
					Incidence, ductal carcinoma	Per 1 g/day	1.04 (-)		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								hormone use	
		659/			Incidence, lobular carcinoma	≥15 vs 0 g/day	1.75 (1.36-2.24)		
					Incidence, lobular carcinoma	Per 1 g/day	1.07 (-)		
		1 947/			Incidence, invasive ER+PR+ ductal cancer	≥15 vs 0 g/day	1.37 (1.17-1.61)		
					Incidence, invasive ER+PR+ ductal cancer	Per 1 g/day	1.05 (-)		
		286/			Incidence, invasive ER+PR+ lobular cancer	≥15 vs 0 g/day	2.28 (1.6-3.24)		
					Incidence, invasive ER+PR+ lobular cancer	Per 1 g/day	1.12 (-)		
Li, 2010 BRE80336 USA	WHI-OS, Prospective cohort, age: 50-79 years,	2 180/ 87 724	Medical record	Self-administered questionnaire	Incidence	Per 1 drinks/day	1.07 (1.02-1.12)	Age, BMI, educational level, ethnicity, family history of breast	RR per increment of 1 drink/day rescaled to an increment

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								cancer, Gail model risk, HRT use, mammography, parity, race, smoking	of 10g ethanol/day
		2 944/			Incidence	≥14 drinks/week vs never drinker	1.24 (1.0-1.55)		
		1 805/			Incidence, ductal	≥14 drinks/week vs never drinker	1.04 (0.78-1.39)		
		720/			Incidence, lobular carcinoma	≥14 drinks/week vs never drinker	2.13 (1.36-3.33)		
		1 803/			Incidence, breast cancer ER+/PR+	≥14 drinks/week vs never drinker	1.27 (0.96-1.68)		
		373/			Incidence, breast cancer ER+/PR-	≥14 drinks/week vs never drinker	1.45 (0.8-2.63)		
		359/			Incidence, breast cancer ER-/PR-	≥14 drinks/week vs never drinker	0.46 (0.19-1.12)		
		1 306/			Incidence, ductal	Per 1 drinks/day	1.06 (1.0-1.13)		
		564/			Incidence,	Per 1	1.13 (1.05-		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
					lobular carcinoma	drinks/day	1.23)		
		1 351/			Incidence, breast cancer ER+/PR+	Per 1 drinks/day	1.08 (1.02-1.15)		
		282/			Incidence, breast cancer ER+/PR-	Per 1 drinks/day	1.12 (1.0-1.25)		
		239/			Incidence, breast cancer ER-/PR-	Per 1 drinks/day	0.85 (0.68-1.05)		
		1 105/			Incidence, invasive ER+PR+ ductal cancer	≥7 vs never drinks/drinker	1.14 (0.87-1.5)		
		497/			Incidence, invasive ER+PR+ lobular cancer	≥7 vs never drinks/drinker	1.82 (1.18-2.81)		
		817/			Incidence, invasive ER+PR+ ductal cancer	Per 1 drinks/day	1.05 (0.97-1.14)		
		385/			Incidence, invasive ER+PR+ lobular cancer	Per 1 drinks/day	1.16 (1.06-1.26)		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Suzuki, 2010 BRE80275 Japan	JPHC, Prospective cohort, age: 40-69 years, W	218/ 13.8 years	Cancer registry	FFQ	Incidence	Per 10 g/day	1.01 (0.87-1.18)	Age, area of residence, BMI, height, hormone use, leisure time physical activity, nutrients, smoking habits	(nothing for the main analysis)
					Incidence	>150 g/week vs never drinkers	1.21 (0.53-2.75)		
		64/			Incidence	Per 10 g/day	1.05 (0.92-1.2)		
		166/			Incidence never used HRT,	Per 10 g/day	1.03 (0.91-1.16)		
		52/			Incidence, ever used HRT,	Per 10 g/day	0.74 (0.33-1.65)		
Trichopoulou, 2010 BRE80320 Greece	EPIC-Greece, Prospective cohort, age: 20-68 years,	127/ 9.8 years	Medical records and pathology reports	FFQ	Incidence	Per 5 g/day	1.01 (0.86-1.17)	Age, age at first child birth, age at menarche, age at menopause, BMI, educational level, energy intake, height, HRT use, menopausal status,	RR rescaled for an increment of 10g/day

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								metabolic equivalents, parity	
Ericson, 2009 BRE80304 Sweden	MDC, Nested case control, age: 45-73 years, W	544/ 1 632 13 years	Cancer registry	Diet history method	Incidence	>30 vs 0 g/day	2.5 (1.2-5.2) ptrend: 0.07	Age, blood sampling date	Mid-points of exposure categories
Nielsen, 2008 BRE80143 Denmark	CCHS, Prospective cohort, W	267/ 5 035	Cancer registry		Incidence	Per drink/day	1.11 (0.99-1.25)	Age, education, physical activity in leisure time, BMI, tobacco smoking, number of children, perceived stress and hormone therapy	Intake in drinks converted to g ethanol using 12 g ethanol/drink as reported in the study, RRs rescaled for an increment of 10g ethanol
						>21 vs <1 drink/week	1.54 (0.77-3.1) ptrend: 0.06		
		85/			HRT use at baseline	Per drink/day	1.27 (1.09-1.49)	Age, education, physical activity in leisure time, BMI, tobacco smoking, perceived stress, number of children	
						>21 vs <1 drink/week	2.17 (0.79-5.93) ptrend: 0.004		
		182/			Incidence, no HRT use at baseline	Per drink/day	0.98 (0.82-1.78)		
						>21 vs <1 drink/week	1.28 (0.46-3.57) ptrend: 0.79		
Zhang, 2007 BRE20023	WHS, Prospective	910/ 10 years	Medical notes	FFQ + questionnaire	Incidence	Per 10 g/day	1.07 (0.99-1.15)	Age, age at first child, age at	None

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
USA	cohort, age: 55 years,							menarche, age at menopause, benign breast disease, BMI, energy intake, family history, hormonal variables, parity/pregnancies, physical activity, randomized treatment assignment, supplements	
		251/			Incidence MHT - never users,	Per 10 g/day	0.99 (0.86-1.15)	Menopausal status	
		112/			Incidence, MHT - past users	Per 10 g/day	0.91 (0.72-1.16)		
		545/			Incidence, MHT - current users	Per 10 g/day	1.15 (1.05-1.26)		
Mellemkjaer, 2006 BRE80039 Denmark	DCH, Prospective cohort, age: 50-65 years,	633/ 23 788 6.1 years	Cancer registry	FFQ	Incidence	Per 12 g/day	1.10 (1.04-1.16)	Age, age at first child birth, benign breast disease, educational level, parity, HRT use	RR rescaled for an increment of 10g/day

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Suzuki, 2005 BRE24245 Sweden	SMC, Prospective cohort, W	1 284/ 51 847 8.3 years	National and Regional Cancer Registries	FFQ	Incidence	≥10 g/day vs nondrinkers	1.43 (1.16-1.76) ptrend: 0.0012	Age, age at first child, age at menarche, age at menopause, benign breast disease, BMI, educational level, energy intake, family history, height, HRT use, OC use, other menstrual characteristics, other nutritional factors, other nutritional factors, parity/pregnancies	Mid-points of exposure categories
		716/			Incidence, ER+/PR+	≥10 g/day vs nondrinkers	1.35 (1.02-1.8) ptrend: 0.049		
		279/			Incidence, ER+/PR-	≥10 g/day vs nondrinkers	2.36 (1.56-3.56) ptrend: 0.001		
		50/			Incidence, ER-/PR+	≥10 g/day vs nondrinkers	0.62 (0.13-2.9) ptrend: 0.57		
		143/			Incidence, ER-/PR-	≥10 g/day vs nondrinkers	0.8 (0.38-1.67) ptrend: 0.45		
		528/			Incidence HRT - no	≥10 g/day vs nondrinkers	1.31 (0.94-1.81)		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Horn-Ross, 2004 BRE15413 USA	CTS, Prospective cohort, W	973/ 5 years	CCR and SEER	FFQ	Incidence	≥20 g/day vs nondrinkers	1.32 (1.06-1.63)	Age, age at menarche, BMI, duration of HRT use, energy intake, ethnicity, family history, other reproductive index, physical activity	Mid-points of exposure categories. only used in the HvL analysis by MHT use (persons per category or person years not given)
		698/			Incidence, lean	≥20 g/day vs nondrinkers	1.4 (1.09-1.79)		
		275/			Incidence, overweight	≥20 g/day vs nondrinkers	1.1 (0.71-1.72)		
		170/			Incidence, HRT - no	≥20 g/day vs nondrinkers	0.98 (0.55-1.73)		
		482/			Incidence, HRT - yes	≥20 g/day vs nondrinkers	1.51 (1.13-2.03)		
	>22 years at baseline						1.07 (0.72-1.58)		
Petri, 2004 BRE16325 Denmark	CCPPS, Prospective cohort, age: 20-91 years, W	397/	Danish Cancer Registry	Questionnaire	Incidence	>27 vs 1-6 drinks/week	0.57 (0.18-1.78)	Age, HRT use, other design issue, parity/pregnancies	Reference category changed using Hamling's method, intake in drinks/week

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
									converted to ethanol g/day, mid points of intake categories.
Sellers, 2004 BRE18027 USA	IWHS, Prospective cohort, age: 55-69 years, W	1 875/ 33 552 14 years	National Death Index, State Health Registry of Iowa	FFQ-semi-quantitative	Incidence	>4 g/day vs never drinkers	1.11 (0.98-1.27) ptrend: 0.09	Age, age at first child, age at menarche, age at menopause, BMI, educational level, energy intake, family history, height, HRT use, nutrients, OC use, parity/pregnancies, physical activity, smoking habits, waist circumference	Mid-points of exposure categories
Feigelson, 2003 BRE02720 USA	CPS II, Prospective cohort, W	1 303/ 66 561 6 years	Medical records, state tumor registries, National Death Index	FFQ-semi-quantitative	Incidence	≥15 vs none	1.26 (1.04-1.53) ptrend: 0.01	Age, age at first child, age at menarche, age at menopause, BMI, body weight, educational level, ethnicity, family history, HRT use, mammography,	Mid-points of exposure categories

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								nutrients, other nutritional factors, parity/pregnancies, physical activity, residual (willet), supplements	
		297/			Incidence, low nutritious food intake	≥15 vs none	1.4 (1.0-1.99)		
		327/			Incidence, high nutritious food intake	≥15 vs none	0.93 (0.56-1.54)		
		307/			Incidence, low nutritious food intake	≥15 vs none	1.33 (0.94-1.88)		
		348/			Incidence, high nutritious food intake	≥15 vs none	1.5 (1.02-2.22)		
Rohan, 2000a BRE16489 Canada	CNBSS, Case cohort, age: 40-59 years, W	542/ 10 years	Pathology reports from provincial cancer registries.	FFQ-quantitative	Incidence, breast cancer, postmenopausal	Per 10 g/day	1.05 (0.98-1.11)	Age, age at menarche, energy intake, family history, other design issue, other specified factor, parity/pregnanci	(nothing estimated in the main analysis)

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								es, recruitment center	
		373/			Incidence, HRT - no	Per 10 g/day	1.05 (0.99-1.11)	Menopausal status	
		946/			Incidence, HRT - yes	Per 10 g/day	1.08 (0.99-1.19)		
Van den Brandt, 1995 BRE12719 Netherlands	NLCS, Case cohort, age: 55-69 years, W	422/ 62 573 3.3 years	Cancer registries and pathology register	Questionnaire	Incidence	≥30 g/day vs nondrinker	1.72 (0.9-3.28) ptrend: 0.047	Age, age at first child, age at menarche, age at menopause, benign breast disease, BMI, educational level, energy intake, family history, family history, OC use, parity/pregnancies, smoking habits	Mid-points of exposure categories
		344/			Incidence, HRT - no	≥15 vs ≤0 g/day	1.24 (-) ptrend: 0.261		
		55/			Incidence, HRT - yes	≥15 vs ≤0 g/day	1.07 (-) ptrend: 0.572		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Barrett-Connor, 1993 BRE00581 USA	Rancho Bernardo, California, Prospective cohort, age: 40-79 years, W	15/ 590 15 years		24h recall	Incidence	Per 18 g/day	0.75 (0.35-1.63)		RR rescaled for an increment of 10g/day

*Studies in postmenopausal women only.

Table 265 Alcohol and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Hvidtfeldt, 2015 Pooled analysis		1 579/ 30 798 392 938 person-years	Danish cancer registry		Absolute Postmenopausal breast cancer risk MHT nonusers	7+ vs <1 drinks/week	72 (12, 131)	Educational level, BMI, smoking, parity, physical activity, age	Excluded, absolute breast cancer risk
					MHT current users		-17 (-133, 118)		
	DCH	1 390/28 533							
	CCHS II	189/ 2 256							
Hastert, 2013 BRE80481 USA	VITAL, Prospective cohort, age: 50-76 years, W	899/ 30 797 6.7 years	SEER registry	FFQ	Incidence	Met vs not met	0.63 (0.53-0.74)	Age, age at first child birth, age at menarche, age at menopause, educational level, energy intake, family history of breast cancer, mammography, other factors, race, years of HRT use	Excluded, met vs not met WCRF/AICR guidelines on alcohol
Loft, 2013 BRE80484 Denmark	DCH, Nested case control,	336/ 672 7 years	Cancer registry	FFQ	Incidence	Per 10 g/day	1.12 (1.0-1.24)	Age at first child birth, BMI,	Superseded by Mellemkjaer, 2006

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	age: 50-64 years, W							education years, HRT use, number of childbirths, parity, smoking	
Poynter, 2013 BRE80453 USA	IWHS, Prospective cohort, age: 55-71 years,	1 593/ 37 459 22 years	Health registers		Incidence, age <75y	Yes vs no	1.2 (1.08-1.33) ptrend: 0.0007	Age at baseline, age at first child birth, age at menarche, age at menopause, BMI, number of childbirths, physical activity, smoking, waist hip ratio	Only two levels of exposure stratified by age, sellers 2004 used instead
		1 071/			Incidence, age >=75y	Yes vs no	0.98 (0.86-1.11) ptrend: 0.73		
Horn-Ross, 2012 BRE80419 USA	CTS, Prospective cohort, W	660/ 40 680 10 years	Cancer registry	Questionnaire	Incidence	≥20 g/day vs non-drinker	1.26 (1.02-1.56)	Age, age at first child birth, BMI, family history of breast cancer, physical inactivity	Superseded by Horn-Ross 2004 with more cases

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Kabat, 2011 BRE80344 USA	WHI, Prospective cohort, age: 50-79 years, W	300/ 148 030 8 years	Mail or telephone questionnaires verified by trained physician adjudicators	FFQ	Incidence, triple negative breast cancer	≥7 drinks/day vs never drank	0.57 (0.34-0.95)	Age, age at first child birth, age at menarche, age at menopause, BMI, breast biopsies, contraception, educational level, ethnicity, family history of breast cancer, HRT use, mammogram in the past 2 years, physical activity, smoking, treatment allocation, waist circumferenc e	Excluded, triple negative postmenopausal breast cancer; analysis by ER+ status was not conducted
		2 471/			Incidence, ER+	≥7 drinks/day vs never drank	1.26 (1.06-1.5)		
Kawai, 2011 BRE80305 Japan	MCS, Prospective cohort, age: 40-64	/ 12.8 years	Cancer registry	FFQ	Incidence	Current vs never drinkers	1.06 (0.66-1.71)	Age, age at menarche, age at menopause,	Excluded, only two levels of exposure, used in HvL analysis

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	years, W							BMI, educational level, energy-adjusted folate intake, energy-adjusted intake of fat, family history of breast cancer, occupation, parity, smoking, use of HRT, walking time	only
Schonfeld, 2011 Pooled analysis		1 612/32 641			Incidence postmenopausal breast cancer nulliparous women	≥7 drinks/week vs none	1.30 (1.11-1.52)	Age, MHT use, BMI, history of benign breast disease, age at menarche, age at natural menopause, ever/never use of oral contraceptive	
		4 719/139 255			Parous women aged <25 years at first birth		1.22 (1.11-1.35)		
		2 856/65 015			Parous women aged ≥25 years at first birth		1.33 (1.19-1.50)		
	BCDDP	2 313							
	NIH-AARP	3 915							

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	PLCO	2 601							
	USRT	963							
Stevens, 2010 BRE80299 USA	CPS II, Prospective cohort, age: 50-74 years, W	3 898/ 70 656 13 years	Medical records	FFQ	Incidence	≥2 vs drinks/day vs non-drinkers	1.29 (1.12-1.49) ptrend: 0.0001	Age, age, age at first child birth, age at menarche, age at menopause, BMI, breast diseases, educational level, energy intake, family history of cancer, HRT use, multivitamin supplement intake, parity, physical activity, race	Excluded, only two levels of exposure, Feigelson, 2003 used instead
Allen, 2009 BRE80227 UK	MWS, Prospective cohort, age: 55 years, W	/ 1 280 296 7.2 years	National health records	Questionnaire (general)	Incidence, HRT - no	Per 10 g/day	1.11 (1.08-1.14)	Age, area of residence, BMI, oral contraceptive use, physical activity, smoking habits, socio-economic status	Only stratified analysis by MHT use
		/			Incidence, HRT - yes	Per 10 g/day	1.12 (1.08-1.15)		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Duffy, 2009 BRE80288 USA	WHI-OS, Prospective cohort, age: 50-79 years, W	1 783/ 88 530 5.5 years	Self report verified by medical record	FFQ	Incidence	Per 1 g/day	1.005 (1.001-1.009)	Age at menarche, age at menopause, BMI, breast biopsies, breastfeeding, educational level, ethnicity, family history, HRT use, income, parity/pregnancies, smoking status	Superseded by Li, 2010
		1 599/			Incidence	≥15 g/day vs no alcohol	1.13 (0.96-1.32)		
Lew, 2009 BRE80256 USA	NIH-AARP, Prospective cohort, age: 50-71 years, W	5 461/ 184 418 7 years	Cancer registry		Incidence	>35 vs 0 g/day	1.35 (1.17-1.56) ptrend: <0.001	Age, age at first child birth, age at menopause, BMI, breast biopsies, energy intake, family history of cancer, fat intake, folate intake, height, HRT use, oral contraceptive	Superseded by Brinton, 2014 in the main analysis

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								use, parity, physical activity, race, smoking habits	
		3 531/			Incidence, ductal	>35 vs 0 g/day	1.46 (1.22-1.75) ptrend: <0.001		
		550/			Incidence, lobular carcinoma	>35 vs 0 g/day	1.52 (0.95-2.44) ptrend: 0.04		
		424/			Incidence, ductal-lobular breast cancer	>35 vs 0 g/day	1.21 (0.66-2.2) ptrend: 0.35		
		1 641/			Incidence, ER+/PR+	>35 vs 0 g/day	1.46 (1.12-1.91) ptrend: 0.003		
		336/			Incidence, ER+/PR-	>20 vs 0 g/day	1.13 (0.73-1.77) ptrend: 0.51		
		366/			Incidence, ER-/PR-	>20 vs 0 g/day	1.21 (0.79-1.84) ptrend: 0.25		
		2 187/			Incidence, HRT never	>35 vs 0 g/day	1.31 (1.04-1.64) ptrend: 0.01		
		2 834/			Incidence, current MHT users	>35 vs 0 g/day	1.4 (1.14-1.71) ptrend: <0.001		
		5 461/			Incidence	Per 10 g/day	1.04 (1.02-1.05)		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		3 531/			Incidence, ductal	Per 10 g/day	1.04 (1.02-1.06)		
		550/			Incidence, lobular carcinoma	Per 10 g/day	1.03 (0.98-1.08)		
		424/			Incidence, ductal-lobular	Per 10 g/day	1.03 (0.97-1.09)		
		3 531/			Incidence, ductal	Per 1 drinks/day	1.05 (1.03-1.08)		
		550/			Incidence, lobular carcinoma	Per 1 drinks/day	1.04 (0.98-1.11)		
		424/			Incidence, ductal-lobular	Per 1 drinks/day	1.04 (0.96-1.12)		
		5 461/			Incidence	≥3vs 0 drinks/day	1.36 (1.16-1.59) ptrend: <0.001		
		2 074/			Incidence, ER+	>35 g/day vs non-drinkers	1.5 (1.19-1.9) ptrend: <0.01		
		1 700/			Incidence, PR+	>35 g/day vs non-drinkers	1.46 (1.12-1.9) ptrend: 0.003		
		418/			Incidence, ER-	>35 g/day vs non-drinkers	0.81 (0.42-1.58) ptrend: 0.90		
		704/			Incidence, PR-	>35 g/day vs non-drinkers	1.17 (0.76-1.81) ptrend: 0.25		
		1 641/			Incidence, ER+/PR+	Per 10 g/day	1.04 (1.01-1.08)		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		366/			Incidence, ER-/PR-	Per 10 g/day	1. (0.93-1.08)		
					Incidence, ER+ ductal	Per 10 g/day	1.05 (1.02-1.08)		
					Incidence, ER+ lobular	Per 10 g/day	1. (0.91-1.09)		
					Incidence, ER- ductal	Per 10 g/day	0.98 (0.9-1.07)		
					Incidence, ER- lobular	Per 10 g/day	1.03 (0.82-1.3)		
Maruti, 2009 BRE80259 USA	VITAL, Prospective cohort, age: 50-76 years, W	730/ 35 023 5 years	SEER registry	Semi-quantitative FFQ	Incidence	≥10 vs <1.5 g/day	1.6 (1.31-1.94) ptrend: <0.0001	Age at first child birth, age at menarche, age at menopause, alcohol intake, benign breast disease, BMI, energy intake, family history of cancer, height, mammography, physical	Superseded by Sczaniecka, 2012

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								activity, postmenopausal hormone use, race	
Rod, 2009 BRE80270 Denmark	CCHS, Prospective cohort, age: 62 years, W	263/ 5 054 20 years	Cancer registry	Self-administered questionnaire	Incidence	>14 vs <1 drink/week	1.67 (1.05-2.65)	Age, alcohol consumption, BMI, educational level, height, marital status, parity, physical activity, postmenopausal hormone use, psychological distress	Superseded by Nielsen, 2008 with more cases
Sonestedt, 2008 BRE80196 Sweden	MDC, Prospective cohort, W	430/ 11 699 10.4 years	Cancer registry	7-day food record & FFQ	Incidence	High consumption vs nonconsumers	2.6 (1.36-4.89)	Age, energy intake, exposure assessment, season of year	Superseded by Ericsson, 2009
Chlebowski, 2007 BRE80607 USA	WHI, Prospective cohort, age: 50-79 years, W	2 409/ 147 916 5 years	Self-reported validated by pathology report	FFQ	Incidence, ER+	>1 vs ≤1 drink/day	1.17 (1.02-1.33)	Age at first child birth, age at menarche, age at menopause, age at screening, BMI, breast biopsies,	Excluded, only two levels of exposure stratified by hormone receptor status

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								breastfeeding, oestrogen use, ethnicity, family history of breast cancer, parity, physical activity, progestin + oestrogen use, smoking	
		458/			Incidence, ER-	>1 vs ≤1 drink/day	1.06 (0.75-1.49)		
Ericson, 2007 BRE80128 Sweden	MDC, Prospective cohort,	392/ 11 699 9.5 years	Cancer registry	Dietary history questionnaire	Incidence	>30 vs ≤0 g/day	2.52 (1.33-4.77) ptrend: 0.06	Age	Superseded by Ericsson, 2009
Visvanathan, 2007 BRE80020 USA	CLUE II, Nested case control, age: 57 years, W	221/		FFQ + questionnaire	Incidence	Drinkers vs nondrinkers	1.25 (0.84-1.87)	Age	Excluded, only two levels of exposure, used in HvL only
Vogel, 2007 BRE80150 Denmark	DCH, Nested case control, age: 50-64 years,	361/ 24 697	Cancer registry	FFQ	Incidence	Per 10 g/day	1.08 (0.98-1.2)	Age at first child birth, benign breast disease, BMI, educational level, HRT use, NSAID	Superseded by Mellemkjaer, 2006

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								use, parity/pregnancies, smoking habits	
Ravn-Haren, 2006 BRE80151 Denmark	DCH, Nested case control, age: 50-64 years,	377/ 24 697	Cancer registry	FFQ	Incidence	Per 10 g/day	1.1 (1.0-1.22)	Age at first child birth, benign breast disease, BMI, educational level, gpx activity, HRT use, number of children, parity	Superseded by Mellemkjaer, 2006
Stolzenberg-Solomon, 2006 BRE80113 USA	PLCO, Prospective cohort, age: 55-74 years, W	691/ 31 411 4.94 years	Cancer screening programme	FFQ	Incidence	>7.62 vs ≤0.01 g/day	1.37 (1.08-1.76) ptrend: 0.02	Age, educational level	Superseded by Falk, 2014
		/			Incidence, Total folate <=335.5 microgram/day,	>7.62 vs ≤0.01 g/day	1.95 (1.03-3.72)	BMI, energy intake, HRT use, residual (willet)	
		115/			Incidence, Total folate <=335.5 microgram/day,	>7.62 vs ≤0.01 g/day	2.1 (1.08-4.07) ptrend: 0.004		
					Incidence, total folate >335.5 microgram/day,	>7.62 vs ≤0.01 g/day	1.23 (0.93-1.62) ptrend: 0.3		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Wirfält, 2005 BRE11111 Sweden	MDC, Nested case control, age: 59 years,	237/ 12 803	Cancer registry	7-day record + questionnaire	Incidence	High vs zero	3.14 (1.17-8.39)		Superseded by Ericsson, 2009
Duffy, 2004 BRE18359 USA	WHI-OS, Prospective cohort, age: 50-79 years, W	/ 93 724 5 years	Medical records	FFQ	Incidence	>15 g/day vs nondrinkers	1.26 (1.07-1.48)	Age, BMI, breast biopsies, breastfeeding, educational level, family history, HRT use, income, physical activity, reproductive factors, smoking habits	Superseded by Li, 2010
Mattisson, 2004a BRE17807 Sweden	MDC, Prospective cohort, W	342/ 11 726 7.6 years	Partially histological - over 80%	7-day record + questionnaire	Incidence	>30 vs ≤15	1.68 (0.91-3.12)	Age, age at first child, age at menarche, educational level, energy intake, height, HRT use, interviewer, leisure time physical activity, other design	Superseded by Ericsson, 2009

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								issue, other nutritional factors, season of interview, smoking habits, waist circumferenc e	
Tjønneland, 2004 BRE12349 Denmark	DCH, Prospective cohort, age: 50-65 years, W	/ 23 683 4.7 years	Direct contact at home	FFQ	Incidence	Per 10 g/day	1.1 (1.03-1.16)	Age at first child, age-underlying cox models, benign breast disease, BMI, duration of HRT use, educational level, HRT use, parity/pregna ncies, parous/nullip arous	Superseded by Mellemkjaer, 2006
Rissanen, 2003 BRE17954 Finland	FMCHES, Nested case control, age: 18-89 years, W	/ 10 years	Partially histological - over 80%		Incidence	(mean exposure)	(-)		Excluded, no risk estimate, only mean intakes
Tjønneland, 2003 BRE12350	DCH, Prospective cohort,	/ 23 778 4.7 years	Partially histological - over 80%	FFQ	Incidence	Per 10 g/day	1.1 (1.04-1.16)	Age at first child, age-underlying	Superseded by Mellemkjaer, 2006 in the

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Denmark	age: 50-64 years, W							cox models, benign breast disease, BMI, duration of HRT use, educational level, HRT use, parity/pregnancies, parous/nulliparous	main analysis
					Incidence, HRT - no	Per 10 g/day	1.07 (0.97-1.18)		
					Incidence, HRT - former	Per 10 g/day	1.2 (1.07-1.36)		
					Incidence, HRT - yes	Per 10 g/day	1.07 (1.0-1.16)		
Chen, 2002 BRE19205 USA	NHS I, Prospective cohort, age: 30-55 years, W	1 722/ 44 187 15.6 years	Pathology report + Self-reported	FFQ-semi-quantitative	Incidence	≥20 vs none	1.33 (1.12-1.58) ptrend: 0.001	Age, age at first child, age at menarche, age at menopause, benign breast disease, body weight, family history, HRT use,	Superseded by Chen, 2011

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								menopausal status, parity/pregnancies	
Pike, 2002 BRE16343 USA	Hawaii and California, 1993, Prospective cohort, W	1 757/ 88 712 6 years	Partially histological - over 80%	Questionnaire	Incidence	≥1 drink/day vs never	1.39 (-) ptrend: 0.002	Age at first child, age at menarche, age at menopause, alcohol, body weight, ethnicity, HRT use, menopausal status, parity/pregnancies	Excluded, no CIs
Sieri, 2002 BRE20941 Italy	ORDET, Nested case control, age: 41-70 years, W	56/ 3 367 5.5 years	Cancer registry + Death certificate	FFQ-semi-quantitative	Incidence	12.9-52.7 vs ≤0.75 g/day	1.04 (0.46-2.33) ptrend: 0.963	Birth cohort, educational level, parity/pregnancies, residual (willet)	
Feigelson, 2001 BRE19514 USA, Puerto Rico	CPS II, Prospective cohort, W	1 054/ 14 years	Death certificate	Questionnaire	Mortality	≥3 drinks/day vs none	1.30 (1.00-1.60) ptrend: 0.16	Age, age at first child, age at menarche, age at menopause, BMI, educational level, ethnicity,	Excluded, outcome is mortality

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								family history, food, height, HRT use, other specified factor, physical activity, smoking habits, supplements	
Jain, 2000 BRE17653 Canada	CNBSS, Prospective cohort, age: 40-59 years, W	98/ 10.3 years	Death certificate	FFQ-quantitative	Mortality	Per 10 g/day	1.006 (0.997-1.016)	Age, age at menarche, BMI, educational level, energy intake, family history, mammography, OC use, other specified factor, parity/pregnancies, recruitment center, smoking habits	Excluded, outcome is mortality
		135/			Mortality, HRT - no	Per 10 g/day	1.012 (1.003-1.021)	Menopausal status	
		39/			Mortality,	Per 10 g/day	1.007 (0.993-		

Author, year, WCRF Code, Country	Study name, characteristics	Cases/ Study size, Follow-up(years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR(95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					HRT - yes		1.021)		
Friedenreich, 1993 BRE17508 Canada	CNBSS, Nested case control, W	284/ 5.5 years	All histology	FFQ	Incidence	≥30 g/day vs nondrinkers	0.86 (0.46-1.59) ptrend: 0.19	Age, energy intake, family history, parity/pregnancies, smoking habits	Superseded by Rohan, 2000a
Gapstur, 1992 BRE03101 USA	IWHS, Prospective cohort, age: 55-69 years, W	459/ 37 105 4 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence	≥15 vs ≤0 g/day	1.46 (1.04-2.04) ptrend: 0.04	Age, age at first child, age at menarche, BMI, family history	
Hiatt, 1988a BRE03888 USA	KPMCP, Case cohort,	226/ 6 years	Hospital discharge records	FFQ	Incidence	≥6 drinks/day vs never drinker	4.2 (1.5-11.5)	Age, BMI, ethnicity, smoking habits	Excluded, no cases or person years per category
Schatzkin, 1987 BRE18010 USA	NHEFS, Prospective cohort, age: 25-74 years, W	76/ 10 years	Medical records + Death certificate	24h recall	Incidence	Any drinking vs nondrinking	1.3 (0.8-2.1)	Age	Excluded, only two levels of exposure, used in HvL only

Figure 334 RR estimates of postmenopausal breast cancer by levels of alcohol (as ethanol) intake

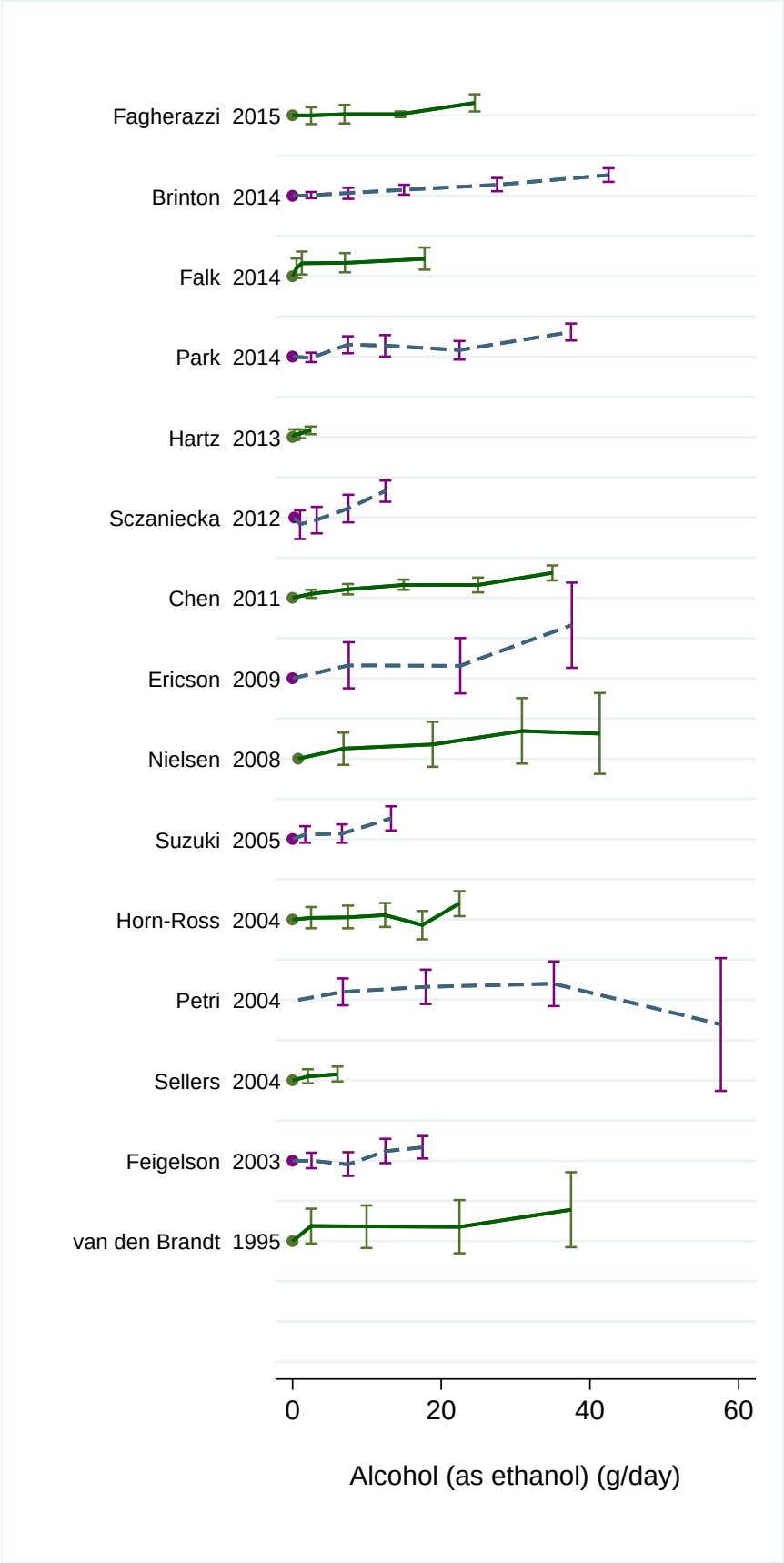


Figure 335 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest level of alcohol intake

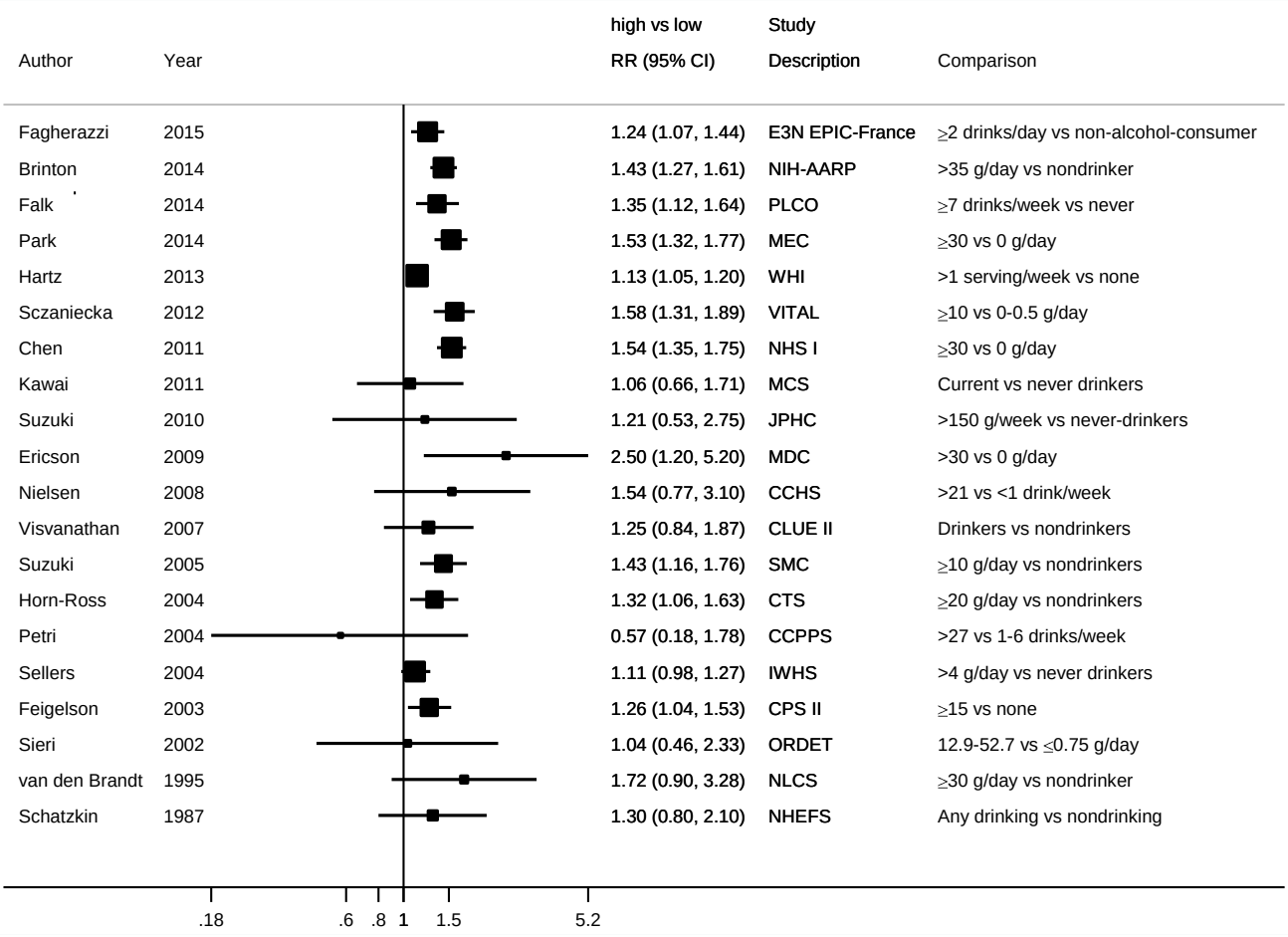


Figure 336 Relative risk of postmenopausal breast cancer incidence for 10g/day increase of alcohol (as ethanol) intake. Studies identified in the CUP

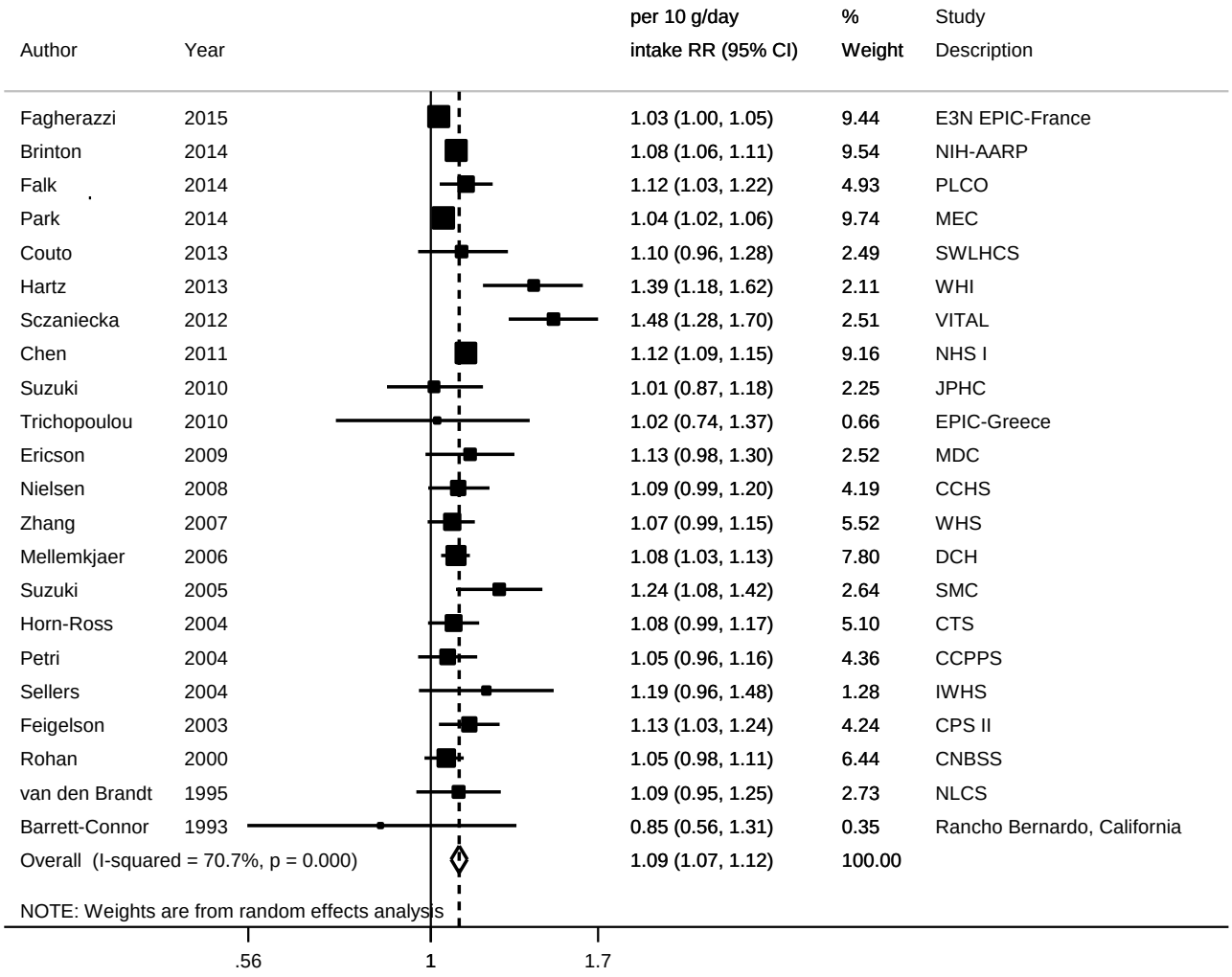


Figure 337 Relative risk of postmenopausal breast cancer incidence for 10g/day increase of alcohol (as ethanol) intake. Studies identified in the CUP and Pooling Project of Cohort Studies

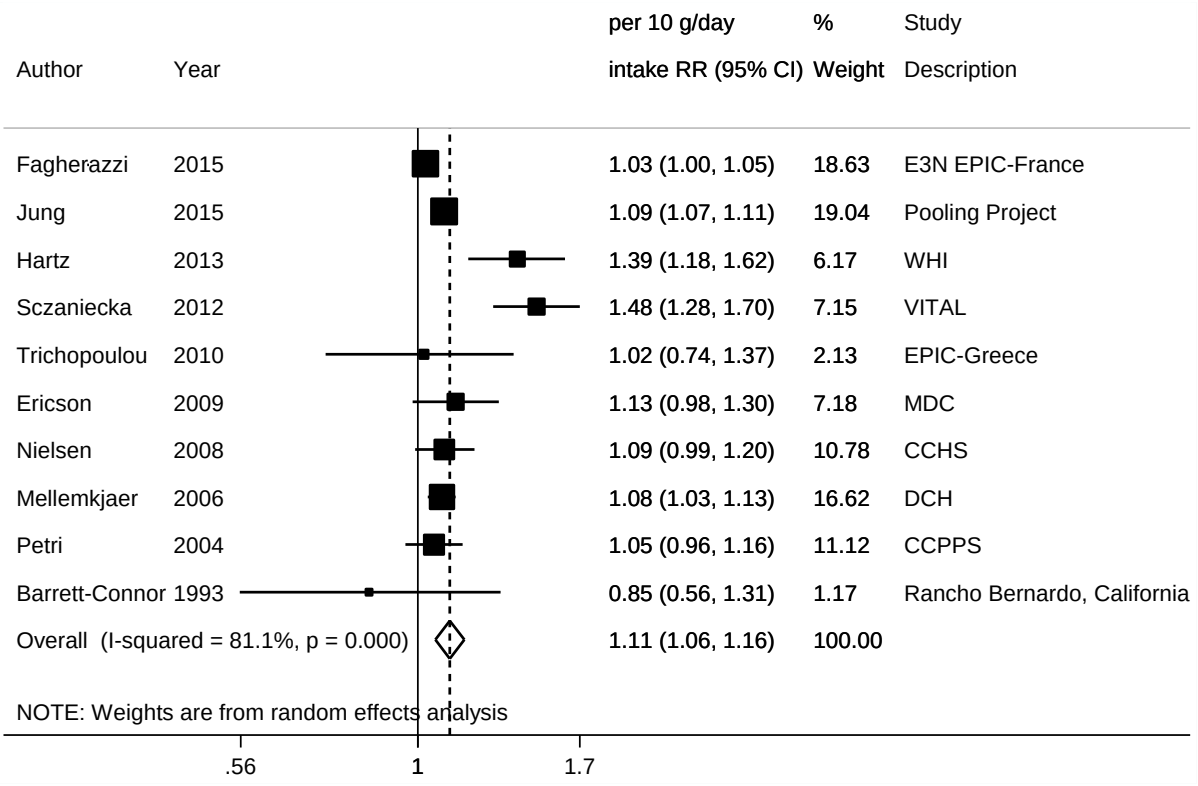


Figure 338 Funnel plot of studies included in the dose response meta-analysis of alcohol as ethanol and postmenopausal breast cancer

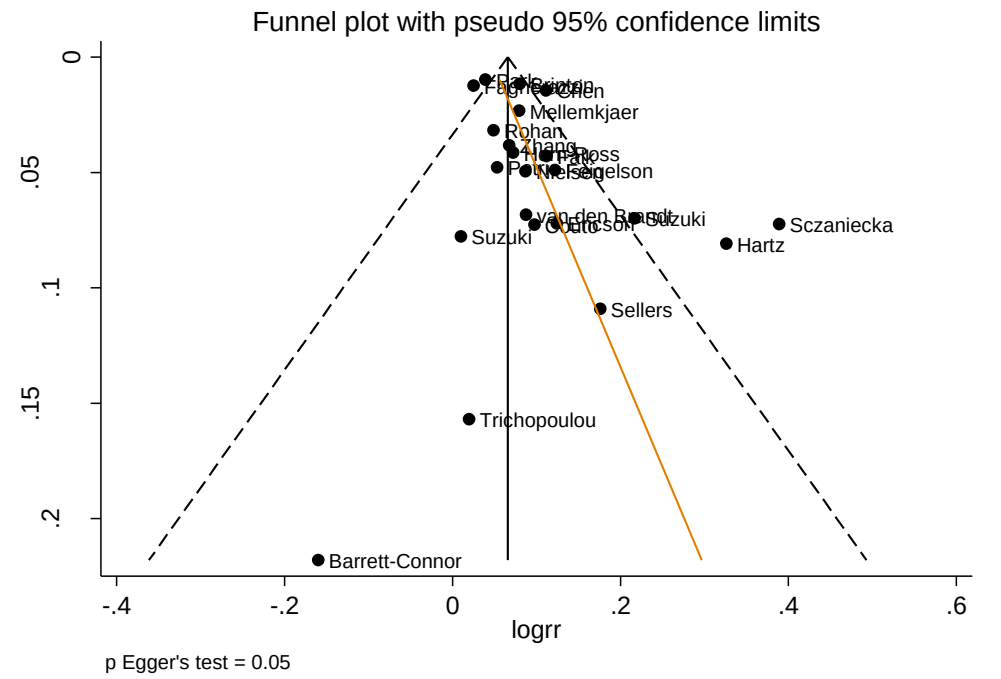


Figure 339 Funnel plot of Pooling Project and nonoverlapping studies identified in the CUP included in the dose response meta-analysis of alcohol and postmenopausal breast cancer

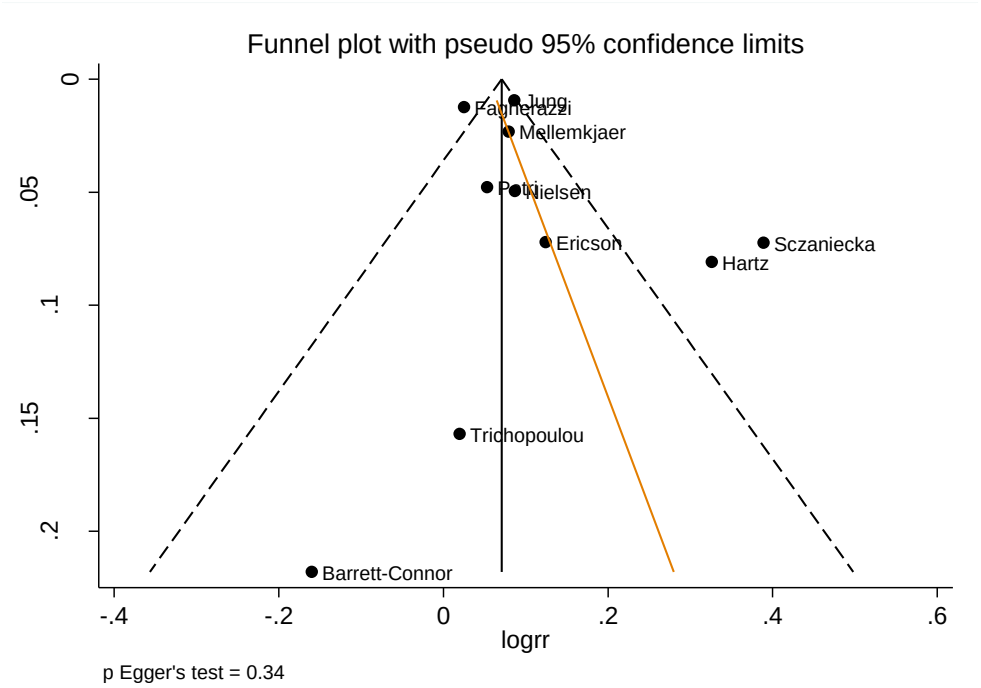


Figure 340 Relative risk of postmenopausal breast cancer mortality for 10g/day increase of alcohol (as ethanol) intake, by geographic location

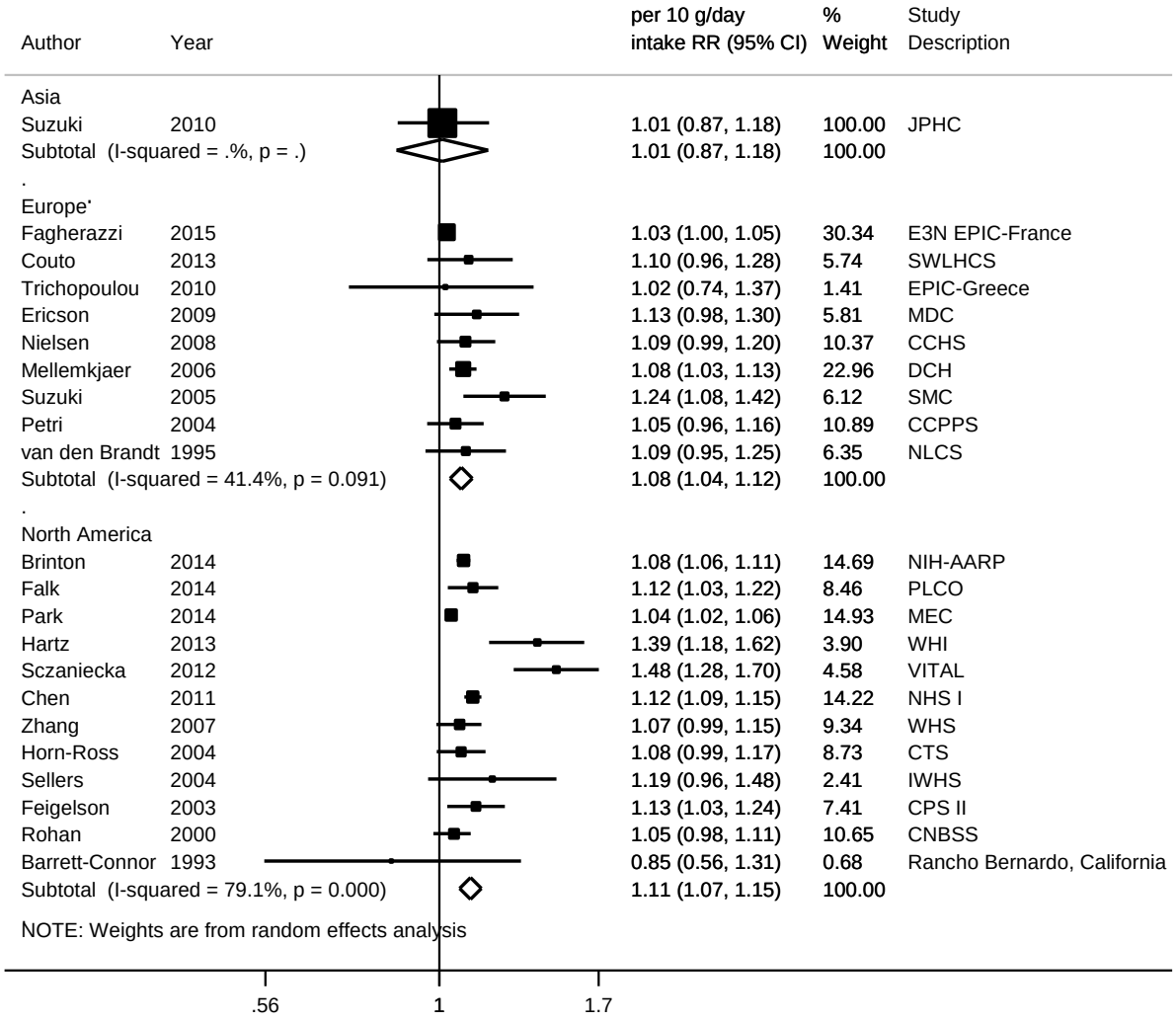


Figure 341 RR (95% CI) of postmenopausal ductal and lobular breast cancer for the highest compared with the lowest level of alcohol as ethanol intake

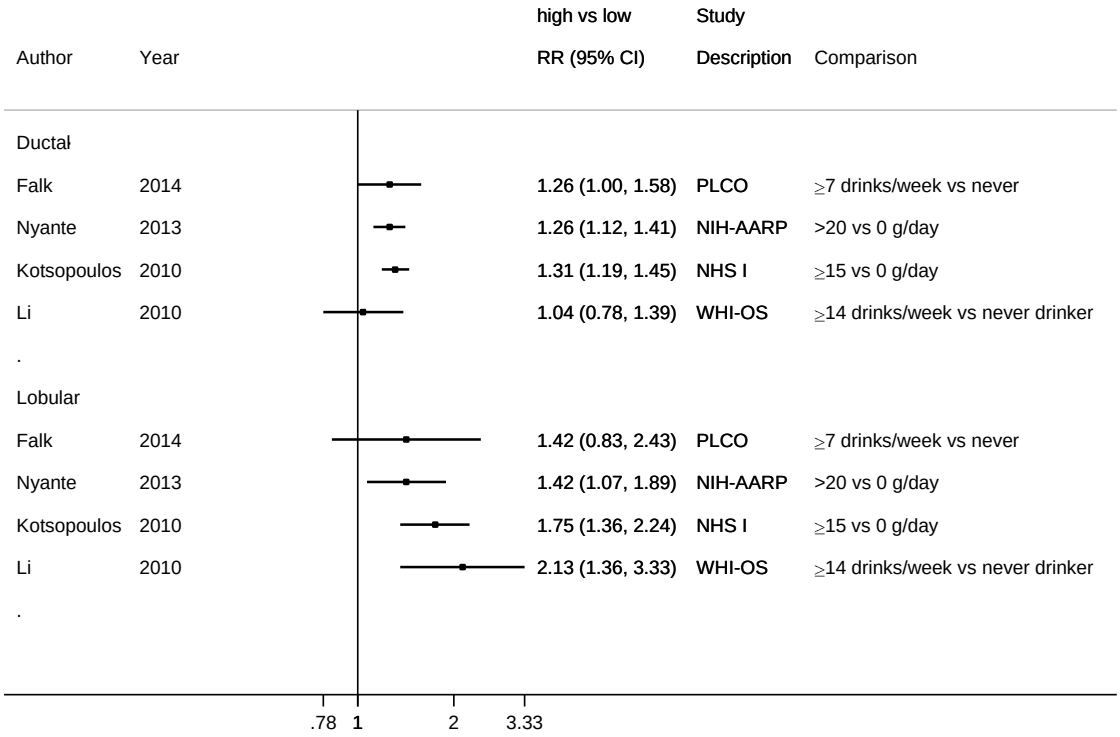


Figure 342 Relative risk of postmenopausal ductal and lobular breast cancer incidence for 10g/day increase of alcohol (as ethanol) intake

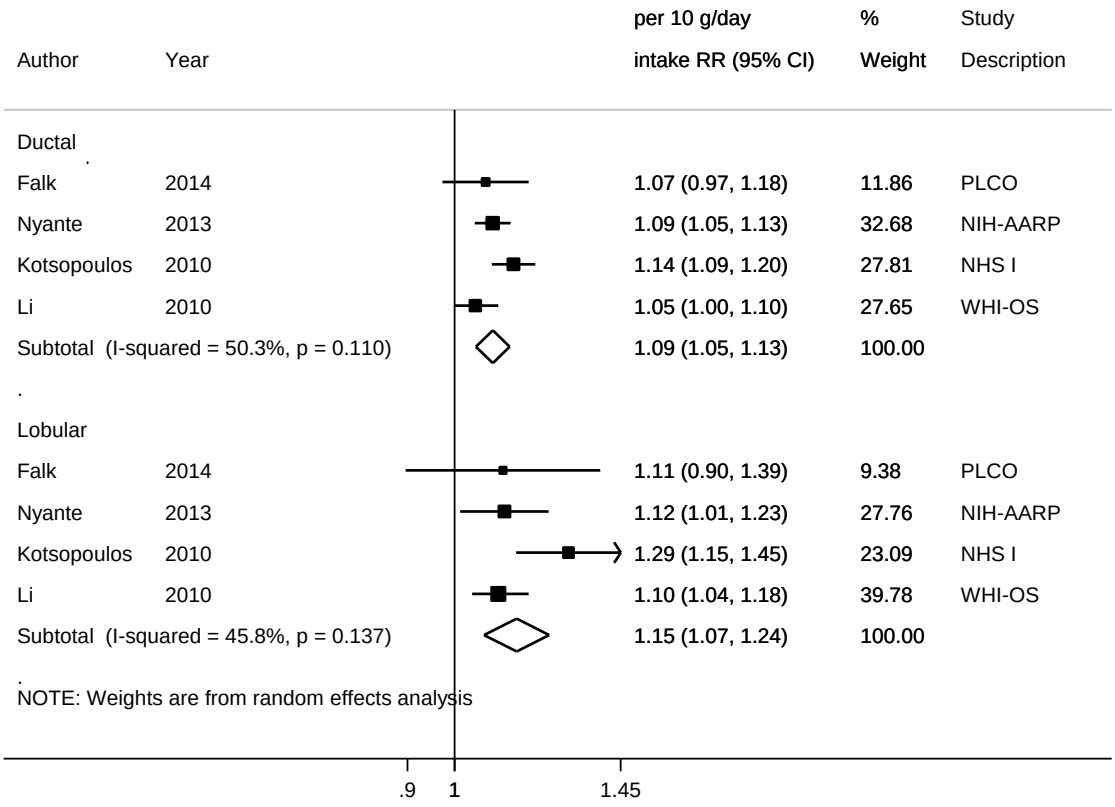


Figure 343 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest level of alcohol as ethanol intake by hormonal status

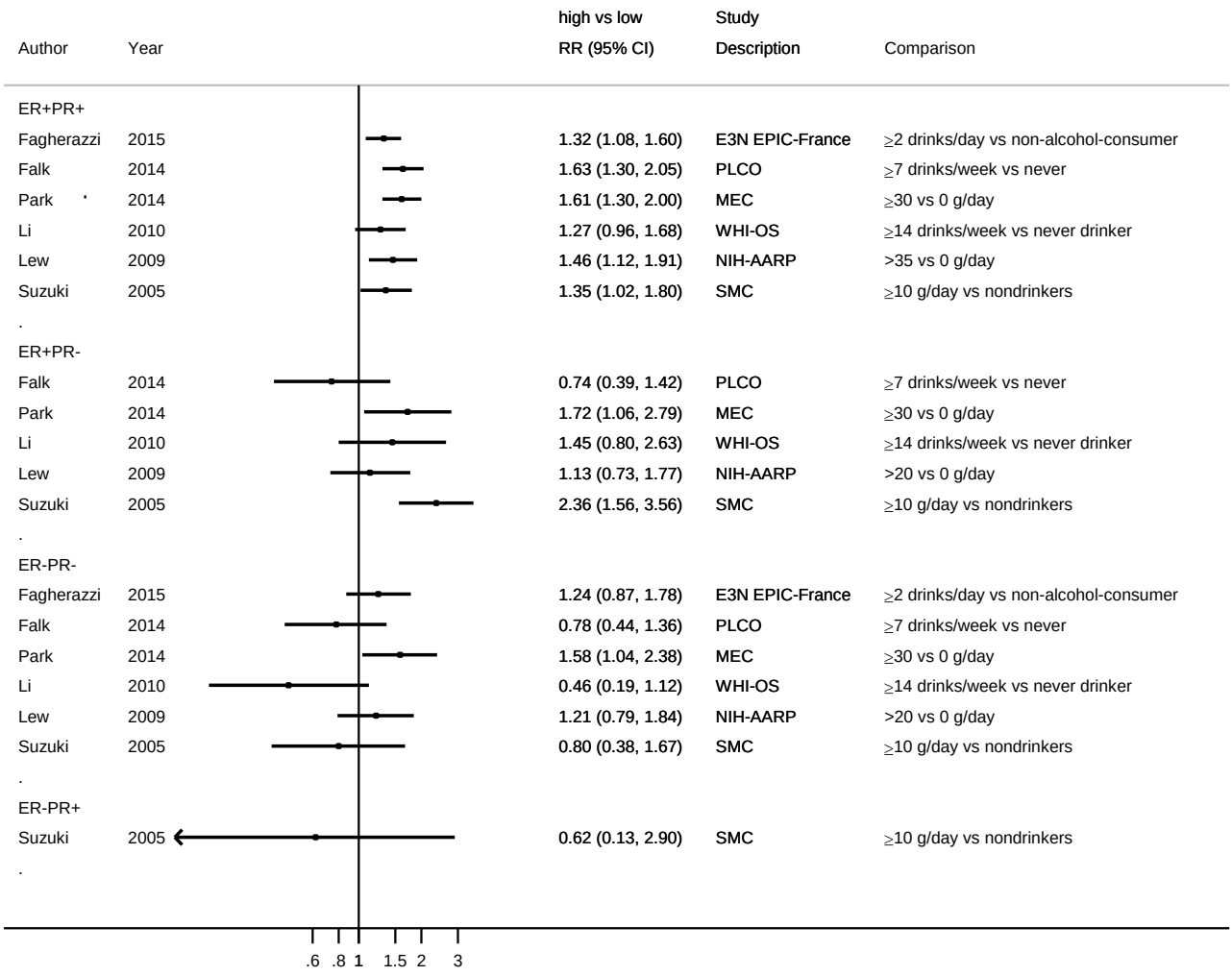


Figure 344 Relative risk of postmenopausal breast cancer incidence for 10g/day increase of alcohol (as ethanol) intake by hormonal status

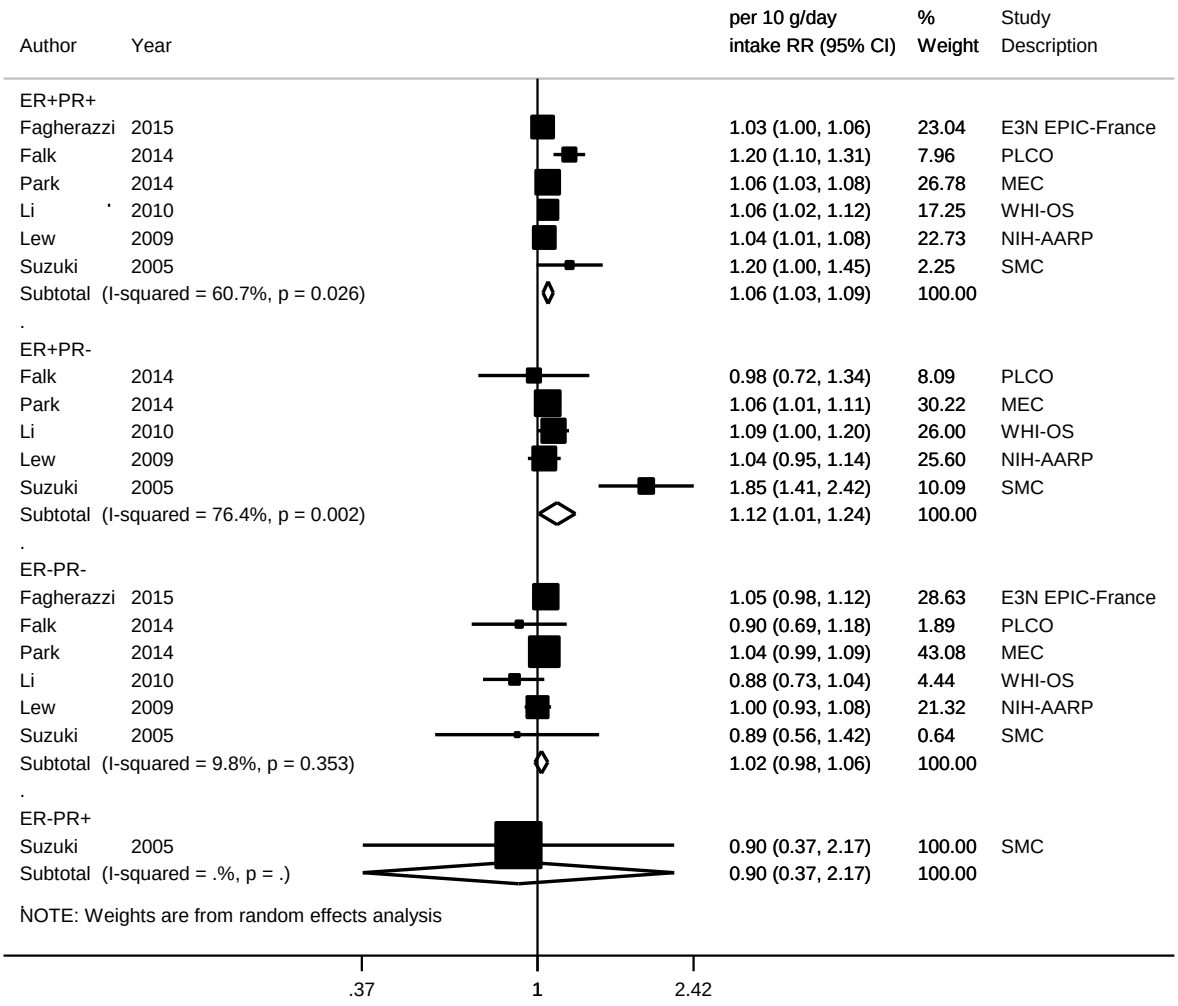
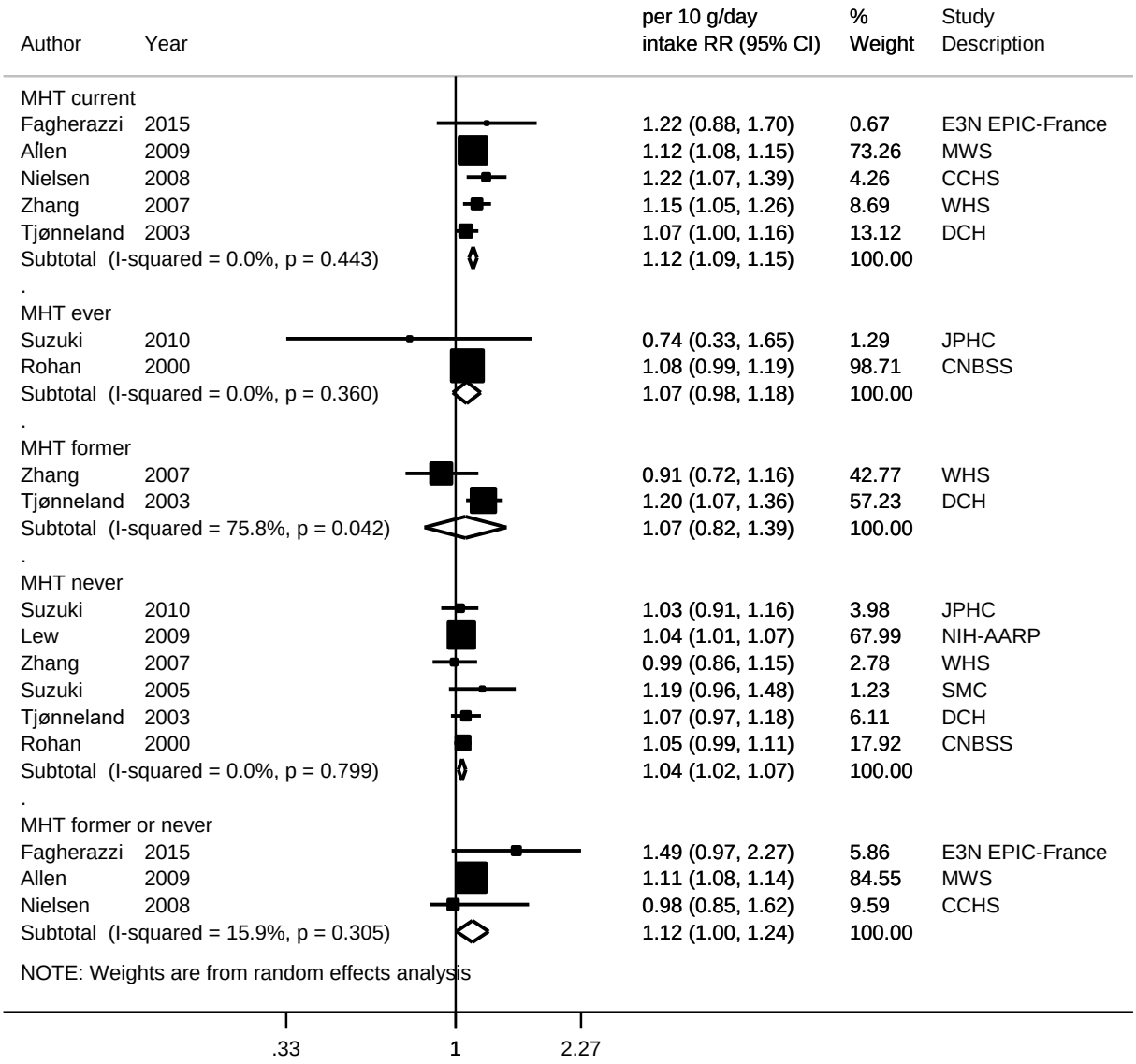
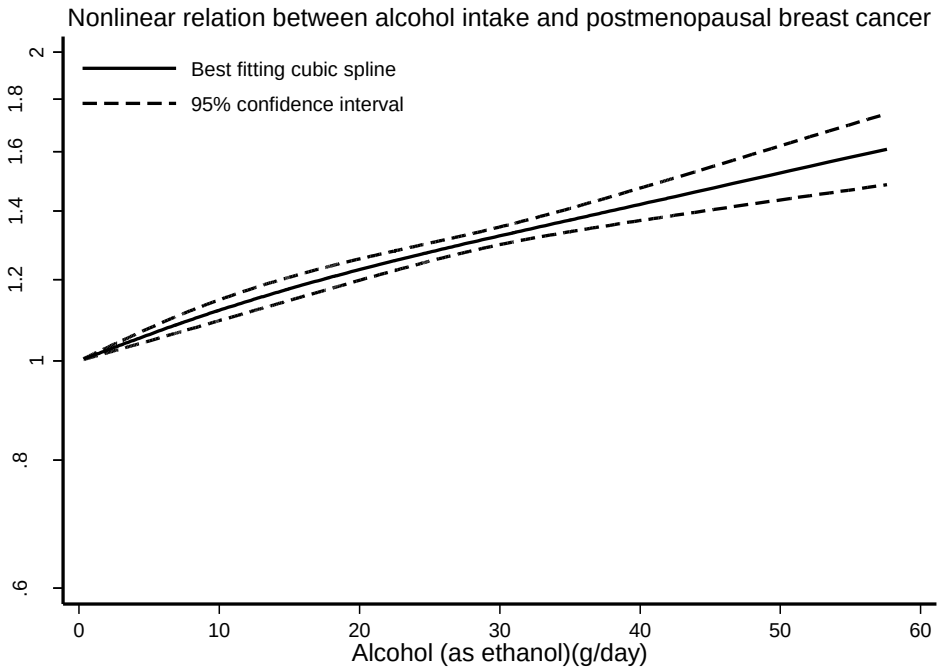


Figure 345 Relative risk of postmenopausal breast cancer for 10g/day increase of alcohol (as ethanol) intake, by menopausal hormone therapy use



Note: Results for MHT ever users (Suzuki, 2005, RR: 1.72 (95% CI=1.30-2.28), comparing ≥10 g/day vs nondrinkers and MHT never users), MHT current users (Lew, 2009, RR: 1.40 (95% CI=1.14-1.71, comparing >35 vs 0g/day) and former MHT users (Lew, 2009, RR: 1.22 (95% CI=0.73-2.03, comparing >35 vs 0 g/day) had missing data and were excluded from the dose-response meta-analysis.

Figure 346 Nonlinear dose-response meta-analysis of alcohol (as ethanol) and postmenopausal breast cancer



P nonlinear = 0.08

Figure 347 Relative risk of postmenopausal breast cancer and alcohol (as ethanol) estimated using non-linear models

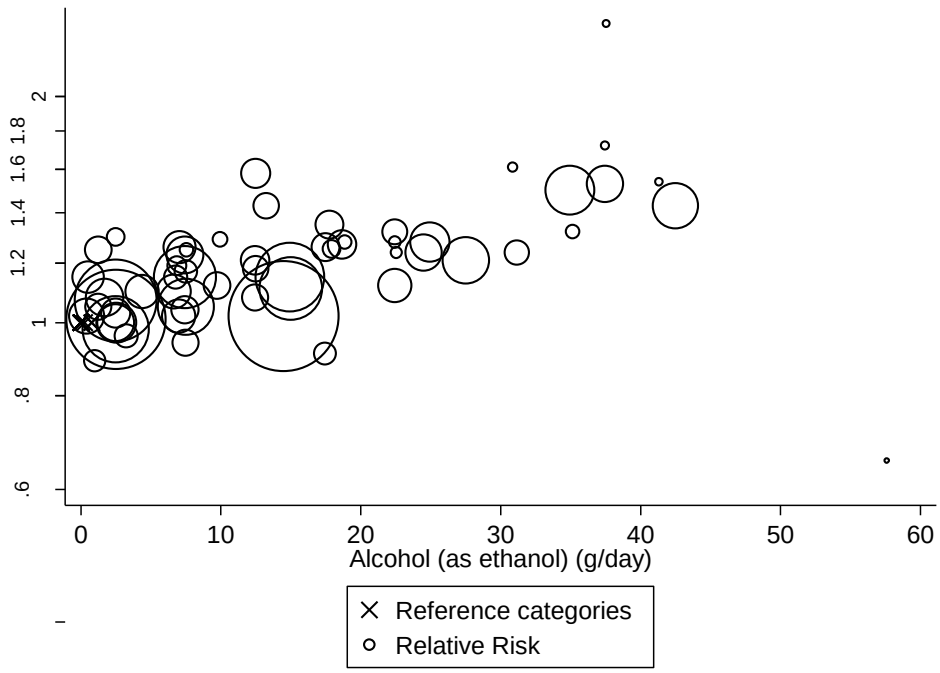


Table 266 Relative risk of postmenopausal breast cancer and alcohol (as ethanol) estimated using non-linear models

Alcohol (as ethanol) (g/day)	RR (95%CI)
0	1.00
2.5	1.03 (1.02-1.04)
7	1.09 (1.07-1.11)
12.5	1.15 (1.12-1.18)
15	1.18 (1.15-1.21)
25	1.28 (1.25-1.30)
35.1	1.37 (1.34-1.41)
42.5	1.45 (1.39-1.51)
57.6	1.61 (1.49-1.74)

5.4.1.1 Alcohol (as ethanol) from beer

Cohort studies

Overall summary

Twenty four publications from 30 studies were identified. Dose-response meta-analyses were conducted to examine the association of alcohol (as ethanol) from beer with risk of breast cancer (any), premenopausal and postmenopausal breast cancer.

Table 267 Summary of results of the dose-response meta-analysis in the CUP SLR

	Breast cancer (any)	Premenopausal breast cancer	Postmenopausal breast cancer
Increment unit used	10 g/day	10 g/day	10 g/day
Pooling Project of Cohort Studies*			
Studies (n)	19	-	-
Cases	35 895	-	-
RR (95%CI)	1.05 (1.03-1.08)	-	-
Heterogeneity (I^2, p-value)	0.27	-	-
Pooling Project and not overlapping studies identified in the CUP			
Studies (n)	23	3	7
Cases	44 780	818	7 798
RR (95%CI)	1.05 (1.03-1.08)	1.32 (1.06-1.64)	1.06 (0.94-1.21)
Heterogeneity (I^2, p-value)	0%, 0.75	0%, 0.71	66%, 0.007
P value Egger test	0.45	-	0.95

*Jung 2015; analyses restricted to women drinking <55g/day.

Breast cancer (any)

Summary

Main results:

Twenty three studies (44 780 cases) (5 publications) were included in the dose-response meta-analysis. Alcohol (as ethanol) intake from beer was associated with a significantly higher risk of breast cancer.

Two studies were excluded from the dose-response meta-analysis (Jain, 2000, Goodman, 1997). Beer intake was nonsignificantly inversely associated with the risk of breast cancer incidence in LSS study (Goodman, 1997). No association with breast cancer mortality was found in the CNBSS study (Jain, 2000).

Breast cancer risk and beer intake by hormone receptor status:

Two studies investigated the association of beer intake and breast cancer risk by tumour hormone receptor status: the Pooling Project of Cohort Studies on Diet and Cancer (Jung, 2015) and E3N EPIC-France (Fagherazzi, 2015).

In the Pooling Project (Jung, 2015), beer consumption was significantly positively associated with risk of both ER^+ and PR+ breast cancers (7737 cases ER^+ and 6342 PR^+). In categorical analysis, the positive association was significant for ER+, ER- (1812 cases), PR+ breast cancer. In E3N EPIC-France (Fagherazzi, 2015), the association with ER-/PR- breast cancer was positive but marginally significant.

No heterogeneity was observed. There was an evidence of a significant publication or small study bias.

Sensitivity and stratified analyses:

The summary RRs ranged from 1.05 (95% CI=1.03-1.07) when Zhang, 1999b was omitted to 1.07 (95% CI=1.01-1.13) when Jung, 2015 was omitted.

All studies were adjusted for age, BMI and reproductive factors. All studies apart from the EPIC (Tjønneland, 2007) were conducted in North America. The association was positive but not significant in the North American studies.

Study quality:

Alcohol consumption was estimated using questionnaires which were country-specific in the EPIC study (Tjønneland, 2007). Risk estimate that were used in the dose-response meta-analysis was among drinkers in one study (Li, 2009). Rohan, 2000a and Tjønneland, 2007 indicated that reference category might have included former/past drinkers along with lifelong abstainers. All remaining studies did not specify if reference category excluded former/past drinkers.

Case ascertainment was through cancer registries or when active follow-up, diagnosis were confirmed through medical records or histologically.

Table 268 Alcohol (as ethanol) from beer and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	25 (15 publications)
Studies included in forest plot of highest compared with lowest exposure	24 (6 publications)
Studies included in linear dose-response meta-analysis	23 (5 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 269 Alcohol (as ethanol) from beer and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR	**CUP SLR**	
Increment unit used	100 g/day of beer	10 g/day	
Studies (n)	3	23	
Cases	N/A	44 780	
RR (95%CI)	1.02 (0.99-1.06)	1.05 (1.03-1.08)	
Heterogeneity (I^2, p-value)	79%	0%, 0.75	
P value Egger test		0.45	
Stratified analyses in CUP SLR			
Geographic area	**Asia**	**Europe**	**North America**
Studies (n)	-	1	6
RR (95%CI)	-	1.05 (0.98-1.12)	1.11 (0.97-1.27)
Heterogeneity (I^2, p-value)	-	-	36%, 0.17
Adjustment for age, BMI and reproductive factors*	**Adjusted**	**Not adjusted**	
Studies (n)	23	-	
RR (95%CI)	1.05 (1.03-1.08)	-	
Heterogeneity (I^2, p-value)	0%, 0.75	-	

Table 270 Alcohol (as ethanol) from beer and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Jung, 2015 North America, Europe, Asia, Australia	19 cohorts: CARET* BCDDP CTS CNBSS CPS II CLUE II IWHS* JPHC I MCCS MEC NLCS* NYUWHS NIH-AARP* NHS (a) NHS (b) NHS II PLCO* SMC WHS SWLHCS	35 895, 6 to 18 years maximum follow-up	Variable in each cohort	Questionnaires	Incidence	≥15 g/day vs non-drinkers of all alcohol	1.29 (1.17-1.43)	Age, energy intake, ethnicity, education, BMI, height, physical activity, smoking status, age at menarche, menopausal status and HRT, parity and age at first birth, oral contraceptive use, family history of breast cancer, personal history of benign breast disease, wine, liquor	None
						10 g/day increase	1.05 (1.03-1.08)		
		13 461			ER+	≥15 g/day vs non-drinkers of all alcohol	1.30 (1.13-1.50)		
						10 g/day increase	1.06 (1.02-1.09)		
		4 915			ER-	≥15 g/day vs non-drinkers of all alcohol	1.37 (1.03-1.82)		
						10 g/day increase	1.06 (0.97-1.16)		
		11 069			PR+	≥15 g/day vs non-drinkers of all alcohol	1.36 (1.17-1.58)		
						10 g/day increase	1.07 (1.02-1.12)		
		4 854			PR-	≥15 g/day vs non-drinkers of all alcohol	1.23 (0.96-1.57)		
						10 g/day increase	1.04 (0.99-1.12)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Li, 2009 BRE80285 USA	KPMCP, Prospective Cohort, Age: 41 years, W	2 829/ 70 033 16 years	SEER cancer registry	Questionnaire	Incidence, breast cancer	Per 1 day/week	1.01 (0.97-1.06)	Age, alcohol consumption, beer consumption, BMI, breast diseases , educational level, ethnicity, family history, liquor consumption, marital status, parity, smoking habits, wine consumption	RR rescaled for an increment of 10g/day
Tjønneland, 2007 BRE80013 Denmark,France ,Germany,Greec e,Italy,Netherlan ds,Norway,Spai n,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	4 285/ 274 688 6.4 years	Population cancer registries and other procedures	FFQ + recall	Incidence, invasive breast cancer	Per 10 g/day	1.05 (0.98-1.12)	Age, age at menarche, parity (yes/no), current oral contraceptive use, current use of HRT, menopausal status, smoking status, education, height and weight	
Zhang, 2007 BRE20023 USA	WHS, Prospective Cohort, Age: 55 years	38 454 10 years	Medical notes	FFQ + questionnaire	Incidence, invasive & in situ breast cancer	Per 10 g/day	1.14 (1.02-1.28)	Age , age at first child, age at menarche, age at menopause, benign breast disease, BMI, energy Intake , family history, hormonal variables , liquor	None

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								consumption, menopausal status, parity/pregnancies , physical activity , randomized treatment assignment, supplements, wine	
Horn-Ross, 2002 BRE15412 USA	CTS, Prospective Cohort, Age: 21-103 years, W, Registered teachers	681/ 111 383 2 years	Cancer registry	FFQ	Incidence, invasive breast cancer	≥5 vs ≤0 g/day	0.90 (0.50-1.60)	Age , age at first child, age at menarche, BMI, energy Intake , ethnicity, family history, menopausal status, physical activity	The Pooling Project, Jung, 2015 was used in the main analysis, mid-points of exposure categories
Rohan, 2000a BRE16489 Canada	CNBSS, Case Cohort, Age: 40-59 years, W, Screening Program	1 336/ 56 837 10 years	All histology	FFQ-quantitative	Incidence, breast cancer	≥20.1 vs ≤0 g/day	0.76 (0.37-1.58)	Age , age at menarche, alcohol, energy Intake , family history, menopausal status, other design Issue, other specified factor, parity/ pregnancies, recruitment center	The Pooling Project, Jung, 2015 was used in the main analysis, mid-points of exposure categories
Zhang, 1999b BRE13965	FHS, Prospective	287/ 5 048	Pathology report + cancer registry	Interview	Incidence, breast cancer	≥3 vs ≤0 drinks/week	1.00 (0.50-2.20)	Age at first child, age at menarche,	Person years per category,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
USA	Cohort, Age: 12-62 years, W, Original and Offspring Cohorts	34.3 years						age at menopause, age-underlying cox models, alcohol, BMI, educational level, height, HRT use, parity/pregnancies, physical activity, smoking habits	intake in drinks/week converted to ethanol g/day using 10g ethanol per drink, mid-points of exposure categories
Willett, 1987a BRE13441 USA	NHS, Prospective Cohort, Age: 34-59 years, W, Registered nurses	327/ 89 538 4 years	Pathology report + self-reported	FFQ-semi-quantitative	Incidence, breast cancer	≥5 vs ≤0 g/day	1.40 (1.10-1.80)	Age , alcohol	The Pooling Project, Jung, 2015 was used in the main analysis, mid-points of exposure categories

*Studies in postmenopausal women only.

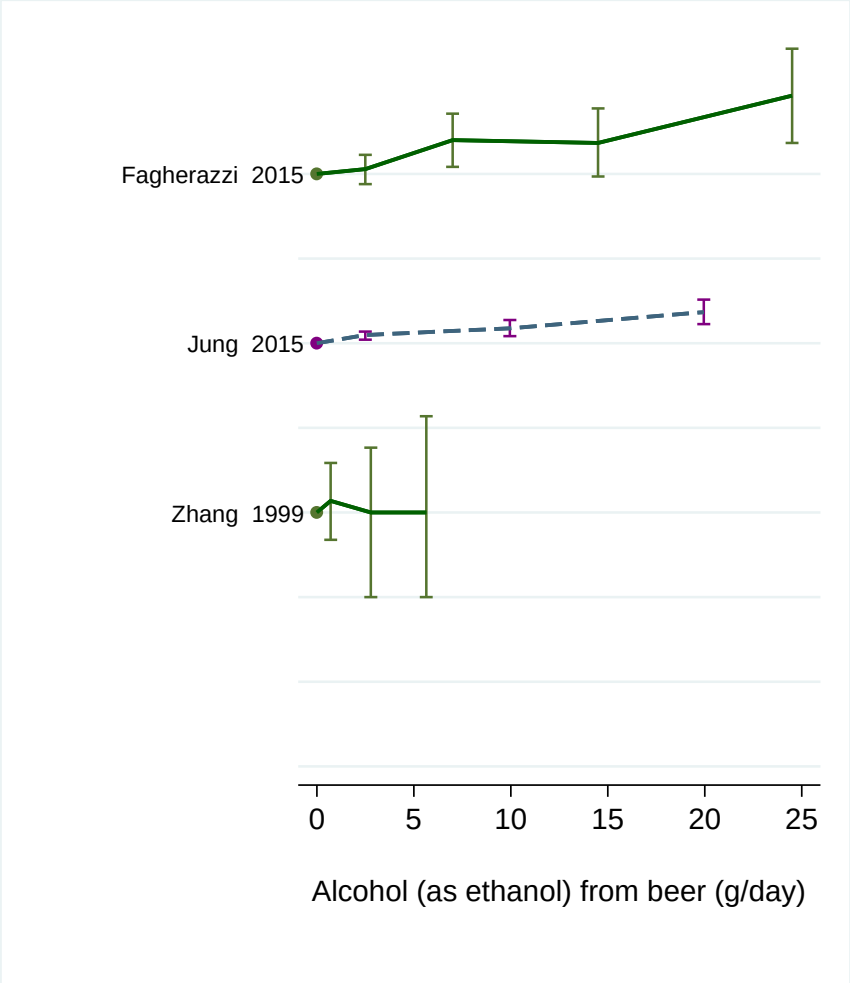
Table 271 Alcohol as (ethanol) from beer and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Fagherazzi, 2015 BRE80543 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W	2 812/ 66 481 16 years	Questionnaire and death certificate	Validated FFQ	Incidence, breast cancer	≥2 drinks/day vs non-alcohol consumers drinks/day	1.90 (1.29-2.79) Ptrend: <0.0001	Age, age at first child, age at menarche, age at menopause, BMI, breastfeeding, educational level, family history of breast cancer, history of benign breast disease, mammography, menopausal women and use of MHT, parity, physical activity, use of oral contraception, use of progestagens in premenopause	Superseded by Tjønneland, 2007
					ER-/PR-	≥2 drinks/day vs non-alcohol consumers	2.52 (1.00-6.36)		Analysis by hormone receptor status was not conducted
Klatsky, 2015 BRE80587	KPMCP, Prospective	69 153	Cancer registry	Questionnaire	Incidence, breast cancer	≥3 vs ≤1 drinks/day	2.00 (1.10-3.40)	Age, alcohol Intake, BMI,	Superseded by Li, 2009 in the

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
USA	Cohort, W	17.8 years						educational level, marital status, race/ethnicity, smoking	dose-response meta-analysis, only used in the highest vs lowest analysis
Visvanathan, 2007 BRE80020 USA	CLUE II, Nested Case Control, Age: 57 years, W	14 624		FFQ + questionnaire	Incidence, breast cancer	Beer drinkers vs non beer drinkers	0.95 (0.56-1.63)	Age , menopausal status	The Pooling Project, Jung, 2015 was used instead, only two levels of exposure
Jain, 2000 BRE17653 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W, Screening Program	223/ 49 165 10.3 years	Death certificate	FFQ-quantitative	Mortality, breast cancer	Per 10 g/day	1.00 (0.98-1.03)	Age , age at menarche, BMI, educational level, energy Intake , family history, mammography, menopausal status, oral contraceptive use, other specified factor, parity/pregnancies, recruitment center, smoking habits	Excluded, study reported on mortality
Goodman, 1997 BRE03352 Japan	LSS, Prospective Cohort, W, Atomic bomb	120/ 22 200 8.31 years	Partially histological - over 80%	Questionnaire	Incidence, breast cancer	Drinker vs never drinker	0.63 (0.36-1.10)	Age , other age Indicator, other specified factor, place of residence	Excluded, only two levels of exposure

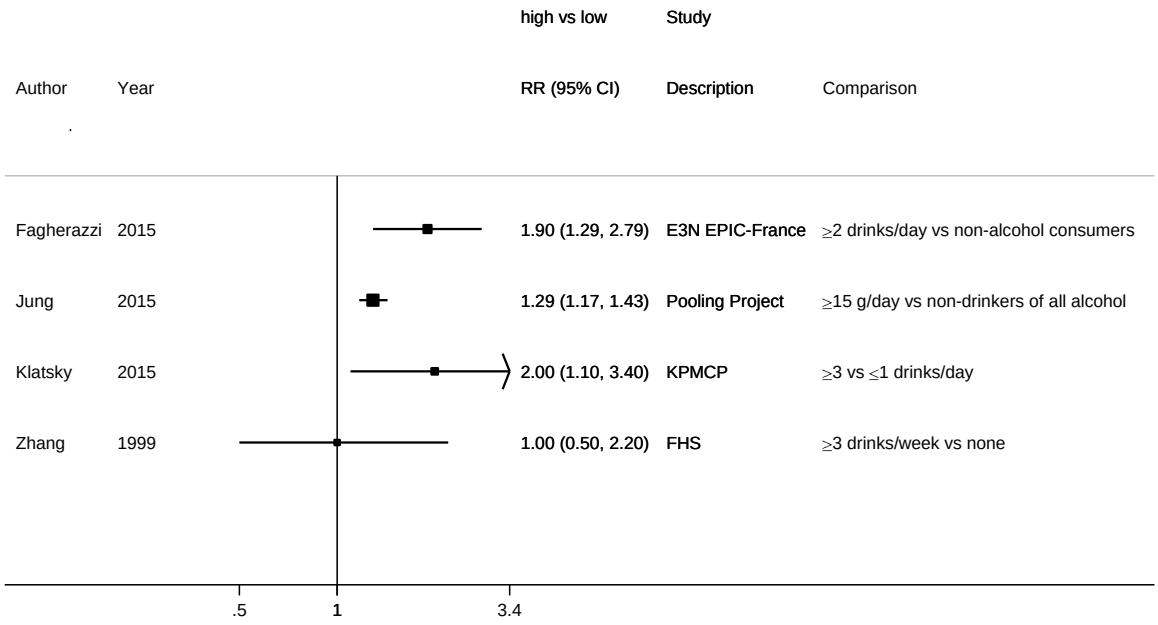
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	survivors								
Friedenreich, 1993 BRE17508 Canada	CNBSS, Nested Case Control, W, Screening Program	519/ 1182 controls 5.5 years	All histology	FFQ	Incidence, breast cancer	≥10 vs ≤ 0 g/day	1.12 (0.62-2.02)	Age , energy Intake , family history, menopausal status, other specified factor, parity/pregnancies, smoking habits	Superseded by Rohan, 2000a
Hiatt, 1988a BRE03888 USA	KPMCP, Case Cohort, W	303/ 58 347 6 years	Hospital discharge records	FFQ	Incidence, breast cancer	Regular drinkers vs lifelong abstainers	1.37 (0.76-2.47)	Age , BMI, ethnicity, smoking habits	Superseded by Li, 2009

Figure 348 RR estimates of breast cancer by levels of alcohol (as ethanol) from beer



NOTE: Fagherazzi, 2015 (E3N EPIC-France) is displayed instead of Tjønneland, 2007 (EPIC) with only a continuous risk estimate available.

Figure 349 RR (95% CI) of breast cancer for the highest compared with the lowest level of alcohol (as ethanol) intake from beer



NOTE: Fagherazzi, 2015 (E3N EPIC-France) is used instead of Tjønneland, 2007 (EPIC) and Klatsky, 2015 (KPMCP) is used instead of Li, 2009 with only continuous risk estimates available.

Figure 350 Relative risk of breast cancer incidence for 10g/day increase of alcohol (as ethanol) intake from beer

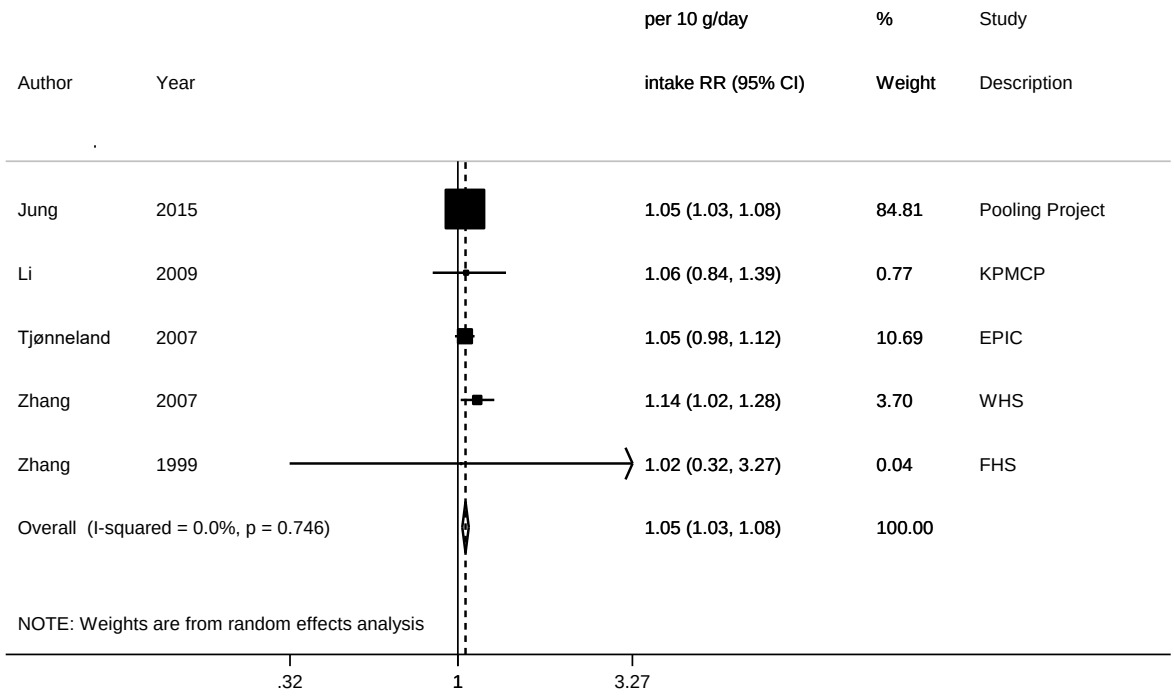


Figure 351 Funnel plot of studies included in the dose response meta-analysis of alcohol (as ethanol) from beer and breast cancer

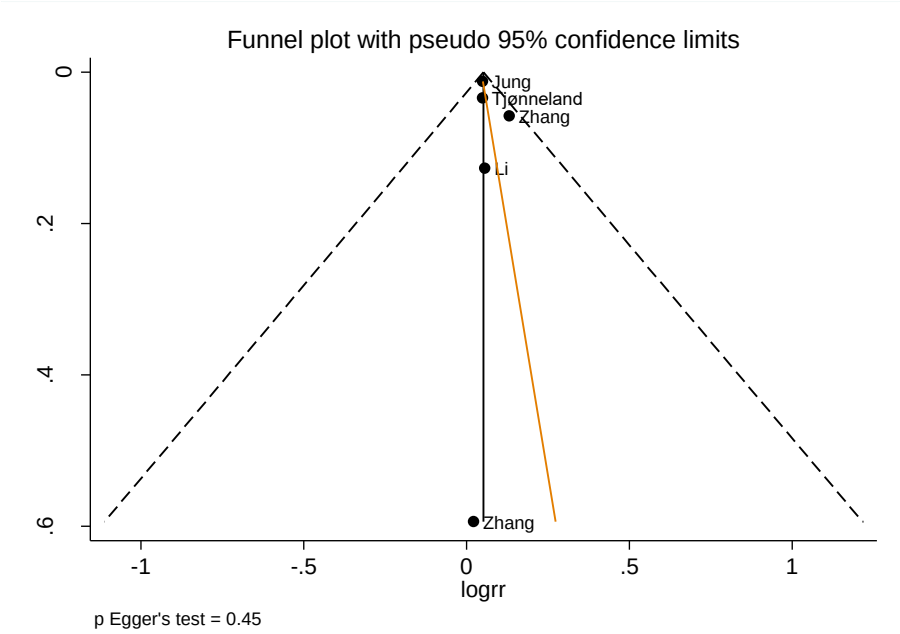
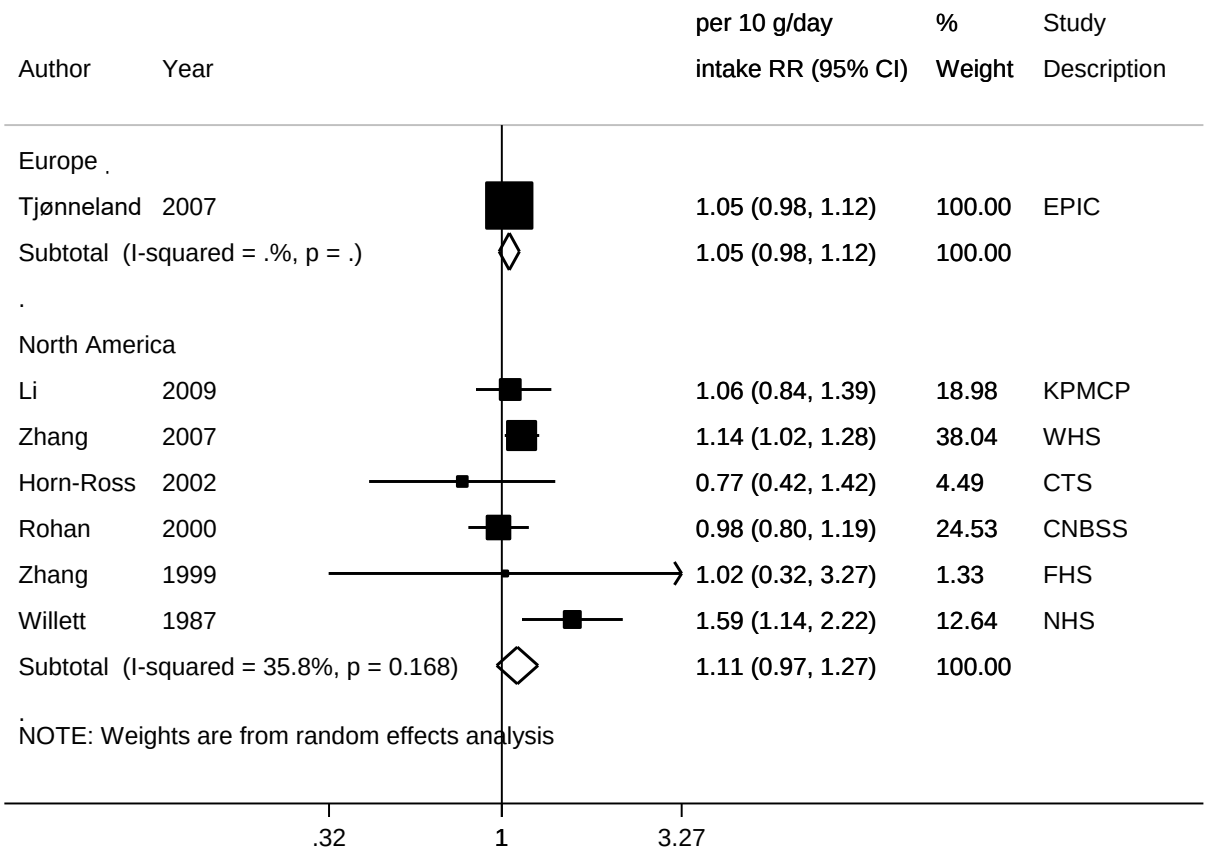


Figure 352 Relative risk of breast cancer (any) incidence for 10g/day increase of alcohol (as ethanol) intake from beer, by geographic location



Premenopausal breast cancer

Summary

Main results:

Summary

Main results:

Three studies (818 cases) (3 publications) were included in the dose-response meta-analysis. Alcohol (as ethanol) intake from beer was associated with a significantly higher risk of premenopausal breast cancer.

Study quality:

Alcohol consumption was estimated using questionnaires in all three studies. Friedenreich, 1993 did not specify if former/past drinkers were excluded from the reference category, Fagherazzi, 2015 indicated that lowest intake (reference) category included 0 g/day consumption over the previous year and one study included above 0 g/day intakes in the lowest category (Petri, 2004).

Table 272 Alcohol (as ethanol) from beer and premenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	3 (3 publications)
Studies included in forest plot of highest compared with lowest exposure	3 (3 publications)
Studies included in linear dose-response meta-analysis	3 (3 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 273 Alcohol (as ethanol) from beer and premenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR	**CUP SLR**
Increment unit used	100 g/day of beer	10 g/day
Studies (n)	2	3
Cases	311	818
RR (95%CI)	1.04 (0.96-1.13)	1.32 (1.06-1.64)
Heterogeneity (I^2, p-value)	0%	0%, 0.71

Table 274 Alcohol (as ethanol) from beer and premenopausal breast cancer risk. Main characteristics of studies identified

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Fagherazzi, 2015 BRE80543 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W	507/ 66 481 16 years	Questionnaire and death certificate	Validated FFQ	Incidence, breast cancer, premenopausal at baseline	≥2 drinks/day vs non-alcohol consumers	2.04 (0.93-4.48)	Age, age at first child, age at menarche, age at menopause, BMI, breastfeeding, educational level, family history of breast cancer, history of benign breast disease, mammography, menopausal women and use of MHT, parity, physical activity, use of oral contraception, use of progestagens in premenopause	Intake in drinks/day converted to ethanol g/day using 10g ethanol/drink, mid-points of exposure categories, person-years per category
Petri, 2004 BRE16325 Denmark	CCPPS, Prospective Cohort, Age: 20-91 years, W	76/ 13 074	Partially histological - over 80%	Questionnaire	Incidence, breast cancer, premenopausal	≥6.1 vs 0-0.9 drinks/week	0.49 (0.15-1.61)	Age, HRT use, other design issue, parity/pregnancies	Drinks/week converted to ethanol g/day using 12g ethanol/drink, mid-points of exposure categories
Friedenreich, 1993 BRE17508 Canada	CNBSS, Nested Case Control, W, Screening Program	235/ 491 controls 5.5 years	All histology	FFQ	Incidence, breast cancer, premenopausal	≥10 g/day vs non-drinkers of beer	2.06 (0.91-4.68)	Age , energy intake, family history, parity/pregnancies, smoking habits	Mid points of exposure categories

Figure 353 RR (95% CI) of premenopausal breast cancer for the highest compared with the lowest level of alcohol (as ethanol) intake from beer

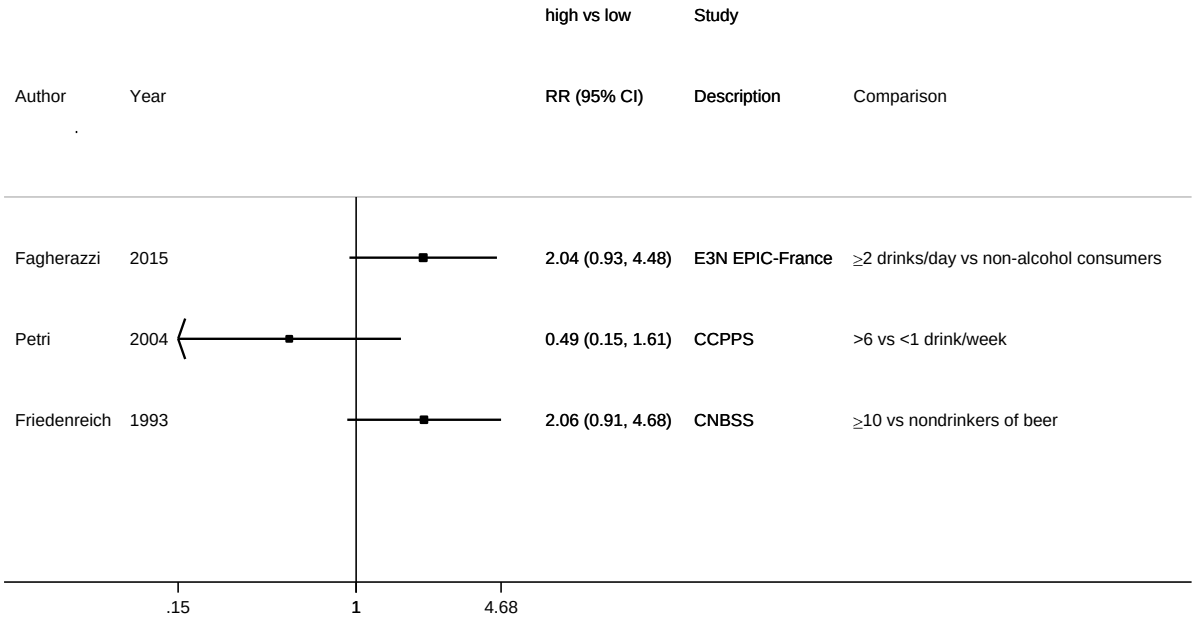


Figure 354 RR estimates of premenopausal breast cancer by levels of alcohol (as ethanol) from beer

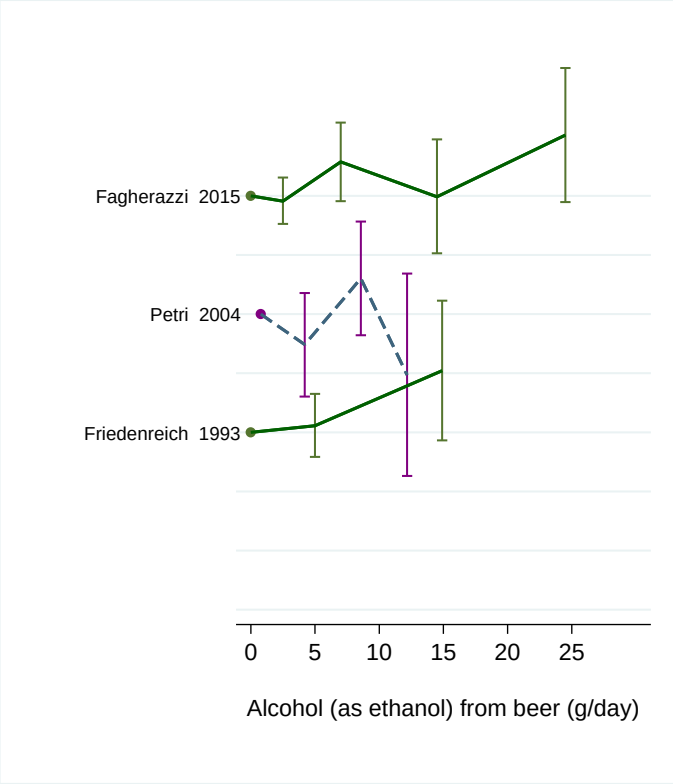
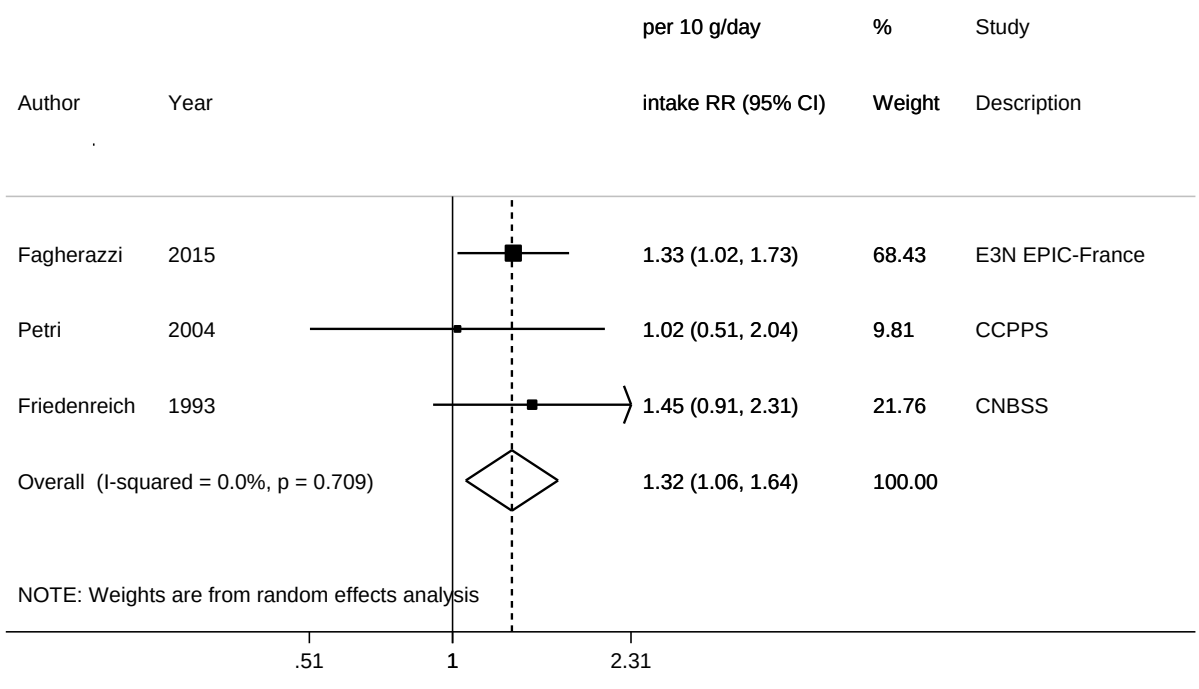


Figure 355 Relative risk of premenopausal breast cancer incidence for 10g/day increase of alcohol (as ethanol) intake from beer



Postmenopausal breast cancer

Summary

Main results:

Seven studies (seven publications) were included in the dose-response meta-analysis. Alcohol (as ethanol) intake from beer was not associated with postmenopausal breast cancer risk.

Two studies were excluded from the dose-response meta-analysis (Lew, 2009, Feigelson, 2001). Lew, 2009 analysed only two levels of alcohol (as ethanol) intake from beer and reported significantly positive association with postmenopausal breast cancer. Feigelson, 2001 reported nonsignificant positive association with breast cancer mortality.

Postmenopausal breast cancer risk and alcohol (as ethanol) intake from beer by hormone receptor status:

Only one study reported results by hormone receptor status and was excluded from the dose-response meta-analysis (Kabat, 2011). In this study, beer intake was nonsignificantly positively associated with postmenopausal ER+ breast cancer and not associated with triple negative postmenopausal breast cancer.

Moderate heterogeneity was observed. There was an evidence of a significant publication or small study bias.

Sensitivity and stratified analyses:

The summary RRs ranged from 1.02 (95% CI=0.91-1.12) when Fagherazzi, 2015 was omitted to 1.09 (95% CI=0.95-1.24) when Friedenreich, 1993 was omitted.

The association remained not significant in stratified analysis by geographical location and study adjustment.

Study quality:

Alcohol consumption was estimated using questionnaires in all studies. In addition, one study used 7 day food record (Mattisson, 2004a). Risk estimate from one study used in the dose-response meta-analysis was in drinkers only (Tjønneland, 2003) and one study included intakes of ≥0 g/day in the reference category (Petri, 2004). Three studies defined reference category as 0 g/day intake over the previous year (Fagherazzi, 2015, Park, 2014, Mattisson, 2004a). All remaining studies did not indicate if lowest category included former drinkers.

Case ascertainment was through cancer registries, death certificates or when active follow-up, diagnosis were confirmed through medical records.

Table 275 Alcohol (as ethanol) from beer and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	10 (11 publications)
Studies included in forest plot of highest compared with lowest exposure	6 (6 publications)
Studies included in linear dose-response meta-analysis	7 (7 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 276 Alcohol (as ethanol) from beer and postmenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR	**CUP SLR**	
Increment unit used	100 g/day of beer	10 g/day	
Studies (n)	4	7	
Cases	N/A	7 798	
RR (95%CI)	1.00 (0.96-1.04)	1.06 (0.94-1.21)	
Heterogeneity (I^2, p-value)	10%	66%, 0.007	
P value Egger test		0.95	
Stratified analyses in CUP SLR			
Geographic area	**Asia**	**Europe**	**North America**
Studies (n)	-	5	2
RR (95%CI)	-	1.10 (0.91-1.34)	0.96 (0.74-1.23)
Heterogeneity (I^2, p-value)	-	65%, 0.02	40%, 0.20

Adjustment for age, BMI and reproductive factors*	**Adjusted**	**Not adjusted**	
Studies (n)	5	2	
RR (95%CI)	1.10 (0.96-1.26)	0.75 (0.51-1.10)	
Heterogeneity (I^2, p-value)	73%, 0.005	0%, 0.96	

Table 277 Alcohol (as ethanol) from beer and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Fagherazzi, 2015 BRE80543 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W	2 305/ 66 481 16 years	Questionnaire and death certificate	Validated FFQ	Incidence, breast cancer, postmenopausal at baseline	≥2 drinks/day vs non-alcohol consumers	1.85 (1.19-2.89)	Age, age at first child, age at menarche, age at menopause, BMI, breastfeeding, educational level, family history of breast cancer, history of benign breast disease, mammography, menopausal women and use of MHT, parity, physical activity, use of oral contraception, use of progestagens in premenopause	Intake in drinks/day converted to ethanol g/day using 10g ethanol/drink, mid-points of exposure categories, person-years per category
Park, 2014 BRE80494 USA	MEC, Prospective Cohort, Age: 60.9 years, W, Postmenopausal	3 885/ 85 089 12.4 years	SEER cancer registry for Hawaii & California & National Death Index	Quantitative FFQ	Incidence, breast cancer	per 10 g/day	1.02 (0.98-1.06)	Age, age at first child birth, age at menarche, age at menopause, BMI, educational level, energy intake, ethnicity, family history of breast cancer, hormone replacement therapy, number	None

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								of children, physical activity, smoking status, type of menopause	
Mattisson, 2004a BRE17807 Sweden	MDCS, Prospective Cohort, Age: 50- years, W, Postmenopausal	342/ 11 726 7.6 years	Partially histological - over 80%	7-day record + questionnaire	Incidence, breast cancer, postmenopausal	≥36.2 vs 0.1-5.6	1.44 (0.75-2.75)	Age , age at first child, age at menarche, educational level, energy Intake , height, HRT use, leisure time physical activity, other design issue, other nutritional factors, season of Interview, smoking habits, waist circumference	Reference category changed using Hamling's method
Petri, 2004 BRE16325 Denmark	CCPPS, Prospective Cohort, Age: 20-91 years, W	144/ 13 074	Partially histological - over 80%	Questionnaire	Incidence, breast cancer, postmenopausal	≥6.1 vs 0-0.9 drinks/week	0.62 (0.25-1.55)	Age , HRT use, other design issue, parity/pregnancies	Drinks/week converted to ethanol g/day using 12g ethanol/drink, mid-points of exposure categories
Tjønneland, 2003 BRE12350	DCH, Prospective Cohort,	416/ 23 778 4.7 years	Partially histological - over 80%	FFQ	Incidence, breast cancer, postmenopausal	24.1-60 vs 0.1-6 g/day	0.89 (0.44-1.81)	Age at first child, age-underlying cox models,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Denmark	Age: 50-64 years, W, Postmenopausal				Postmenopausal	Per 10 g/day	0.98 (0.85-1.14)	alcohol, benign breast disease, BMI, duration of HRT use, educational level, HRT use, parity/pregnancies	None
van den Brandt, 1995 BRE12719 Netherlands	NLCS, Case Cohort, Age: 55-69 years, W, Postmenopausal	422/ 62 573 3.3 years	All histology	Questionnaire	Incidence, breast cancer, postmenopausal	Per 1 g/day	0.93 (0.82-1.05)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, educational level, energy Intake , family history, family history, oral contraceptive use, parity/pregnancies , smoking habits	RR rescaled for an increment of 10g/day
Friedenreich, 1993 BRE17508 Canada	CNBSS, Nested Case Control, W, Screening Program	284/ 691 controls 5.5 years	All histology	FFQ	Incidence, breast cancer, postmenopausal	≥10 vs ≤0 g/day	0.58 (0.23-1.46)	Age, energy intake, family history of breast cancer, parity/pregnancies , smoking habits	Mid points of exposure categories

Table 278 Alcohol as (ethanol) from beer and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Kabat, 2011 BRE80344 USA	WHI, Prospective Cohort, Age: 50-79 years, W	2 479/ 148 030 8 years	Mail or telephone questionnaires verified by trained physician adjudicators	FFQ	Incidence, breast cancer ER+	≥3 vs 0 serving/week	1.01 (0.73-1.38)	Age, age at first child birth, age at menarche, age at menopause, BMI, breast biopsies, contraception, educational level, ethnicity, family history of breast cancer, HRT use, mammogram In the past 2 years, physical activity, smoking, treatment allocation, waist circumference	Excluded, analysis by hormone receptor status was not conducted
		300/			Incidence, triple negative breast cancer	≥3 vs 0 serving/week	1.60 (0.79-3.26)		
Li, 2010 BRE80336	WHI-OS, Prospective Cohort, Age: 50-79 years, Postmenopausal	2 459/ 87 724	Medical record	Self-administered questionnaire	Incidence, invasive cancer	≥1 drink/day vs never drinker	1.90 (1.34-2.70)	Age, BMI, educational level, ethnicity, family history of breast cancer, Gail model risk, HRT use, mammography, parity, race, smoking	Superseded by Kabat, 2011, no cases or person-years per category
		1 805			ductal carcinomas		1.65 (1.04-2.60)		
		720			lobular carcinomas		3.55 (1.85-6.82)		
Lew, 2009 BRE80256 USA	NIH-AARP, Prospective Cohort,	5 461/ 184 418 7 years	Cancer registry		Incidence, breast cancer	3 vs 0 drinks/day	1.73 (1.22-2.47)	Age, age at first child birth, age at menopause, BMI,	Excluded, only two levels of exposure,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 50-71 years, W, Postmenopausal							breast biopsies, energy Intake, family history of cancer, fat intake, folate intake, height, HRT use, liquor consumption, oral contraceptive use, parity, physical activity, race, smoking habits, wine	used in the HvL analysis only
Feigelson, 2001 BRE19514 USA, Puerto Rico	CPS II, Prospective Cohort, W	463/ 242 010 14 years	Death certificate	Questionnaire	Mortality, breast cancer, postmenopausal	≥3 vs ≤0 drinks/day	1.29 (0.68-2.45)	Age , age at first child, age at menarche, age at menopause, BMI, educational level, ethnicity, family history, food, height, HRT use, other specified factor, physical activity, smoking habits, supplements	Excluded, outcome is mortality

Figure 356 RR estimates of postmenopausal breast cancer by levels of alcohol (as ethanol) from beer

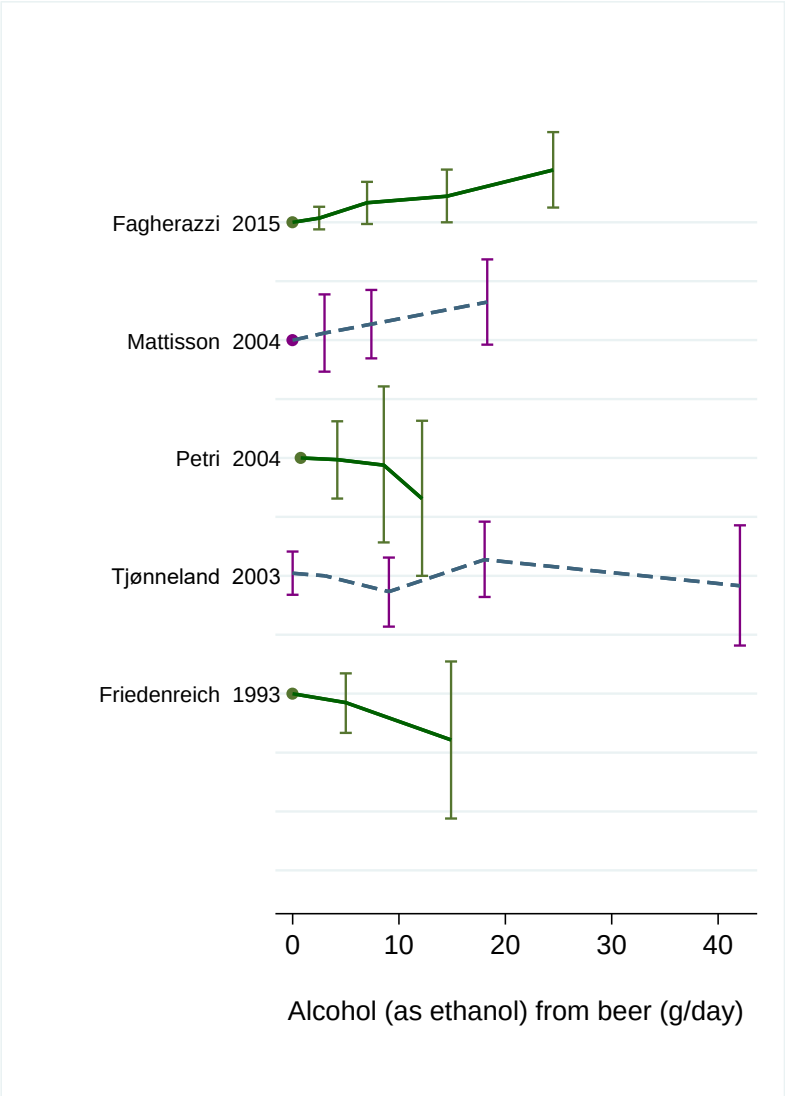


Figure 357 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest level of alcohol (as ethanol) intake from beer

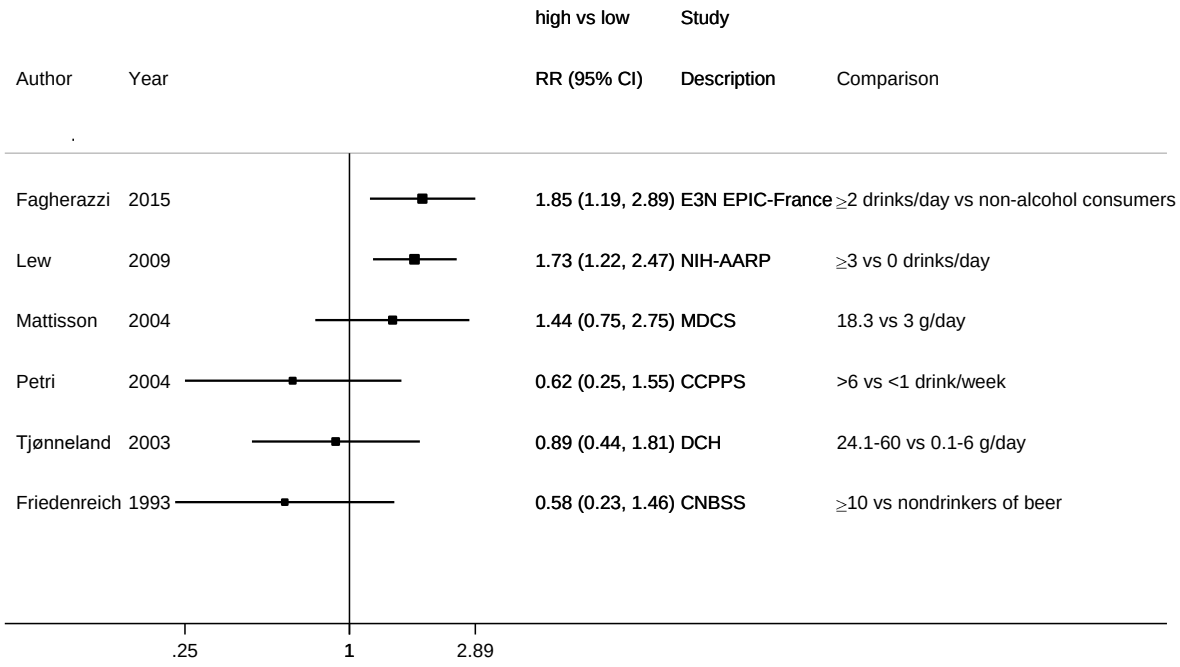


Figure 358 Relative risk of postmenopausal breast cancer incidence for 10g/day increase of alcohol (as ethanol) intake from beer

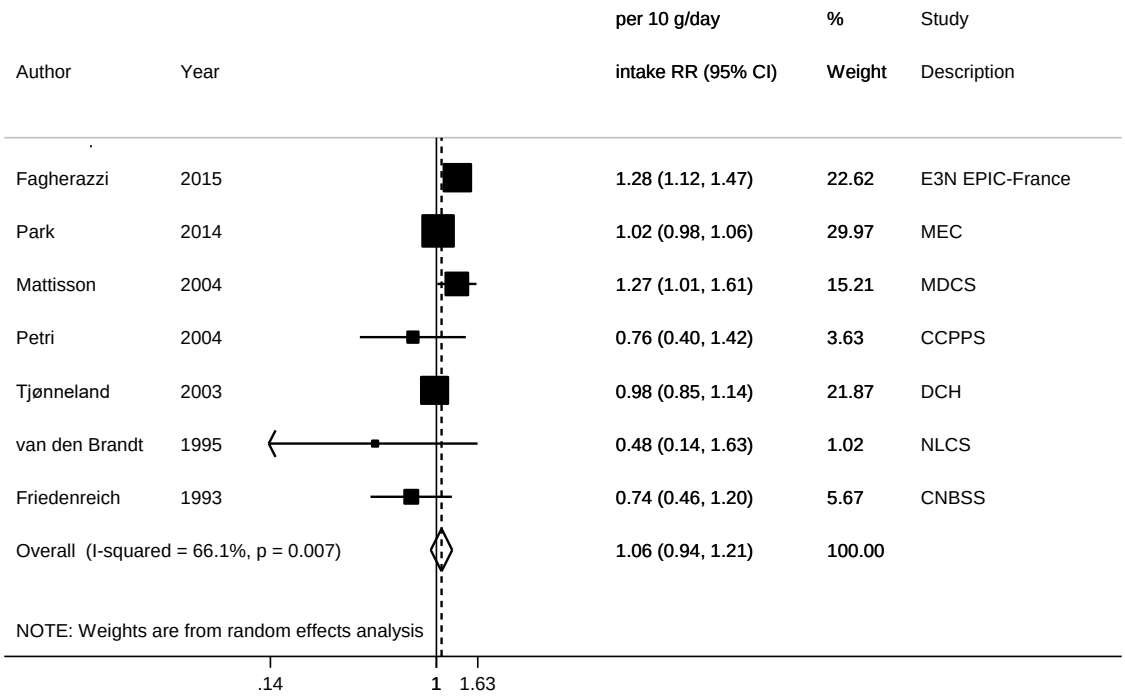


Figure 359 Funnel plot of studies included in the dose response meta-analysis of alcohol (as ethanol) from beer and postmenopausal breast cancer

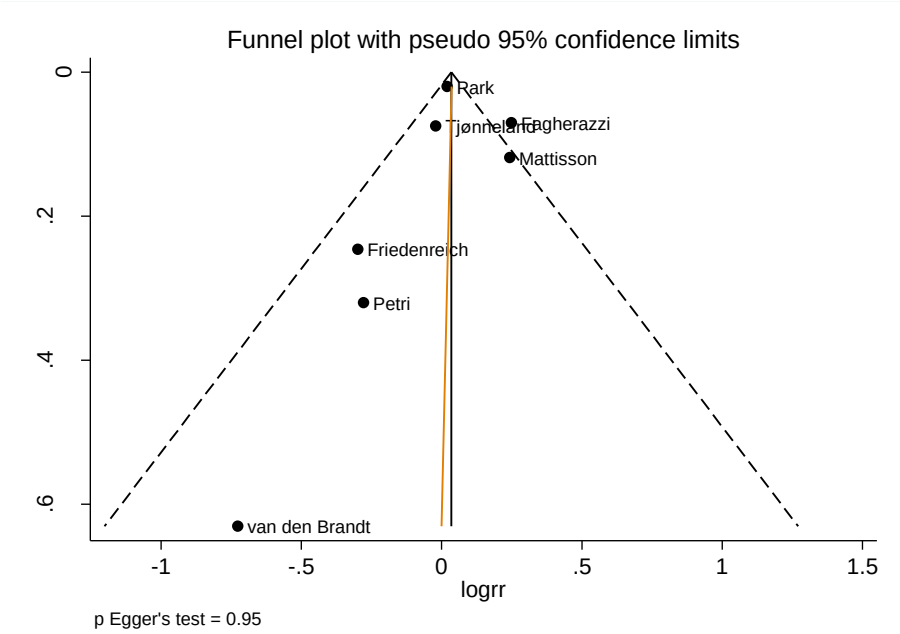
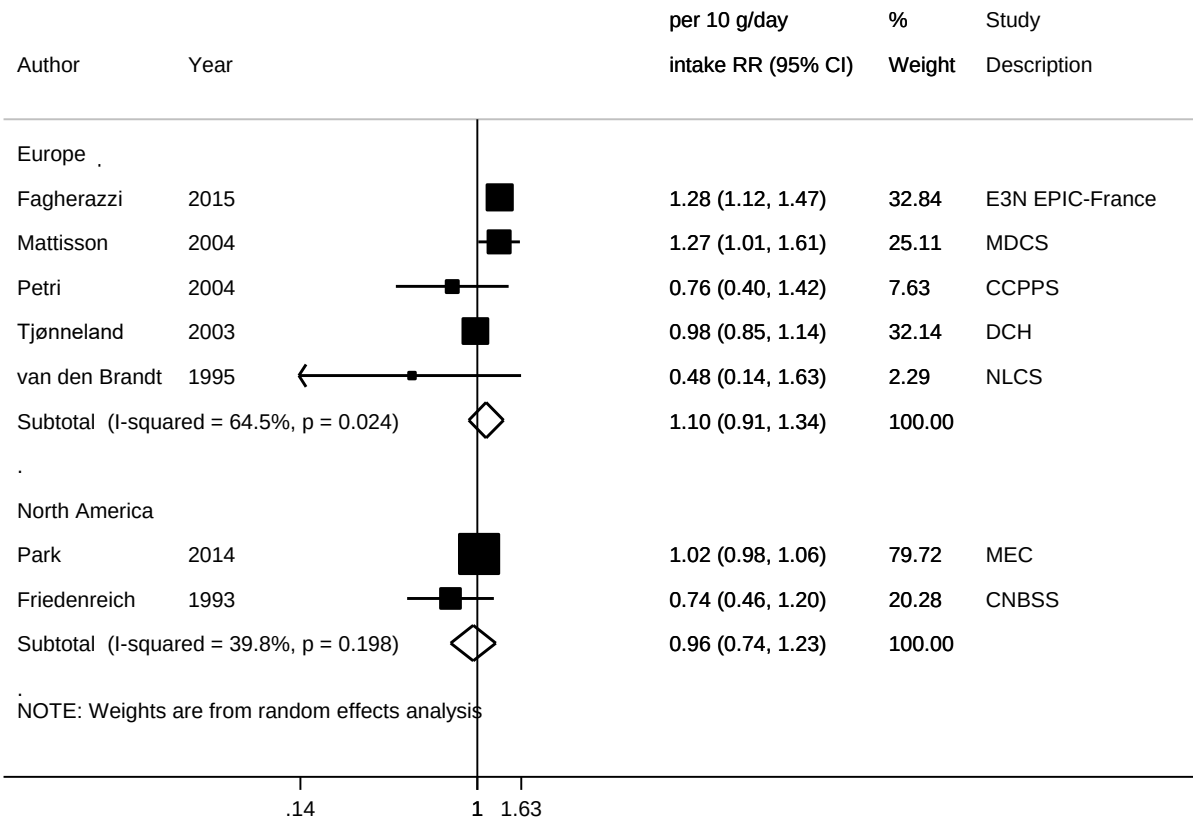


Figure 360 Relative risk of postmenopausal breast cancer incidence for 10g/day increase of alcohol (as ethanol) intake from beer, by geographic location



5.4.1.2 Alcohol (as ethanol) from wine

Cohort studies

Overall summary

Twenty six publications from 33 studies were identified. Dose-response meta-analyses were conducted to examine the association of alcohol (as ethanol) from wine with risk of breast cancer (any), premenopausal and postmenopausal breast cancer.

Table 279 Summary of results of the dose-response meta-analysis in the CUP SLR

	Breast cancer (any)	Premenopausal breast cancer	Postmenopausal breast cancer
Increment unit used	10 g/day	10 g/day	10 g/day
Pooling Project of Cohort Studies*			
Studies (n)	20	-	-
Cases	36 177	-	-
RR (95%CI)	1.07 (1.05-1.09)	-	-
Heterogeneity (I^2, p-value)	0.47	-	-
Pooling Project and not overlapping studies identified in the CUP			
Studies (n)	24	3	6
Cases	66 318	818	3 913
RR (95%CI)	1.06 (1.02-1.10)	1.17 (0.79-1.73)	1.12 (1.08-1.17)
Heterogeneity (I^2, p-value)	60%, 0.04	74%, 0.02	0%, 0.96
P value Egger test	0.79	-	0.008

*Jung 2015; analyses restricted to women drinking <55g/day.

Breast cancer (any)

Summary

Main results:

Twenty four studies (66 318 cases) (5 publications) were included in the dose-response meta-analysis. Alcohol (as ethanol) intake from wine was associated with a significantly higher risk of breast cancer.

Two studies were excluded from the dose-response meta-analysis (Hirvonen, 2006, Jain, 2000). One study reported that wine intake is associated with a significantly increased risk of breast cancer mortality (Jain, 2000). Hirvonen, 2006 reported positive but not significant association between white or red wine intake and breast cancer risk.

Moderate and significant heterogeneity was observed. There was no evidence of a significant publication or small study bias.

Breast cancer risk and alcohol (as ethanol) intake from wine by hormone receptor status:

Only one study reported breast cancer risk by hormone receptor status (Fagherazzi, 2015). Wine intake was associated with a significantly positively higher risk of ER+/PR+ breast cancer, comparing intake of ≥2 drinks/day vs non-alcohol consumers. The Pooling Project (Jung, 2015) reported significantly higher risk of ER+, PR-, PR+, PR- breast cancer in the dose-response meta-analysis and comparing highest versus lowest intakes of wine.

Sensitivity and stratified analyses:

The summary RRs ranged from 1.05 (95% CI=1.01-1.09) when Allen, 2009 was omitted to 1.07 (95% CI=1.05-1.09) when Tjønneland, 2007 was omitted.

Study quality:

Alcohol consumption was estimated using questionnaires which were country-specific in the EPIC study (Tjønneland, 2007). Risk estimates that were used in the dose-response meta-analysis were among drinkers in two studies (Allen, 2009 (MWS), Li, 2009 (KPMCP)). Rohan, 2000a and Tjønneland, 2007 indicated that reference category might have included former/past drinkers along with lifelong abstainers. All remaining studies did not specify if reference category excluded former/past drinkers.

Case ascertainment was through cancer registries or when active follow-up, diagnosis were confirmed through medical records.

Table 280 Alcohol (as ethanol) from wine and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	26 (16 publications)
Studies included in forest plot of highest compared with lowest exposure	23 (4 publications)
Studies included in linear dose-response meta-analysis	24 (5 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 281 Alcohol (as ethanol) from wine and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR	CUP SLR	
Increment unit used	1 time/day	10 g/day	
Studies (n)	3	24	
Cases	2 182	66 318	
RR (95%CI)	1.08 (0.96-1.22)	1.06 (1.02-1.10)	
Heterogeneity (I^2, p-value)	66%	60%, 0.04	
		0.79	
Stratified analyses in CUP SLR			
Geographic area	**Asia**	**Europe**	**North America**
Studies (n)	-	2	5
RR (95%CI)	-	1.06 (0.96-1.17)	1.10 (1.00-1.22)
Heterogeneity (I^2, p-value)	-	79%, 0.03	40%, 0.16
Adjustment for age, BMI and reproductive factors*	**Adjusted**	**Not adjusted**	
Studies (n)	23	1	
RR (95%CI)	1.05 (1.01-1.09)	1.13 (1.04-1.24)	
Heterogeneity (I^2, p-value)	62%, 0.05	-	

* Pooling Project and not overlapping studies identified in the CUP. Only one study (Allen, 2009) was unadjusted for reproductive factors.

Table 282 Alcohol (as ethanol) from wine and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Jung, 2015 North America, Europe, Asia, Australia	20 cohorts: CARET* BCDDP CTS CNBSS CPS II CLUE II IWHS* JPHC I MCCS MEC NLCS* NYUWHS NIH-AARP* NHS (a) NHS (b) NHS II Prospective Study on Hormones, Diet and Breast Cancer (Italy) PLCO* SMC WHS SWLHCS	36 177, 6 to 18 years maximum follow-up	Variable in each cohort	Questionnaires	Incidence	≥15 g/day vs non-drinkers of all alcohol	1.23 (1.13-1.33)	Age, energy intake, ethnicity, education, BMI, height, physical activity, smoking status, age at menarche, menopausal status and HRT, parity and age at first birth, oral contraceptive use, family history of breast cancer, personal history of benign breast disease, wine, liquor	None
						10 g/day increase	1.07 (1.05-1.09)		
		21 199			ER+	≥15 g/day vs non-drinkers of all alcohol	1.34 (1.19-1.52)		
						10 g/day increase	1.12 (1.09-1.15)		
		4 981			ER-	≥15 g/day vs non-drinkers of all alcohol	1.21 (1.02-1.43)		
						10 g/day increase	1.10 (1.03-1.18)		
		15 368			PR+	≥15 g/day vs non-drinkers of all alcohol	1.31 (1.12-1.53)		
						10 g/day increase	1.11 (1.07-1.15)		
		6 818			PR-	≥15 g/day vs non-drinkers of all alcohol	1.35 (1.19-1.54)		
						10 g/day increase	1.11 (1.07-1.16)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Allen, 2009 BRE80227 UK	MWS, Prospective Cohort, Age: 55 years, W	21 971/ 1 280 296 7.2 years	National health records	Questionnaire (general), wine drinkers only	Incidence, breast cancer	Per 10 g/day	1.13 (1.04-1.24)	Age, area of residence, BMI, HRT use, OC use, physical activity, smoking habits, socio-economic status	
Li, 2009 BRE80285 USA	KPMCP, Prospective Cohort, Age: 41 years, W	2 829/ 70 033 16 years	SEER registry	Questionnaire, drinkers only	Incidence, breast cancer	Per 1 day/week	1.02 (0.99-1.04)	Age, alcohol consumption, beer consumption, BMI, breast diseases , educational level, ethnicity, family history, liquor consumption, marital status, parity, smoking habits	RR rescaled for an increment of 10g/day
Tjønneland, 2007 BRE80013 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	/274 688 6.4 years	Population cancer registries and other procedures	FFQ + recall	Incidence, Invasive breast cancer	Per 10 g/day	1.02 (0.99-1.05)	Age, age at menarche, parity (yes/no), current oral contraceptive use, current use of HRT, menopausal status, smoking status,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								education, height and weight	
Horn-Ross, 2002 BRE15412 USA	CTS, Prospective Cohort, Age: 21-103 years, W, Registered teachers	681/ 111 383 2 years	Cancer registry	FFQ	Incidence, Invasive breast cancer	≥20 vs ≤0 g/day	1.70 (1.20-2.40)	Age, age at first child, age at menarche, BMI, energy Intake , ethnicity, family history, menopausal status, physical activity	The Pooling Project, Jung, 2015 was used in the main analysis, mid-points of exposure categories
Rohan, 2000a BRE16489 Canada	CNBSS, Case Cohort, Age: 40-59 years, W, Screening Program	1 336/ 56 837 10 years	All histology	FFQ-quantitative, ex-drinkers not identified for exclusion	Incidence, breast cancer	≥20.1 vs ≤0 g/day	0.79 (0.53-1.19)	Age, age at menarche, alcohol, energy Intake , family history, menopausal status, parity/pregnancies, recruitment center, RR remained similar after adjustment for Quetelet's index	The Pooling Project, Jung, 2015 was used in the main analysis, mid-points of exposure categories
Zhang, 1999b BRE13965 USA	FHS, Prospective Cohort, Age: 12-62 years, W,	287/ 5 048 34.3 years	Pathology report + cancer registry	Interview	Incidence, breast cancer,	≥3 vs ≤0 drinks/week	1.00 (0.70-1.30)	Age at first child, age at menarche, age at menopause, age-underlying cox models, alcohol,	Person years per category, intake in drinks/week converted to ethanol g/day using 10g

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
	Original and Offspring Cohorts							BMI, educational level, height, HRT use, parity/pregnancies, physical activity , smoking habits	ethanol per drink, mid-points of exposure categories
Willett, 1987a BRE13441 USA	NHS, Prospective Cohort, Age: 34-59 years, W, Registered nurses	327/ 89 538 4 years	Pathology report + self-reported	FFQ-semi-quantitative	Incidence, breast cancer,	≥5 vs ≤0 g/day	1.10 (0.80-1.40)	Age	The Pooling Project, Jung, 2015 was used in the main analysis, mid-points of exposure categories

*Studies in postmenopausal women only.

Table 283 Alcohol as (ethanol) from wine and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Fagherazzi, 2015 BRE80543 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W	2 812/ 66 481 16 years	Questionnaire and death certificate	Validated FFQ	Incidence, breast cancer	≥2 drinks/day vs non-alcohol consumers	1.25 (1.06-1.47)	Age, age at first child, age at menarche, age at menopause, BMI, breastfeeding, educational level, family history of breast cancer, history of benign breast disease, mammography, menopausal women and use of MHT, parity, physical activity, use of oral contraception, use of progestagens in premenopause	Superseded by Tjønneland, 2007
					ER+/PR+		1.54 (1.23-1.93)		Analysis by hormone receptor status was not conducted
Klatsky, 2015 BRE80587 USA	KPMCP, Prospective Cohort, W	69 153 17.8 years	Cancer registry	Questionnaire	Incidence, breast cancer	≥3 vs ≤1 drinks/day	1.10 (0.80-1.50)	Age, alcohol Intake, BMI, educational level, marital status, race/ethnicity, smoking	Superseded by Li, 2009 in the dose-response meta-analysis, only used in the highest vs lowest analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Visvanathan, 2007 BRE80020 USA	CLUE II, Nested Case Control, Age: 57 years, W	14 624		FFQ + questionnaire	Incidence, breast cancer	Wine drinkers vs non wine drinkers	1.60 (1.01-2.54)	Age, menopausal status	The Pooling Project, Jung, 2015 was used, only two levels of exposure
Zhang, 2007 BRE20023 USA	WHS, Prospective Cohort, Age: 55 years	/38 454 10 years	Medical notes	FFQ + questionnaire	Incidence, Invasive & in situ breast cancer	Per 10 g/day, red wine	0.99 (0.79-1.24)	Age, age at first child, age at menarche, age at menopause, beer consumption, benign breast disease, BMI, energy Intake , family history, hormonal variables , liquor consumption, menopausal status, parity/pregnancies, physical activity , randomized treatment assignment, supplements, wine	The Pooling Project, Jung, 2015 was used for dose-response meta-analysis, reported separately by red and white wine
						Per 10 g/day, white wine	1.07 (0.94-1.21)		
Hirvonen, 2006 BRE80105 France	SU.VI.MAX, Prospective Cohort, Age: 35-60 years,	95/ 4 396 6.6 years	Medical records	24h recall	Incidence, breast cancer	≥150 vs ≤0 ml/day, red wine	1.24 (0.76-2.03)	Age, family history, menopausal status, OC use, parity/	Excluded, reported separately by red and white wine
						≥150 vs ≤0 ml/day,	1.09 (0.64-1.84)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	W, participants of a RCT					white wine		pregnancies, smoking habits	
Jain, 2000 BRE17653 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W, Screening Program	223/ 49 165 10.3 years	Death certificate	FFQ	Mortality, breast cancer	≥10.1 vs ≤0 g/day	1.15 (1.11-1.18)	Age, age at menarche, BMI, educational level, energy Intake , family history, mammography, menopausal status, OC use, other specified factor, parity/pregnancies, recruitment center, smoking habits	Excluded, study reported on mortality
						Per 10 g/day	1.06 (1.04-1.10)	Alcohol	
Friedenreich, 1993 BRE17508 Canada	CNBSS, Nested Case Control, W, Screening Program	519/ 1182 controls 5.5 years	All histology	FFQ	Incidence, breast cancer	≥10 vs ≤0 g/day	1.46 (0.99-2.14)	Age, energy Intake , family history, menopausal status, other specified factor, parity/pregnancies, smoking habits	Superseded by Rohan, 2000a
Hiatt, 1988a BRE03888 USA	KPMCP, Case Cohort, W	303/ 58 347 6 years	Hospital discharge records	FFQ	Incidence, breast cancer	Regular drinkers vs lifelong abstainers	1.36 (0.86-2.17)	Age, BMI, ethnicity, smoking habits	Superseded by Li, 2009

Figure 361 RR estimates of breast cancer (any) by levels of alcohol (as ethanol) from wine.

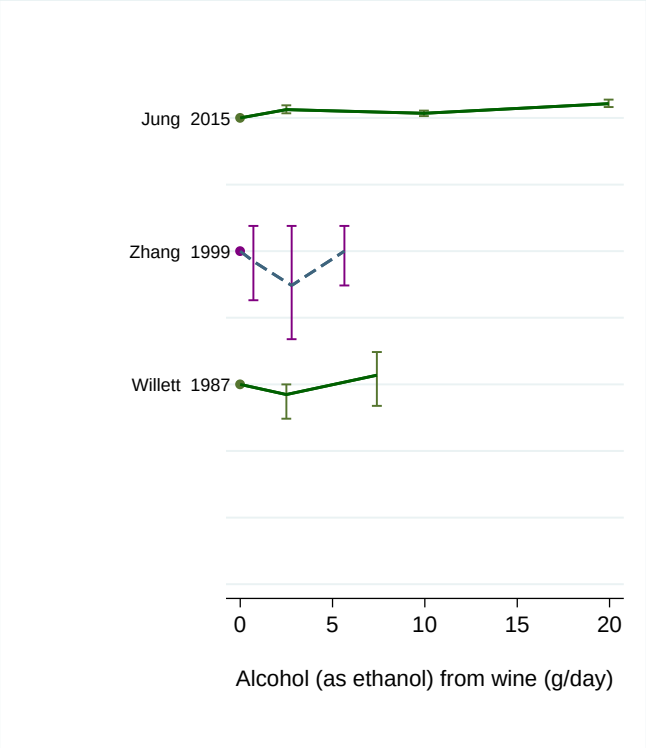
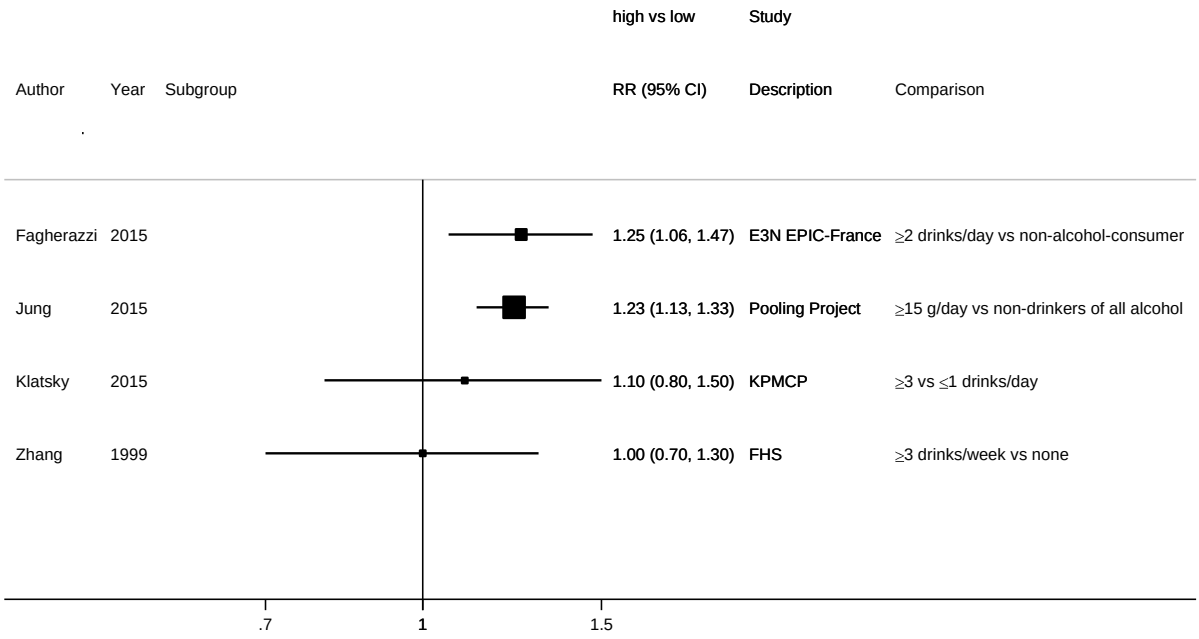


Figure 362 RR (95% CI) of breast cancer for the highest compared with the lowest level of alcohol (as ethanol) intake from wine.



NOTE: Fagherazzi, 2015 (E3N EPIC-France) is used instead of Tjønneland, 2007 (EPIC) and Klatsky, 2015 (KPMCP) is used instead of Li, 2009 with only continuous risk estimates available.

Figure 363 Relative risk of breast cancer incidence for 10g/day increase of alcohol (as ethanol) intake from wine

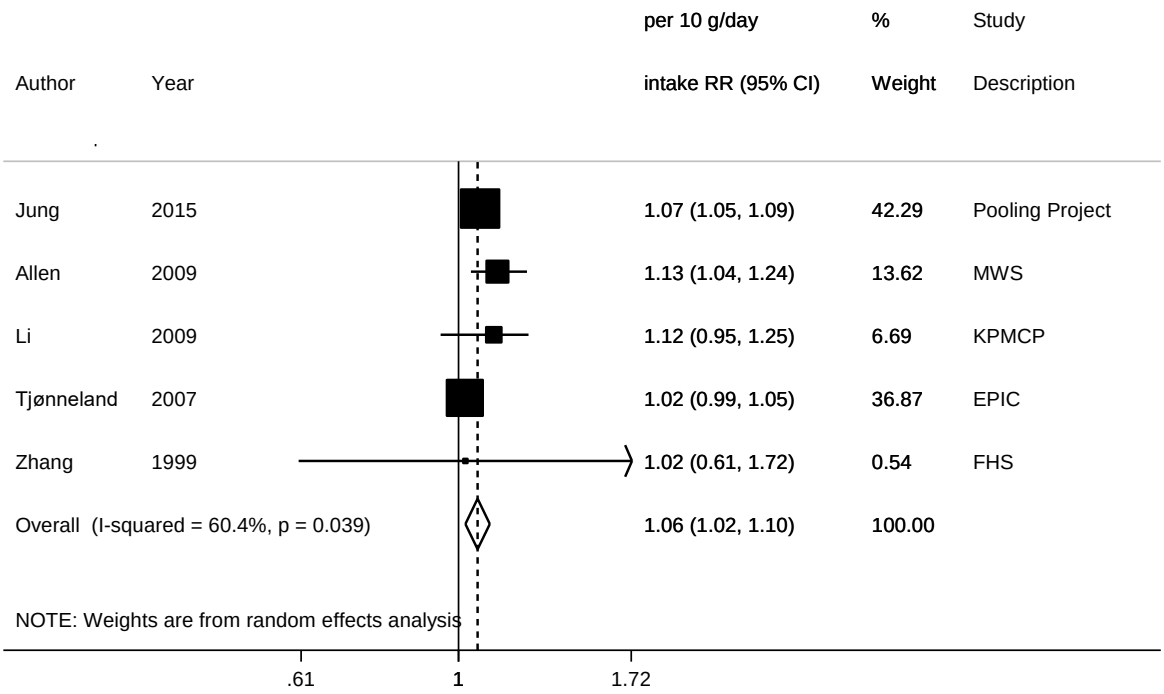


Figure 364 Funnel plot of studies included in the dose response meta-analysis of alcohol (as ethanol) from wine and breast cancer

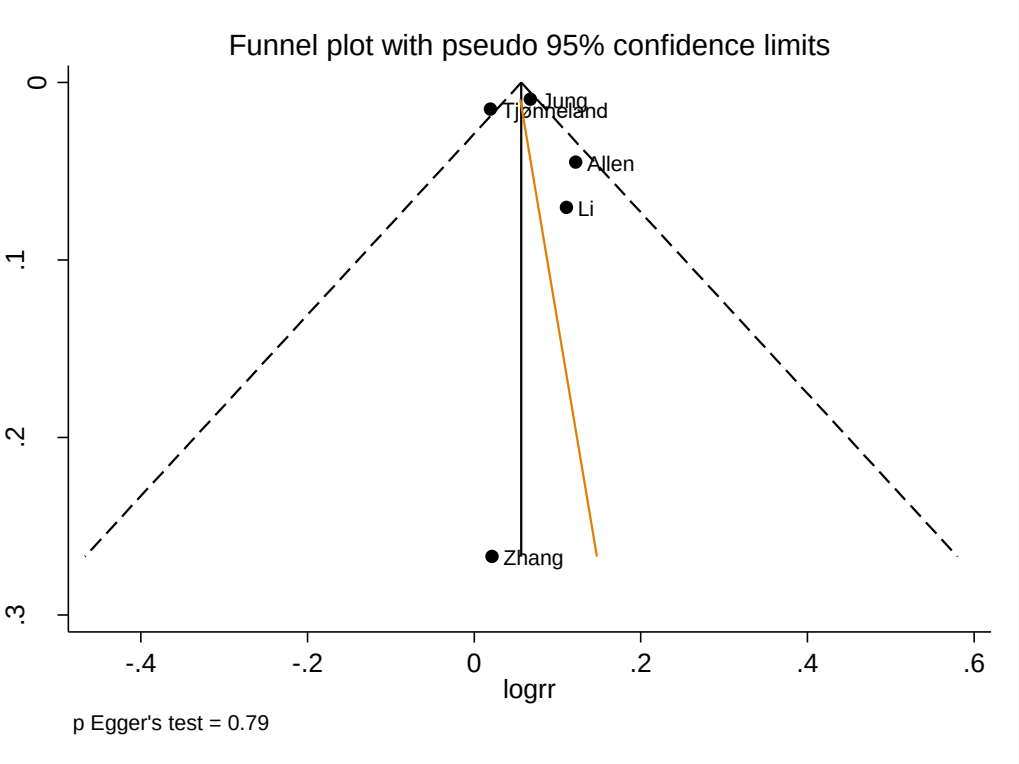
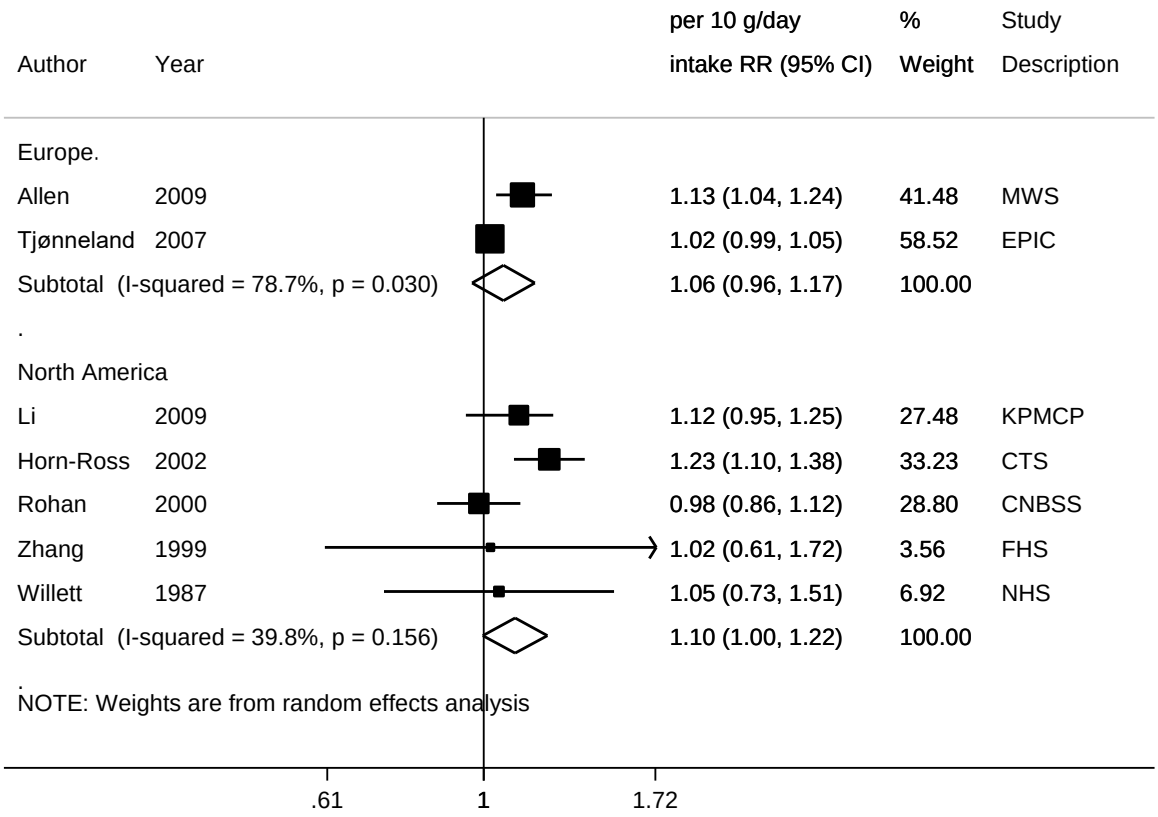


Figure 365 Relative risk of breast cancer incidence for 10g/day increase of alcohol (as ethanol) intake from wine, by geographic location



Premenopausal breast cancer

Summary

Main results:

Three studies (818 cases) (3 publications) were included in the dose-response meta-analysis. Alcohol (as ethanol) intake from beer was positively but not significantly associated with a higher risk of premenopausal breast cancer.

Study quality:

Alcohol consumption was estimated using questionnaires in all three studies. Friedenreich, 1993 did not specify if former/past drinkers were excluded from the reference category, Fagherazzi, 2015 indicated that lowest intake (reference) category included 0 g/day consumption over the previous year and one study included above 0 g/day intakes in the lowest category (Petri, 2004).

Table 284 Alcohol (as ethanol) from wine and premenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	3 (3 publications)
Studies included in forest plot of highest compared with lowest exposure	3 (3 publications)
Studies included in linear dose-response meta-analysis	3 (3 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 285 Alcohol (as ethanol) from wine and premenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR	**CUP SLR**
Increment unit used	1 time/day	10 g/day
Studies (n)	2	3
Cases	311	818
RR (95%CI)	1.36 (0.98-1.88)	1.17 (0.79-1.73)
Heterogeneity (I^2, p-value)	0%	74%, 0.02

Table 286 Alcohol as (ethanol) from wine and premenopausal breast cancer risk. Main characteristics of studies identified

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Fagherazzi, 2015 BRE80543 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W	507/ 29 740 16 years	Questionnaire and death certificate	Validated FFQ	Incidence, breast cancer, premenopausal at baseline	≥2 drinks/day vs non-alcohol consumers	0.95 (0.68-1.32)	Age, age at first child, age at menarche, age at menopause, BMI, breastfeeding, educational level, family history of breast cancer, history of benign breast disease, mammography, menopausal women and use of MHT, parity, physical activity, use of oral contraception, use of progestagens in premenopause	Intake in drinks/day converted to ethanol g/day using 10g ethanol/drink, mid-points of exposure categories, person-years per category
Petri, 2004 BRE16325 Denmark	CCPPS, Prospective Cohort, Age: 20-91 years, W	76/ 5 420	Partially histological - over 80%	Questionnaire	Incidence, breast cancer, premenopausal	≥6.1 vs 0-0.9 drinks/ week	1.43 (0.67-3.01)	Age , HRT use, other design Issue, parity/pregnancies	Drinks/week converted to ethanol g/day using 12g ethanol/drink, mid-points of exposure categories
Friedenreich, 1993 BRE17508 Canada	CNBSS, Nested Case Control, W, Screening Program	235/ 726 5.5 years	Histologically	FFQ	Incidence, breast cancer, premenopausal	≥10 vs ≤0 g/day	1.99 (1.15-3.43)	Age , energy intake , family history, parity/pregnancies, smoking habits	Mid points of exposure categories

Figure 366 RR estimates of premenopausal breast cancer by levels of alcohol (as ethanol) from wine

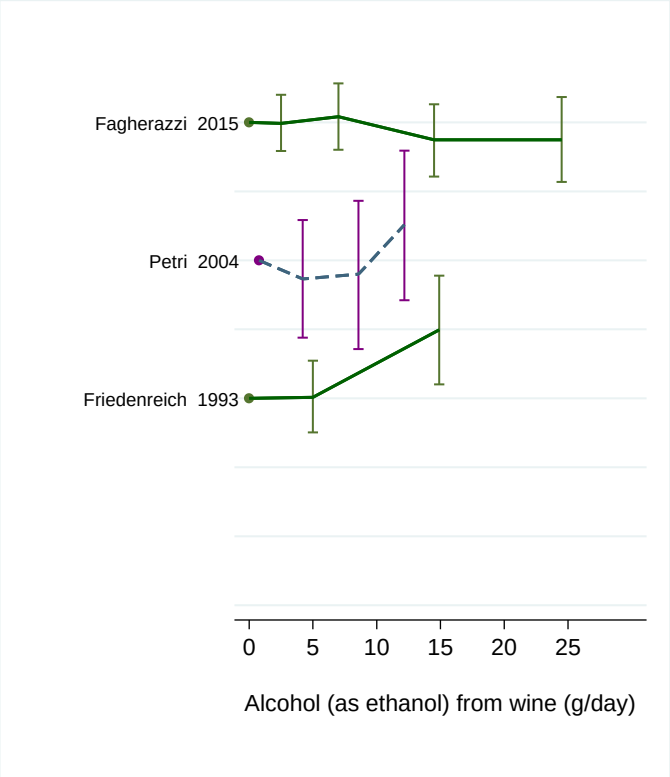


Figure 367 RR (95% CI) of premenopausal breast cancer for the highest compared with the lowest level of alcohol (as ethanol) intake from wine

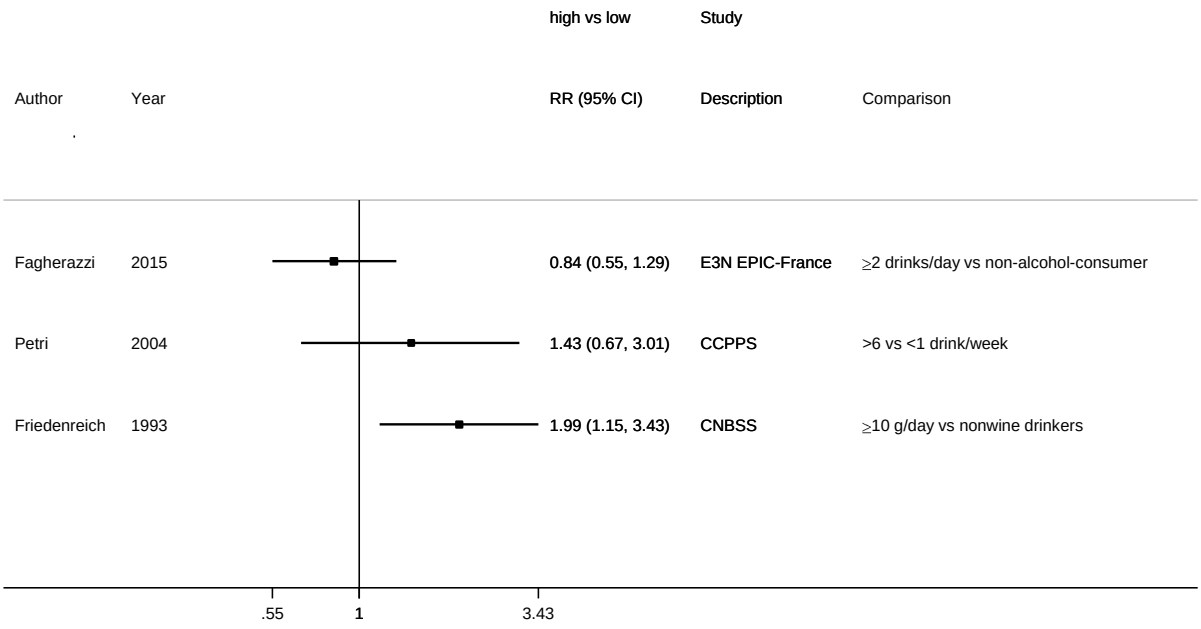
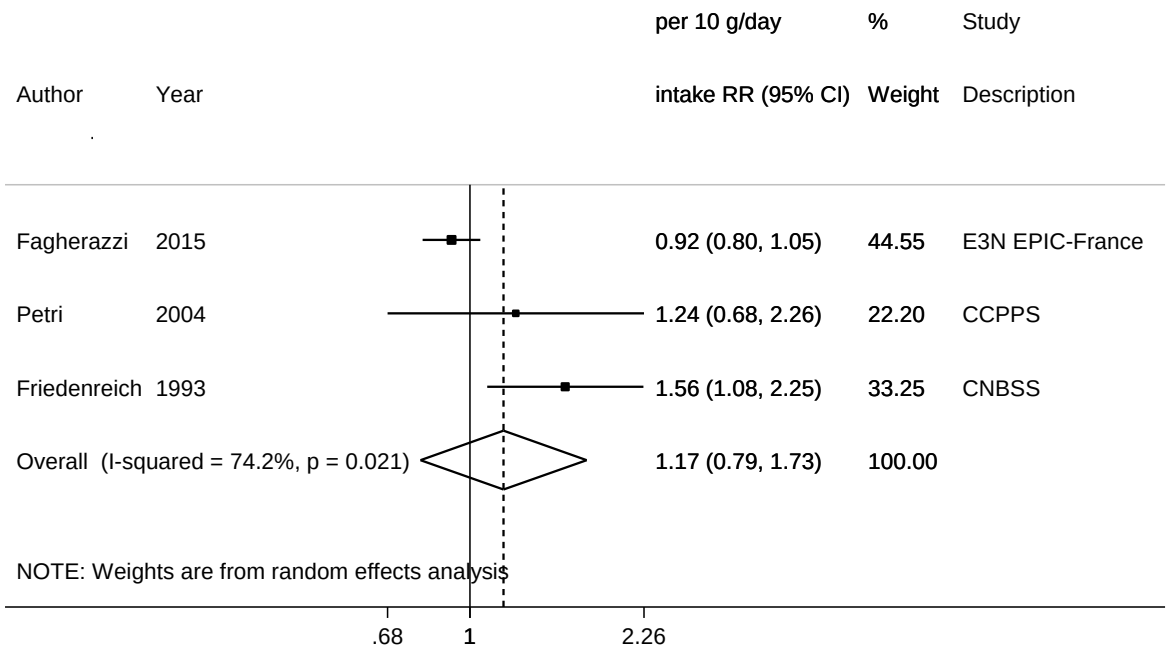


Figure 368 Relative risk of premenopausal breast cancer incidence for 10g/day increase of alcohol (as ethanol) intake from wine



Postmenopausal breast cancer

Summary

Main results:

Six studies (3 913 cases) (six publications) were included in the dose-response meta-analysis. Alcohol (as ethanol) intake from wine was associated with a significantly higher risk of postmenopausal breast cancer.

Four studies (five publications) were excluded from the dose-response meta-analysis. One study reported risk estimates for red and white wine separately (Park, 2014). In this study, postmenopausal breast cancer risk was significantly positively associated with white but not red wine intake. One study on mortality (Feigelson, 2001) and one study with only two levels of intake (Lew, 2009) reported non-significant inverse and positive association, respectively.

Postmenopausal breast cancer risk and alcohol (as ethanol) intake from wine by hormone receptor status:

Analysis by hormone receptor status (Kabat, 2011) and by histological types (Li, 2010) of postmenopausal breast cancer was not conducted due to low number of studies. Wine intake was associated with significantly increased risk of ER+ (Kabat, 2011) and lobular breast cancer (Li, 2010) but not with other subtypes of postmenopausal breast cancer.

No heterogeneity was observed. There was an evidence of a significant publication or small study bias.

Sensitivity and stratified analyses:

The summary RRs ranged from 1.11 (95% CI=1.06-1.17) when Tjønneland, 2003 was omitted to 1.12 (95% CI=1.08-1.17) when Friedenreich, 1993 was omitted.

Study quality:

Alcohol consumption was estimated using questionnaires in all studies. In addition, one study used 7 day food record (Mattisson, 2004a). Risk estimate from one study used in the dose-response meta-analysis was in drinkers only (Tjønneland, 2003) and one study included intakes of ≥0 g/day in the reference category (Petri, 2004). Fagherazzi, 2015 and Mattisson, 2004a defined reference category as 0 g/day intake over the previous year. All remaining studies did not indicate if lowest category included former drinkers.

Case ascertainment was through cancer registries, death certificates or when active follow-up, diagnosis were confirmed through medical records.

Table 287 Alcohol (as ethanol) from wine and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	10 (11 publications)
Studies included in forest plot of highest compared with lowest exposure	7 (7 publications)
Studies included in linear dose-response meta-analysis	6 (6 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 288 Alcohol (as ethanol) from wine and postmenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR	**CUP SLR**	
Increment unit used	1 time/day	10 g/day	
Studies (n)	5	6	
Cases	1 608	3 913	
RR (95%CI)	1.14 (1.06-1.23)	1.12 (1.08-1.17)	
Heterogeneity (I^2, p-value)	0%	0%, 0.96	
P value Egger test		0.008	
Stratified analyses in CUP SLR			
Geographic area	**Asia**	**Europe**	**North America**
Studies (n)	-	5	1
RR (95%CI)	-	1.12 (1.08-1.17)	1.00 (0.69-1.43)

Heterogeneity (I^2, p-value)	-	0%, 0.95	-
Adjustment for age, BMI and reproductive factors	**Adjusted**	**Not adjusted**	
Studies (n)	4	2	
RR (95%CI)	1.12 (1.08-1.17)	0.97 (0.72-1.31)	
Heterogeneity (I^2, p-value)	0%, 0.99	0%, 0.80	

Table 289 Alcohol (as ethanol) from wine and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Fagherazzi, 2015 BRE80543 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W	2 305/ 36 741 16 years	Questionnaire and death certificate	Validated FFQ	Incidence, breast cancer, postmenopausal at baseline	≥2 drinks/day vs non-alcohol consumers	1.33 (1.11-1.58)	Age, age at first child, age at menarche, age at menopause, BMI, breastfeeding, educational level, family history of breast cancer, history of benign breast disease, mammography, menopausal women and use of MHT, parity, physical activity, use of oral contraception, use of progestagens in premenopause	Intake in drinks/day converted to ethanol g/day using 10g ethanol/drink, mid-points of exposure categories, person-years per category
Mattisson, 2004a BRE17807 Sweden	MDCS, Prospective Cohort, Age: 50- years, W, Postmenopausal	342/ 11 328 7.6 years	Partially histological - over 80%	7-day record + questionnaire	Incidence, postmenopausal breast cancer	31.6 vs 1.7 g/day	2.11 (1.24-3.60)	Age , age at first child, age at menarche, educational level, energy Intake , height, HRT use,	Reference category changed using Hamling's method

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								Interviewer, leisure time physical activity, other design issues, other nutritional factors, season of interview, smoking habits, waist circumference	
Petri, 2004 BRE16325 Denmark	CCPPS, Prospective Cohort, Age: 20-91 years, W	144/ 10 997	Partially histological - over 80%	Questionnaire	Incidence, postmenopausal breast cancer, ≥70 years	≥6.1 vs 0-0.9 drinks/week	0.81 (0.40-1.65)	Age , HRT use, other design issues, parity/ pregnancies	Drinks/week converted to ethanol g/day using 12g ethanol/drink, mid-points of exposure categories
Tjønneland, 2003 BRE12350 Denmark	DCH, Prospective Cohort, Age: 50-64 years, W, Postmenopausal	416/ 23 328 4.7 years	Partially histological - over 80%	FFQ	Incidence postmenopausal breast cancer	≥60.1 vs 0.1-6 g/day	2.74 (1.01-7.47)	Age at first child, age-underlying cox models, alcohol, benign breast disease, BMI, duration of HRT use, educational level, HRT use, parity/ pregnancies, parous/nulliparous	
						per 10 g/day	1.13 (1.06-1.22)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
van den Brandt, 1995 BRE12719 Netherlands	NLCS, Case Cohort, Age: 55-69 years, W, Postmenopausal	422/ 62 573 3.3 years	All histology	Questionnaire	Incidence, postmenopausal, breast cancer	per 1 g/day	1.01 (0.99-1.02)	Age, age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, educational level, energy Intake , family history, family history, oral contraceptive use, parity/ pregnancies, smoking habits	RR rescaled for an increment of 10g/day
Friedenreich, 1993 BRE17508 Canada	CNBSS, Nested Case Control, W, Screening Program	284/ 975 5.5 years	All histology	FFQ	Incidence, postmenopausal breast cancer	≥10 g/day vs wine non-drinkers	1.10 (0.62-1.94)	Age, energy intake, family history, parity/ pregnancies, smoking habits	Mid points of exposure categories

Table 290 Alcohol (as ethanol) from wine and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Park, 2014 BRE80494 USA	MEC, Prospective Cohort, Age: 60.9 years, W, Postmenopausal	/ 85 089 12.4 years	SEER cancer registry for Hawaii & California & National Death Index	Quantitative FFQ	Incidence, postmenopausal breast cancer	per 10 g/day, red wine	1.08 (0.98-1.18)	Age, age at first child birth, age at menarche, age at menopause, BMI, educational level, energy Intake, ethnicity, family history of breast cancer, hormone replacement therapy, number of children, physical activity, smoking status, type of menopause	Excluded, reported separately by red and white wine
						per 10 g/day, white wine	1.11 (1.06-1.15)		
Kabat, 2011 BRE80344 USA	WHI, Prospective Cohort, Age: 50-79 years, W	2 479/ 148 030 8 years	Mail or telephone questionnaires verified by trained physician adjudicators	FFQ	Incidence, postmenopausal breast cancer ER+	≥3 vs 0 serving/week	1.16 (1.02-1.32)	Age, age at first child birth, age at menarche, age at menopause, BMI, breast biopsies, contraception, educational level, ethnicity, family history of breast cancer,	Excluded, analysis by ER+ status was not conducted
		300/			Triple negative postmenopausal breast cancer	≥3 vs 0 serving/week	0.75 (0.48-1.17)		Excluded, triple negative breast cancer

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								HRT use, mammogram In the past 2 years, physical activity, smoking, treatment allocation, waist circumference	
Li, 2010 BRE80336	WHI - OS, Prospective Cohort, Age: 50-79 years, Postmenopausal	87 724 13 years maximum	Medical record	Self-administered questionnaire	Incidence, postmenopausal breast cancer	≥1 drink/day vs never drinker	1.15 (0.94-1.41)	Age, BMI, educational level, ethnicity, family history of breast cancer, Gail model risk, HRT use, mammography, parity, race, smoking	Superseded by Kabat, 2011, no cases or person-years per category
					Ductal		1.05 (0.81-1.36)		
					Lobular		1.87 (1.22-2.87)		
Lew, 2009 BRE80256 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W, Postmenopausal	5 461/ 184 418 7 years	Cancer registry		Incidence, postmenopausal breast cancer	≥3 vs 0 drinks/day	1.39 (0.86-2.24)	Age, age at first child birth, age at menopause, beer consumption, BMI, breast biopsies, energy Intake, family history of cancer, fat Intake, folate Intake, height, HRT use, liquor	Excluded, only two levels of exposure, used in the HvL analysis only

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								consumption, oral contraception use, parity, physical activity, race, smoking habits	
Feigelson, 2001 BRE19514 USA, Puerto Rico	CPS II, Prospective Cohort, W	573/ 14 years	Death certificate	Questionnaire	Mortality, postmenopausal breast cancer	≥3 vs ≤0 drinks/day	0.79 (0.39-1.60)	Age , age at first child, age at menarche, age at menopause, BMI, educational level, ethnicity, family history, food, height, HRT use, other specified factor, physical activity , smoking habits, supplements	Excluded, outcome is mortality

Figure 369 RR estimates of postmenopausal breast cancer by levels of alcohol (as ethanol) from wine

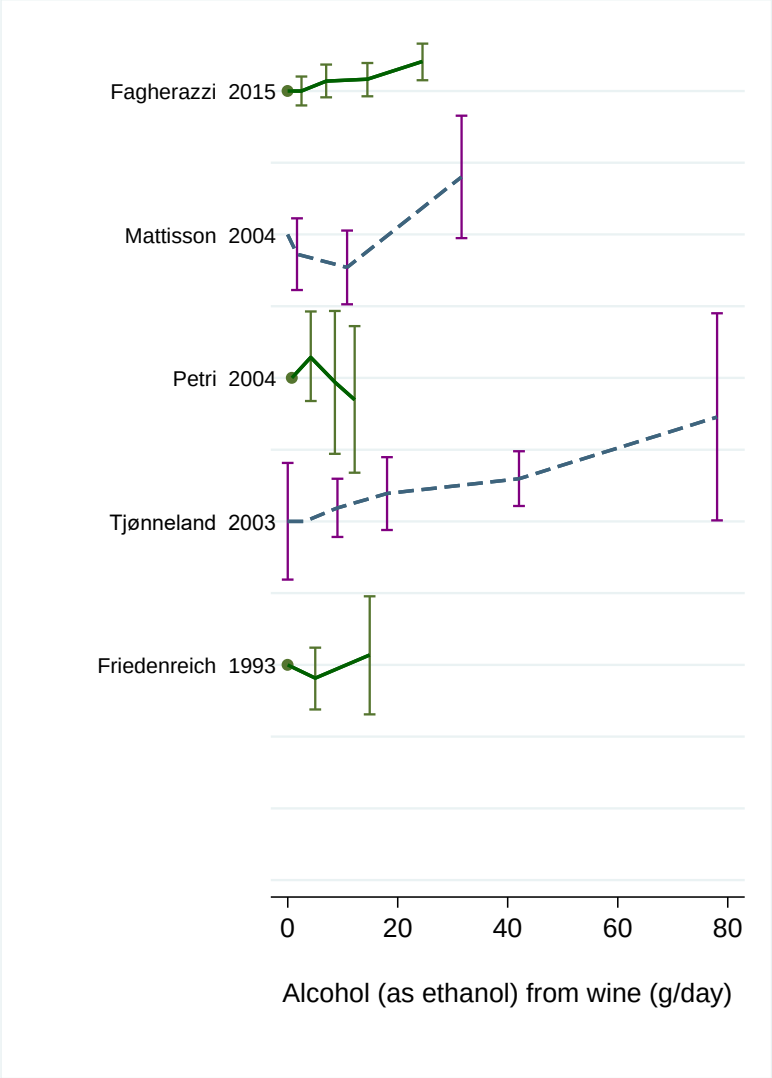


Figure 370 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest level of alcohol (as ethanol) intake from wine

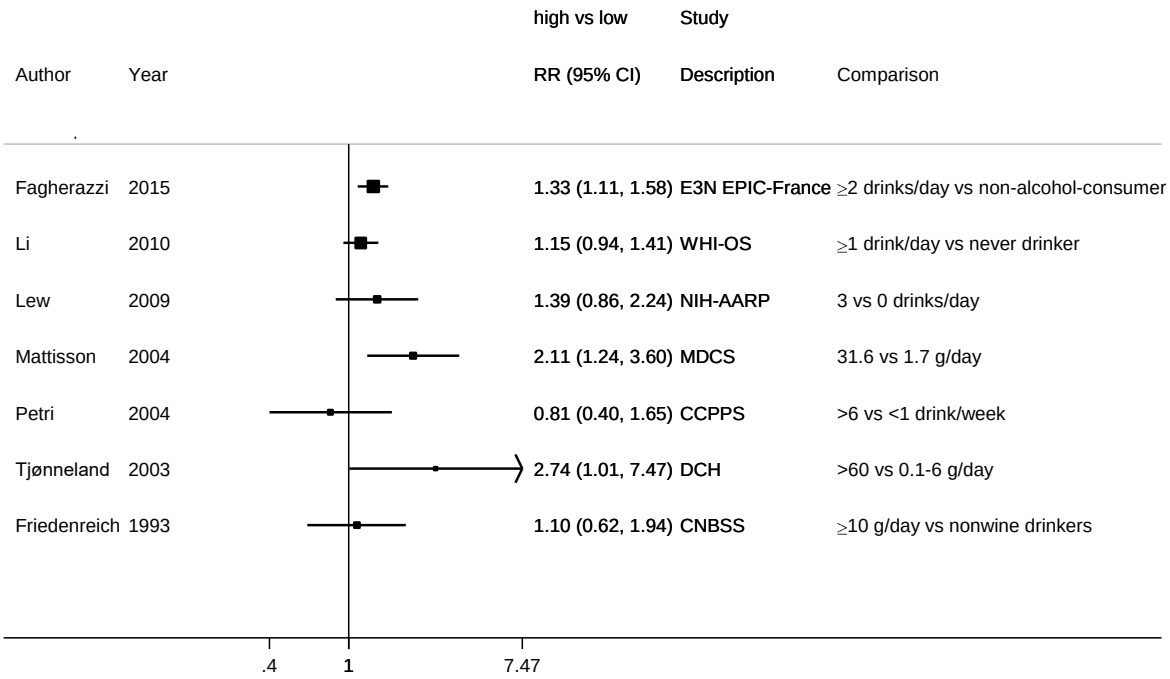


Figure 371 Relative risk of postmenopausal breast cancer incidence for 10g/day increase of alcohol (as ethanol) intake from wine

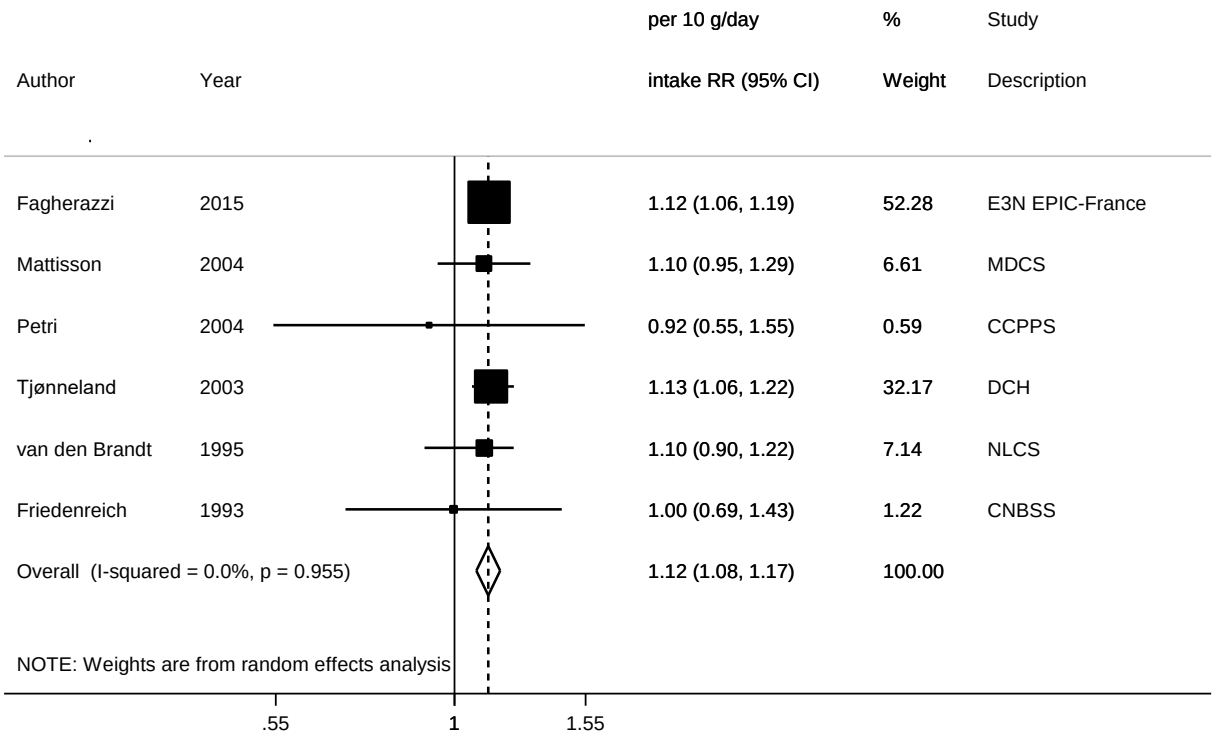


Figure 372 Funnel plot of studies included in the dose response meta-analysis of alcohol (as ethanol) from wine and postmenopausal breast cancer

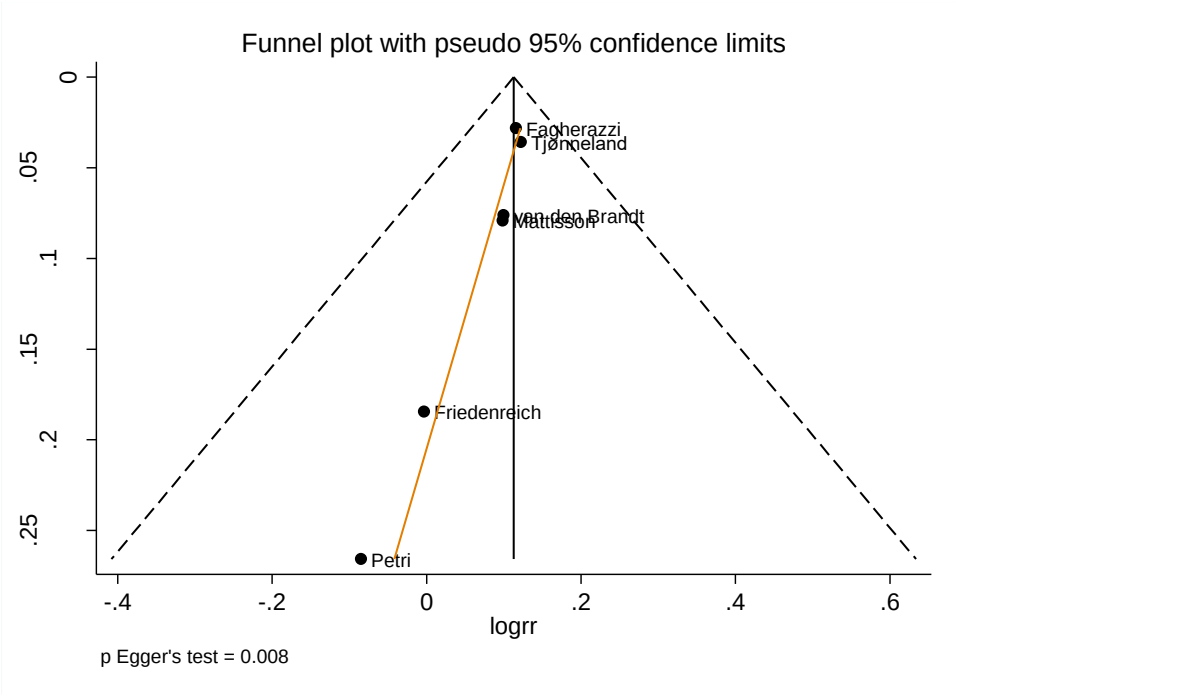
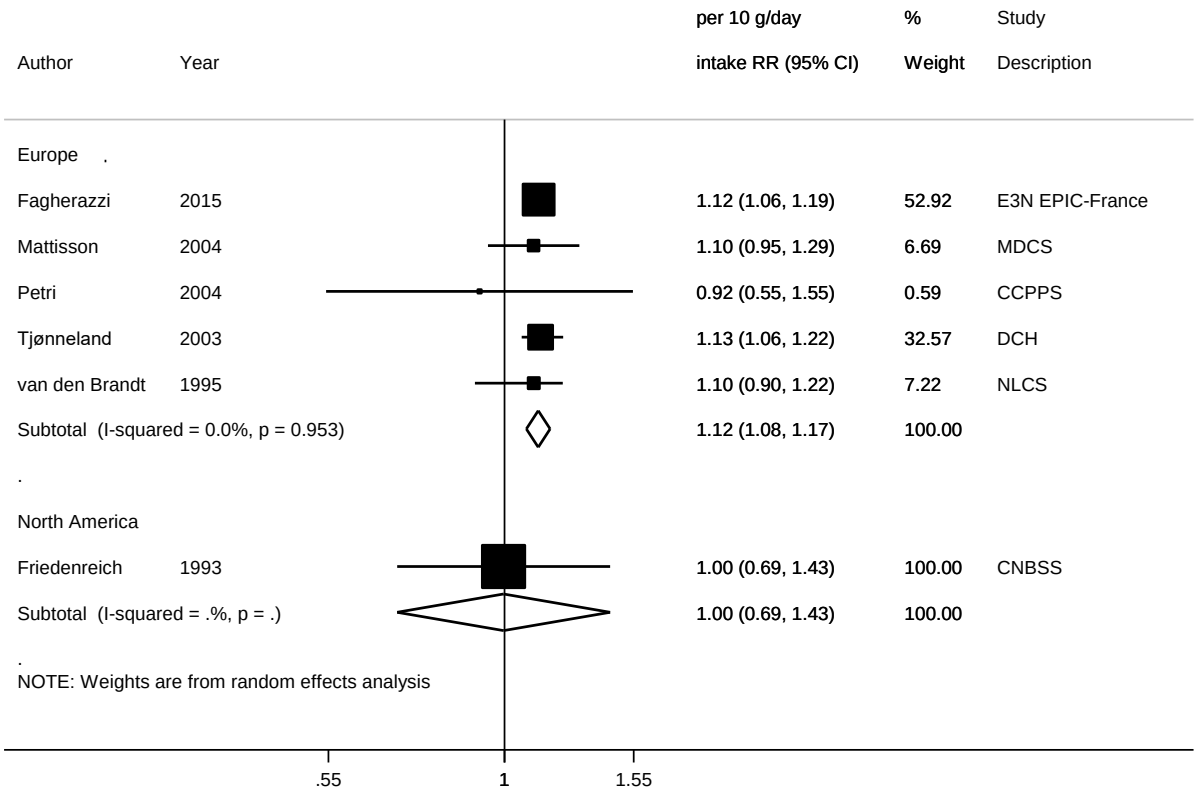


Figure 373 Relative risk of postmenopausal breast cancer incidence for 10g/day increase of alcohol (as ethanol) intake from wine, by geographic location



5.4.1.3 Alcohol (as ethanol) from liquor

Cohort studies

Overall summary

Twenty four publications from 32 studies were identified. Dose-response meta-analyses were conducted to examine the association of alcohol (as ethanol) from liquor with risk of breast cancer (any), premenopausal and postmenopausal breast cancer.

Table 291 Summary of results of the dose-response meta-analysis in the CUP SLR

	Breast cancer (any)	**Premenopausal breast cancer**	**Postmenopausal breast cancer**
Increment unit used	10 g/day	10g/day	10 g/day
Pooling Project of Cohort Studies*			
Studies (n)	20	-	-
Cases	36 177	-	-
RR (95%CI)	1.06 (1.04-1.08)	-	-
Heterogeneity (I^2, p-value)	0.05	-	-
Pooling Project and not overlapping studies identified in the CUP			
Studies (n)	23	3	7
Cases	43 574	818	7 798
RR (95%CI)	1.04 (0.99-1.09)	1.10 (0.92-1.30)	1.05 (0.93-1.17)
Heterogeneity (I^2, p-value)	80%, 0.002	0%, 0.92	73%, 0.001
P value Egger test	0.61	-	0.78

*Jung 2015; analyses restricted to women drinking <55g/day.

Breast cancer (any)

Summary

Main results:

Twenty three studies (43 574 cases) (4 publications) were included in the dose-response meta-analysis. Alcohol (as ethanol) intake from liquor was associated with a significantly higher risk of breast cancer.

Two studies were excluded from the dose-response meta-analysis (Mørch, 2005, Jain, 2000). Mørch, 2005 reported significantly positive association between liquor intake and breast cancer incidence and Jain, 2000 reported significant inverse association for breast cancer mortality.

High and significant heterogeneity was observed. There was no evidence of a significant publication or small study bias.

Breast cancer risk and alcohol (as ethanol) intake from liquor by hormone receptor status:

In the Pooling Project (Jung, 2015), alcohol (as ethanol) intake from liquor was significantly positively associated with risk of ER^+ (14 965 cases), ER^- (3 490 cases), PR^+ (12 312 cases), PR^- (5 344 cases) breast cancers in the dose-response as well as in the highest versus lowest analysis.

Influence and stratified analyses:

In influence analysis including the Pooling Project and no overlapping studies, the summary relative risk changed from 1.02 (95% CI, 0.91-1.14) when the Pooling Project (Jung, 2015) was excluded to 1.04 (1.00-1.09) when Zhang, 1999b was excluded.

All studies were adjusted for age, BMI and reproductive factors and all studies apart from the EPIC (Tjønneland, 2007) were conducted in North America.

Study quality:

Alcohol consumption was estimated using questionnaires which were country-specific in the EPIC study (Tjønneland, 2007). Tjønneland, 2007 Rohan, 2000a indicated that reference category might have included ex-drinkers. One study reported that lowest intake category included 0 g/day intakes over the previous year only (Horn-Ross, 2002). All remaining studies did not specify if former drinkers were identified for exclusion from the reference category.

Case ascertainment was through cancer registries or when active follow-up, diagnosis were confirmed through medical records or histologically.

Table 292 Alcohol (as ethanol) from liquor and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	26 (15 publications)
Studies included in forest plot of highest compared with lowest exposure	24 (5 publications)
Studies included in linear dose-response meta-analysis	23 (4 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 293 Alcohol (as ethanol) from liquor and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR	**CUP SLR**	
Increment unit used	Times/day	10 g/day	
Studies (n)	3	23	
Cases	N/A	43 574	
RR (95%CI)	1.18 (1.06-1.32)	1.04 (0.99-1.09)	
Heterogeneity (I^2, p-value)	67%	80%, 0.002	
P value Egger test		0.61	
Stratified analyses in CUP SLR			
Geographic area	**Asia**	**Europe**	**North America**
Studies (n)	-	1	6
RR (95%CI)	-	1.09 (0.99-1.21)	1.12 (0.99-1.26)
Heterogeneity (I^2, p-value)	-	-	81%, <0.0001
Adjustment for age, BMI and reproductive factors*	**Adjusted**	**Not adjusted**	
Studies (n)	23	-	
RR (95%CI)	1.04 (0.99-1.09)	-	
Heterogeneity (I^2, p-value)	80%, 0.002	-	

Table 294 Alcohol (as ethanol) from liquor and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Jung, 2015 North America, Europe, Asia, Australia	20 cohorts: CARET* BCDDP CTS CNBSS CPS II CLUE II IWHS* JPHC I MCCS MEC NLCS* NYUWHS NIH-AARP* NHS (a) NHS (b) NHS II Prospective Study on Hormones, Diet and Breast Cancer (Italy) PLCO* SMC WHS SWLHCS	25 630, 6 to 18 years maximum follow-up	Variable in each cohort	Questionnaires	Incidence	≥15 g/day vs non-drinkers of all alcohol	1.33 (1.25-1.42)	Age, energy intake, ethnicity, education, BMI, height, physical activity, smoking status, age at menarche, menopausal status and HRT, parity and age at first birth, oral contraceptive use, family history of breast cancer, personal history of benign breast disease, wine, liquor	None
						10 g/day increase	1.06 (1.04-1.08)		
		14 965			ER+	≥15 g/day vs non-drinkers of all alcohol	1.39 (1.25-1.56)		
						10 g/day increase	1.10 (1.07-1.13)		
		3 490			ER-	≥15 g/day vs non-drinkers of all alcohol	1.28 (1.06-1.54)		
						10 g/day increase	1.08 (1.02-1.14)		
		12 312			PR+	≥15 g/day vs non-drinkers of all alcohol	1.43 (1.28-1.60)		
						10 g/day increase	1.05 (1.03-1.07)		
		5 344			PR-	≥15 g/day vs non-drinkers of all alcohol	1.24 (1.06-1.43)		
						10 g/day increase	1.05 (1.01-1.10)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Li, 2009 BRE80285 USA	KPMCP, Prospective Cohort, Age: 41 years, W	2 829/ 70 033 16 years	SEER cancer registry	Questionnaire	Incidence, breast cancer	Per 1 time/week	1.01 (0.98-1.04)	Age, alcohol consumption, beer consumption, BMI, breast diseases , educational level, ethnicity, family history, liquor consumption, marital status, parity, smoking habits	RR rescaled for an increment of 10g/day
Tjønneland, 2007 BRE80013 Denmark,France ,Germany,Greec e,Italy,Netherlan ds,Norway,Spai n,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	274 688 6.4 years	Population cancer registries and other procedures	FFQ + recall	Incidence, invasive breast cancer	Per 10 g/day	1.09 (0.99-1.21)	Age at menarche, educational level, height, HRT use, menopausal status, oral contraceptive use, parity, smoking status, weight	None
Zhang, 2007 BRE20023 USA	WHS, Prospective Cohort, Age: 55 years	38 454 10 years	Medical notes	FFQ + questionnaire	Incidence, invasive & in situ breast cancer	Per 10 g/day	1.05 (0.95-1.17)	Age , age at first child, age at menarche, age at menopause, beer consumption, benign breast disease, BMI,	None

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								energy Intake , family history, hormonal variables , menopausal status, parity/pregnancies, physical activity , randomized treatment assignment, supplements, wine, wine	
Horn-Ross, 2002 BRE15412 USA	CTS, Prospective Cohort, Age: 21-103 years, W, Registered teachers	681/ 111 383 2 years	Cancer registry	FFQ	Incidence, invasive breast cancer	≥20 vs ≤0 g/day	1.70 (1.00-2.80)	Age , age at first child, age at menarche, BMI, energy Intake , ethnicity, family history, menopausal status, physical activity	The Pooling Project, Jung, 2015 was used in the main analysis, mid-points of exposure categories
Rohan, 2000a BRE16489 Canada	CNBSS, Case Cohort, Age: 40-59 years, W, Screening Program	1 336/ 56 837 10 years	All histology	FFQ-quantitative	Incidence, breast cancer	≥20.1 vs ≤0 g/day	1.42 (0.96-2.11)	Age , age at menarche, alcohol, energy Intake , family history, menopausal status, other design Issue, other specified	The Pooling Project, Jung, 2015 was used in the main analysis, mid-points of exposure categories

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								factor, parity/pregnancies, recruitment center	
Zhang, 1999b BRE13965 USA	FHS, Prospective Cohort, Age: 12-62 years, W, Original and Offspring Cohorts	287/ 5 048 34.3 years	Pathology report + cancer registry	Interview	Incidence, breast cancer	≥3 vs ≤0 drinks/week	0.70 (0.50-1.00)	Age at first child, age at menarche, age at menopause, age-underlying cox models, alcohol, BMI, educational level, height, HRT use, parity/pregnancies, physical activity , smoking habits	Person years per category, intake in drinks/week converted to ethanol g/day using 10g ethanol per drink, mid-points of exposure categories
Willett, 1987a BRE13441 USA	NHS, Prospective Cohort, Age: 34-59 years, W, Registered nurses	447/ 89 538 4 years	Pathology report + self-reported	FFQ-semi-quantitative	Incidence, breast cancer	≥5 vs ≤0 g/day	1.40 (1.10-1.70)	Age , alcohol	The Pooling Project, Jung, 2015 was used in the main analysis, mid-points of exposure categories

Table 295 Alcohol (as ethanol) from liquor and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Fagherazzi, 2015 BRE80543 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W	2 812/ 66 481 16 years	Questionnaire and death certificate	Validated FFQ	Incidence, breast cancer	≥2 drinks/day vs non-alcohol consumers	1.11 (0.80-1.53)	Age, age at first child, age at menarche, age at menopause, BMI, breastfeeding, educational level, family history of breast cancer, history of benign breast disease, mammography, menopausal women and use of MHT, parity, physical activity, use of oral contraception, use of progestagens in premenopause	Superseded by Tjønneland, 2007
Klatsky, 2015 BRE80587 USA	KPMCP, Prospective Cohort, W	/69 153 17.8 years	Cancer registry	Questionnaire	Incidence, breast cancer	≥3 vs ≤1 drinks/day	1.10 (0.80-1.60)	Age, alcohol Intake, BMI, educational level, marital status, race/ethnicity, smoking	Superseded by Li, 2009 in the dose-response meta-analysis, only used in the highest vs lowest analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Visvanathan, 2007 BRE80020 USA	CLUE II, Nested Case Control, Age: 57 years, W	14 624		FFQ + questionnaire	Incidence, breast cancer	Liquor drinkers vs non liquor drinkers	1.10 (0.65-1.86)	Age, menopausal status	The Pooling Project, Jung, 2015 was used instead, only two levels of exposure
Mørch, 2005 BRE23480 Denmark	DNCS, Prospective Cohort, Age: 44- years, W, Registered nurses	/17 647 10 years	Not specified	Questionnaire	Incidence, breast cancer	High vs low	1.60 (1.10-2.32)		Excluded, only two levels of intake
Jain, 2000 BRE17653 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W, Screening Program	223/ 49 165 10.3 years	Death certificate	FFQ-quantitative	Mortality, breast cancer	Per 10 g/day	0.94 (0.93-0.96)	Age, age at menarche, BMI, educational level, energy Intake , family history, mammography, menopausal status, oral contraceptive use, other specified factor, parity/pregnancies, recruitment center, smoking habits, total alcohol intake	Excluded, study reported on mortality
Friedenreich, 1993	CNBSS, Nested Case	519/ 1 182 controls	All histology	FFQ	Incidence, breast cancer	≥10 vs ≤0 g/day	1.10 (0.79-1.52)	Age, energy Intake, family	Superseded by Rohan, 2000a

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
BRE17508 Canada	Control, W, Screening Program	5.5 years						history, menopausal status, other specified factor, parity/pregnancies, smoking habits	
Hiatt, 1988a BRE03888 USA	KPMCP, Case Cohort, W	303/ 58 347 6 years	Hospital discharge records	FFQ	Incidence, breast cancer	Regular drinkers vs abstainers lifelong	1.46 (0.93-2.29)	Age , BMI, ethnicity, smoking habits	Superseded by Li, 2009

Figure 374 RR estimates of breast cancer by levels of alcohol (as ethanol) from liquor

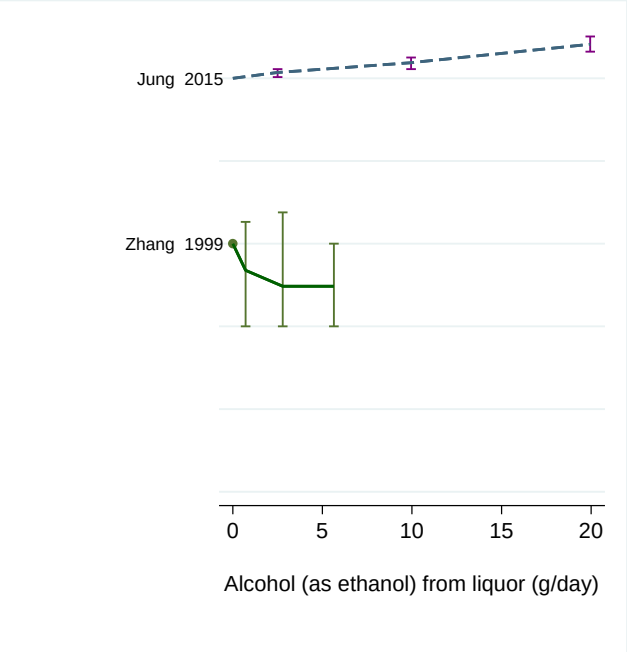
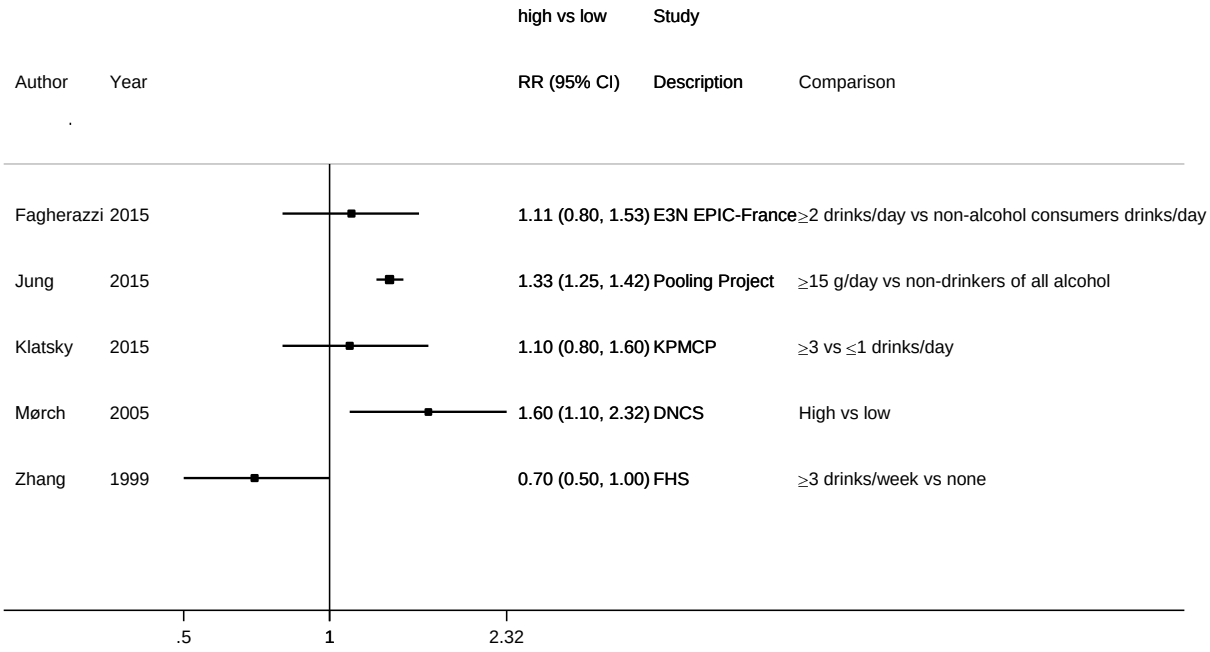


Figure 375 RR (95% CI) of breast cancer for the highest compared with the lowest level of alcohol (as ethanol) from liquor intake



NOTE: Fagherazzi, 2015 (E3N EPIC-France) is used instead of Tjønneland, 2007 (EPIC) and Klatsky, 2015 (KPMCP) is used instead of Li, 2009 with only continuous risk estimates available.

Figure 376 Relative risk of breast cancer incidence for 10g/day increase of alcohol (as ethanol) from liquor intake

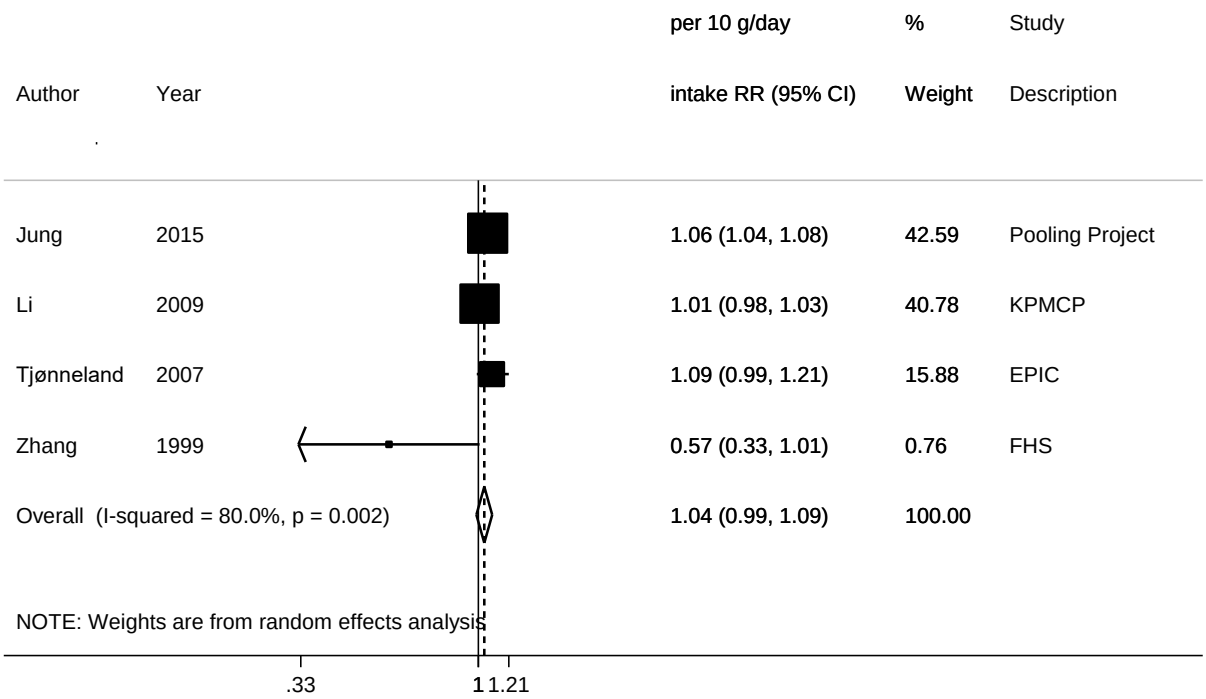


Figure 377 Funnel plot of studies included in the dose response meta-analysis of alcohol (as ethanol) from liquor and breast cancer

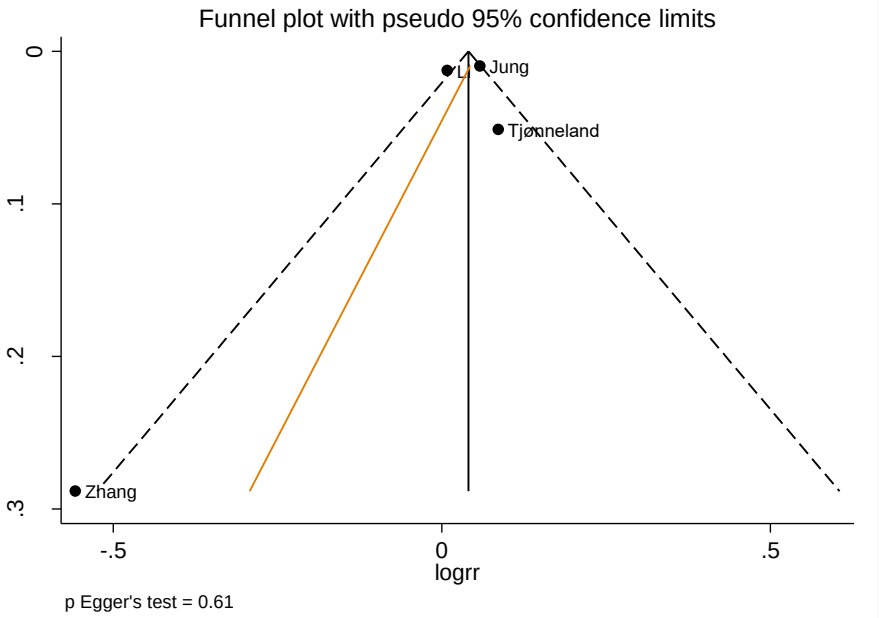
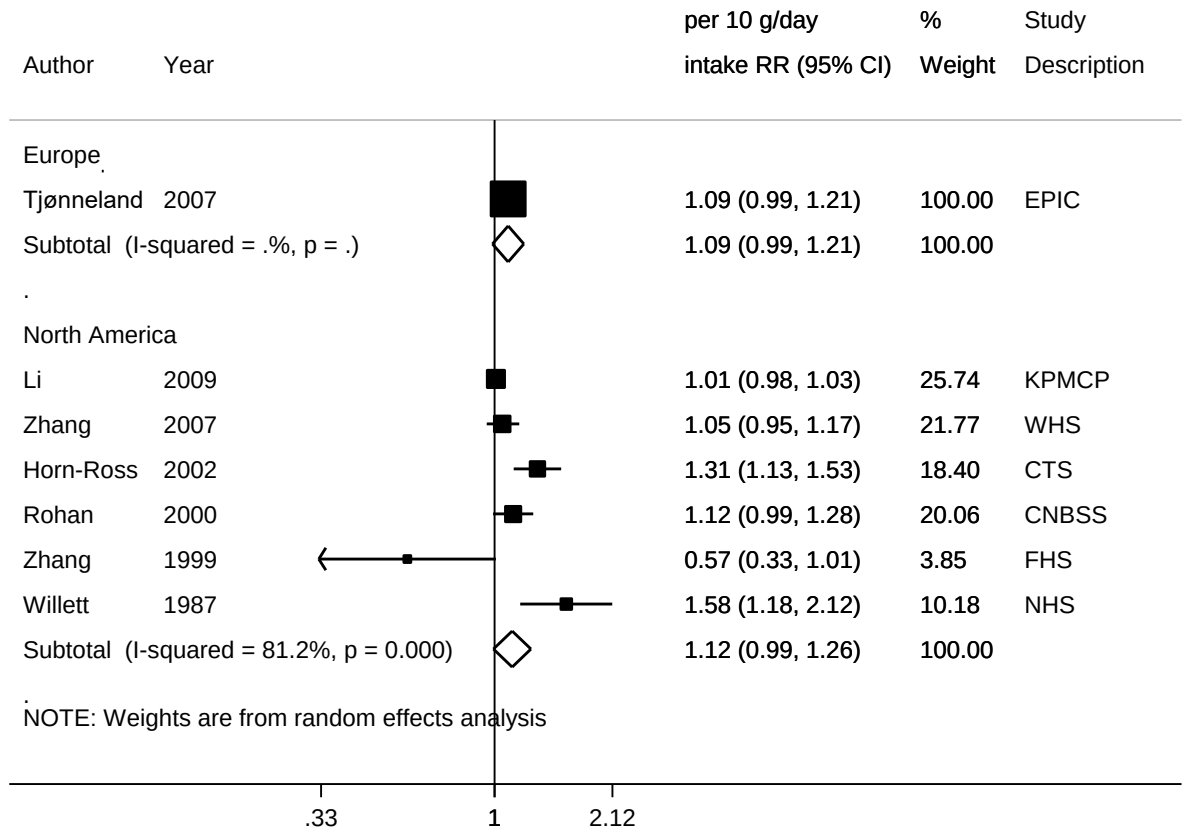


Figure 378 Relative risk of breast cancer (any) incidence for 10g/day increase of alcohol (as ethanol) from liquor intake, by geographic location



Premenopausal breast cancer

Summary

Main results:

Three studies (818 cases) (3 publications) were included in the dose-response meta-analysis. Alcohol (as ethanol) intake from liquor was positively but not significantly associated with a higher risk of premenopausal breast cancer.

Study quality:

Acohol consumption was estimated using questionnaires in all three studies. Friedenreich, 1993 did not specify if former/past drinkers were excluded from the reference category, Fagherazzi, 2015 indicated that lowest intake (reference) category included 0 g/day consumption over the previous year and Petri, 2004 included above 0 g/day intakes in the lowest category.

Table 296 Alcohol (as ethanol) from liquor and premenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	3 (3 publications)
Studies included in forest plot of highest compared with lowest exposure	3 (3 publications)
Studies included in linear dose-response meta-analysis	3 (3 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 297 Alcohol (as ethanol) from liquor and premenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR	**CUP SLR**
Increment unit used	1 time/day	10 g/day
Studies (n)	2	3
Cases	311	818
RR (95%CI)	1.17 (0.86-1.58)	1.10 (0.92-1.30)
Heterogeneity (I^2, p-value)	0%	0%, 0.92

Table 298 Alcohol as (ethanol) from liquor and premenopausal breast cancer risk. Main characteristics of studies identified.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Fagherazzi, 2015 BRE80543 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W	507/ 66 481 16 years	Questionnaire and death certificate	Validated FFQ	Incidence, breast cancer, premenopausal	≥2 drinks/day vs non-alcohol consumers	0.76 (0.33-1.75)	Age, age at first child, age at menarche, age at menopause, BMI, breastfeeding, educational level, family history of breast cancer, history of benign breast disease, mammography, menopausal women and use of MHT, parity, physical activity, use of oral contraception, use of progestagens in premenopause	Intake in drinks/day converted to ethanol g/day using 10g ethanol/drink, mid-points of exposure categories, person-years per category
Petri, 2004 BRE16325 Denmark	CCPPS, Prospective Cohort, Age: 20-91 years, W	76/ 13 074	Partially histological - over 80%	Questionnaire	Incidence, breast cancer, premenopausal	≥6.1 vs 0-0.9 drinks/week	1.34 (0.39-4.55)	Age, HRT use, other design issue, parity/ pregnancies	Drinks/week converted to ethanol g/day using 12g ethanol/drink, mid-points of exposure categories

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Friedenreich, 1993 BRE17508 Canada	CNBSS, Nested Case Control, W, Screening Program	235/ 491 controls 5.5 years	All histology	FFQ	Incidence, breast cancer, premenopausal	≥10 g/day vs liquor nondrinkers	1.21 (0.75-1.96)	Age, energy intake, family history, parity/ pregnancies, smoking habits	Mid points of exposure categories

Figure 379 RR (95% CI) of premenopausal breast cancer for the highest compared with the lowest level of alcohol (as ethanol) intake from liquor.

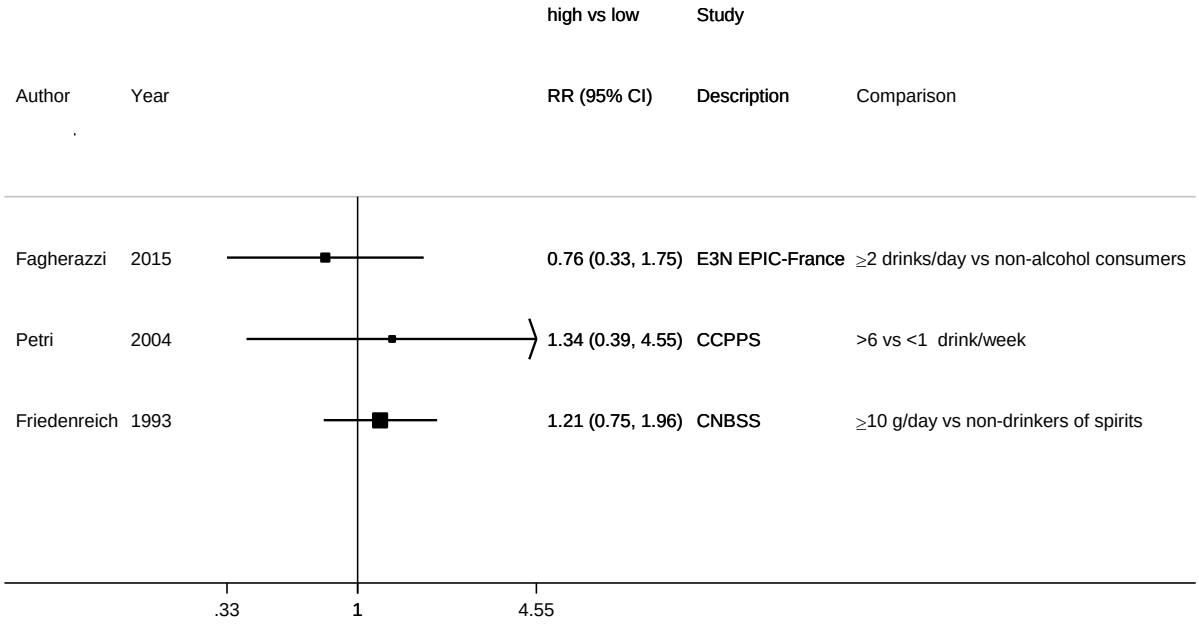


Figure 380 RR estimates of premenopausal breast cancer by levels of alcohol (as ethanol) from liquor

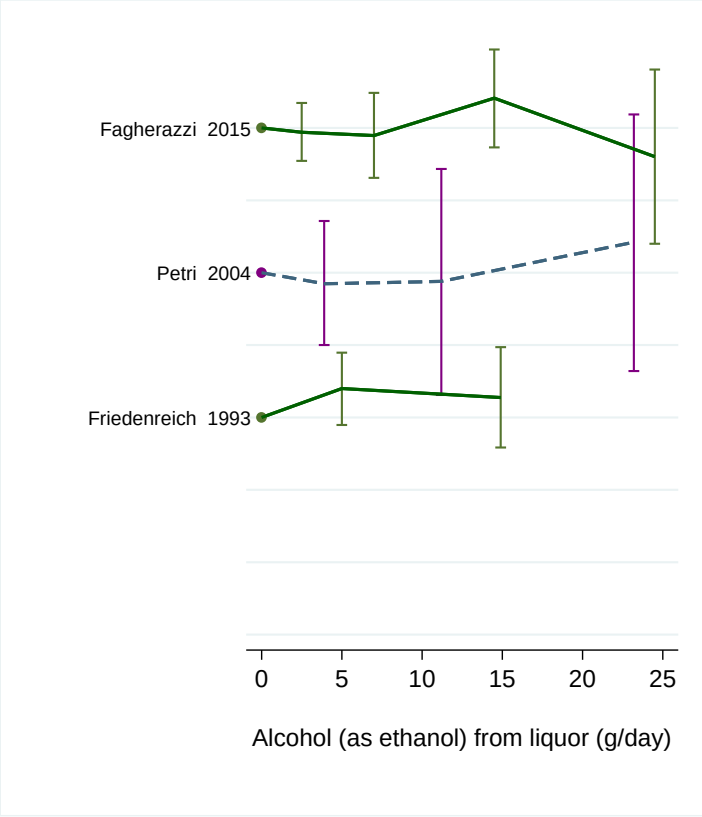
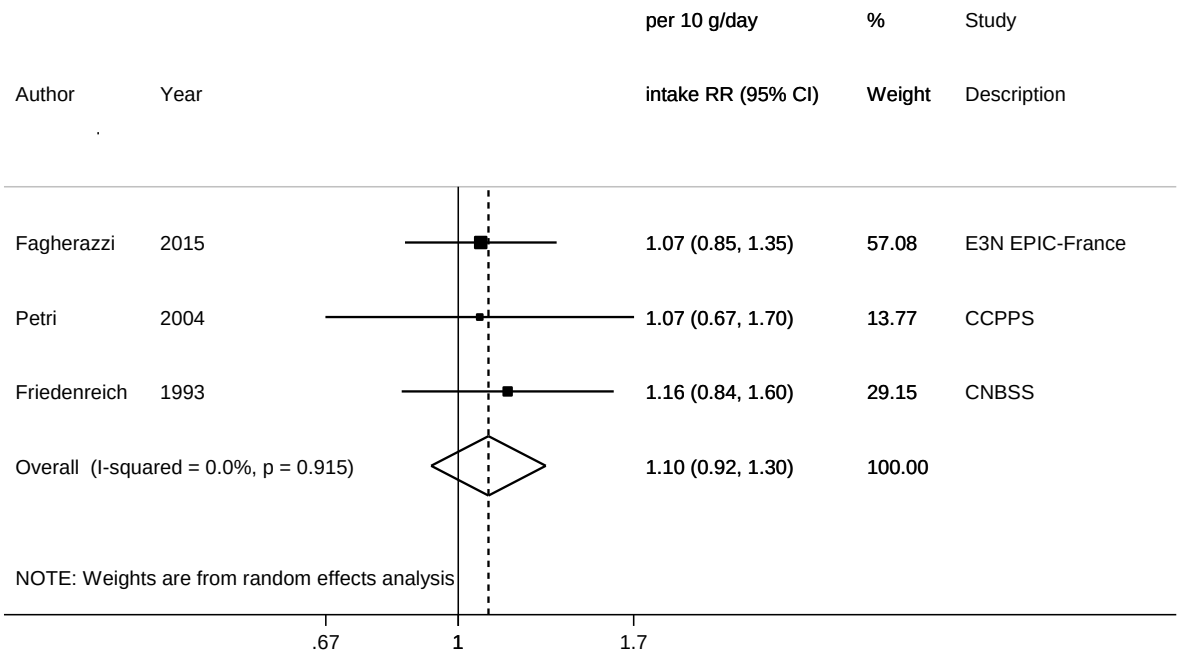


Figure 381 Relative risk of premenopausal breast cancer incidence for 10g/day increase of alcohol (as ethanol) intake from liquor



Postmenopausal breast cancer

Summary

Main results:

Seven studies (7 798 cases) (7 publications) were included in the dose-response meta-analysis. Alcohol (as ethanol) intake from liquor was positively but not significantly associated with a higher risk of postmenopausal breast cancer.

Two studies were excluded from the dose-response meta-analysis. Lew, 2009 and Feigelson, 2001 reported that liquor consumption was significantly positively associated with breast cancer incidence and mortality, respectively.

Postmenopausal breast cancer risk and alcohol (as ethanol) intake from liquor by cancer type:

Kabat, 2011 (WHI) reported that liquor intake was significantly positively associated with ER+ postmenopausal breast cancer and non-significantly inversely associated with triple negative postmenopausal breast cancer. Li, 2010 (WHI-OS) reported that liquor intake was significantly positively associated with lobular but not with ductal cancer.

Influence and stratified analyses:

In influence analysis, the summary relative risk ranged from 1.01 (95% CI, 0.92-1.12) when Petri, 2004 was excluded to 1.09 (1.00-1.18) when Mattisson, 2004a was excluded.

Study quality:

Alcohol consumption was estimated using questionnaires in all studies. In addition, one study used 7 day food record (Mattisson, 2004a). The reference category included intakes of ≥0

g/day in one study (Petri, 2004). Risk estimate from one study used in the dose-response meta-analysis was in drinkers only (Tjønneland, 2003). All remaining studies did not specify if former/past drinkers were excluded from the reference category with three studies indicating that lowest intake category included 0 g/day consumption over the previous year (Fagherazzi, 2015, Park, 2014, Mattisson, 2004a).

Case ascertainment was through cancer registries, death certificates or when active follow-up, diagnosis were confirmed through medical records.

Table 299 Alcohol (as ethanol) from liquor and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	10 (11 publications)
Studies included in forest plot of highest compared with lowest exposure	7 (7 publications)
Studies included in linear dose-response meta-analysis	7 (7 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 300 Alcohol (as ethanol) from wine and postmenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR	**CUP SLR**
Increment unit used	1 time/day	10 g/day
Studies (n)	5	7
Cases	N/A	7 798
RR (95%CI)	1.03 (0.94-1.13)	1.05 (0.93-1.17)
Heterogeneity (I^2, p-value)	64%	73%, 0.001
P value Egger test		0.78

Stratified analyses in CUP SLR			
Geographic area	**Asia**	**Europe**	**North America**
Studies (n)	-	5	2
RR (95%CI)	-	1.09 (0.88-1.36)	1.04 (1.01-1.07)
Heterogeneity (I^2, p-value)	-	82%, <0.001	0%, 0.89
Adjustment for age, BMI and reproductive factors	**Adjusted**	**Not adjusted**	

Studies (n)	5	2	
RR (95%CI)	1.01 (0.91-1.13)	1.38 (0.73-2.60)	
Heterogeneity (I^2, p-value)	73%, 0.005	82%, 0.02	

Table 301 Alcohol (as ethanol) from liquor and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Fagherazzi, 2015 BRE80543 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W	2 305/ 66 481 16 years	Questionnaire and death certificate	Validated FFQ	Incidence, breast cancer, postmenopause	≥2 drinks/day vs non-alcohol consumers	1.19 (0.84-1.69)	Age, age at first child, age at menarche, age at menopause, BMI, breastfeeding, educational level, family history of breast cancer, history of benign breast disease, mammography, menopausal women and use of MHT, parity, physical activity, use of oral contraception, use of progestagens in premenopause	Intake in drinks/day converted to ethanol g/day using 10g ethanol/drink, mid-points of exposure categories, person-years per category
Park, 2014 BRE80494 USA	MEC, Prospective Cohort, Age: 60.9 years, W, Postmenopausal	3 885/ 85 089 12.4 years	SEER cancer registry for Hawaii & California & National Death Index	Quantitative FFQ	Incidence, breast cancer	Per 10 g/day	1.04 (1.01-1.07)	Age, age at first child birth, age at menarche, age at menopause, BMI, educational level, energy	None

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								Intake, ethnicity, family history of breast cancer, hormone replacement therapy, number of children, physical activity, smoking status, type of menopause	
Mattisson, 2004a BRE17807 Sweden	MDCS, Prospective Cohort, Age: 50- years, W, Postmenopausal	342/ 11 726 7.6 years	Partially histological - over 80%	7-day record + questionnaire	Incidence, breast cancer, postmenopausal	23.2 vs 0 g/day	1.05 (0.54-2.07)	Age, age at first child, age at menarche, educational level, energy Intake , height, HRT use, Interviewer, leisure time physical activity, other design issue, other nutritional factors, season of interview, smoking habits, waist circumference	Reference category changed using Hamling's method
Petri, 2004 BRE16325	CCPPS, Prospective	144/ 13 074	Partially histological -	Questionnaire	Incidence, breast cancer,	≥6.1 vs 0-0.9 drinks/week	2.43 (1.41-4.20)	Age, HRT use, other design	Drinks/week converted to

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Denmark	Cohort, Age: 20-91 years, W		over 80%		postmenopausal			issue, parity/ pregnancies	ethanol g/day using 12g ethanol/drink, mid-points of exposure categories
Tjønneland, 2003 BRE12350 Denmark	DCH, Prospective Cohort, Age: 50-64 years, W, Postmenopausal	416/ 23 778 4.7 years	Partially histological - over 80%	FFQ	Incidence, breast cancer, postmenopausal	12.1-60 vs 0.1-6 g/day	1.47 (0.65-3.31)	Age at first child, age-underlying cox models, alcohol, benign breast disease, BMI, duration of HRT use, educational level, HRT use, parity/ pregnancies, parous/ nulliparous	
						Per 10 g/day	1.09 (0.87-1.36)		
van den Brandt, 1995 BRE12719 Netherlands	NLCS, Case Cohort, Age: 55-69 years, W, Postmenopausal	422/ 62 573 3.3 years	All histology	Questionnaire	Incidence, breast cancer, postmenopausal	Per 1 g/day	1.02 (0.99-1.04)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, educational level, energy Intake , family history, family history, oral contraceptive	RR rescaled for an increment of 10g/day

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								use, parity/pregnancies, smoking habits	
Friedenreich, 1993 BRE17508 Canada	CNBSS, Nested Case Control, W, Screening Program	284/ 691 controls 5.5 years	All histology	FFQ	Incidence, breast cancer, postmenopausal	≥10 vs ≤0 g/day	1.00 (0.64-1.56)	Age, energy intake, family history, parity/ pregnancies, smoking habits	Mid points of exposure categories

Table 302 Alcohol (as ethanol) from liquor and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Kabat, 2011 BRE80344 USA	WHI, Prospective Cohort, Age: 50-79 years, W	2 479/ 148 030 8 years	Mail or telephone questionnaires verified by trained physician adjudicators	FFQ	Incidence, breast cancer ER+	≥3 vs 0 servings/week	1.36 (1.17-1.58)	Age, age at first child birth, age at menarche, age at menopause, BMI, breast biopsies, contraception, educational level, ethnicity, family history of breast cancer, HRT use, mammogram In the past 2 years, physical activity, smoking, treatment allocation, waist circumference	Excluded, analysis by hormone receptor status was not conducted
		300/			Incidence, triple negative breast cancer	≥3 vs 0 servings/week	0.84 (0.47-1.52)		
Li, 2010 BRE80336	WHI-OS, Prospective Cohort, Age: 50-79 years, Postmenopausal	2 459/ 87 724	Medical record	Self-administered questionnaire	Incidence, breast cancer, postmenopausal	≥1 vs never drinks	1.45 (1.14-1.83)	Age, BMI, educational level, ethnicity, family history of breast cancer, Gail model risk, HRT use, mammography, parity, race, smoking	Superseded by Kabat, 2011, no cases or person-years per category
		1 805			ductal carcinomas		1.28 (0.94-1.72)		
		720			lobular carcinomas		2.46 (1.51-4.00)		
Lew, 2009 BRE80256 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W, Postmenopausal	5 461/ 184 418 7 years	Cancer registry		Incidence, breast cancer	3 vs 0 drinks/day	1.24 (1.03-1.49)	Age, age at first child birth, age at menopause, beer consumption, BMI, breast biopsies, energy Intake, family history of cancer, fat Intake, folate	Excluded, only two levels of exposure, used in the HvL analysis only

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								Intake, height, HRT use, oral contraceptive use, parity, physical activity, race, smoking habits, wine	
Feigelson, 2001 BRE19514 USA, Puerto Rico	CPS II, Prospective Cohort, W	590/ 242 010 14 years	Death certificate	Questionnaire	Mortality, breast cancer, postmenopausal	≥3 vs ≤0 drinks/day	1.66 (1.12-2.46)	Age, age at first child, age at menarche, age at menopause, BMI, educational level, ethnicity, family history, food, height, HRT use, other specified factor, physical activity, smoking habits, supplements	Excluded, outcome is mortality

Figure 382 RR estimates of postmenopausal breast cancer by levels of alcohol (as ethanol) from liquor

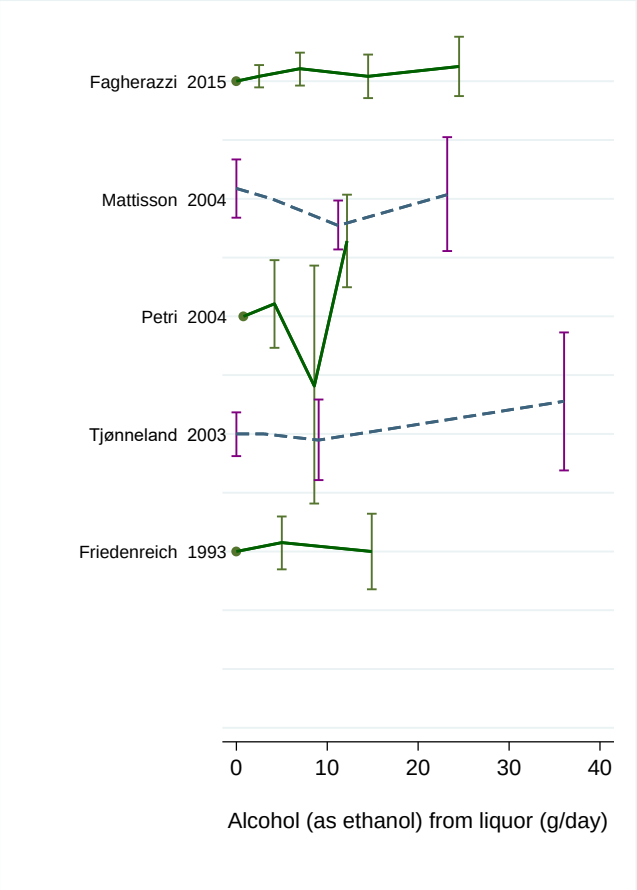


Figure 383 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest level of liquor intake

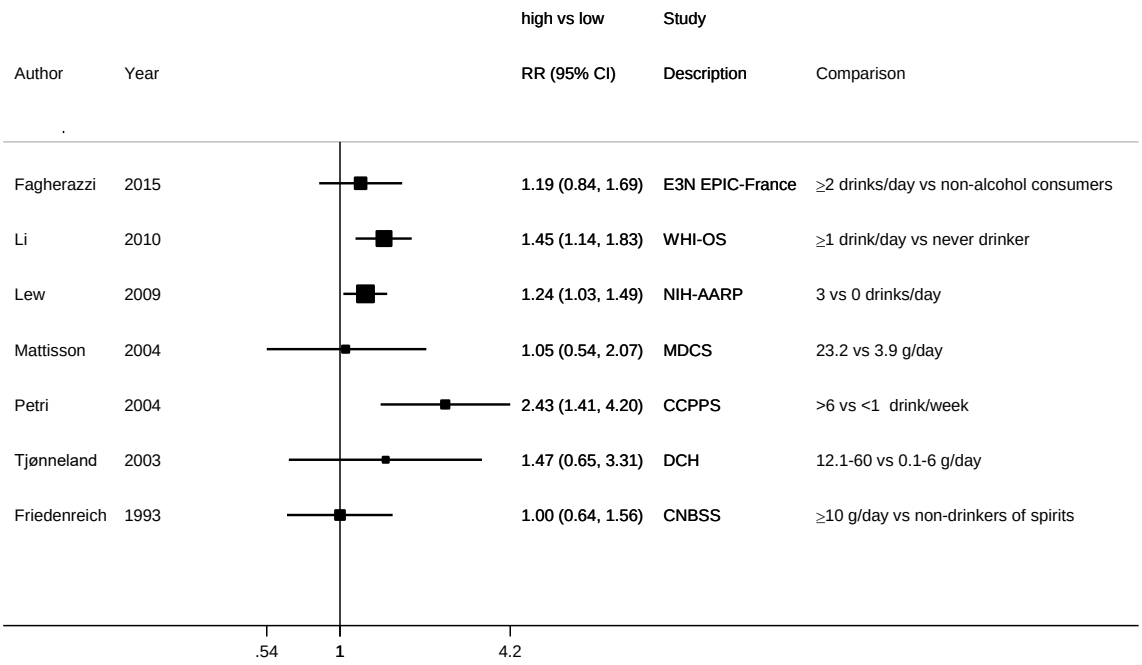


Figure 384 Funnel plot of studies included in the dose response meta-analysis of alcohol (as ethanol) from liquor and postmenopausal breast cancer

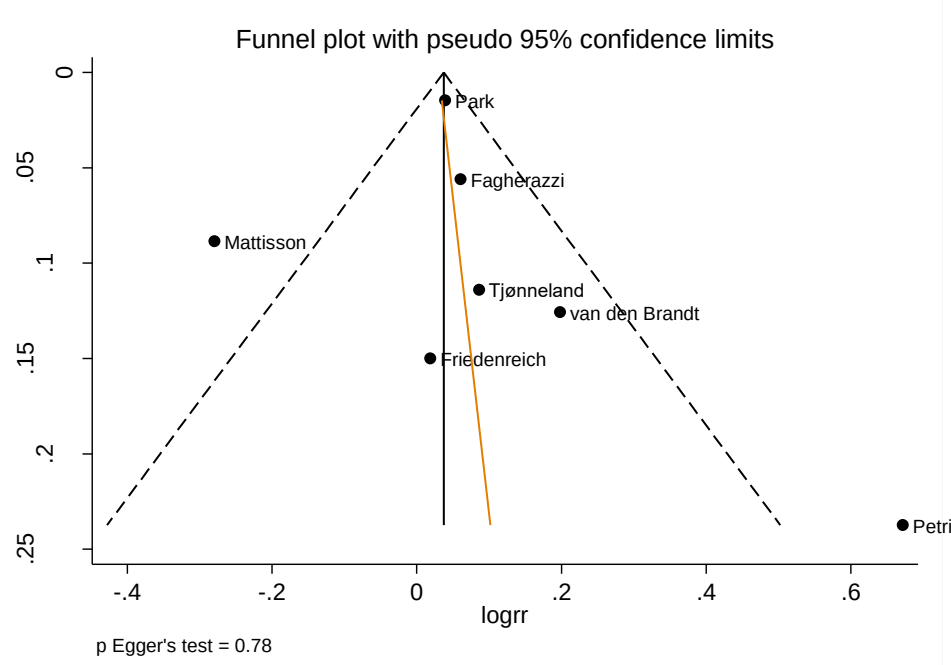


Figure 385 Relative risk of postmenopausal breast cancer incidence for 10g/day increase of alcohol (as ethanol) intake from liquor

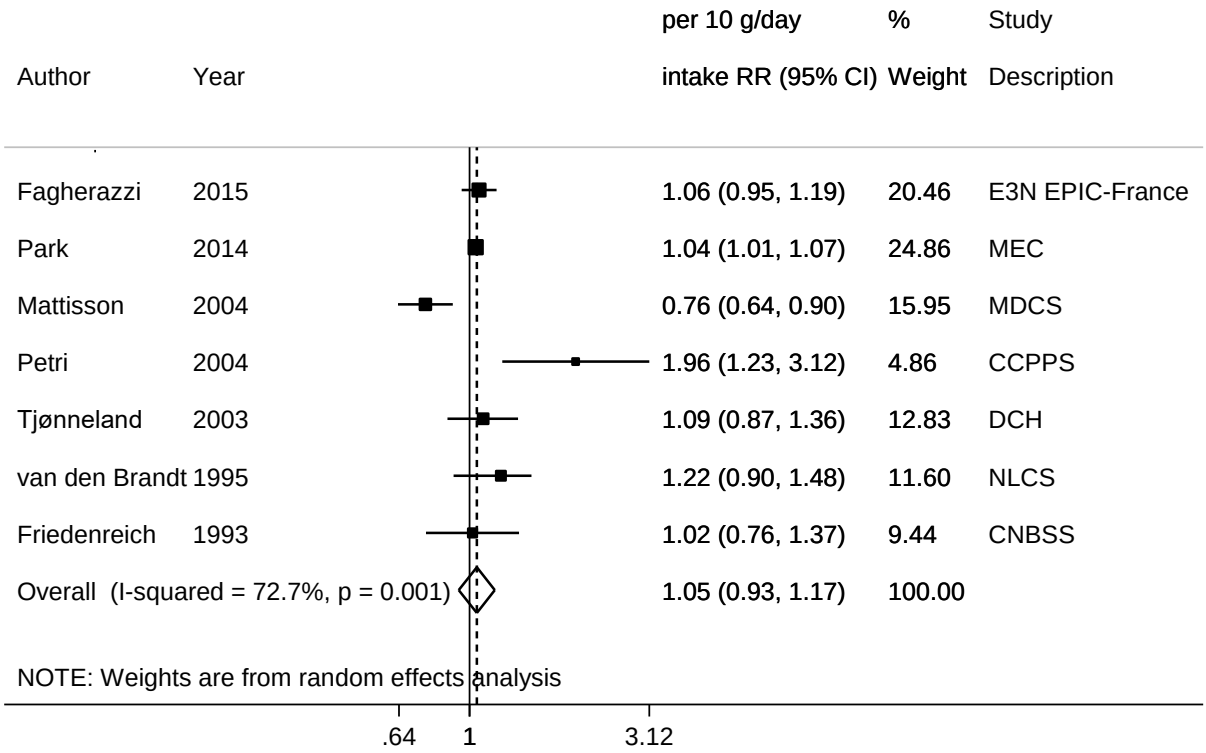
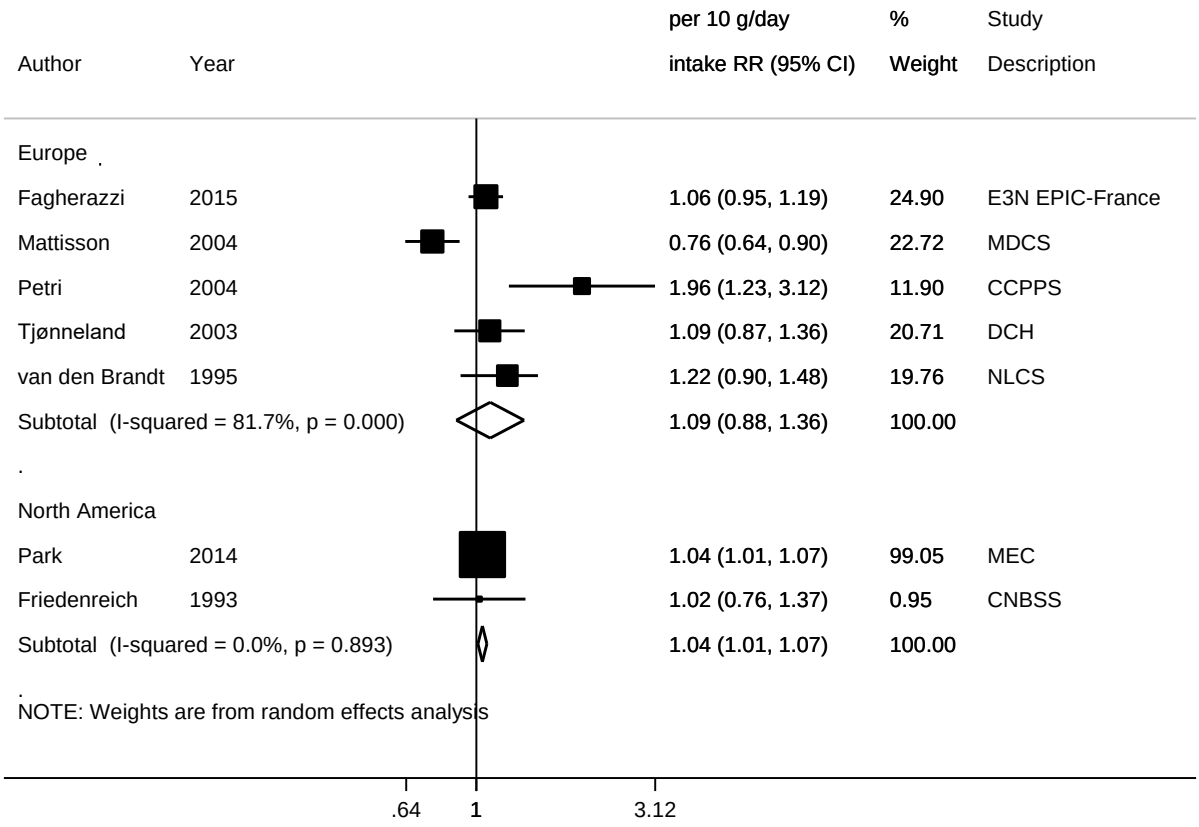


Figure 386 Relative risk of postmenopausal breast cancer incidence for 10g/day increase of alcohol (as ethanol) intake from liquor, by geographic location



5.5 Vitamins

5.5.1.2.1 Circulating alpha-carotene

Breast cancer (any)

A pooled analysis of eight prospective cohorts (Columbia, MO; Umeå; CLUE I and II; NHS; WHS; NYUWHS; SWHS; MEC) (Eliassen, 2012) and two French cohorts (Maillard, 2010, E3N; Pouchieu, 2014, SU.VI.MAX) were identified and included in the dose-response meta-analysis. Overall, a non-significant inverse association was observed (summary RR for 10 μg/dL: 0.90, 95% CI: 0.77-1.05), with no evidence of heterogeneity (I^2=0%, Pheterogeneity=0.79). Other published reports were superseded by the pooled analysis.

The NHS study was included in the pooled analysis with 962 cases (Eliassen, 2012). In a more recent publication of the same cohort (Eliassen, 2015, 2188 cases), circulating alpha-carotene was significantly related to lower risk of breast cancer (any) (RR: 0.74, 95% CI: 0.60-0.91, ptrend=0.01), comparing highest vs lowest concentrations of alpha-carotene. The pooled analysis reported a no significant relative risk estimate for the highest compared to the lowest quartile but a significant linear trend was observed (p=0.04).

The EPIC study examined the association of plasma alpha carotene with breast cancer by ER status and age at diagnosis (less or more than 50 years) but was not included in the dose-response meta-analysis (Bakker, 2016). This study was published after the end of the literature search.

Hormone receptor status

In the pooled analysis of eight prospective cohorts (Eliassen, 2012) a statistically significant association was observed for ER-negative breast cancer (RR for Q5 vs Q1=0.61, 95% CI=0.40-0.93, Ptrend: 0.04) but not for ER-positive; RR=0.85, 95% CI=0.65-1.12, Ptrend=0.16; Pheterogeneity=0.11).

In the EPIC study, plasma alpha carotene was significantly inversely related to ER-negative breast cancer (RR for highest vs lowest concentrations: 0.61, 95% CI: 0.39-0.98, ptrend=0.02) but not with ER-positive breast cancer (RR: 0.77, 95% CI: 0.49-1.19, ptrend=0.28).

Premenopausal breast cancer

Three cohorts from two publications (Sisti, 2015; Hulten, 2001) were identified and all were included in the dose-response meta-analysis. Circulating alpha-carotene was non-significantly positively associated with premenopausal breast cancer (summary RR for 10 μg/dL: 1.04, 95% CI: 0.78-1.39), with no evidence of heterogeneity (I^2=0%, Pheterogeneity=0.53).

Postmenopausal breast cancer

Six cohorts from four publications (Sisti, 2015; Epplein, 2009; Kabat, 2009; Hulten, 2001) were identified and all were included in the dose-response meta-analysis. Circulating alpha-carotene was significantly inversely associated with postmenopausal breast cancer (summary

RR for 10 μg/dL: 0.80, 95% CI: 0.65-0.98), with no evidence of heterogeneity (I^2=0%, Pheterogeneity=0.89).

The summary RR became non-significant when Sisti, 2015 (39.2% weight) was omitted in influence analysis (summary RR for 10 μg/dL: 0.80, 95% CI: 0.62-1.04). There was no evidence of small study or publication bias (P Egger's test=0.62).

Table 303 Circulating alpha-carotene and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	11 (17 publications)
Studies included in forest plot of highest compared with lowest intake	Breast cancer: 9 (2 publications) Premenopausal: 3 (2 publications) Postmenopausal: 6 (4 publications)
Studies included in linear dose-response meta-analysis	Breast cancer: 10 (3 publications) Premenopausal: 3 (2 publications) Postmenopausal: 6 (4 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 304 Circulating alpha-carotene and breast cancer risk. Summary of the linear dose-response meta-analysis in the CUP

	Breast cancer (any)	**Premenopausal**	**Postmenopausal**
Increment unit used	10 μg/dL		
Studies (n)	10	3	6
Cases (total number)	3 506	592	1 101
RR (95%CI)	0.90 (0.77-1.05)	1.04 (0.78-1.39)	0.80 (0.65-0.98)
Heterogeneity (I^2, p-value)	0%, p=0.79	0%, p=0.53	0%, p=0.89
P value Egger test	-	-	0.62

Table 305 Circulating alpha-carotene and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR

Author, Year	**Number of studies**	**Total number of cases**	**Studies country, area**	**Outcome**	**Comparison**	**RR (95%CI)**	**P trend**	**Heterogeneity (I^2, p value)**
Meta-analysis								
Aune et al, 2012	13	3 531	North America, Europe, Asia	Incidence, breast cancer	High vs. low Per 10 μg/dL	0.80 (0.68-0.95) 0.82 (0.73-0.92)	- -	15% 3%

Table 306 Circulating alpha-carotene and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Sisti, 2015 BRE80597 USA	NHS I and II, Nested Case Control, Age: 25-55 years, W, Premenopausal	535/ 1 179	Biennial follow-up questionnaires and medical records	Blood: participants collected follicular phase blood samples during days 3–5 of their menstrual cycle, and blood and urine samples during the luteal phase, 7–9 days before the anticipated start of their next cycle.	Incidence, breast cancer, premenopausal at diagnosis	≥12 vs ≤4.5 µg/dl	1.17 (0.81-1.68) Ptrend:0.49	Age at menarche, alcohol intake, BMI, family history of breast cancer, history of benign breast disease, matching variables, parity and age at first birth	Included, premenopausal breast cancer; midpoints of exposure quartiles
		491/			Postmenopausal at diagnosis		0.73 (0.49-1.06) Ptrend:0.10		Included, postmenopausal breast cancer; midpoints of exposure quartiles
		1 133/ 1133 controls			Breast cancer		0.93 (0.73-1.19) Ptrend:0.62		Superseded by pooled analysis, Eliassen, 2012
		616/			ER+		0.92 (0.69-1.23) Ptrend:0.50		Not analysed
		150/			ER-		0.87 (0.51-1.47) Ptrend:0.38		
Pouchieu, 2014 BRE80565 France	SU.VI.MAX, Nested Case Control, Age: 49.8 years, W	100/ 100 controls 8 years	Self report verified by medical record	Plasma: HPLC	Incidence, breast cancer	per 0.1 µmol/l	0.94 (0.77-1.15)	Age, alcohol intake, BMI, dietary records, educational level, energy intake, family history of breast cancer, fat intake, fruits and	Included, all breast cancer, RR rescaled for an increment used, units converted to µg/dl

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								vegetables consumption, height, HRT use, intervention group, menopausal status, number of children, physical activity, smoking status	
		50/ 50 controls			Intervention group	per 0.1 µmol/l	0.61 (0.35-1.06)		
					Placebo-group	per 0.1 µmol/l	0.89 (0.62-1.30)		
Eliassen, 2012 China, Sweden, USA	Pooled analysis of 8 prospective studies*, Mean age ranged from 51.3-66.0 years, W *Columbia, MO; Umeå; CLUE I and II; NHS; WHS; NYUWHS; SWHS; MEC	3,055 cases/ 3,956 controls		Plasma, recalibrated values, reverse-phase HPLC, median time between blood collection and diagnosis was 4.3 years	Incidence, breast cancer	≥11.3 vs <2.6 µg/dl	0.87 (0.71-1.05) Ptrend:0.04	Menopausal status, age at menopause, age at menarche, parous, age at first birth, exogenous hormone use, BMI, current smoking, race, personal history of benign breast disease, family history of breast cancer Matching factors included age at	Included, all breast cancer; midpoints of exposure quintiles
		1,481			ER+ breast cancer	Q5 vs Q1	0.85 (0.65-1.12) Ptrend:0.16		Not analysed
		417			ER- breast cancer	Q5 vs Q1	0.61 (0.40-0.93) Ptrend:0.04		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								blood collection, date, time, and fasting status at blood collection, menopausal status, date of last menstrual period and/or phase and day of menstrual cycle (premenopausal women), PMH use, race or ethnicity, study centre, smoking status, follow-up time, availability of FFQ, use of antibiotics, number of blood collections within the cohort, diagnosis of benign breast disease	
Maillard, 2010 BRE80258 France	E3N EPIC-France, Nested Case Control, Age: 40-65 years, W	366/ 720 controls 7 years	Self report verified by medical record	Serum: HPLC	Incidence, breast cancer	Q 5 vs Q 1	0.99 (0.62-1.56) Ptrend:0.95	Age, age at first child birth, alcohol consumption, benign breast disease, blood collection	Included, all breast cancer; intakes estimated from mean and standard deviation,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								centre, date of blood collection, educational level, family history of cancer, fasting condition, height, menopausal hormone use, menopausal status, parity	midpoints of exposure quantiles
					Alcohol <=10g/day		0.95 (0.47-1.91) Ptrend:0.73		
					Alcohol 10+ g/day		2.34 (0.71-7.71) Ptrend:0.42		
Epplein, 2009 BRE80236 USA	MEC, Nested Case Control, Age: 45-75 years, W, Postmenopausal	286/ 535 controls	Cancer registry	Plasma: HPLC with photodiode array detection	Incidence, breast cancer, postmenopausal	≥101.8 vs ≤42 ng/ml	0.88 (0.56-1.39) Ptrend:0.64	Age at first child birth, age at interview, age at menarche, age at menopause, alcohol consumption, BMI, date of blood collection, ethnicity, fasting condition, geographic area, HRT use, parity, year of birth	Included, postmenopausal breast cancer; converted units, midpoints of exposure quintiles
Kabat, 2009	Women's Health	190/	Self report,	Serum: reverse-	Incidence,	≥0.09 vs ≤0.03	0.75 (0.49-1.15)	Age, age at first	Included,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
BRE80250 USA	Initiative - Dietary Modification Trial, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	5 450 8 years	medical record and pathology report reviewed by centrally trained physician	phase HPLC	invasive & in situ breast cancer, postmenopausal	µg/ml	Ptrend:0.19	child birth, age at menarche, age at menopause, alcohol consumption, benign breast disease, BMI, calcium intake, educational level, energy intake, ethnicity, family history of cancer, HRT use, OC use, physical activity, randomized treatment assignment	postmenopausal breast cancer; converted units, midpoints
		153/			Incidence, invasive breast cancer, postmenopausal	≥0.09 vs ≤0.03 µg/ml	0.55 (0.34-0.90) Ptrend:0.02		
Hulten, 2001 BRE04155 Sweden	VIP-MONICA-MSP, Nested Case Control, W	201/ 390 controls	Partially histological - over 80%	Plasma: HPLC	Incidence, breast cancer	Q4 vs Q1	0.70 (0.40-1.20) Ptrend:0.21	BMI, total cholesterol, triglycerides, age at menarche, parity, age at first full-term pregnancy, use of hormone replacement therapy, menopausal status, cotinine (a marker of recent exposure	Superseded by pooled analysis, Eliassen, 2012
	VIP-MONICA	57/ 93 controls			Premenopausal	>0.35 vs ≤0.16 µmol/L	0.70 (0.20-2.40) Ptrend:0.59		Included, premenopausal breast cancer; converted units, midpoints
	VIP-MONICA	67/ 109 controls			Postmenopausal		0.50 (0.20-1.40) Ptrend:0.17		Included, postmenopausal

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								to tobacco smoke), and hours of fasting	breast cancer; converted units, midpoints
	MSP	67/ 127 controls				>0.36 vs ≤0.15 µmol/L	0.60 (0.20-1.60) Ptrend:0.25		

Table 307 Circulating alpha-carotene and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Bakker, 2016 Europe	EPIC, Nested Case Control, Mean age: 50 years, W	636/ 632 controls	Linkage to population cancer registries in most countries, a combination of methods in some countries, including health insurance records, cancer and pathology registries, and active follow-up	Plasma: HPLC	Incidence, invasive breast cancer, ER+	≥266.43 vs ≤36.10 nmol/l	0.77 (0.49-1.19) Ptrend:0.28	BMI, height, age at menarche, age at first full-term pregnancy, OC use, HRT use, smoking status, alcohol consumption, educational level, intake of saturated fatty acids, energy intake, season of blood collection Matching factors: study centre, age,	Identified after end of search, analysis by tumour receptor status was not conducted due to low number of studies
		515/ 514 controls			ER-	≥279.56 vs ≤38.33 nmol/l	0.61 (0.39-0.98) Ptrend:0.02		
					ER+PR+	Q5 vs Q1	1.01 (0.55-1.86)		
					ER-PR-		0.64 (0.36-1.13)		
					ER- , never/past smokers	Q3 vs Q1	0.70 (0.48-1.04)		
					ER- , current		0.81 (0.32-2.03)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					smokers			menopausal status, use of exogenous hormones, phase of menstrual cycle, fasting status at blood collection, time of blood collection	
Eliassen, 2015 BRE80598 USA	NHS, Nested Case Control, Age: 43-67 years, W	894/ 897 controls 20 years	Biennial follow-up questionnaires and medical records	Plasma: reverse-phase HPLC, first sample collected 1989-1990 second sample collected 2000-2002	Incidence, breast cancer	≥111 vs ≤37.6 µg/dl	0.74 (0.60-0.91) Ptrend:0.01	Age at first child birth, age at menarche, age at menopause, alcohol intake, BMI at age 18 years, family history of breast cancer, history of benign breast disease, matching variables, parity	Superseded by pooled analysis, Eliassen, 2012
		1 316/			Incidence, breast cancer ER+		0.74 (0.59-0.93) Ptrend:0.02		
		292/			Incidence, breast cancer ER-		0.68 (0.45-1.02) Ptrend:0.15		
		350/			Incidence, well differentiated breast cancer		0.82 (0.56-1.20) Ptrend:0.34		
		596/			Incidence,		0.89 (0.66-1.20)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					moderate differentiated breast cancer		Ptrend:0.39		
		373/			Incidence, poorly differentiated breast cancer		0.58 (0.39-0.86) Ptrend:0.02		
		646/			Incidence, luminal a breast cancer		0.80 (0.59-1.08) Ptrend:0.13		
		216/			Incidence, luminal b breast cancer		0.54 (0.33-0.88) Ptrend:0.02		
		108/			Incidence, triple negative breast cancer		0.91 (0.46-1.80) Ptrend:0.84		
		1 850/			Incidence, nonrecurrent and nonlethal breast cancer		0.78 (0.63-0.96) Ptrend:0.04		
		301/			Incidence, recurrent or lethal breast cancer		0.54 (0.35-0.83) Ptrend:0.01		
		1 121/ 1209 controls			Incidence, breast cancer, BMI<25.0		0.65 (0.49-0.86) Ptrend:0.005		
		695/ 644 controls			BMI 25- <30		0.94 (0.65-1.37) Ptrend:0.87		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		334/ 298 controls			BMI >=30		0.76 (0.37-1.55) Ptrend:0.52		
		1 880/ 1926 controls			Nonsmokers		0.74 (0.60-0.92) Ptrend:0.01		
		271/ 226 controls			Current smokers		1.23 (0.54-2.80) Ptrend:0.22		
		1 828/ 1828 controls			Follow up <10 years		0.73 (0.59-0.91) Ptrend:0.02		
		894/ 897 controls			Follow up >=10 years		0.77 (0.56-1.05) Ptrend:0.21		
Dorjgochoo, 2009 BRE80289 China	SWHS, Nested Case Control, Age: 40-70 years, W	365/ 726 controls 7.5 person-years	Cancer registry	Plasma: HPLC	Incidence, breast cancer	Q4 vs Q1	0.98 (0.62-1.54) Ptrend:0.95	Age, age at first child birth, age at menarche, antioxidant intake, benign breast disease, educational level, energy intake, family history of cancer, fish, fruit intake, laboratory batch, menopausal status, occupation, physical activity, red meat intake, smoking status, tea intake,	Superseded by pooled analysis, Eliassen, 2012

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								vegetable intake, waist-hip ratio	
Tamimi, 2009 BRE80276 USA	NHS, Nested Case Control, W, Postmenopausal	604/ 626 controls 9 years	Self report verified by medical record	Plasma: reverse-phase HPLC	Incidence, breast cancer	Q5 vs Q1	0.70 (0.40-1.00) Ptrend:0.004	Age, age at first child birth, alcohol, benign breast disease, BMI, family history of cancer, parity, postmenopausal hormone use	Superseded by pooled analysis, Eliassen, 2012
						Q5 vs Q1	0.60 (0.40-0.90) Ptrend:0.0008		
Sesso, 2005 BRE24061 USA	WHS, Nested Case Control, W, Health professionals	480 7 years	Medical records + self-reported	Plasma: reverse-phase HPLC	Incidence, breast cancer	15.9 vs 2.2 µg/dl	1.06 (0.61-1.84) Ptrend:0.85	Age at first child, age at menarche, alcohol, biomarkers, BMI, design , design , design , family history, HRT use, menopausal status, nutrients, nutrients, nutrients, nutrients, OC use, parity/pregnancies, physical activity	Superseded by pooled analysis, Eliassen, 2012

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Tamimi, 2005 BRE24274 USA	NHS, Nested Case Control, Age: 43-70 years, W, Registered nurses	325 22 years	All morphology (histology or cytology)	Plasma: reverse-phase HPLC	Incidence, invasive & in situ breast cancer	Q5 vs Q1	0.64 (0.47-0.88) Ptrend:0.01	Age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, family history, fasting condition, HRT use, laboratory variables , other anthropometric index	Superseded by pooled analysis, Eliassen, 2012
		165/			Incidence, breast cancer ER-		0.50 (0.28-0.91) Ptrend:0.48	Age , parous/ nulliparous	
		564/			Incidence, breast cancer ER+		0.72 (0.50-1.04) Ptrend:0.03		
Tamimi, 2004 BRE12084 USA	NHS, Nested Case Control, Age: 30-55 years, W, Registered nurses	254/ 235 controls 8 years	Partially histological - over 80%	Plasma: reverse-phase HPLC	Incidence, breast cancer	Q3 vs ≥Q1	0.96 (0.60-1.52)	Age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, duration of HRT use, family history, parity/pregnancies, smoking habits	Superseded by pooled analysis, Eliassen, 2012
Han, 2003	NHS,	881/	Partially	Plasma: reverse-	Incidence, breast	Q4 vs Q1	0.68 (0.50-0.92)	Age at first	Superseded by

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
BRE18435 USA	Nested Case Control, Age: 57 years, W, Registered nurses	844 controls 8 years	histological - over 80%	phase HPLC	cancer, ^{194}Trp non carriers (XRCCI Arg Trp)		Ptrend:0.008	child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, duration of HRT use, family history, parity/pregnancies, parous/nulliparous, smoking habits	pooled analysis, Eliassen, 2012
Sato, 2002 BRE20839 USA	CLUE I, Nested Case Control, Age: 51 years, W, blood donors	231/ 235 controls 20 years	Partially histological - over 80%	Serum: reverse-phase HPLC	Incidence, breast cancer	≥3.5 vs ≤0.8 µg/dl	0.69 (0.36-1.34) Ptrend:0.09	Matched on age (within 1 year), race, menopausal status, and month and year of blood donation; premenopausal women were also matched on date of last menstrual cycle	Superseded by pooled analysis, Eliassen, 2012
	CLUE II, Nested Case Control, Age: 60 years, W,	115/ 113 controls 3 years	Partially histological - over 80%			≥4.9 vs ≤1.4 µg/dl	0.84 (0.34-2.08) Ptrend:0.59		Superseded by pooled analysis, Eliassen, 2012

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	blood donors								
Toniolo, 2001 BRE12399 USA	NYUWHS, Nested Case Control, Age: 35-65 years, W	14 275	Partially histological - over 80%	Serum: HPLC, Steghens et al. method	Incidence, breast cancer	Q4 vs Q1	1.00 Ptrend:0.0006	Age at first child, benign breast disease, biomarkers, family history	Superseded by pooled analysis, Eliassen, 2012
Dorgan, 1998 BRE14889 USA	Columbia, MO cohort, Nested Case Control, Age: 41-73 years, W	105/ 209 controls 9.5 years	All histology	Serum	Incidence, invasive breast cancer	0.14-0.84 vs ≤0.05 µmol/l	1.80 (0.80-4.10) Ptrend:0.11	Biomarkers, BMI, smoking habits	Superseded by pooled analysis, Eliassen, 2012

Figure 387 RR estimates of breast cancer by levels of plasma alpha-carotene concentration

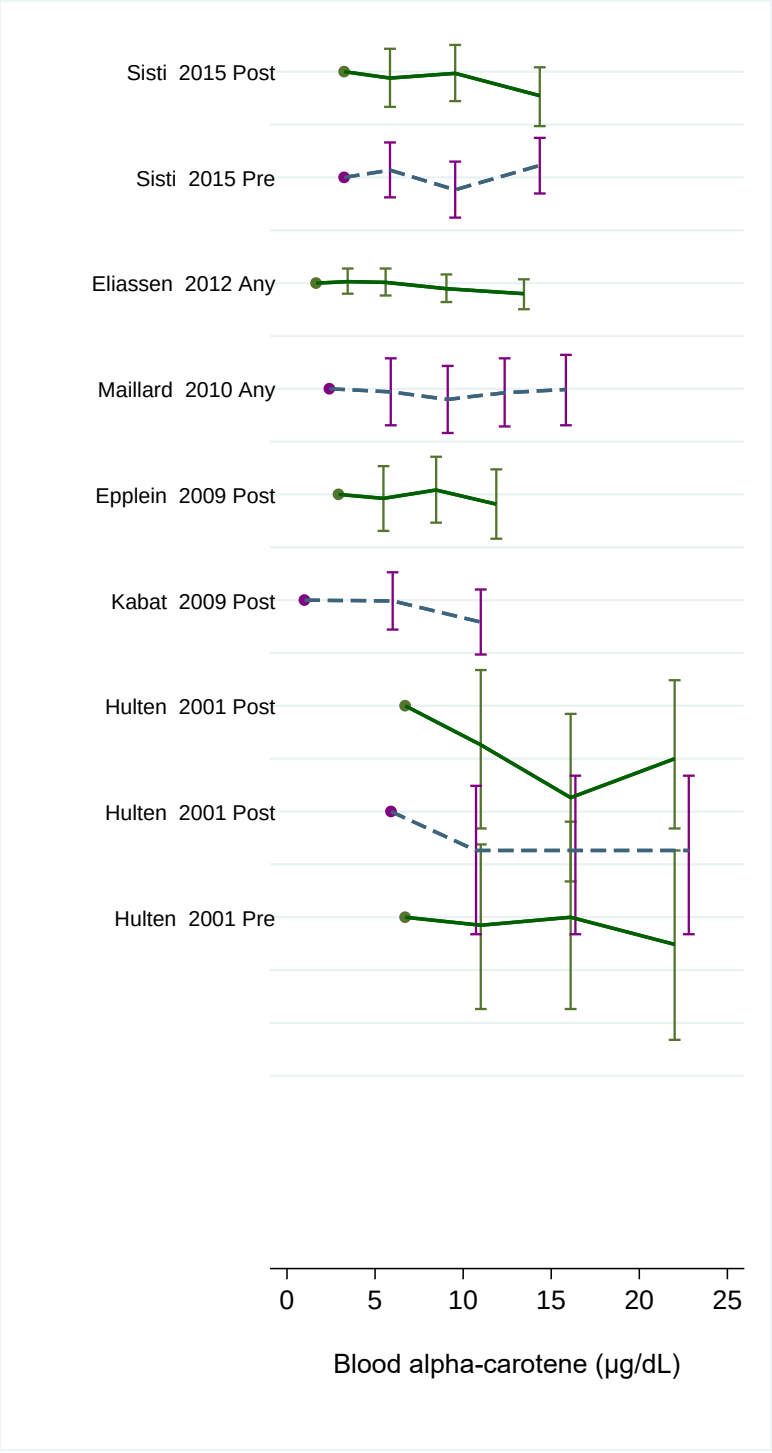


Figure 388 RR (95% CI) of breast cancer for the highest compared with the lowest level of plasma alpha-carotene concentration

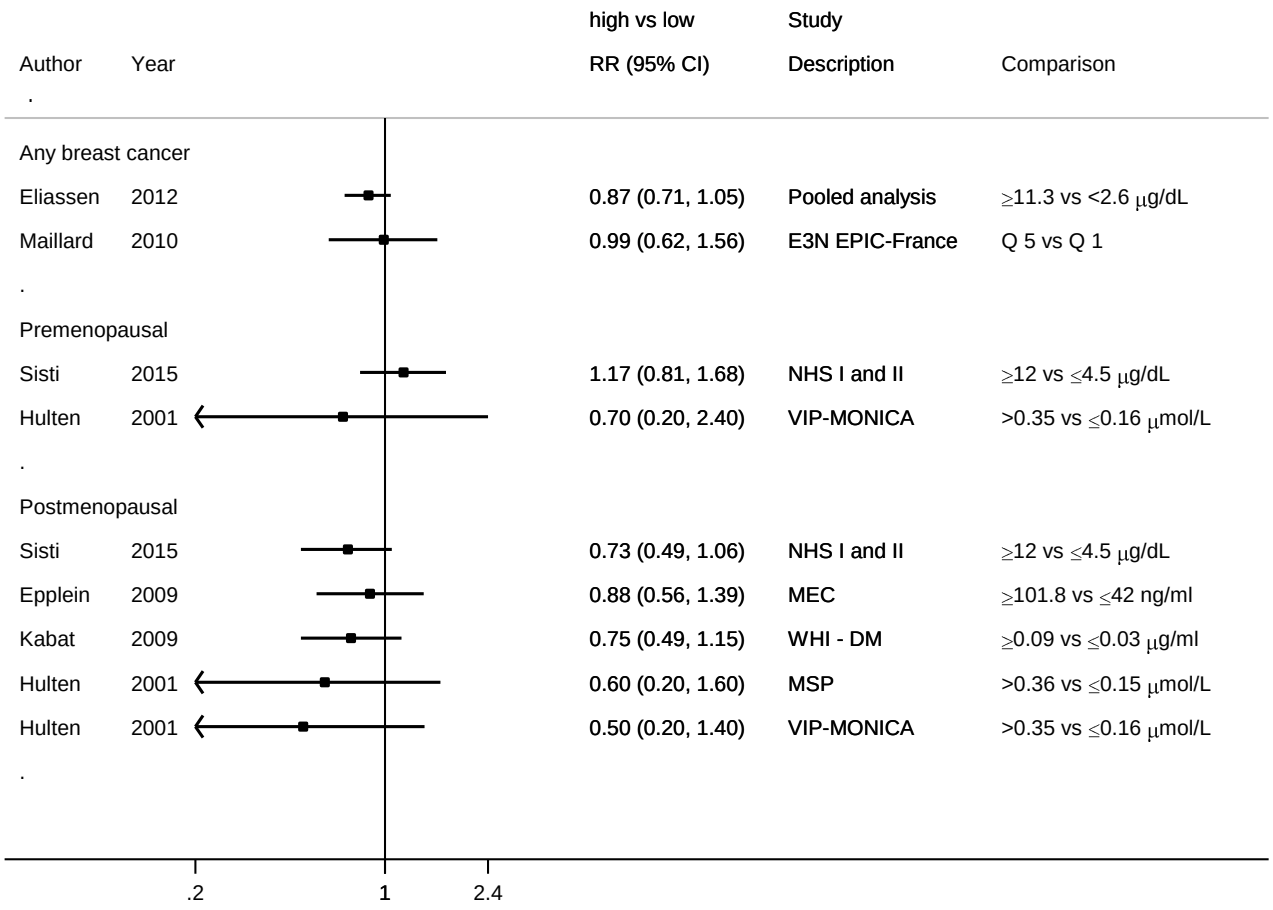


Figure 389 Relative risk of breast cancer (any) for 10 µg/dl increase of plasma alpha-carotene concentration

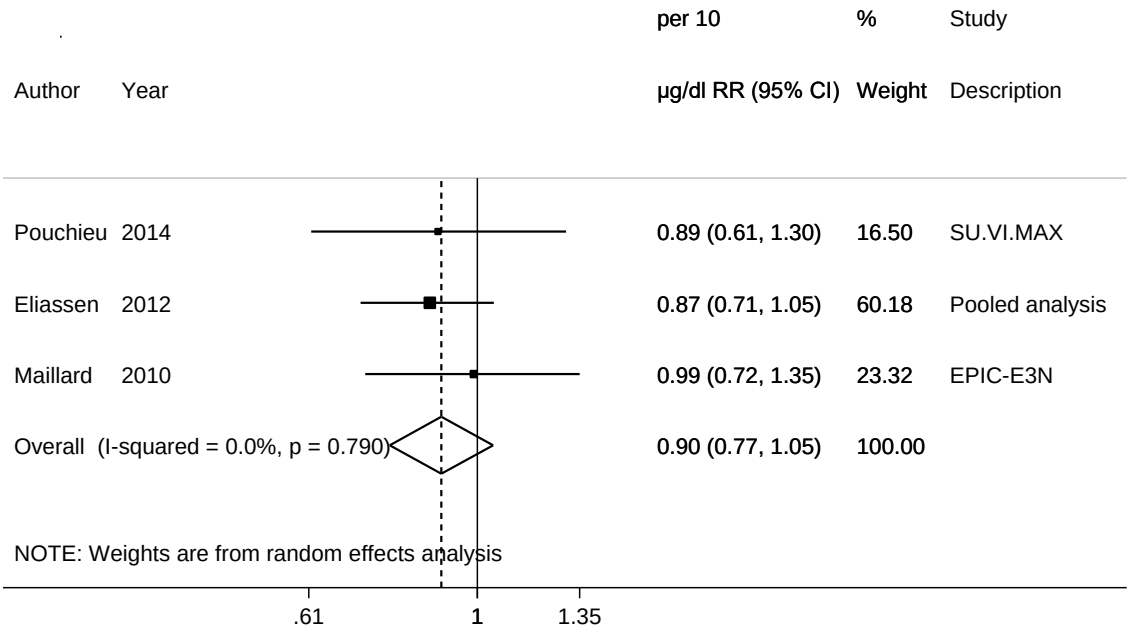


Figure 390 Relative risk of premenopausal breast cancer for 10 µg/dl increase of plasma alpha-carotene concentration

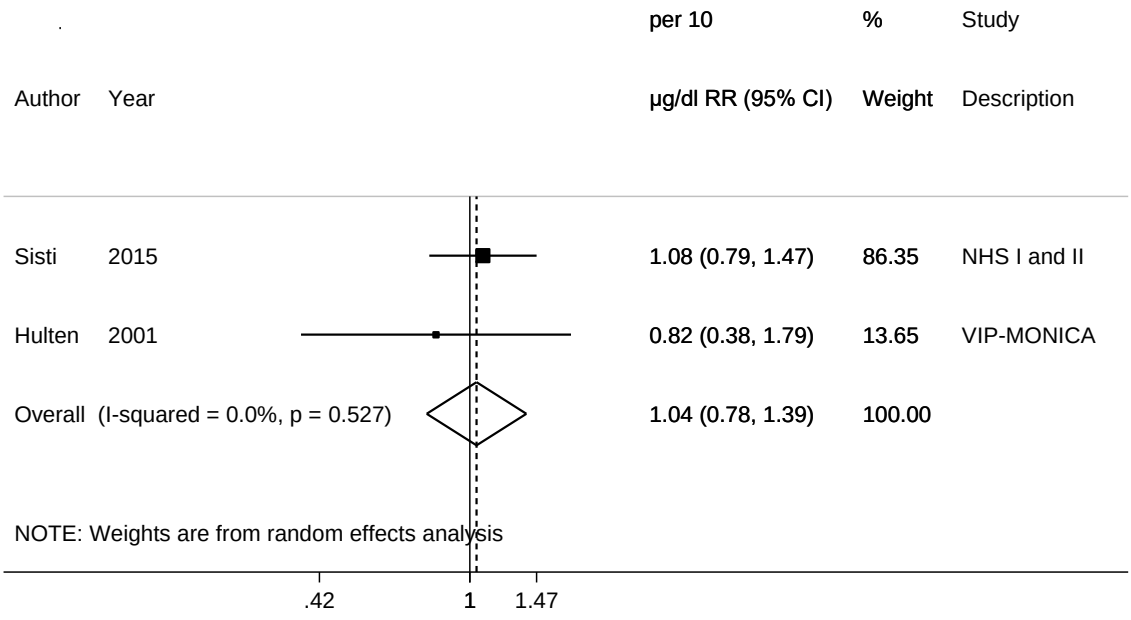


Figure 391 Relative risk of postmenopausal breast cancer for 10 µg/dl increase of plasma alpha-carotene concentration

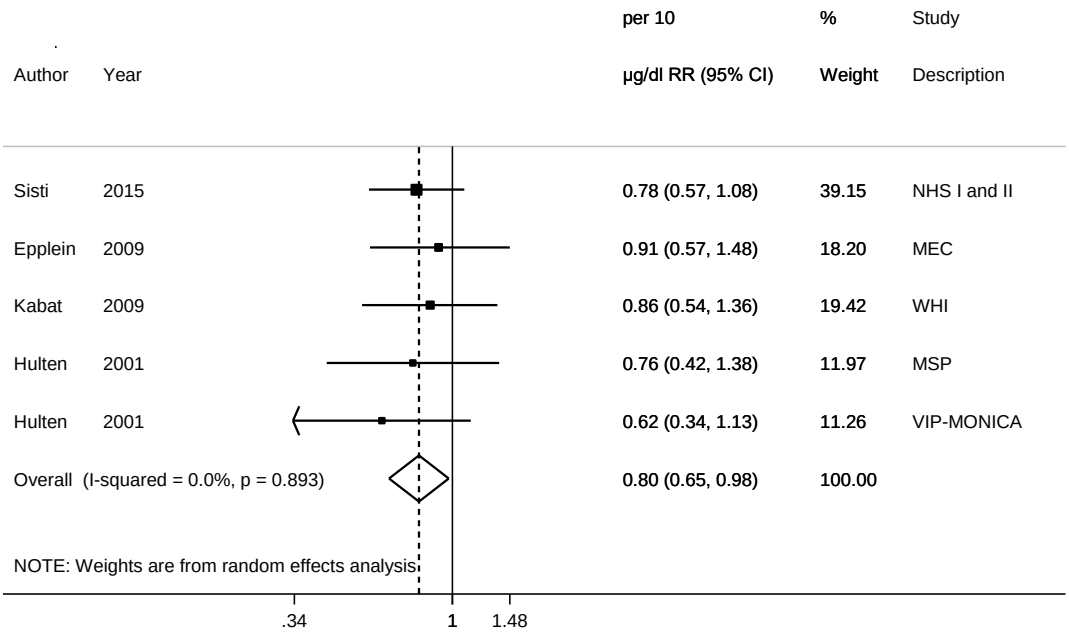
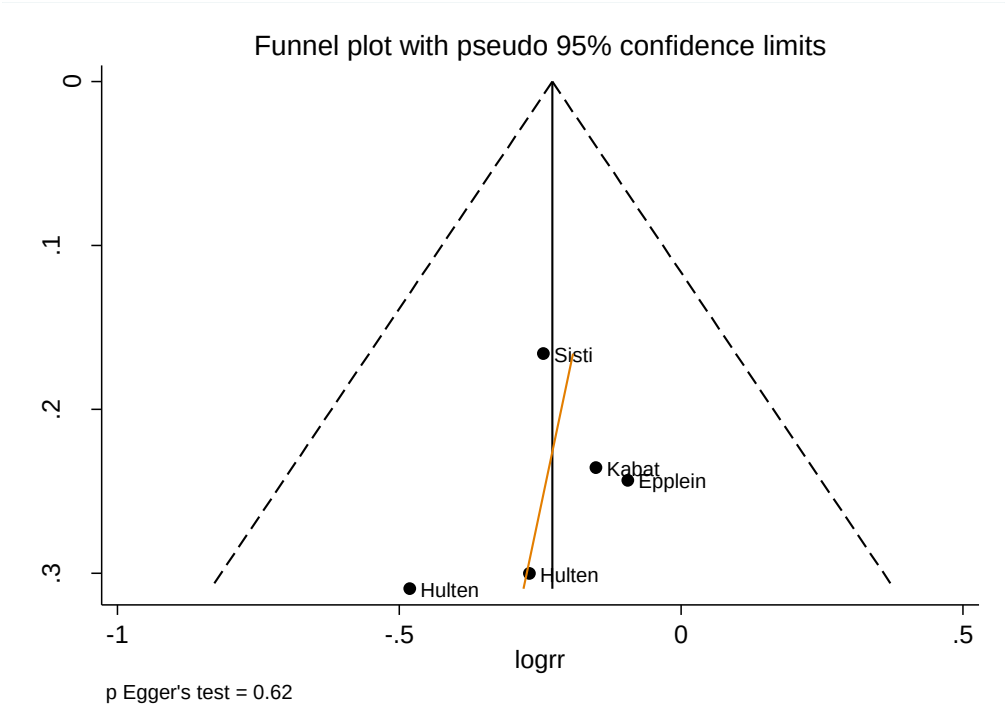


Figure 392 Funnel plot of studies included in the dose response meta-analysis of plasma alpha -carotene concentration and postmenopausal breast cancer



5.5.1.2.2 Dietary beta-carotene and other carotenoids

16 publications (24 prospective studies) on dietary beta-carotene intake and breast cancer were identified, including a pooled analysis of 18 cohort studies. The pooled analysis superseded all identified studies on breast cancer (any) and no dose-response meta-analysis was conducted in the CUP. The summary RR for 5000 μg/day in the Pooling Project was (1.00, 95% CI: 0.98-1.02) with no significant evidence of heterogeneity (Pheterogeneity=0.98) (Zhang, 2012). Study characteristics and results of all identified studies are shown in study inclusion and exclusion tables.

Hormone receptor status

In the Pooling Project (Zhang, 2012) dietary beta-carotene intake was inversely associated with the risk of ER-negative breast cancer (pooled multivariable RRs of the comparison between the highest and lowest quintiles: 0.84; 95% CI: 0.77- 0.93 and RR for 5000 μg/d; 0.93; 95% CI:0.88- 0.99) but not inversely associated with the risk of ER-positive breast cancer (pooled multivariable RRs for the same comparison: 1.04; 95% CI: 0.98- 1.10). Nonsignificant associations were observed for PR-positive and PR-negative breast cancer. The observed associations were not modified by menopausal status.

Premenopausal breast cancer

Three studies were identified and all were included in the dose-response meta-analysis. Dietary beta-carotene was non-significantly inversely associated with premenopausal breast cancer (summary RR for 5000 μg/day: 0.95, 95% CI: 0.81-1.10), with moderate heterogeneity (I^2=42%, Pheterogeneity=0.18).

In the Pooling Project (Zhang, 2012) dietary beta-carotene intake was inversely but not significantly associated with premenopausal ER-positive and ER-negative breast cancer, also the inverse association is more evident for ER-negative cancers.

Postmenopausal breast cancer

Seven studies from eight publications were identified and all were included in the dose-response meta-analysis. Dietary beta-carotene was inversely and marginally significantly associated with postmenopausal breast cancer risk (summary RR for 5000 μg/day: 0.94, 95% CI: 0.89-1.00), with no evidence of heterogeneity (I^2=0%, Pheterogeneity=0.75).

Two studies (Roswall, 2010, DCH and Cui, 2008, WHI-OS) reported risk estimates for ER/PR breast cancer types. Both studies are included in the Pooling Project.

Other carotenoids and breast cancer (any)

All identified studies on dietary alpha-carotene, lycopene, lutein and zeaxanthin, beta-cryptoxanthin and risk of any type of breast cancer were superseded by the Pooling Project (Zhang, 2012). In the Pooling Project, alpha carotene, lutein and zeaxanthin were significantly inversely associated with ER- breast cancer risk, RR: 0.87, 95% CI: 0.78-0.97 and RR: 0.87, 95% CI: 0.79-0.95, respectively. Alpha carotene and lycopene were significantly inversely associated with ER-PR+ breast cancer, RR: 0.64, 95% CI: 0.47-0.86 and RR: 0.73, 95% CI: 0.55-0.97, respectively. Significant inverse association was also

reported for lutein and zeaxanthing intake and ER-PR- breast cancer (RR: 0.89, 95% CI: 0.81-0.99).

Other carotenoids and premenopausal breast cancer

No new studies were identified in the CUP. Pooling Project of 18 cohort studies (Zhang, 2012) reported no significant associations between dietary alpha-carotene, beta-cryptoxanthin, lutein/zeaxanthin, lycopene and premenopausal ER+ and ER- breast cancer.

Other carotenoids and postmenopausal breast cancer

Two new studies (two publications) were identified during the CUP. In the Rotterdam Study (199 cases), dietary intake of alpha-carotene, lutein, zeaxanthin, beta-cryptoxanthin, and lycopene were not associated with postmenopausal breast cancer risk (Panatavos, 2012). In the WHI-OS (2 879 cases), dietary alpha-carotene was inversely associated with ER+PR+ postmenopausal breast cancer (RRs of the comparison between the highest and lowest quintiles: 0.83, 95% CI: 0.70-0.99); the RR for lycopene was similar: 0.85, 95% CI: 0.73-1.00 (Cui, 2008). Beta-cryptoxanthin, lutein and zeaxanthin were not associated with postmenopausal, ER+PR+, ER+PR-, or ER-PR- postmenopausal breast cancer. Pooling Project of 16 (NHS II and WLHS excluded) cohort studies reported no significant associations between dietary alpha-carotene, beta-cryptoxanthin, lutein/zeaxanthin, lycopene and postmenopausal ER+ and ER- breast cancer (Zhang, 2012).

Table 308 Dietary carotenoid intake and breast cancer (any) risk. Results of meta-analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analysis								
Aune et al, 2012	3	4 290	North America, Europe, Asia	Incidence	Total carotenoids High vs. low Per 10 000 µg/d	 0.95 (0.84-1.08) 0.98 (0.79-1.22)		 17% 66%
	10	18 191			Beta-carotene High vs. low Per 5000 µg/d	 0.93 (0.88-0.98) 0.95 (0.91-0.99)		0% 0%
	6	9 461			Alpha-carotene High vs. low Per 1000 µg/d	 0.93 (0.86-1.01) 0.96 (0.90-1.02)		 16% 44%
	6	9 461			Beta-cryptoxanthin High vs. low Per 150 µg/d	 1.02 (0.95-1.09) 1.01 (0.96-1.06)		 0% 18%
	5	8 750			Lutein and zeaxanthin High vs. low Per 5000 µg/d	 0.94 (0.87-1.02) 0.94 (0.87-1.01)		 0% 5%
	7	10 537			Lycopene High vs. low Per 10 000 µg/d	 1.00 (0.93-1.07) 1.02 (0.97-1.08)		 2% 3%

Table 309 Dietary beta-carotene intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis by menopausal status

Author, Yea WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Pantavos, 2015 BRE80573 Netherlands	Rotterdam, Netherlands, Prospective Cohort, Age: 55- years, W	199/ 3 209 17 years	Annual linkage to the Netherlands cancer registry and the nationwide network of histopathology and cytopathology	Validated FFQ	Incidence, breast cancer postmenopausal	high vs low µg/day	0.87 (0.61-1.24)	Age, alcohol consumption, BMI, educational level, family history of breast cancer, multivitamin supplement Intake, smoking status	Included, postmenopausal breast cancer, corrected intake units
Larsson, 2010 BRE80300 Sweden	SMC, Prospective Cohort, Age: 62 years, W	1 008/ 36 664 9.4 years	Self report verified by medical record	FFQ	Incidence, breast cancer	≥4783 vs ≤1773 µg/day	0.87 (0.71-1.06)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, benign breast disease, BMI, educational level, energy Intake, family history of cancer, multivitamin supplement Intake, OC use, parity, physical activity, postmenopausal	Included, breast cancer (any)
		562/			Incidence, breast cancer ER+/PR+		0.93 (0.71-1.22) Ptrend:0.90		Not analysed, included in the highest vs lowest analysis
		244/			Incidence, breast cancer ER+/PR-		0.79 (0.52-1.19) Ptrend:0.12		
		110/			Incidence, breast cancer ER-/PR-		0.57 (0.31-1.02) Ptrend:0.11		

Author, Yea WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								hormone use, smoking status	
Nagel, 2010 BRE80257 Europe	EPIC, Prospective Cohort, Age: 35-70 years, W	3 606/ 334 493 8.8 years	Cancer registry and death certificates	Dietary record + FFQ	Incidence, Invasive breast cancer, postmenopausal	per 2 mg/day	0.98 (0.92-1.04)	Age, age at first child birth, age at menarche, alcohol consumption, educational level, energy from carbohydrates, energy from other sources, height, HRT use, mono-unsaturated fat, parity, physical activity, polyunsaturated fat, saturated fat, smoking status, study center, weight	Included, postmenopausal breast cancer
						7.28 vs 1.2 mg/day	0.93 (0.82-1.04) Ptrend:0.292		
		1 480/			Incidence, Invasive breast cancer, premenopausal	per 2 mg/day	1.02 (0.92-1.14)		Included, premenopausal breast cancer
						7.28 vs 1.2 mg/day	1.04 (0.85-1.27) Ptrend:0.945		
Cui, 2008 BRE80182 USA	Women's Health Initiative - Observational study, Prospective Cohort, Age: 50-79 years, Postmenopausal	2 879/ 84 805 7.6 years	Self report/ hospital records/pathology reports	Semi-quantitative FFQ	Incidence, Invasive breast cancer, postmenopausal	≥5835 vs 0-2154.9 µg/day	0.86 (0.75-0.99) Ptrend:0.073	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, benign breast disease, BMI, educational level, energy	Included, postmenopausal breast cancer
		1 760/			ER+/PR+		0.78 (0.66-0.94) Ptrend:0.021		Not analysed, included in the highest vs lowest analysis
		362/			ER+/PR-		0.84 (0.57-1.22) Ptrend:0.96		

Author, Yea WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		350/			ER-/PR-		1.12 (0.75-1.68) Ptrend:0.62	Intake, ethnicity, family history of cancer, folate Intake, hysterectomy, OC use, oophorectomy/hysterectomy, parity, physical activity, postmenopausal hormone use, smoking habits, supplement use	
Cho, 2003 BRE01652 USA	NHS, Prospective Cohort, Age: 26-46 years, W, Registered nurses	714/ 90 655 8 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, Invasive breast cancer, premenopausal	7701 vs 1675 µg/day	0.96 (0.75-1.22) Ptrend:0.97	Age at first child, age at menarche, alcohol, benign breast disease, BMI, family history, height, menopausal status, nutrients, OC use, parity/pregnancies, residual (willet), smoking habits	Included, breast cancer (any)
Horn-Ross, 2002 BRE15412 USA	CTS, Prospective Cohort, Age: 21-103	111 383 2 years	Partially histological - over 80%	FFQ	Incidence, Invasive breast cancer	≤4652 vs ≤1465 µg/day	1.10 (0.90-1.40) Ptrend:0.2	Age , age at first child, age at menarche, BMI, energy Intake ,	Included, breast cancer (any)

Author, Yea WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	years, W, Registered teachers							ethnicity, family history, menopausal status, physical activity	
Terry, 2002 BRE12200 Canada	CNBSS, Case Cohort, W, Screening Program	1 452/ 56 837	Partially histological - over 80%	FFQ-quantitative	Incidence, breast cancer	per 3556 µg/day	1.01(0.70-1.33)	Age , age at menarche, alcohol, benign breast disease, BMI, educational level, energy Intake , family history, HRT use, nutrients, nutrients, nutrients, OC use, parity/pregnancies, physical activity , recruitment center, residual (willet), smoking habits, supplements	Included, breast cancer (any)
		672/			Premenopausal		1.01 (0.89-1.15)		Included, premenopausal breast cancer
		575/			Postmenopausal		1.01 (0.89-1.15)		Included, postmenopausal breast cancer
Zhang, 1999 BRE13953 USA	NHS, Prospective Cohort, Age: 33-60 years, W,	1 913/ 83 234 14 years	Temp	FFQ-semi-quantitative	Incidence, Invasive breast cancer, postmenopausal	7609 vs 1677 µg/day	0.94 (0.81-1.09) Ptrend:0.42	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease,	Included, postmenopausal breast cancer
		784/ 83 234			Incidence, Invasive breast		0.84 (0.67-1.05) Ptrend:0.07		Included, premenopausal

Author, Yea WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Registered nurses	14 years			cancer, premenopausal			BMI, body weight, energy Intake , family history, height, HRT use, length of follow-up, parity/ pregnancies	breast cancer
Verhoeven, 1997 BRE12868 Netherlands	NLCS, Case Cohort, Age: 55-69 years, W	519/ 62 573 4.3 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, Invasive breast cancer	0.72 vs 0.2 mg/day	1.01 (0.72-1.42) Ptrend:0.96	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, energy Intake , family history, parity/ pregnancies	Included, breast cancer (any)
Shibata, 1992 BRE80361 USA	Leisure World Cohort, Prospective Cohort, M/W, retirement community, upper middle social class	219/ 11 580 70 159 person-years	Community registry	FFQ	Incidence, breast cancer	≥9800 vs ≤4799 µg/day	0.79 (0.57-1.10)	Age, smoking status	Included, postmenopausal breast cancer

Table 310 Dietary beta-carotene intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Zhang, 2012*	Pooled analysis of 18 prospective cohorts (CARET, BWHS, BCDDP, CTS, CPS II, CNBSS, CLUE II, IWHS, JPHC I, MCCS, NLCS, NIH-AARP, NHS, NHS II, PLCO, SMC, WHS, WLHS)	33 380/ 1 028 438 14.9 (mean)	Study specific		Incidence, breast cancer	**Q5 vs Q1** Beta-carotene Alpha-carotene Beta-cryptoxanthin Lutein/zeaxanthin Lycopene	 1.00 (0.97-1.04) 0.98 (0.94-101) 0.95 (0.91-0.99) 0.98 (0.93-1.02) 0.99 (0.96-1.03)	Age, ethnicity, family history of breast cancer, personal history of benign breast disease, alcohol consumption, smoking status, education, physical activity, age at menarche, BMI, height, oral contraceptive use, menopausal status (in total breast cancer analysis), energy intake, parity, age of first birth	Superseded all identified studies
						Per 5000 µg Beta-carotene Alpha-carotene Beta-cryptoxanthin Lutein/zeaxanthin Lycopene	 1.00 (0.98-1.02) 0.99 (0.98-1.01) 0.99 (0.97-1.00) 1.00 (0.99-1.02) 1.00 (0.99-1.02)		
		19 282/			ER+	**Q5 vs Q1** Beta-carotene Alpha-carotene Beta-cryptoxanthin Lutein/zeaxanthin Lycopene	 1.04 (0.98-1.10) 1.04 (0.99-1.09) 0.96 (0.92-1.00) 1.00 (0.93-1.08) 0.99 (0.94-1.04)		Analysis by tumour hormone receptor status was not conducted
						Per 5000 µg Beta-carotene Alpha-carotene Beta-cryptoxanthin Lutein/zeaxanthin Lycopene	 1.02 (0.99-1.05) 1.01 (0.99-1.03) 0.99 (0.97-1.00) 1.01 (0.98-1.04) 1.01 (0.99-1.03)		
		4 643/			ER-	**Q5 vs Q1** Beta-carotene Alpha-carotene	 0.84 (0.77-0.93) 0.87 (0.78-0.97)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
						Beta-cryptoxanthin Lutein/zeaxanthin Lycopene	0.90 (0.81-1.00) 0.87 (0.79-0.95) 0.92 (0.83-1.02)		
						Per 5000 µg Beta-carotene Alpha-carotene Beta-cryptoxanthin Lutein/zeaxanthin Lycopene	 0.93 (0.88-0.99) 0.95 (0.90-1.01) 0.97 (0.93-1.00) 0.95 (0.91-1.00) 0.98 (0.93-1.03)		
		15 696/			PR+	**Q5 vs Q1** Beta-carotene Alpha-carotene Beta-cryptoxanthin Lutein/zeaxanthin Lycopene	 1.01 (0.96-1.07) 1.00 (0.95-1.05) 0.96 (0.91-1.01) 0.97 (0.90-1.05) 0.99 (0.92-1.07)		
						Per 5000 µg Beta-carotene Alpha-carotene Beta-cryptoxanthin Lutein/zeaxanthin Lycopene	 1.00 (0.97-1.04) 1.00 (0.98-1.03) 1.00 (0.97-1.03) 1.00 (0.97-1.03) 0.99 (0.97-1.02)		
		7 203/			PR-	**Q5 vs Q1** Beta-carotene Alpha-carotene Beta-cryptoxanthin Lutein/zeaxanthin Lycopene	 0.94 (0.87-1.02) 0.97 (0.88-1.07) 0.93 (0.83-1.04) 0.97 (0.90-1.06) 0.96 (0.88-1.05)		
						Per 5000 µg Beta-carotene Alpha-carotene	 0.97 (0.91-1.03) 0.99 (0.94-1.04)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
						Beta-cryptoxanthin	0.96 (0.92-1.00)		
						Lutein/zeaxanthin	0.99 (0.96-1.03)		
						Lycopene	1.02 (0.98-1.05)		
					ER+PR+	**Q5 vs Q1**			
						Beta-carotene	1.02 (0.98-1.09)		
						Alpha-carotene	1.03 (0.97-1.08)		
						Beta-cryptoxanthin	0.96 (0.92-1.01)		
						Lutein/zeaxanthin	0.99 (0.93-1.07)		
						Lycopene	1.00 (0.93-1.08)		
						Per 5000 µg			
						Beta-carotene	1.01 (0.98-1.04)		
						Alpha-carotene	1.01 (0.99-1.04)		
						Beta-cryptoxanthin	1.00 (0.97-1.03)		
						Lutein/zeaxanthin	1.01 (0.98-1.04)		
						Lycopene	1.00 (0.98-1.02)		
					ER+PR-	**Q5 vs Q1**			
						Beta-carotene	1.05 (0.91-1.22)		
						Alpha-carotene	1.06 (0.91-1.25)		
						Beta-cryptoxanthin	0.91 (0.80-1.05)		
						Lutein/zeaxanthin	1.07 (0.93-1.23)		
						Lycopene	0.96 (0.84-1.10)		
						Per 5000 µg			
						Beta-carotene	1.01 (0.92-1.13)		
						Alpha-carotene	1.03 (0.94-1.12)		
						Beta-cryptoxanthin	0.97 (0.93-1.00)		
						Lutein/zeaxanthin	1.04 (0.98-1.10)		
						Lycopene	1.04 (0.98-1.10)		
					ER-PR+	**Q5 vs Q1**			
						Beta-carotene	0.70 (0.51-0.96)		
						Alpha-carotene	0.64 (0.47-0.86)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
						Beta-cryptoxanthin Lutein/zeaxanthin Lycopene	0.78 (0.59-1.03) 0.72 (0.51-1.02) 0.73 (0.55-0.97)		
						Per 5000 µg Beta-carotene Alpha-carotene Beta-cryptoxanthin Lutein/zeaxanthin Lycopene	 0.89 (0.75-1.05) 0.86 (0.74-1.00) 0.94 (0.86-1.02) 0.94 (0.83-1.07) 0.90 (0.75-1.07)		
					ER-PR-	**Q5 vs Q1** Beta-carotene Alpha-carotene Beta-cryptoxanthin Lutein/zeaxanthin Lycopene	 0.87 (0.78-0.96) 0.90 (0.80-1.01) 0.95 (0.84-1.07) 0.89 (0.81-0.99) 0.95 (0.85-1.07)		
						Per 5000 µg Beta-carotene Alpha-carotene Beta-cryptoxanthin Lutein/zeaxanthin Lycopene	 0.94 (0.88-1.01) 0.98 (0.92-1.04) 0.97 (0.94-1.01) 0.96 (0.91-1.01) 0.99 (0.95-1.04)		
		2 247 (2 220 lutein/ zeaxanthin)/			Incidence, premenopausal breast cancer ER+	**Per 5000 µg** Beta-carotene Alpha-carotene Beta-cryptoxanthin Lutein/zeaxanthin Lycopene	 0.98 (0.89-1.08) 1.01 (0.93-1.09) 1.01 (0.94-1.09) 1.00 (0.94-1.07) 1.01 (0.94-1.08)		
		987 (962 lutein/ zeaxanthin)/			ER-	**Per 5000 µg** Beta-carotene Alpha-carotene	 0.92 (0.78-1.08) 0.91 (0.78-1.06)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
						Beta-cryptoxanthin Lutein/zeaxanthin Lycopene	1.02 (0.93-1.12) 0.99 (0.89-1.10) 0.92 (0.77-1.10)		
		15 252 (15 202 lutein/ zeaxanthin)/			Incidence, postmenopausal breast cancer ER+	**Per 5000 µg** Beta-carotene Alpha-carotene Beta-cryptoxanthin Lutein/zeaxanthin Lycopene	 1.02 (0.99-1.06) 1.01 (0.99-1.04) 0.99 (0.96-1.02) 1.03 (1.00-1.06) 1.02 (0.99-1.04)		
		3 162 (3 131 lutein/ zeaxanthin)/			ER-	**Per 5000 µg** Beta-carotene Alpha-carotene Beta-cryptoxanthin Lutein/zeaxanthin Lycopene	 0.94 (0.87-1.01) 0.94 (0.87-1.02) 0.97 (0.93-1.02) 0.95 (0.89-1.01) 1.00 (0.95-1.06)		
Roswall, 2010 BRE80338 Denmark	DCH, Prospective Cohort, Age: 50-64 years, Postmenopausal	1 072/ 26 224 10.6 years	Cancer registry	FFQ	Incidence, postmenopausal breast cancer	≥73553.3 vs 0-2115.7 µg	0.91 (0.75-1.11) Ptrend:0.07	Age at first child birth, alcohol, beta carotene from supplement, BMI, educational level, folate Intake, hormone replacement therapy, HRT use, number of childbirths, parity, vitamin C (diet), vitamin C supplement, vitamin E intake	Superseded by Nagel, 2010
						per 5,000 µg	0.94 (0.88-1.01)		
		269/			ER+/PR+	≥73553.3 vs 0-2115.7 µg	0.96 (0.85-1.10)		Not analysed, included in the highest vs lowest analysis
		103/			ER-/PR-		0.90 (0.72-1.12)		
		87/			ER+/PR-		0.93 (0.75-1.14)		
		8/			ER-/PR+		1.30 (0.83-2.05)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Michels, 2001 BRE17830 Sweden	Prospective Cohort, Age: 40-76 years, W, Screening Program	59 039 130 months	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, Invasive breast cancer	5.1 vs 0.97 mg/day	1.01 (0.84-1.22) Ptrend:0.53	Age , age at first child, alcohol, BMI, body weight, educational level, energy Intake , family history, nutrients, nutrients, parous/nulliparous	Superseded by Larsson, 2010
Giovannucci, 1993 BRE03262 USA	NHS, Nested Case Control, Age: 30-55 years, W, Registered nurses	392/ 786 controls 2 years	Medical records + death certificate	FFQ-semi-quantitative	Incidence, breast cancer	Q 5 vs Q 1	1.00 (0.68-1.48) Ptrend:0.65	Age	Superseded by Cho, 2003
Rohan, 1993 BRE17965 Canada	CNBSS, Nested Case Control, Age: 40-59 years, W, Screening Program	519/ 1182 controls 6 years	All histology	Dietary history questionnaire	Mortality, breast cancer	≥8441.1 vs ≤3446 IU/day	0.86 (0.57-1.31) Ptrend:0.322	Age , age at first child, age at menarche, benign breast disease, educational level, energy Intake , family history, menopausal status, nutrients	Excluded, outcome is mortality

*Risk estimates for other carotenoids are only included from the Pooling Project (Zhang, 2012).

Figure 393 RR estimates of breast cancer by levels of dietary beta-carotene intake

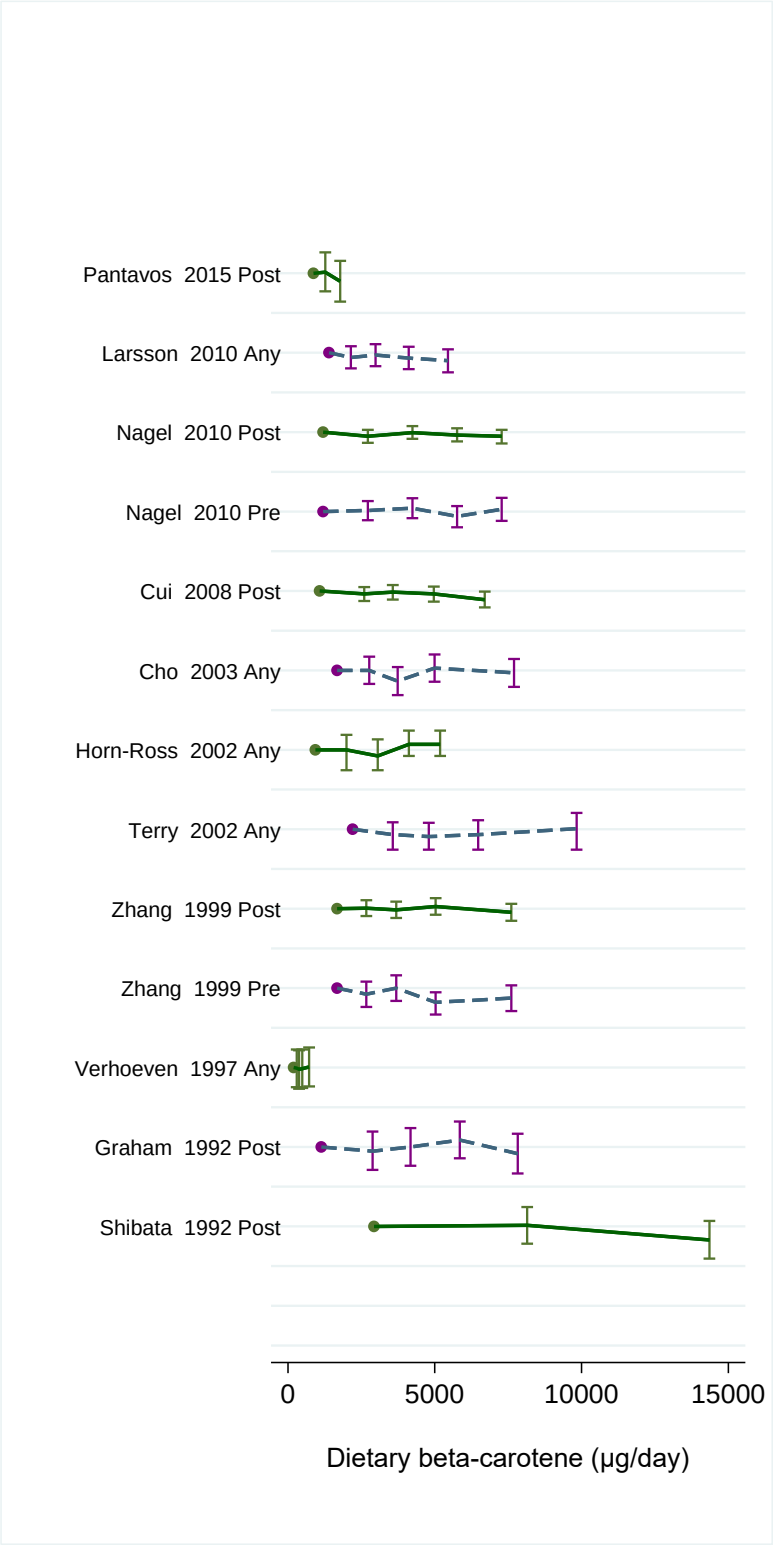


Figure 394 RR (95% CI) of breast cancer for the highest compared with the lowest level of dietary beta-carotene intake

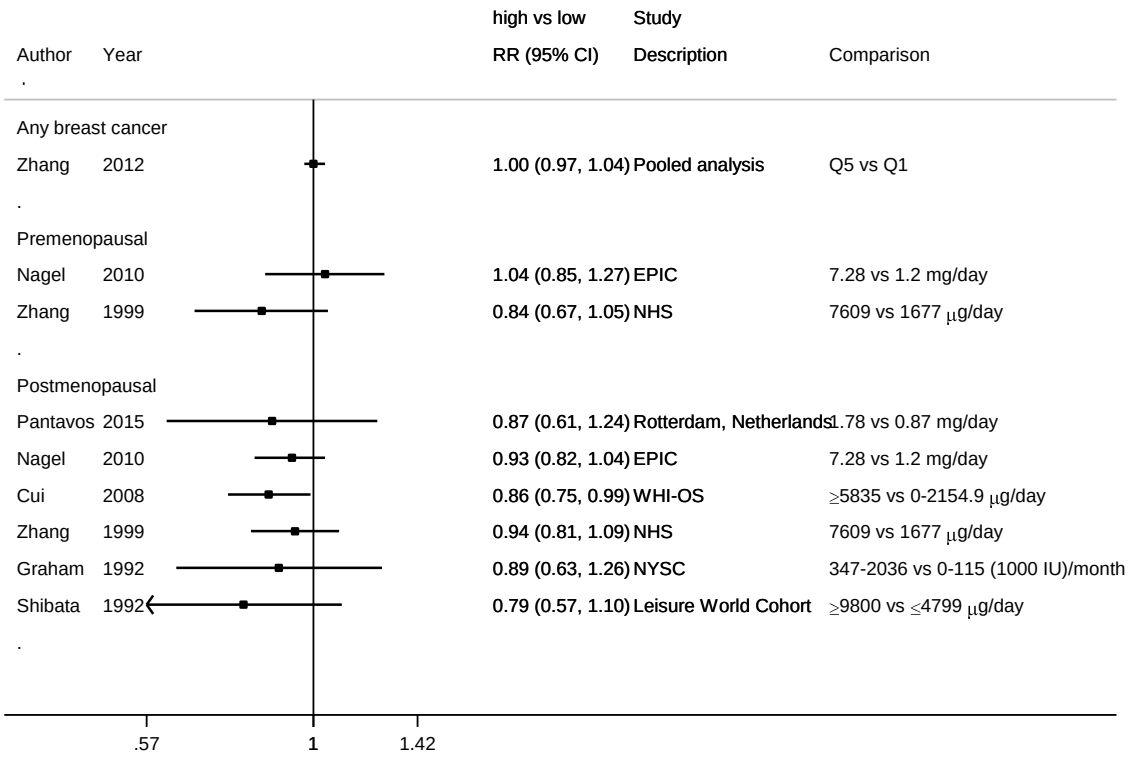


Figure 395 Relative risk of premenopausal breast cancer for 5000 μg/day increase of dietary beta-carotene intake

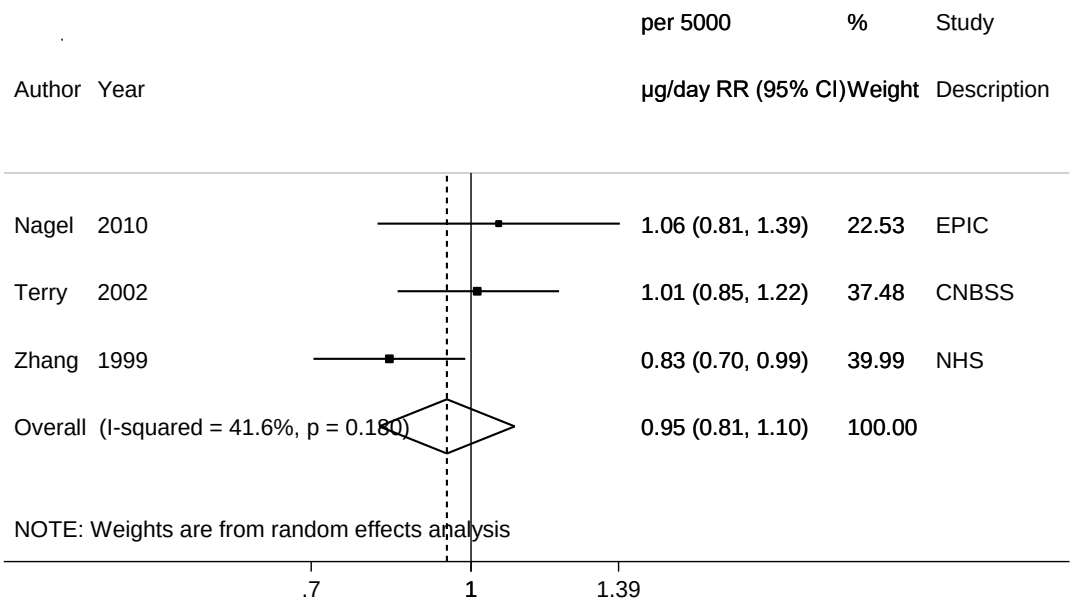


Figure 396 Relative risk of postmenopausal breast cancer for 5000 µg/day increase of dietary beta-carotene intake

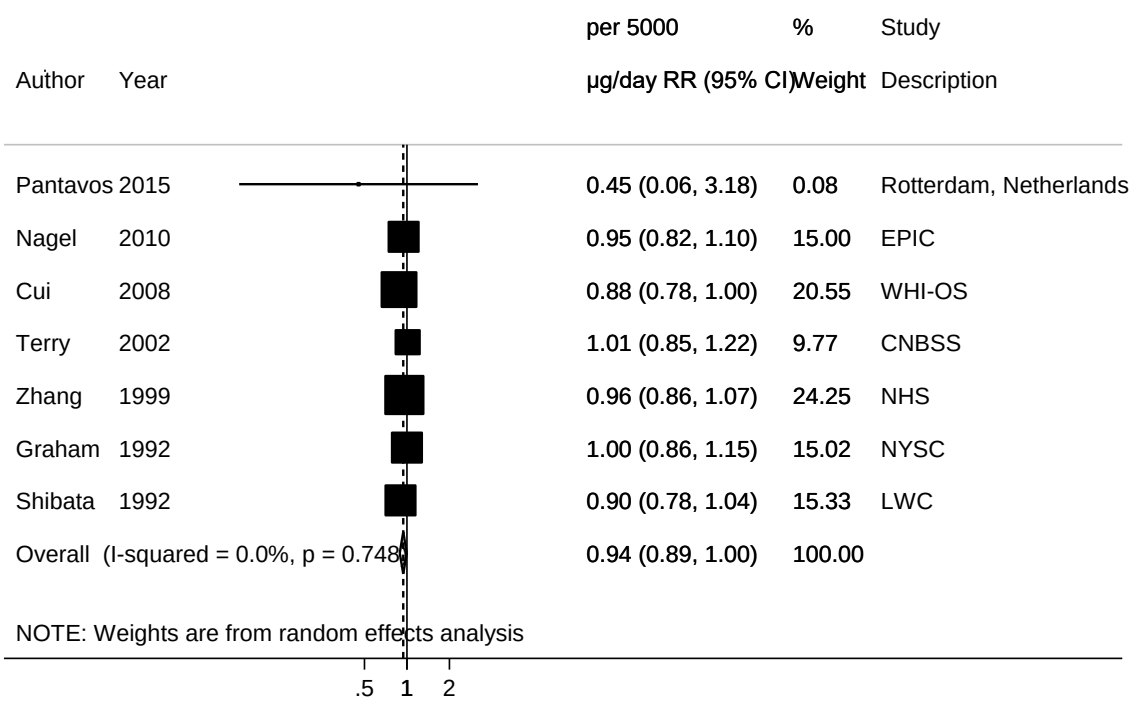


Figure 397 Funnel plot of studies included in the dose response meta-analysis of dietary beta-carotene intake and postmenopausal breast cancer

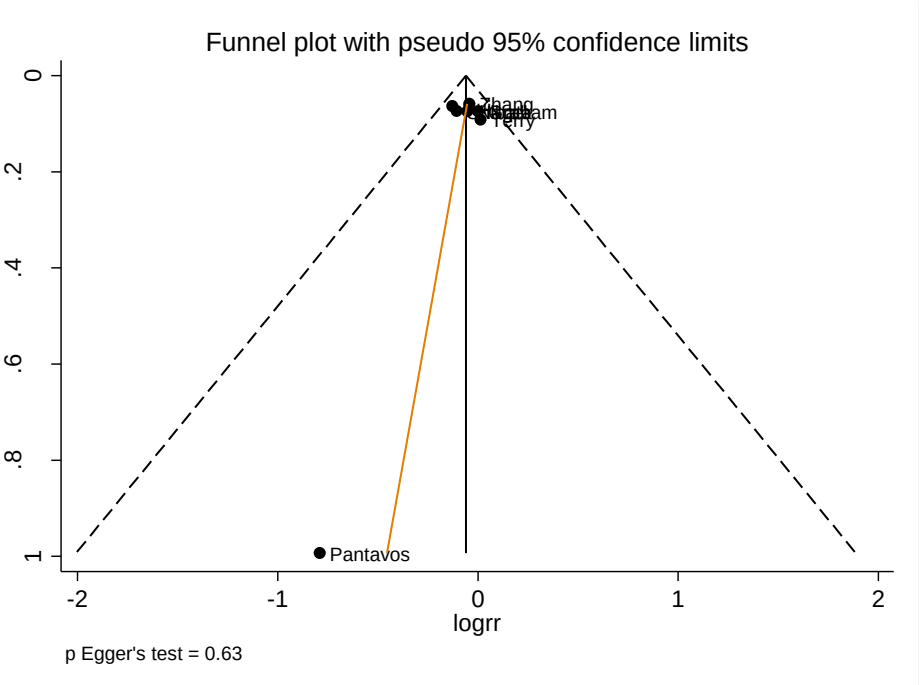


Figure 398 RR (95% CI) of breast cancer for the highest compared with the lowest level of dietary beta-carotene intake, by tumour receptor status and menopausal status

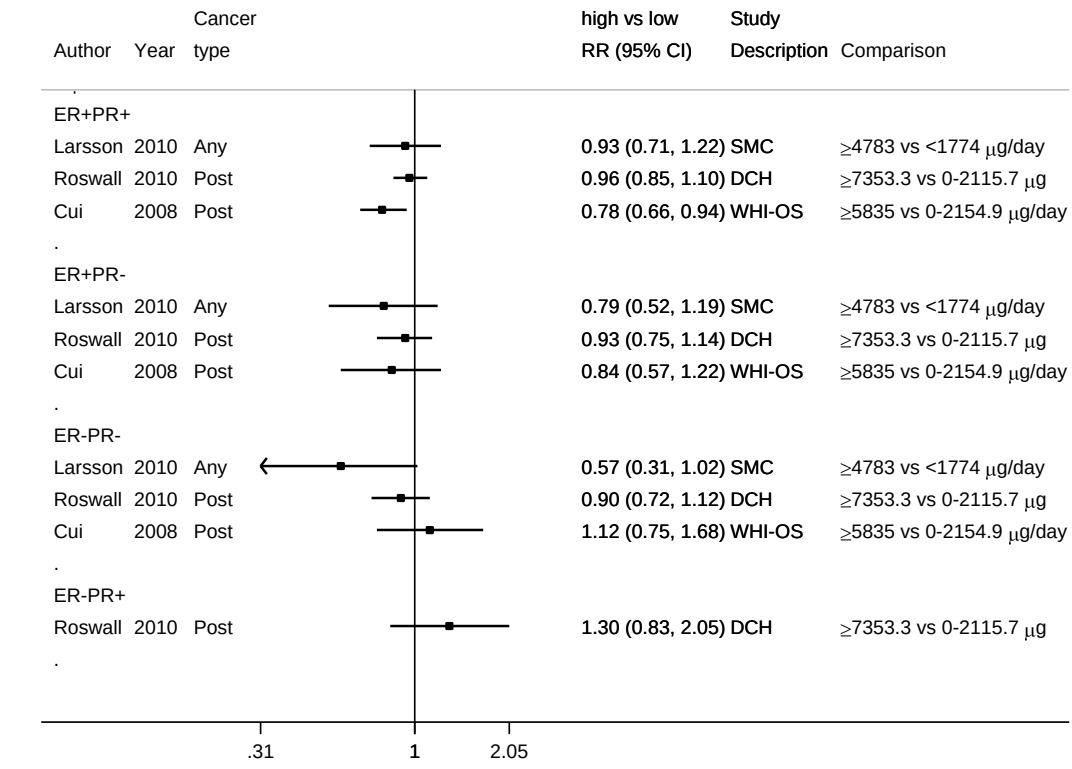
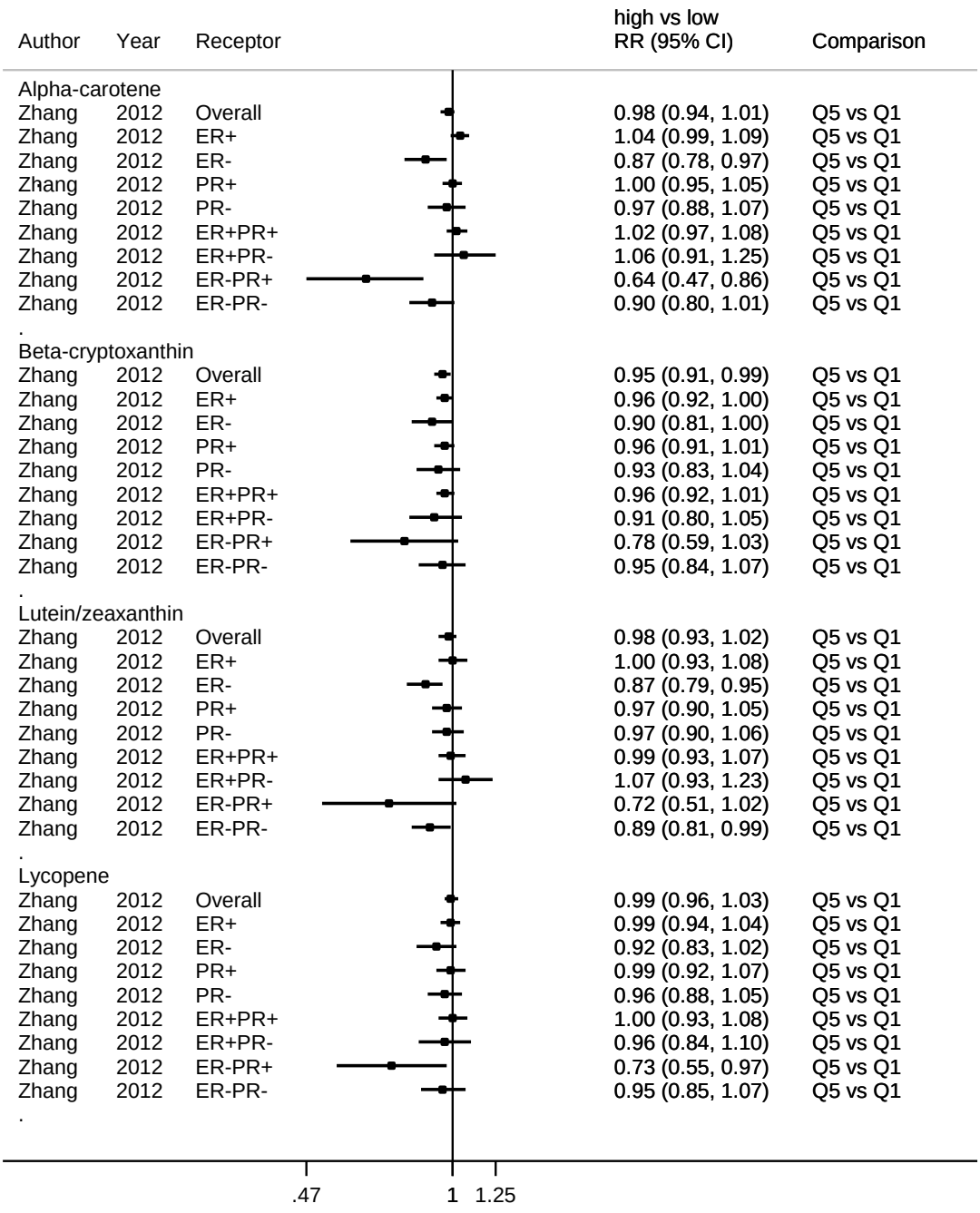


Figure 399 RR (95% CI) of breast cancer for the highest compared with the lowest level of dietary intake of other carotenoids in the Pooling Project (Zhang, 2012)



5.5.1.2.2 Circulating beta-carotene

Breast cancer (any)

The pooled analysis of eight prospective cohorts (Columbia, MO; Umeå; CLUE I and II; NHS; WHS; NYUWHS; SWHS; MEC) (Eliassen, 2012) and three other cohorts (Pouchieu, 2014, SU.VI.MAX; Maillard, 2010, E3N French cohort; Wald, 1984, Guernsey Study) were identified and included in the dose-response meta-analysis. Overall, a significant inverse association was observed (summary RR for 50 μg/dl: 0.78, 95% CI: 0.66-0.92), with no evidence of heterogeneity (I2=0%, Pheterogeneity=0.77).

One study (Knekt, 1990) could not be included in the meta-analysis (RR for Q5 vs Q1=0.30, 95% CI=0.10-1.00). All other publications were superseded by the pooled analysis (Eliassen, 2012).

The EPIC study examined the association of plasma beta-carotene with breast cancer by ER status and age at diagnosis (less or more than 50 years). The study was published after the end of the literature search and was not included in the dose-response meta-analysis (Bakker, 2016).

Analysis by hormone receptor status

In the pooled analysis (Eliassen, 2012) the inverse association was significant in ER-negative tumours (RR for Q5 vs Q1=0.52, 95% CI=0.36-0.77, Ptrend: 0.001) but not in ER-positive (RR=0.83, 95% CI=0.66-1.04, Ptrend=0.06) breast cancers (Pheterogeneity=0.01).

In EPIC, plasma beta-carotene was significantly inversely related to ER-negative breast cancer (RR for highest vs lowest concentrations: 0.41, 95% CI: 0.26-0.65, ptrend=0.002) but not ER-positive breast cancer (RR: 1.02, 95% CI: 0.66-1.57, ptrend=0.91) (Pheterogeneity=0.03). When stratified by smoking status, the inverse association with ER-negative breast cancer was only significant in never/past smokers.

Premenopausal breast cancer

Four cohorts from three publications (Sisti, 2015; Dorjgochoo, 2009; Hulten, 2001) were identified and included in the dose-response meta-analysis. Circulating beta-carotene was non-significantly positively associated with premenopausal breast cancer (summary RR for 50 μg/dL: 1.24, 95% CI: 0.75-2.03), with no evidence of heterogeneity (I2=0%, Pheterogeneity=0.41).

Postmenopausal breast cancer

Seven cohorts from five publications (Sisti, 2015; Dorjgochoo, 2009; Epplein, 2009; Kabat, 2009; Hulten, 2001) were identified and were all included in the dose-response meta-analysis. Circulating beta-carotene was non-significantly inversely associated with postmenopausal breast cancer (summary RR for 50 μg/dL=0.81, 95% CI=0.59-1.11), with low heterogeneity (I2=0%, Pheterogeneity=0.65).

The inverse association became significant when Dorjgochoo, 2009 was omitted in influence analysis (summary RR for 50 μg/dL: 0.65, 95% CI: 0.43-0.98). There was no significant evidence of small study or publication bias (P Egger's test=0.45). Visual inspection of the

funnel plot showed asymmetry, which may be driven by smaller studies with stronger inverse associations (Sato, 2002; Hulten, 2001).

Table 311 Circulating beta-carotene and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	13 (19 publications)
Studies included in forest plot of highest compared with lowest intake	Breast cancer: 9 (2 publications) Premenopausal: 4 (3 publications) Postmenopausal: 7 (5 publications)
Studies included in linear dose-response meta-analysis	Breast cancer: 11 (4 publications) Premenopausal: 4 (3 publications) Postmenopausal: 7 (5 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 312 Circulating beta-carotene and breast cancer risk. Summary of the linear dose-response meta-analysis in the CUP

	Breast cancer (any)	**Premenopausal**	**Postmenopausal**
Increment unit used	50 µg/dL		
Studies (n)	11	4	7
Cases (total number)	3 558	776	1 283
RR (95%CI)	0.78 (0.66-0.92)	1.24 (0.75-2.03)	0.81 (0.59-1.11)
Heterogeneity (I^2, p-value)	0%, p=0.77	0%, p=0.41	0%, p=0.65
P value Egger test	-	-	0.45

Table 313 Circulating beta-carotene and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR

Author, Year	**Number of studies**	**Total number of cases**	**Studies country, area**	**Outcome**	**Comparison**	**RR (95%CI)**	**P trend**	**Heterogeneity (I^2, p value)**
Meta-analysis								
Aune et al, 2012	15	3 609	North America, Europe, Asia	Incidence, breast cancer	High vs. low Per 50 µg/dL	0.82 (0.64-1.04) 0.74 (0.57-0.97)	- -	55% 43%

Table 314 Circulating beta-carotene and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Sisti, 2015 BRE80597 USA	NHS I and II, Nested Case Control, Age: 25-55 years, W, Premenopausal	535/	Biennial follow-up questionnaires and medical records	Blood: participants collected follicular phase blood samples during days 3–5 of their menstrual cycle, and blood and urine samples during the luteal phase, 7–9 days before the anticipated start of their next cycle.	Premenopausal at diagnosis	≥36 vs ≤14.9 µg/dl	0.98 (0.68-1.41) Ptrend:0.88	Age at menarche, alcohol intake, BMI, family history of breast cancer, history of benign breast disease, matching variables, parity and age at first birth	Included, premenopausal breast cancer; midpoints of exposure quartiles
		492/			Postmenopausal at diagnosis		0.95 (0.63-1.42) Ptrend:0.82		Included, postmenopausal breast cancer; midpoints of exposure quartiles
		1 132/ 1132 controls			Incidence, breast cancer		0.99 (0.77-1.28) Ptrend:0.98		Superseded by pooled analysis, Eliassen, 2012
		615/			ER+		0.99 (0.74-1.33) Ptrend:0.95		Not analysed
		150/			ER-		0.96 (0.56-1.65) Ptrend:0.83		
Pouchieu, 2014 BRE80565 France	SU.VI.MAX, Nested Case Control,	100/ 100 controls 8 years	Self report verified by medical record	Plasma: HPLC	Incidence, breast cancer	per 0.1 µmol/l	0.96 (0.89-1.03)	Age, alcohol intake, BMI, dietary records,	Included, all breast cancer, RR rescaled for

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Age: 49.8 years, W							educational level, energy intake, family history of breast cancer, fat intake, fruits and vegetables consumption, height, HRT use, intervention group, menopausal status, number of children, physical activity, smoking status	an increment used, units converted to µg/dl
		50/ 50 controls			Intervention group	per 0.1 µmol/l	0.89 (0.78-1.03)		
					Placebo-group	per 0.1 µmol/l	0.95 (0.81-1.12)		
Eliassen, 2012 China, Sweden, USA	Pooled analysis of 8 prospective studies*, Mean age ranged from 51.3-66.0 years, W *Columbia, MO; Umeå; CLUE I and II; NHS; WHS;	3,055 cases/ 3,956 controls		Plasma, recalibrated values, reverse-phase HPLC, median time between blood collection and diagnosis was 4.3 years	Incidence, breast cancer	≥39.9 vs <11.9 µg/dl	0.83 (0.70-0.98) Ptrend:0.02	Menopausal status, age at menopause, age at menarche, parous, age at first birth, exogenous hormone use, BMI, current smoking, race, personal history of benign breast	Included, all breast cancer; midpoints of exposure quintiles
		1,481			ER+ breast cancer	Q5 vs Q1	0.83 (0.66-1.04) Ptrend:0.06		
		417			ER- breast cancer	Q5 vs Q1	0.52 (0.36-0.77) Ptrend:0.001		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	NYUWHS; SWHS; MEC							disease, family history of breast cancer Matching factors included age at blood collection, date, time, and fasting status at blood collection, menopausal status, date of last menstrual period and/or phase and day of menstrual cycle (premenopausal women), PMH use, race or ethnicity, study centre, smoking status, follow-up time, availability of FFQ, use of antibiotics, number of blood collections within the cohort, diagnosis of benign breast disease	
Maillard, 2010	E3N EPIC-	366/	Self report	Serum: HPLC	Incidence, breast	Q5 vs Q1	0.85 (0.53-1.35)	Age, age at first	Included, all

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
BRE80258 France	France, Nested Case Control, Age: 40-65 years, W	720 controls 7 years	verified by medical record		cancer		Ptrend:0.39	child birth, alcohol consumption, benign breast disease, blood collection centre, date of blood collection, educational level, family history of cancer, fasting condition, height, menopausal hormone use, menopausal status, parity	breast cancer; intakes estimated from mean and standard deviation, midpoints of exposure quantiles
					Alcohol <=10g/day		0.71 (0.34-1.48) Ptrend:0.31		
					Alcohol 10+ g/day		0.70 (0.21-2.34) Ptrend:0.84		
Dorjgochoo, 2009 BRE80289 China	SWHS, Nested Case Control, Age: 40-70 years, W	365/ 726 controls 7.5 person-years	Cancer registry	Plasma: reverse-phase HPLC	Incidence, breast cancer	Q4 vs Q1	1.47 (0.92-2.35) Ptrend:0.19	Age, age at first child birth, age at menarche, antioxidant intake, benign breast disease, educational level, energy	Superseded by pooled analysis, Eliassen, 2012
		184/ 358 controls			Premenopausal		1.44 (0.73-2.82) Ptrend:0.22		Included, premenopausal breast cancer; midpoints of

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								intake, family history of cancer, fish, fruit intake, laboratory batch, menopausal status, occupation, physical activity, red meat intake, smoking status, tea intake, vegetable intake, waist-hip ratio	exposure quintiles
		181/ 368 controls			Post menopause		1.58 (0.78-3.19) Ptrend:0.56		Included, postmenopausal breast cancer; midpoints of exposure quintiles
Epplein, 2009 BRE80236 USA	MEC, Nested Case Control, Age: 45-75 years, W, Postmenopausal	286/ 535 controls	Cancer registry	Plasma: HPLC with photodiode array detection	Incidence, breast cancer, postmenopausal	≥460.9 vs ≤180.4 ng/ml	0.73 (0.46-1.15) Ptrend:0.30	Age at first child birth, age at interview, age at menarche, age at menopause, alcohol consumption, BMI, date of blood collection, ethnicity, fasting condition, geographic area, HRT use, parity, year of birth	Included, postmenopausal breast cancer; converted units, midpoints of exposure quintiles
Kabat, 2009 BRE80250 USA	Women's Health Initiative - Dietary	190/ 5 450 8 years	Self report, medical record and pathology	Serum: reverse-phase HPLC	Incidence, invasive & in situ breast	≥0.33 vs ≤0.16 µg/ml	0.95 (0.63-1.43) Ptrend:0.82	Age, age at first child birth, age at menarche, age	Included, postmenopausal breast cancer;

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Modification Trial, Prospective Cohort, Age: 50-79 years, W, Postmenopausal		report reviewed by centrally trained physician		cancer, postmenopausal			at menopause, alcohol consumption, benign breast disease, BMI, calcium intake, educational level, energy intake, ethnicity, family history of cancer, HRT use, OC use, physical activity, randomized treatment assignment	converted units, midpoints of exposure quintiles
Sato, 2002 BRE20839 USA	CLUE I, Nested Case Control, Age: 51 years, W, blood donors	243/ 244 controls 20 years	Partially histological - over 80%	Serum: reverse-phase HPLC	Incidence, breast cancer, postmenopausal	≥22.2 vs ≤7.2 µg/dl	0.41 (0.22-0.79) Ptrend:0.007	Matched on age (within 1 year), race, menopausal status, and month and year of blood donation; premenopausal women were also matched on date of last menstrual cycle	Included, postmenopausal breast cancer; midpoints
	CLUE II, Nested Case Control, Age: 60 years, W, blood donors	115/ 115 controls 3 years	Partially histological - over 80%		Incidence, breast cancer, postmenopausal	≥22.6 vs ≤7.1 µg/dl	0.62 (0.27-1.42) Ptrend:0.26		Included, postmenopausal breast cancer; midpoints
Hulten, 2001 BRE04155	VIP-MONICA-MSP,	201/ 390 controls	Partially histological -	Plasma: HPLC	Incidence, breast cancer	Q4 vs Q1	0.80 (0.50-1.40) Ptrend:0.40	BMI, total cholesterol,	Superseded by pooled analysis,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Sweden	Nested Case Control, W		over 80%					triglycerides, age at menarche, parity, age at first full-term pregnancy, use of hormone replacement therapy, menopausal status, cotinine (a marker of recent exposure to tobacco smoke), and hours of fasting	Eliassen, 2012
	VIP-MONICA	57/ 93 controls			Premenopausal	>0.51 vs ≤0.25 µmol/l	1.60 (0.50-5.40) Ptrend:0.28		Included, premenopausal breast cancer; converted units, midpoints
		67/ 109 controls			Postmenopausal		0.70 (0.20-1.90) Ptrend:0.25		Included, postmenopausal breast cancer; converted units, midpoints
	MSP	67/ 127 controls				>0.55 vs ≤0.26 µmol/l	0.40 (0.10-1.20)		
Wald, 1984	Guernsey Study	39/ 78 controls		Plasma	Incidence, breast cancer	Q5 vs Q1	0.54	Age, duration of sample storage	Included, all breast cancer

Table 315 Circulating beta-carotene and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Bakker, 2016 Europe	EPIC, Nested Case Control, Mean age: 50 years,	636/ 632 controls	Linkage to population cancer registries in most countries, a	Plasma: HPLC	Incidence, invasive breast cancer, ER+	≥1373.03 vs ≤249.33 nmol/l	1.02 (0.66-1.57) Ptrend:0.91	BMI, height, age at menarche, age at first full-term pregnancy, OC use, HRT use, smoking status,	Identified after end of search, analysis by tumour
		515/			ER-	≥1426.18 vs	0.41 (0.26-0.65)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	W	514 controls	combination of methods in some countries, including health insurance records, cancer and pathology registries, and active follow-up			≤253.18 nmol/l	Ptrend:0.002	alcohol consumption, educational level, intake of saturated fatty acids, energy intake, season of blood collection Matching factors: study centre, age, menopausal status, use of exogenous hormones, phase of menstrual cycle, fasting status at blood collection, time of blood collection	hormone receptor status was not conducted
					ER+PR+	Q5 vs Q1	0.86 (0.47-1.56)		
					ER-PR-		0.45 (0.26-0.80)		
					ER- , never/past smokers	Q3 vs Q1	0.64 (0.43-0.96)		
					ER- , current smokers		0.94 (0.44-2.02)		
Eliassen, 2015 BRE80598 USA	NHS, Nested Case Control, Age: 43-67 years, W	2 151/ 2153 controls 20 years	Biennial follow-up questionnaires and medical records	Blood: first sample collected 1989-1990 second sample collected 2000-2002	Incidence, breast cancer	≥419 vs ≤135.9 µg/dl	0.72 (0.59-0.88) Ptrend:<0.001	Age at first child birth, age at menarche, age at menopause, alcohol intake, BMI at age 18 years, family history of breast cancer, history of benign breast disease, matching variables, parity	Superseded by pooled analysis, Eliassen, 2012
		1 316/			Incidence, breast cancer ER+	≥419 vs ≤135.9 µg/dl	0.70 (0.56-0.89) Ptrend:0.002		
		292/			Incidence,	≥419 vs ≤135.9	0.72 (0.47-1.10)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					breast cancer ER-	µg/dl	Ptrend:0.14		
		350/			Incidence, well differentiated breast cancer	≥419 vs ≤135.9 µg/dl	0.79 (0.54-1.16) Ptrend:0.26		
		596/			Incidence, moderate differentiated breast cancer	≥419 vs ≤135.9 µg/dl	0.74 (0.55-1.01) Ptrend:0.11		
		373/			Incidence, poorly differentiated breast cancer	≥419 vs ≤135.9 µg/dl	0.53 (0.35-0.80) Ptrend:<0.001		
		646/			Incidence, luminal a breast cancer	≥419 vs ≤135.9 µg/dl	0.80 (0.59-1.09) Ptrend:0.08		
		216/			Incidence, luminal b breast cancer	≥419 vs ≤135.9 µg/dl	0.47 (0.28-0.77) Ptrend:0.003		
		108/			Incidence, triple negative breast cancer	≥419 vs ≤135.9 µg/dl	0.81 (0.40-1.62) Ptrend:0.48		
		1 850/			Incidence, nonrecurrent and nonlethal breast cancer	≥419 vs ≤135.9 µg/dl	0.82 (0.67-1.02) Ptrend:0.03		
		301/			Incidence,	≥419 vs ≤135.9	0.32 (0.21-0.51)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					recurrent or lethal breast cancer	µg/dl	Ptrend:<0.001		
		1 121/ 1209 controls			Incidence, breast cancer, BMI <25	≥419 vs ≤135.9 µg/dl	0.62 (0.47-0.83) Ptrend:<0.001		
		696/ 644 controls			BMI 25- <30	≥419 vs ≤135.9 µg/dl	0.86 (0.59-1.26) Ptrend:0.48		
		333/ 299 controls			BMI >=30	≥419 vs ≤135.9 µg/dl	0.96 (0.45-2.04) Ptrend:0.86		
		1 880/ 1927 controls			Nonsmokers	≥419 vs ≤135.9 µg/dl	0.73 (0.59-0.91) Ptrend:0.002		
		271/ 226 controls			Current smokers	≥419 vs ≤135.9 µg/dl	0.99 (0.45-2.16) Ptrend:0.95		
		1 828/ 1829 controls			Follow up <10 years	≥419 vs ≤135.9 µg/dl	0.77 (0.62-0.96) Ptrend:0.01		
		895/ 900 controls			Follow up >=10 years	≥419 vs ≤135.9 µg/dl	0.70 (0.51-0.97) Ptrend:0.05		
Tamimi, 2009 BRE80276 USA	NHS, Nested Case Control, W, Postmenopausal	604/ 626 controls 9 years	Self report verified by medical record	Plasma: reverse-phase HPLC	Incidence, breast cancer	Q5 vs Q 1	0.60 (0.40-1.00) Ptrend:0.001	Age, age at first child birth, alcohol, benign breast disease, BMI, family history of cancer, parity, postmenopausal hormone use	Superseded by pooled analysis, Eliassen, 2012
							0.60 (0.40-0.90) Ptrend:0.0004	Mammographic density	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Sesso, 2005 BRE24061 USA	WHS, Nested Case Control, W, Health professionals	480 7 years	Medical records + self-reported	Plasma: reverse-phase HPLC	Incidence, breast cancer	45.6 vs 8.3 g/dl	1.36 (0.79-2.33) Ptrend:0.36	Age at first child, age at menarche, alcohol, biomarkers, BMI, design , design , design , family history, HRT use, menopausal status, nutrients, nutrients, nutrients, nutrients, OC use, parity/pregnancies, physical activity	Superseded by pooled analysis, Eliassen, 2012
Tamimi, 2005 BRE24274 USA	NHS, Nested Case Control, Age: 43-70 years, W, Registered nurses	325 22 years	All morphology (histology or cytology)	Plasma: reverse-phase HPLC	Incidence, invasive & in situ breast cancer	Q5 vs Q1	0.73 (0.53-1.02) Ptrend:0.01	Age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, family history, fasting condition, HRT use, laboratory variables , other anthropometric index	Superseded by pooled analysis, Eliassen, 2012
Tamimi, 2004 BRE12084 USA	NHS, Nested Case Control, Age: 30-55 years, W, Registered nurses	254/ 234 controls 8 years	Partially histological - over 80%	Plasma: reverse-phase HPLC	Incidence, breast cancer, Val/Val (MnSOD)	Q3 vs ≥Q1	0.81 (0.50-1.31)	Age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, duration of HRT use, family history, parity/pregnancies, smoking habits	Superseded by pooled analysis, Eliassen, 2012

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Han, 2003 BRE18435 USA	NHS, Nested Case Control, Age: 57 years, W, Registered nurses	881/ 844 controls 8 years	Partially histological - over 80%	Plasma: reverse-phase HPLC	Incidence, breast cancer, ^{194}Trp non carriers (XRCCI Arg Trp)	Q4 vs Q1	0.84 (0.62-1.14) Ptrend:0.07	Age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, duration of HRT use, family history, parity/pregnancies, parous/nulliparous, smoking habits	Superseded by pooled analysis, Eliassen, 2012
Toniolo, 2001 BRE12399 USA	NYUWHS, Nested Case Control, Age: 35-65 years, W	14 275	Partially histological - over 80%	Serum: HPLC, Steghens et al. method	Incidence, breast cancer	Q4 vs Q1	1.00 Ptrend:0.006	Age at first child, benign breast disease, biomarkers, family history	Superseded by pooled analysis, Eliassen, 2012
Dorgan, 1998 BRE14889 USA	Columbia, MO cohort, Nested Case Control, Age: 41-73 years, W	105/ 209 controls 9.5 years	All histology	Serum	Incidence, invasive breast cancer	0.69-2.2 vs ≤0.29 µmol/l	1.10 (0.50-2.40) Ptrend:0.97	Biomarkers, BMI, smoking habits	Superseded by pooled analysis, Eliassen, 2012
Knekt, 1990 BRE80617 Finland	FMCHES, Nested Case Control, Age: 15-99 years, M/W	52/ 93 controls 8 years	Cancer registry	Serum	Incidence, breast cancer, women	Q5 vs Q1	0.30 (0.10-1.00)	Smoking habits	Excluded, only two categories

Figure 400 RR estimates of breast cancer by levels of circulating beta-carotene concentration

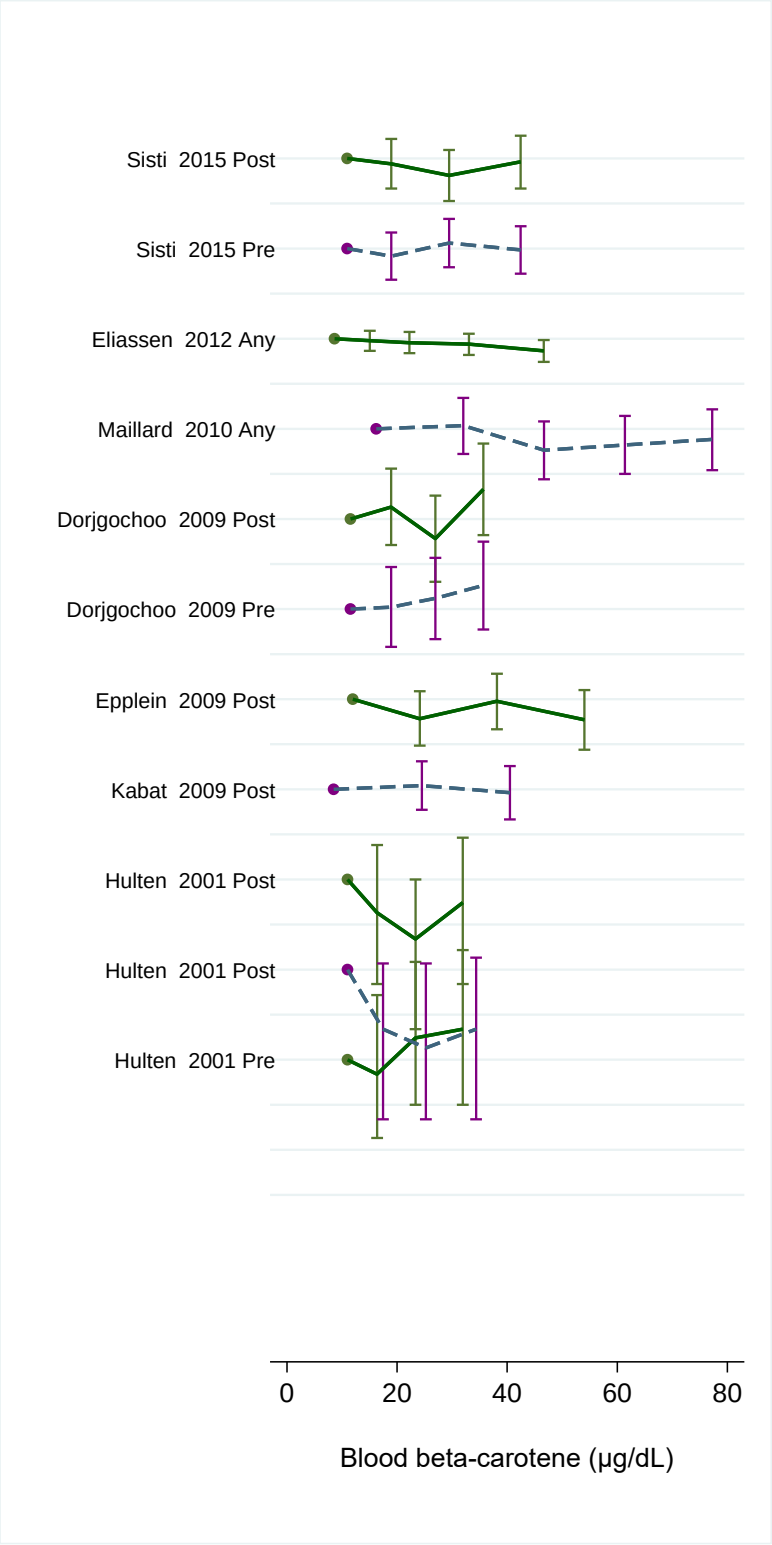


Figure 401 RR (95% CI) of breast cancer for the highest compared with the lowest level of circulating beta-carotene concentration

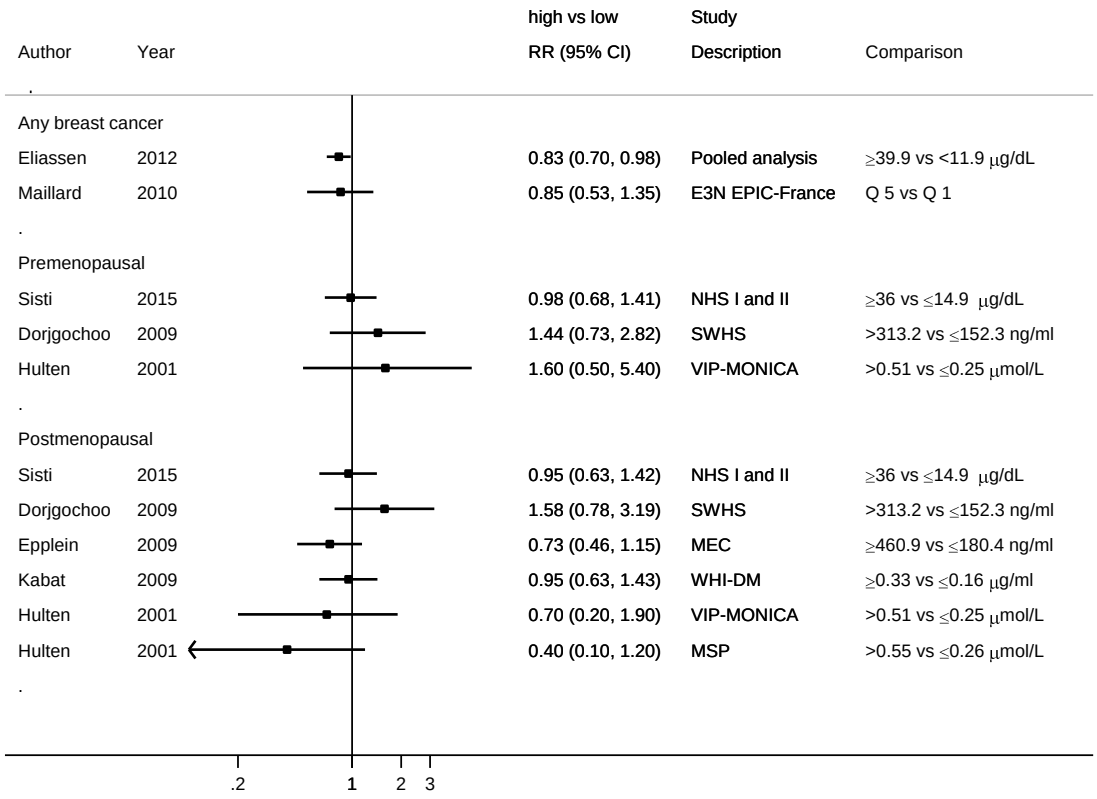


Figure 402 Relative risk of breast cancer (any) for 50 µg/dl increase of circulating beta-carotene concentration

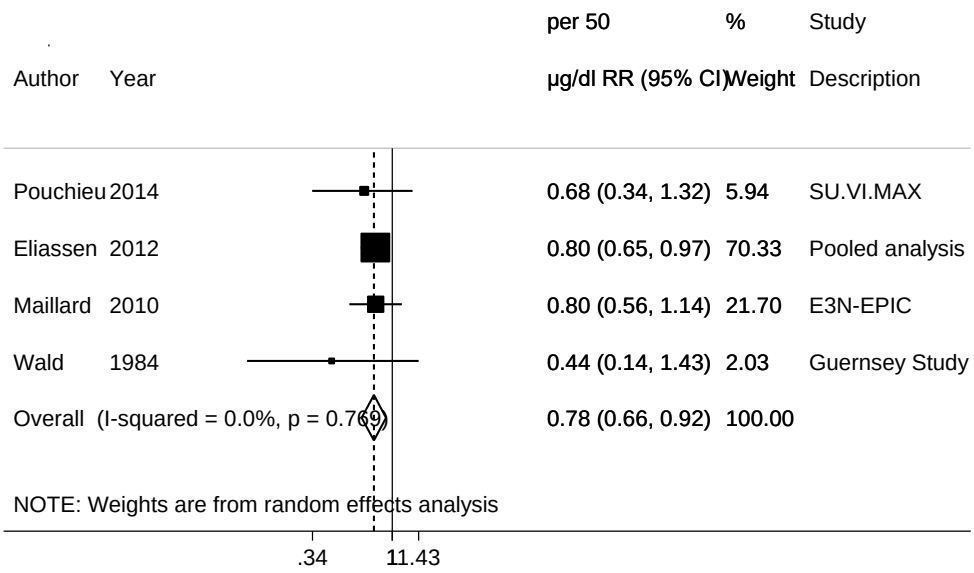


Figure 403 Relative risk of premenopausal breast cancer for 50 µg/dl increase of circulating beta-carotene concentration

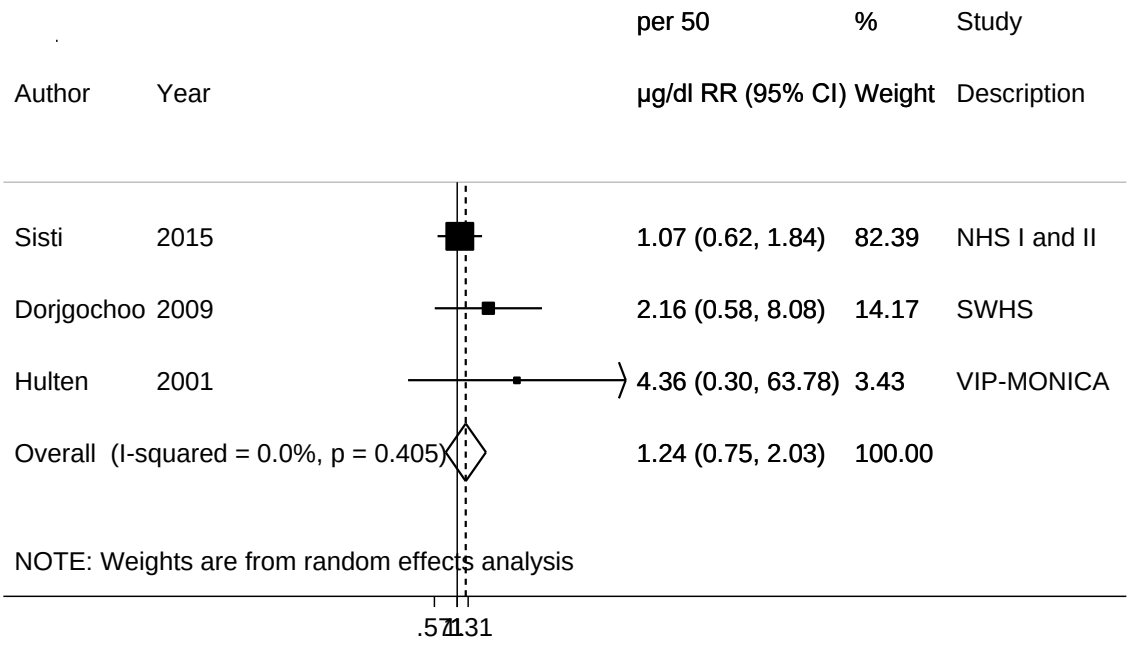


Figure 404 Relative risk of postmenopausal breast cancer for 50 µg/dl increase of circulating beta-carotene concentration

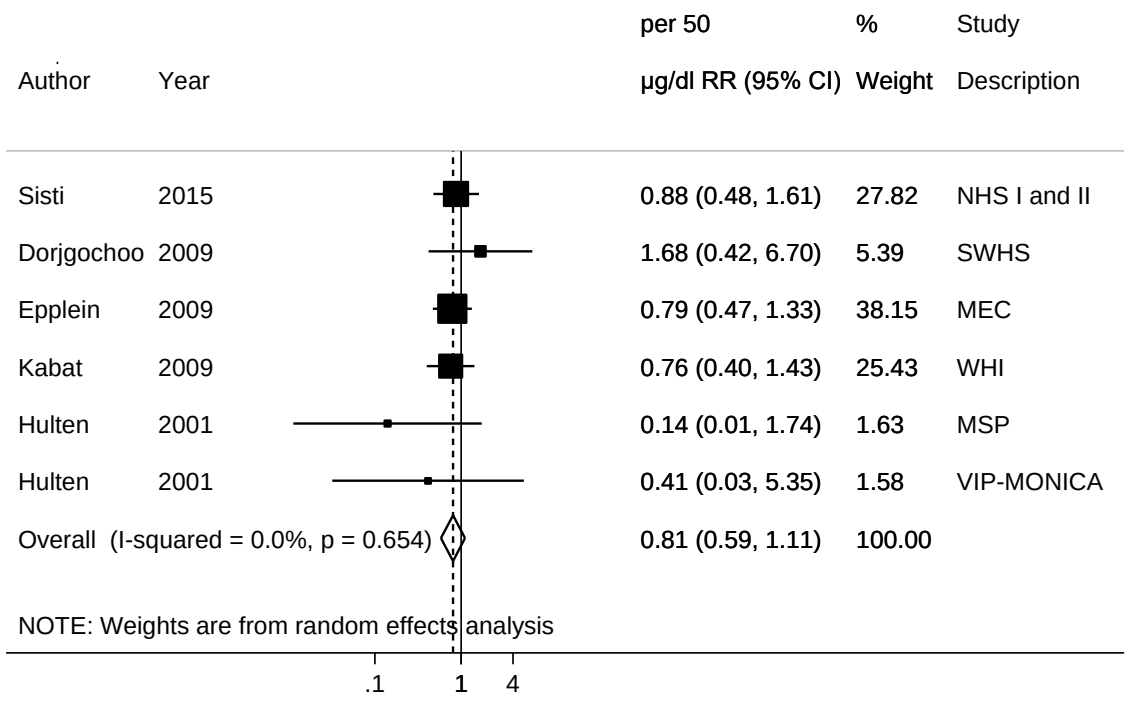
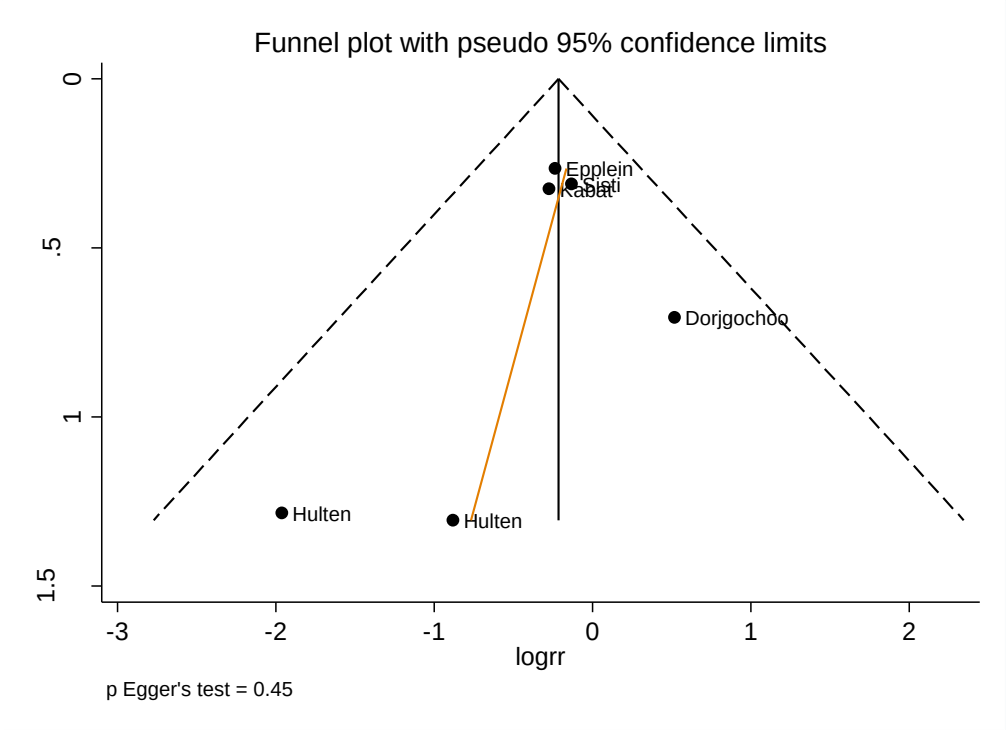


Figure 405 Funnel plot of studies included in the dose response meta-analysis of circulating beta -carotene concentration and postmenopausal breast cancer



5.5.1.2.3 Circulating beta-cryptoxanthin

Breast cancer (any)

The pooled analysis of eight prospective cohorts (Columbia, MO; Umeå; CLUE I and II; NHS; WHS; NYUWHS; SWHS; MEC) (Eliassen, 2012) and two other cohorts (Pouchieu, 2014, SU.VI.MAX; Maillard, 2010, E3N French cohort) were identified and included in the dose-response meta-analysis. Overall, no association was observed (summary RR for 15 µg/dL=0.87, 95% CI=0.68-1.11, with high heterogeneity (I^2=59%, Pheterogeneity=0.09).

The EPIC study (Bakker, 2016) examined the association of plasma beta-cryptoxanthin with breast cancer by ER status and age at diagnosis (less or more than 50 years). This study was published after the end date of search. All other publications were superseded by the pooled analysis (Eliassen, 2012).

Hormone receptor status

The pooled analysis (Eliassen, 2012) reported non-significant positive associations (RR for Q5 vs Q1=1.03, 95% CI=0.69-1.53, Ptrend=0.68 for ER-negative breast cancer; RR=1.09, 95% CI=0.86-1.39, Ptrend=0.57 for ER-positive breast cancer) (Pheterogeneity=0.50).

In EPIC, plasma beta-cryptoxanthin was non-significantly inversely associated with ER-negative breast cancer (RR for highest vs lowest concentrations=0.84, 95% CI=0.51-1.37, Ptrend=0.29) and ER-positive breast cancer (RR=0.70, 95% CI=0.45-1.10, ptrend=0.68)

(Pheterogeneity=0.66). Similar results were observed in the analysis with women >50 years (data not shown in the publication).

Premenopausal breast cancer

Three cohorts from two publications (Sisti, 2015; Hulten, 2001) were included in the dose-response meta-analysis. Circulating beta-cryptoxanthin was non-significantly inversely associated with premenopausal breast cancer (summary RR for 50 μg/dL: 0.89, 95% CI: 0.54-1.47), with no evidence of heterogeneity (I^2=0%, Pheterogeneity=0.62).

Postmenopausal breast cancer

Five cohorts from three publications (Sisti, 2015; Kabat, 2009; Hulten, 2001) were included in the dose-response meta-analysis. Circulating beta-cryptoxanthin was non-significantly inversely associated with postmenopausal breast cancer (summary RR for 15 μg/dL=0.87, 95% CI=0.60-1.27; I^2=0%, Pheterogeneity=0.74).

Table 316 Circulating beta-cryptoxanthin and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	11 (14 publications)
Studies included in forest plot of highest compared with lowest intake	Breast cancer: 9 (2 publications) Premenopausal: 3 (2 publications) Postmenopausal: 5 (3 publications)
Studies included in linear dose-response meta-analysis	Breast cancer: 10 (3 publications) Premenopausal: 3 (2 publications) Postmenopausal: 5 (3 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 317 Circulating beta-cryptoxanthin and breast cancer risk. Summary of the linear dose-response meta-analysis in the CUP

	Breast cancer (any)	**Premenopausal**	**Postmenopausal**
Increment unit used	15 μg/dL		
Studies (n)	10	3	5
Cases (total number)	3 517	588	815
RR (95%CI)	0.87 (0.68-1.11)	0.89 (0.54-1.47)	0.87 (0.60-1.27)
Heterogeneity (I^2, p-value)	59%, p=0.09	0%, p=0.62	0%, p=0.74
P value Egger test	-	-	-

Table 318 Circulating beta-cryptoxanthin and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analysis								
Aune et al, 2012	11	2 861	North America, Europe, Asia	Incidence, breast cancer	High vs. low Per 15 µg/dL	0.89 (0.76-1.05) 0.86 (0.72-1.01)	- -	0% 0%

Table 319 Circulating beta-cryptoxanthin and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Sisti, 2015 BRE80597 USA	NHS I and II, Nested Case Control, Age: 25-55 years, W, Premenopausal	531/ 1 179	Biennial follow-up questionnaires and medical records	Blood: participants collected follicular phase blood samples during days 3–5 of their menstrual cycle, and blood and urine samples during the luteal phase, 7–9 days before the anticipated start of their next cycle.	Incidence, breast cancer, premenopausal at diagnosis	≥14 vs ≤7.2 µg/dl	0.87 (0.59-1.27) Ptrend:0.61	Age at menarche, alcohol intake, BMI, family history of breast cancer, history of benign breast disease, matching variables, parity and age at first birth	Included, premenopausal; midpoints of exposure quartiles
		491/			Postmenopausal at diagnosis	≥14 vs ≤7.2 µg/dl	0.85 (0.57-1.26) Ptrend:0.48		Included, postmenopausal; midpoints of exposure quartiles
		1 129/ 1129 controls			Incidence, breast cancer	≥14 vs ≤7.2 µg/dl	0.83 (0.64-1.07) Ptrend:0.27		Superseded by Eliassen, 2012
		612/			ER+	≥14 vs ≤7.2 µg/dl	0.88 (0.66-1.19) Ptrend:0.51		Not analysed
		149/			ER-	≥14 vs ≤7.2 µg/dl	0.78 (0.45-1.33) Ptrend:0.35		
Pouchieu, 2014 BRE80565 France	SU.VI.MAX, Nested Case Control, Age: 49.8 years, W	100/ 100 controls 8 years	Self-report verified by medical record	Plasma: HPLC	Incidence, breast cancer	per 0.1 µmol/l	0.83 (0.71-0.96)	Age, alcohol intake, BMI, dietary records, educational level, energy intake, family history of breast cancer, fat intake, fruits and vegetables consumption,	Included, all breast cancer, RR rescaled for an increment used, units converted to µg/dl

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								height, HRT use, intervention group, menopausal status, number of children, physical activity, smoking status	
		50/ 50 controls			Intervention group	per 0.1 µmol/l	0.76 (0.56-1.01)		
					Placebo-group	per 0.1 µmol/l	0.75 (0.54-1.04)		
Eliassen, 2012 China, Sweden, USA	Pooled analysis of 8 prospective studies*, Mean age ranged from 51.3-66.0 years, W *Columbia, MO; Umeå; CLUE I and II; NHS; WHS; NYUWHS; SWHS; MEC	3,055 cases/ 3,956 controls		Plasma, recalibrated values, reserve-phase HPLC, median time between blood collection and diagnosis was 4.3 years	Incidence, breast cancer	≥19.4 vs <6.1 µg/dl	0.98 (0.82-1.18) Ptrend:0.21	Menopausal status, age at menopause, age at menarche, parous, age at first birth, exogenous hormone use, BMI, current smoking, race, personal history of benign breast disease, family history of breast cancer Matching factors included age at blood collection, date, time, and	Included, all breast cancer; midpoints of exposure quintiles

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								fasting status at blood collection, menopausal status, date of last menstrual period and/or phase and day of menstrual cycle (premenopausal women), PMH use, race or ethnicity, study centre, smoking status, follow-up time, availability of FFQ, use of antibiotics, number of blood collections within the cohort, diagnosis of benign breast disease	
		1,481			ER+ breast cancer	Q5 vs Q1	1.09 (0.86-1.39) Ptrend:0.57		Not analysed
		417			ER- breast cancer	Q5 vs Q1	1.03 (0.69-1.53) Ptrend:0.68		Not analysed
Maillard, 2010 BRE80258 France	E3N EPIC-France, Nested Case Control,	366/ 720 controls 7 years	Self report verified by medical record	Serum: HPLC	Incidence, breast cancer	Q5 vs Q1	1.02 (0.65-1.60) Ptrend:0.83	Age, age at first child birth, alcohol consumption,	Included, all breast cancer; intakes estimated from

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Age: 40-65 years, W							benign breast disease, blood collection centre, date of blood collection, educational level, family history of cancer, fasting condition, height, menopausal hormone use, menopausal status, parity	mean and standard deviation, midpoints of exposure quantiles
					Alcohol <=10g/day	Q5 vs Q1	0.94 (0.47-1.86) Ptrend:0.91		
					Alcohol 10+ g/day	Q5 vs Q1	1.28 (0.36-4.52) Ptrend:0.52		
Kabat, 2009 BRE80250 USA	Women's Health Initiative - Dietary Modification Trial, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	190/ 5 450 8 years	Self-report, medical record and pathology report reviewed by centrally trained physician	Fasting serum: reverse-phase HPLC	Incidence, invasive & in situ breast cancer, postmenopausal	≥0.1 vs ≤0.05 µg/ml	1.28 (0.86-1.92) Ptrend:0.23	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, benign breast disease, BMI, calcium intake, educational level, energy intake, ethnicity, family history of	Included, postmenopausal; converted units, midpoints
		153/			Incidence, invasive breast cancer	≥0.1 vs ≤0.05 µg/ml	1.14 (0.73-1.79) Ptrend:0.56		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								cancer, HRT use, OC use, physical activity, randomized treatment assignment	
Hulten, 2001 BRE04155 Sweden	VIP-MONICA-MSP, Nested Case Control, W	201/ 390 controls	Partially histological - over 80%	Plasma: HPLC	Incidence, breast cancer	Q4 vs Q1	0.90 (0.50-1.60) Ptrend:0.60	BMI, total cholesterol, triglycerides, age at menarche, parity, age at first full-term pregnancy, use of hormone replacement therapy, menopausal status, cotinine (a marker of recent exposure to tobacco smoke), and hours of fasting	Superseded by pooled analysis, Eliassen, 2012
	VIP-MONICA	57/ 93 controls			Premenopausal	≥0.30 vs ≤0.14 µmol/	1.00 (0.30-3.60) Ptrend:0.49		Included, premenopausal; converted units, midpoints
	VIP-MONICA	67/ 109 controls			Postmenopausal	≥0.30 vs ≤0.14 µmol/	0.80 (0.30-2.30) Ptrend:0.41		Included, postmenopausal; converted units, midpoints
	MSP	67/ 127 controls			Postmenopausal	≥0.38 vs ≤0.15 µmol/	0.70 (0.20-2.00) Ptrend:0.85		

Table 320 Circulating beta-cryptoxanthin and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Bakker, 2016 Europe	EPIC, Nested Case Control, Mean age: 50 years, W	636/ 632 controls	Linkage to population cancer registries in most countries, a combination of methods in some countries, including health insurance records, cancer and pathology registries, and active follow-up	Plasma, sum of carotenoids, HPLC	Incidence, invasive breast cancer, ER+	≥1005.58 vs ≤123.52 nmol/l	0.70 (0.45-1.10) Ptrend:0.68	BMI, height, age at menarche, age at first full-term pregnancy, OC use, HRT use, smoking status, alcohol consumption, educational level, intake of saturated fatty acids, energy intake, season of blood collection Matching factors: study centre, age, menopausal status, use of exogenous hormones, phase of menstrual cycle, fasting status at blood collection, time of blood collection	Excluded, identified after end of search, analysis by tumour receptor status was not conducted
		515/ 514 controls			ER-	≥983.98 vs ≤118.54 nmol/l	0.84 (0.51-1.37) Ptrend:0.29		
Eliassen, 2015 BRE80598	NHS, Nested Case	2 149/ 2153 controls	Biennial follow-up	Blood: first sample collected	Incidence, breast cancer	≥126 vs ≤50.8 µg/dl	0.86 (0.70-1.06) Ptrend:0.12	Age at first child birth, age at	Superseded by pooled analysis,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
USA	Control, Age: 43-67 years, W	20 years	questionnaires and medical records	1989-1990 second sample collected 2000-2002				menarche, age at menopause, alcohol intake, BMI at age 18 years, family history of breast cancer, history of benign breast disease, matching variables, parity	Eliassen, 2012
		1 313/			Incidence, breast cancer ER+	≥126 vs ≤50.8 µg/dl	0.93 (0.74-1.17) Ptrend:0.36		
		292/			Incidence, breast cancer ER-	≥126 vs ≤50.8 µg/dl	0.90 (0.60-1.35) Ptrend:0.79		
		349/			Incidence, well differentiated breast cancer	≥126 vs ≤50.8 µg/dl	1.09 (0.74-1.59) Ptrend:0.64		
		595/			Incidence, moderate differentiated breast cancer	≥126 vs ≤50.8 µg/dl	0.82 (0.60-1.12) Ptrend:0.19		
		373/			Incidence, poorly differentiated breast cancer	≥126 vs ≤50.8 µg/dl	0.93 (0.65-1.35) Ptrend:0.40		
		646/			Incidence, luminal a breast cancer	≥126 vs ≤50.8 µg/dl	1.06 (0.78-1.44) Ptrend:0.93		
		215/			Incidence,	≥126 vs ≤50.8	0.98 (0.61-1.58)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					luminal b breast cancer	µg/dl	Ptrend:0.85		
		108/			Incidence, triple negative breast cancer	≥126 vs ≤50.8 µg/dl	0.91 (0.48-1.76) Ptrend:0.99		
		1 849/			Incidence, nonrecurrent and nonlethal breast cancer	≥126 vs ≤50.8 µg/dl	0.89 (0.72-1.10) Ptrend:0.29		
		300/			Incidence, recurrent or lethal breast cancer	≥126 vs ≤50.8 µg/dl	0.68 (0.45-1.04) Ptrend:0.008		
		1 121/ 1209 controls			Incidence, breast cancer, BMI <25	≥126 vs ≤50.8 µg/dl	0.70 (0.53-0.92) Ptrend:0.05		
		695/ 644 controls			BMI 25- <30	≥126 vs ≤50.8 µg/dl	1.12 (0.76-1.67) Ptrend:0.84		
		332/ 299 controls			BMI >=30	≥126 vs ≤50.8 µg/dl	1.41 (0.74-2.68) Ptrend:0.62		
		1 880/ 1927 controls			Nonsmokers	≥126 vs ≤50.8 µg/dl	0.89 (0.71-1.10) Ptrend:0.25		
		269/ 226 controls			Current smokers	≥126 vs ≤50.8 µg/dl	0.97 (0.45-2.11) Ptrend:0.53		
		1 824/ 1828 controls			Follow up <10 years	≥126 vs ≤50.8 µg/dl	0.90 (0.72-1.11) Ptrend:0.21		
		895/ 900 controls			Follow up >=10 years	≥126 vs ≤50.8 µg/dl	0.76 (0.55-1.05) Ptrend:0.12		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Tamimi, 2009 BRE80276 USA	NHS, Nested Case Control, W, Postmenopausal	604/ 626 controls 9 years	Self-report verified by medical record	Plasma: reverse-phase HPLC	Incidence, breast cancer, postmenopausal	Q5 vs Q1	0.90 (0.60-1.30) Ptrend:0.11	Age, age at first child birth, alcohol, benign breast disease, BMI, family history of cancer, parity, postmenopausal hormone use	Superseded by Sisti, 2015
							0.80 (0.50-1.20) Ptrend:0.04	Mammographic density	
Sesso, 2005 BRE24061 USA	WHS, Nested Case Control, W, Health professionals	480 7 years	Medical records + self-reported	Plasma: reverse-phase HPLC	Incidence, breast cancer	20.6 vs 3.5 µg/dl	0.82 (0.46-1.44) Ptrend:0.21	Age at first child, age at menarche, alcohol, biomarkers, BMI, design , design , family history, HRT use, menopausal status, nutrients, nutrients, nutrients, nutrients, OC use, parity/pregnancies, physical activity	Superseded by pooled analysis, Eliassen, 2012
Tamimi, 2005 BRE24274 USA	NHS, Nested Case Control,	325 22 years	All morphology (histology or cytology)	Plasma: reverse-phase HPLC	Incidence, invasive & in situ breast	Q5 vs Q1	0.95 (0.69-1.31) Ptrend:0.08	Age at first child, age at menarche, age at	Superseded by pooled analysis, Eliassen, 2012

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 43-70 years, W, Registered nurses				cancer			menopause, alcohol, benign breast disease, BMI, family history, fasting condition, HRT use, laboratory variables , other anthropometric index	
Tamimi, 2004 BRE12084 USA	NHS, Nested Case Control, Age: 30-55 years, W, Registered nurses	254/ 235 controls 8 years	Partially histological - over 80%	Plasma: reverse-phase HPLC	Incidence, breast cancer, Val/Val (MnSOD)	T3 vs T1	0.53 (0.34-0.84)	Age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, duration of HRT use, family history, parity/pregnancies, smoking habits	Superseded by pooled analysis, Eliassen, 2012
Sato, 2002 BRE20839 USA	CLUE I, Nested Case Control, Age: 51 years, W, blood donors	244/ 244 controls 20 years	Partially histological - over 80%	Serum: reverse-phase HPLC	Incidence, breast cancer	≥15.8 vs ≤4.4 µg/dl	0.98 (0.55-1.75) Ptrend:.67	Matched on age (within 1 year), race, menopausal status, and month and year of blood donation; premenopausal	Superseded by pooled analysis, Eliassen, 2012
	CLUE II, Nested Case Control,	115/ 115 controls 3 years			Incidence, breast cancer	≥17.3 vs ≤6.5 µg/dl	0.70 (0.29-1.73) Ptrend:0.68		Superseded by pooled analysis, Eliassen, 2012

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 60 years, W, blood donors							women were also matched on date of last menstrual cycle	
Toniolo, 2001 BRE12399 USA	NYUWHS, Nested Case Control, Age: 35-65 years, W	14 275	Partially histological - over 80%	Serum: HPLC, Steghens et al. method	Incidence, breast cancer	Q4 vs Q1	1.00 Ptrend:0.05	Age at first child, benign breast disease, biomarkers, family history	Superseded by pooled analysis, Eliassen, 2012
Dorgan, 1998 BRE14889 USA	Columbia, MO cohort, Nested Case Control, Age: 41-73 years, W	105/ 209 controls 9.5 years	All histology	Serum	Incidence, invasive breast cancer	0.28-1.07 vs ≤0.1 µmol/l	0.60 (0.30-1.20) Ptrend:0.41	Biomarkers, BMI, smoking habits	Superseded by pooled analysis, Eliassen, 2012

Figure 406 RR estimates of breast cancer by levels of circulating beta-cryptoxanthin concentration

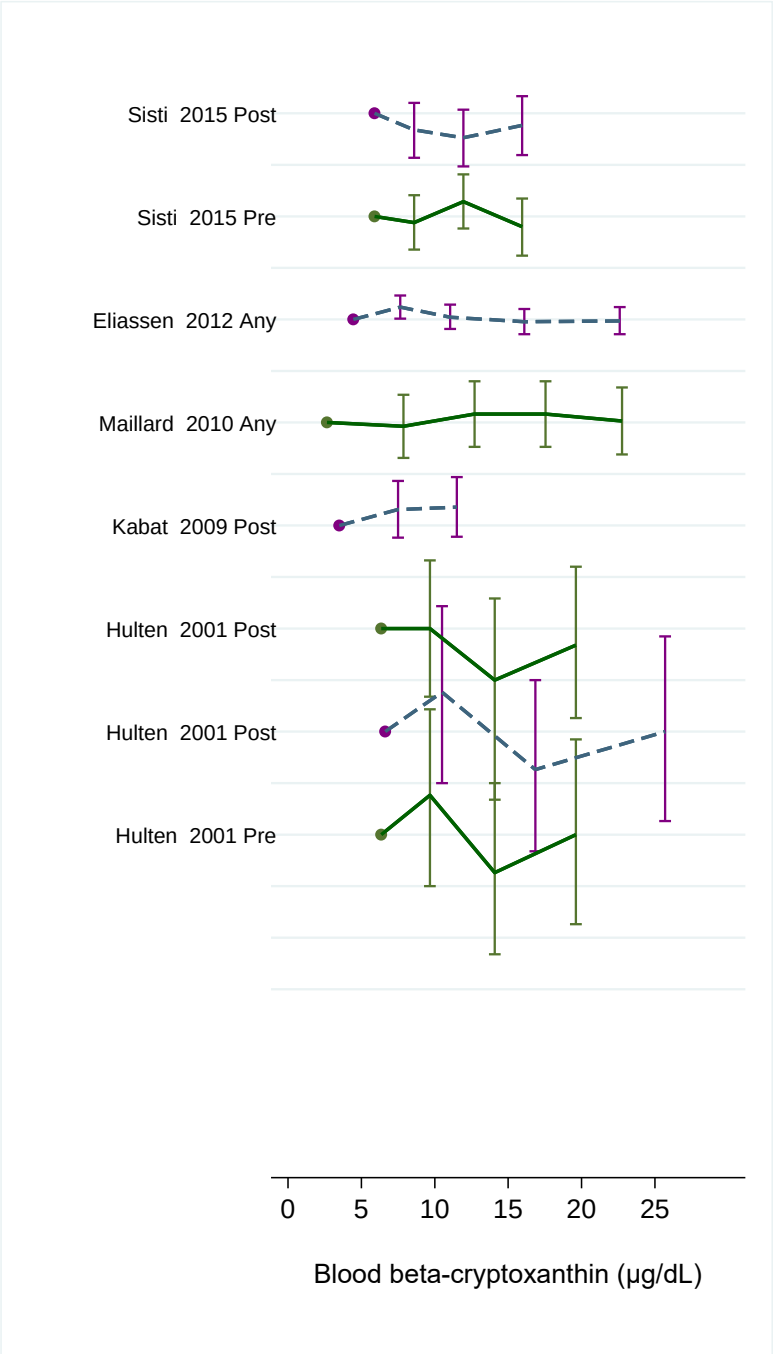


Figure 407 RR (95% CI) of breast cancer for the highest compared with the lowest level of circulating beta-cryptoxanthin concentration

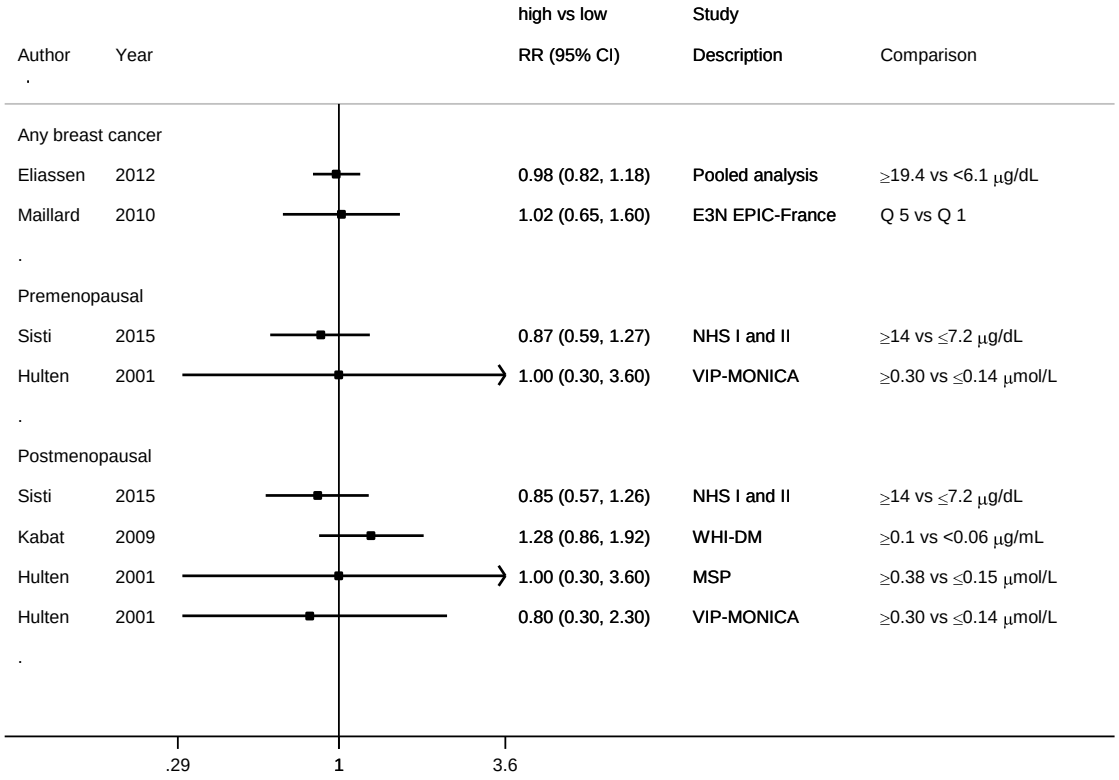


Figure 408 Relative risk of breast cancer (any) for 15 µg/dl increase of circulating beta-cryptoxanthin concentration

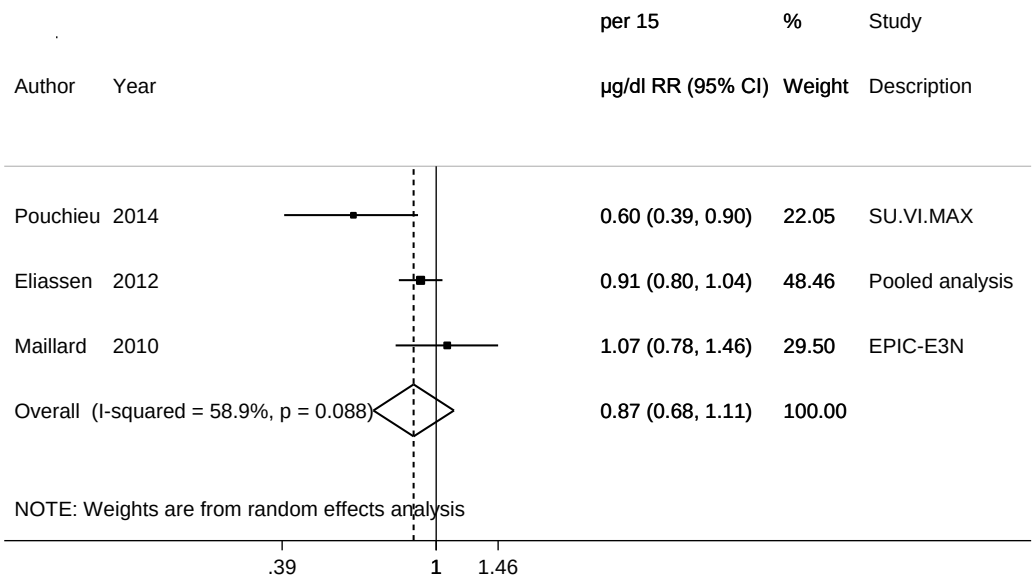


Figure 409 Relative risk of premenopausal breast cancer for 15 µg/dl increase of circulating beta-cryptoxanthin concentration

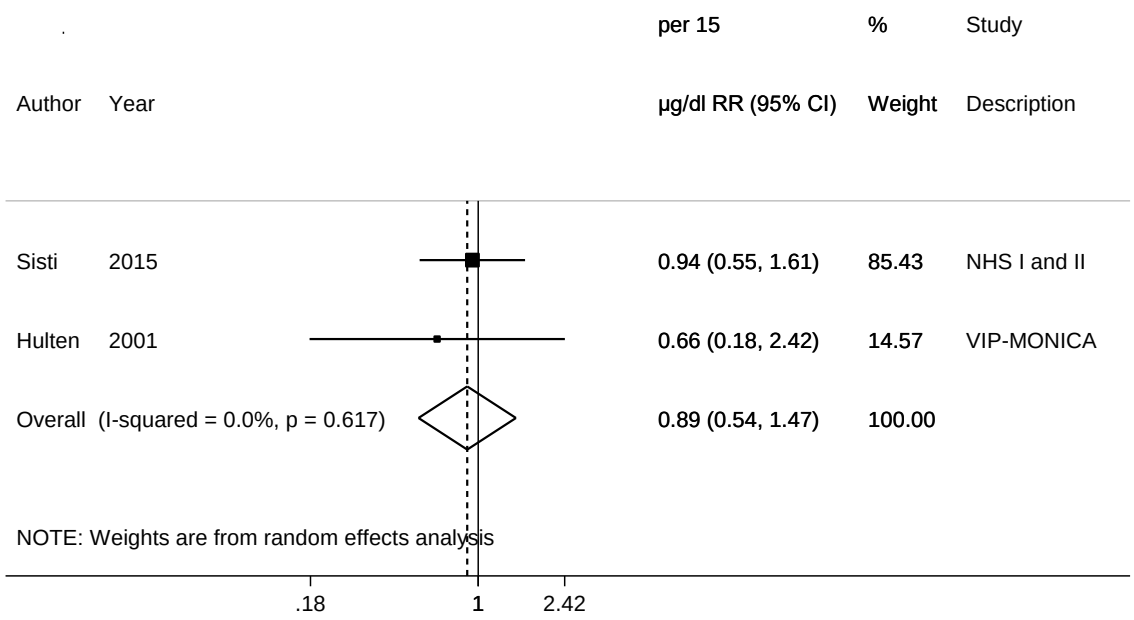
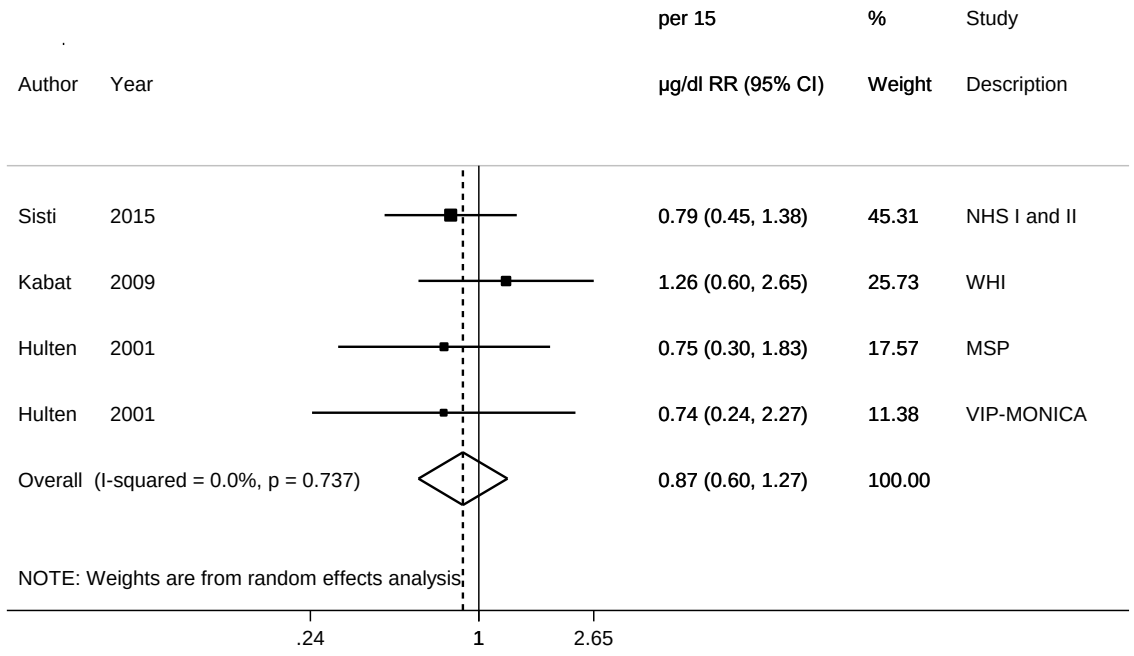


Figure 410 Relative risk of postmenopausal breast cancer for 15 µg/dl increase of circulating beta-cryptoxanthin concentration



5.5.2 Circulating total carotenoids

Breast cancer (any)

A pooled analysis of eight prospective cohorts (Columbia, MO; Umeå; CLUE I and II; NHS; WHS; NYUWHS; SWHS; MEC) (Eliassen, 2012) and one report from the E3N French cohort were identified (Maillard, 2010). A significant inverse association was observed in the dose-response meta-analysis (summary RR for 100 μg/dL=0.82; 95% CI 0.71-0.96) with no evidence of heterogeneity (I^2=0%). The pooled analysis had 86% weight in the meta-analysis and in this study, the association of breast cancer with total carotenoids was more evident in women with BMI<25 kg/m^2 and in current smokers (p-value interaction <0.01 for both variables).

Other published reports were superseded by the pooled analysis (Eliassen, 2012). The NHS I study was included in the pooled analysis (962 cases). In a larger and more recent study in the same cohort (Eliassen, 2015, 2188 cases) blood circulating carotenoids were significantly related to lower risk of breast cancer (any) (RR for highest vs lowest concentrations of total carotenoids: 0.77, 95%CI: 0.63-0.94, p_{trend}<0.01). These results are consistent with those of the pooled analysis.

Not included in the dose-response meta-analysis was also a nested case-control study in the EPIC study in which the association of plasma carotenoids with breast cancer was examined by ER status and age at diagnosis (less or more than 50 years) (Bakker, 2016). The study was published after the end date of the review search. A total of 1502 breast cancer cases in EPIC were selected from the cohort with oversampling of cases with ER- tumours and of premenopausal women.

Hormone receptor status

The pooled analysis (Eliassen, 2012), two publications of the NHS cohorts (Eliassen, 2015, Sisti, 2015) and the EPIC study (Bakker, 2016) reported results by hormone receptor status.

In the pooled analysis (Eliassen, 2012) the association appeared stronger for ER- negative than for ER-positive but the associations were nto statistically significant (RR for top vs bottom quintile = 0.81, 95% CI = 0.56 -1.16, ptrend =0 .008 for ER-negative, and 0.86, 95% CI = 0.69-1.07, ptrend = 0.21for ER-positive).

In the EPIC study (Bakker, 2016), the RR for ≥ 3707 vs ≤ 979 nmol/l was 0.85; 95% CI: 0.53-1.37, p_{trend}<0.66 for ER+ cancers (636 cases) and 0.64, 95% CI: 0.37-1.09, p_{trend}<0.23 for ER- cancers (515 cases).

In a recent publication of the NHS study a significant inverse association was observed for ER-positive tumours (RR for ≥1379 vs ≤728.9 μg /dl: 0.73, 95% CI: 0.58-0.92, p_{trend}<0.01, 1309 cases) and not significant for ER- negative (RR: 0.90, 95% CI: 0.60-1.35, p_{trend}<0.76, 291 cases) but there was no significant heterogeneity (p=0.02). Women with high plasma carotenoids were at reduced breast cancer risk for more aggressive and fatal disease (RR: 0.48; 95% CI: 0.31, 0.73; P-trend = 0.001). In another publication from NHS I and II (Sisti, 2015), premenopausal total carotenoids levels were not inversely associated with breast cancer risk. No differences by estrogen receptor status were observed. The RR for the

comparison of 136 vs ≤84.9 μg/dl was 0.88, 95% CI: 0.66-1.18 for ER-positive (606 cases) and 0.95, 95%CI: 0.55-1.62, for ER- negative breast cancer (148 cases). [NHS cohorts included in the pooled analysis by Eliassen, 2015].

Premenopausal breast cancer

In the pooled analysis of eight cohort studies, there was no significant interaction of menopausal status and circulating carotenoids in relation to breast cancer risk (Eliassen, 2012) [data not shown in the publication]. Most participants in the pooled analysis were postmenopausal at blood collection. Three studies (two publications) included in the pooled analysis reported data on premenopausal breast cancer and circulating carotenoids and were included in the dose-response meta-analysis. No significant association was observed.

Postmenopausal breast cancer

Four studies (three publications) were identified and all were included in the dose-response meta-analysis. No association with total circulating carotenoids was observed. All studies were included in the published pooled analysis (Eliassen, 2012) [see note on Premenopausal section].

Table 321 Circulating total carotenoids and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	9 (11 publications)
Studies included in forest plot of highest compared with lowest intake	Breast cancer: 9 (2 publications) Premenopausal: 3 (2 publications) Postmenopausal: 4 (3 publications)
Studies included in linear dose-response meta-analysis	Breast cancer: 9 (2 publications) Premenopausal: 3 (2 publications) Postmenopausal: 4 (3 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 322 Circulating total carotenoids and breast cancer risk. Summary of the linear dose-response meta-analysis in the CUP

	Breast cancer (any)	**Premenopausal**	**Postmenopausal**
Increment unit used	100 μg/dl		
Studies (n)	9	3	4
Cases (total number)	3 407	710	949
RR (95%CI)	0.82 (0.71-0.96)	1.07 (0.72-1.60)	1.06 (0.55-2.03)
Heterogeneity (I^2, p-value)	0%, 0.78	0%, 0.97	79%, 0.01
P value Egger test	-	-	-

Table 323 Total circulating carotenoids and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analysis								
Aune et al, 2012	7	2 518	North America, Europe, Asia	Incidence, breast cancer	High vs. low Per 100 µg/dl	0.74 (0.57-0.96) 0.78 (0.61-0.99)	- -	52% 53%

Table 324 Circulating total carotenoid intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Sisti, 2015 BRE80597 USA	NHS I and II, Nested Case Control, Age: 25-55 years, W, Premenopausal	1 111/ 1111 controls	Biennial follow-up questionnaires and medical records	Blood: participants collected follicular phase blood samples during days 3–5 of their menstrual cycle, and blood and urine samples during the luteal phase, 7–9 days before the anticipated start of their next cycle.	Incidence, breast cancer	≥136 vs ≤84.9 µg/dl	.99 (0.77-1.28) Ptrend:0.67	Age at menarche, alcohol intake, BMI, family history of breast cancer, history of benign breast disease, matching variables, parity and age at first birth	Superseded by pooled analysis Eliassen, 2012
		526/			Incidence, breast cancer, premenopausal at diagnosis		1.13 (0.78-1.62) Ptrend:0.61		Included in analysis in premenopausal and postmenopausal only; midpoints of exposure quartiles
		482/			Postmenopausal at diagnosis		0.79 (0.53-1.19) Ptrend:0.12		
		606/			ER+		0.88 (0.66-1.18) Ptrend:0.24		No meta-analysis by ER status
		148/			ER-		0.95 (0.55-1.62) Ptrend:0.63		
Eliassen, 2012 China, Sweden, USA	Pooled analysis of 8 prospective studies*, Mean age ranged from 51.3-66.0 years, W	3,055 cases/ 3,956 controls	Plasma, recalibrated values, reverse-phase HPLC, median time between blood collection and diagnosis was 4.3 years	Plasma, recalibrated values, reverse-phase HPLC, median time between blood collection and diagnosis was 4.3 years	Incidence, breast cancer	≥139 vs <70.1 µg/dl	0.81 (0.68-0.96) Ptrend:0.01	Menopausal status, age at menopause, age at menarche, parous, age at first birth, exogenous hormone use, BMI, current smoking, race, personal history of benign breast disease, family history of breast cancer	Included, all breast cancer; midpoints of exposure quintiles
		1,481			ER+	Q5 vs Q1	0.86 (0.69-1.07) Ptrend:0.21		No meta-analysis by ER status
	*Columbia, MO; Umeå; CLUE I and II; NHS; WHS; NYUWHS;	417			ER-		0.81 (0.56-1.16) Ptrend:0.08		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	SWHS; MEC							Matching factors included age at blood collection, date, time, and fasting status at blood collection, menopausal status, date of last menstrual period and/or phase and day of menstrual cycle (premenopausal women), PMH use, race or ethnicity, study centre, smoking status, follow-up time, availability of FFQ, use of antibiotics, number of blood collections within the cohort, diagnosis of benign breast disease	
Maillard, 2010 BRE80258 France	E3N EPIC-France, Nested Case Control, Age: 40-65 years, W	366/ 720 controls 7 years	Self report verified by medical record	Serum: HPLC	Incidence, breast cancer	Q5 vs Q1	0.74 (0.47-1.16) Ptrend:0.38	Age, age at first child birth, alcohol consumption, benign breast disease, blood collection centre, date of blood	Included, all breast cancer; intakes estimated from mean and standard deviation,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								collection, educational level, family history of cancer, fasting condition, height, menopausal hormone use, menopausal status, parity	midpoints of exposure quantiles
					alcohol 10+ g/day		1.15 (0.35-3.74) Ptrend:0.54		
					alcohol <=10g/day		0.73 (0.35-1.55) Ptrend:0.40		
Dorjgochoo, 2009 BRE80289 China	SWHS, Nested Case Control, Age: 40-70 years, W	365/ 726 controls 7.5 person-years	Cancer registry	Plasma: reverse-phase HPLC	Incidence, breast cancer	Q4 vs Q1	1.30 (0.87-1.93) Ptrend:0.14	Age, age at first child birth, age at menarche, benign breast disease, educational level, energy intake, family history of cancer, fish, fruit intake, laboratory batch, occupation, physical activity, red meat intake, smoking status, tea intake, vegetable intake, waist-hip ratio, other plasma lipophilic antioxidants	Superseded by pooled analysis Eliassen, 2012
		184/			Incidence, breast cancer, premenopausal		1.06 (0.51-1.91) Ptrend:0.75		Included, premenopausal; converted units, midpoints of exposure quantiles
		181/			Postmenopausal		1.77 (0.96-3.25) Ptrend:0.05		Included, postmenopausal; converted units, midpoints of exposure quantiles
Epplein, 2009 BRE80236	MEC, Nested Case	286/ 535 controls	Cancer registry	Plasma: HPLC with	Incidence, breast cancer,	≥1953.1 vs ≤1129.4	0.80 (0.51-1.26) Ptrend:0.39	Age at first child birth, age at	Included, postmenopausal;

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
USA	Control, Age: 45-75 years, W, Postmenopausal			photodiode array detection	postmenopausal	ng/ml		menarche, age at menopause, alcohol consumption, BMI, date of blood collection, ethnicity, fasting condition, geographic area, HRT use, parity, year of birth	converted units, midpoints of exposure quintiles
					Ever smokers		0.29 (0.10-0.85)		
					Never smokers		1.19 (0.62-2.27)		

Table 325 Circulating total carotenoid intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Bakker, 2016 Europe	EPIC, Nested Case Control, Mean age: 50 years, W	636/ 632 controls	Linkage to population cancer registries in most countries, a combination of methods in some countries, including health insurance records, cancer and pathology	Plasma, sum of carotenoids, HPLC	Incidence, invasive breast cancer, ER+	≥3707.60 vs ≤979.60 nmol/l	0.85 (0.53-1.37) Ptrend:0.66	BMI, height, age at menarche, age at first full-term pregnancy, OC use, HRT use, smoking status, alcohol consumption, educational level, intake of saturated fatty acids, energy	Identified after end of search, analysis was not conducted by tumour hormone receptor status due to low number of studies

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
			registries, and active follow-up					intake, season of blood collection	
		515/ 514 controls			ER-	≥3716.75 vs ≤987.08 nmol/l	0.64 (0.37-1.09) Ptrend:0.23	Matching factors: study centre, age, menopausal status, use of exogenous hormones, phase of menstrual cycle, fasting status at blood collection, time of blood collection	
Eliassen, 2015 BRE80598 USA	NHS, Nested Case Control, Age: 43-67 years, W	2 141/ 2143 controls 20 years	Biennial follow-up questionnaires and medical records	Blood: first sample collected 1989-1990 second sample collected 2000-2002	Incidence, breast cancer	≥1379 vs ≤728.9 µg /dl	0.77 (0.63-0.94) Ptrend:0.005	Age at first child birth, age at menarche, age at menopause, alcohol intake, BMI at age 18 years, family history of breast cancer, history of benign breast disease, matching variables, parity	Superseded by pooled analysis Eliassen, 2012
		1 309/			Incidence, breast cancer ER+	≥1379 vs ≤728.9 µg /dl	0.73 (0.58-0.92) Ptrend:0.003		Not analysed
		291/			Incidence, breast	≥1379 vs ≤728.9	0.90 (0.60-1.35)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					cancer ER-	µg /dl	Ptrend:0.76		
		349/			Incidence, well differentiated breast cancer	≥1379 vs ≤728.9 µg /dl	0.61 (0.41-0.89) Ptrend:0.02		
		594/			Incidence, moderate differentiated breast cancer	≥1379 vs ≤728.9 µg /dl	0.86 (0.64-1.16) Ptrend:0.15		
		370/			Incidence, poorly differentiated breast cancer	≥1379 vs ≤728.9 µg /dl	0.69 (0.47-1.01) Ptrend:0.06		
		645/			Incidence, luminal a breast cancer	≥1379 vs ≤728.9 µg /dl	0.77 (0.57-1.04) Ptrend:0.03		
		215/			Incidence, luminal b breast cancer	≥1379 vs ≤728.9 µg /dl	0.61 (0.38-1.00) Ptrend:0.02		
		107/			Incidence, triple negative breast cancer	≥1379 vs ≤728.9 µg /dl	1.40 (0.73-2.70) Ptrend:0.41		
		1 844/			Incidence, no recurrent and non lethal breast cancer	≥1379 vs ≤728.9 µg /dl	0.83 (0.68-1.02) Ptrend:0.04		
		297/			Incidence, recurrent or lethal breast cancer	≥1379 vs ≤728.9 µg /dl	0.48 (0.31-0.73) Ptrend:0.001		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		1 118/ 1204 controls			Incidence, breast cancer, BMI <25	≥1379 vs ≤728.9 µg /dl	0.64 (0.48-0.84) Ptrend:<0.001		
		693/ 640 controls			BMI 25- <30	≥1379 vs ≤728.9 µg /dl	1.08 (0.74-1.58) Ptrend:0.73		
		329/ 298 controls			BMI <30	≥1379 vs ≤728.9 µg /dl	0.98 (0.49-1.97) Ptrend:0.75		
		1 873/ 1920 controls			Nonsmokers	≥1379 vs ≤728.9 µg /dl	0.82 (0.66-1.01) Ptrend:0.04		
		268/ 223 controls			Current smokers	≥1379 vs ≤728.9 µg /dl	0.60 (0.28-1.28) Ptrend:0.09		
		1 814/ 1818 controls			Follow up <10 years	≥1379 vs ≤728.9 µg /dl	0.79 (0.64-0.98) Ptrend:0.04		
		889/ 896 controls			Follow up >=10 years	≥1379 vs ≤728.9 µg /dl	0.69 (0.50-0.95) Ptrend:0.01		
Tamimi, 2009 BRE80276 USA	NHS, Nested Case Control, W, Postmenopausal	604/ 626 controls 9 years	Self report verified by medical record	Plasma: reverse-phase HPLC	Incidence, breast cancer, postmenopausal	Q 5 vs Q 1	0.70 (0.50-1.00) Ptrend:0.01	Age, age at first child birth, alcohol, benign breast disease, BMI, family history of cancer, parity, postmenopausal hormone use	Superseded by Sisti, 2015
							0.60 (0.40-0.90) Ptrend:0.002	Mammographic density	
Tamimi, 2005 BRE24274 USA	NHS, Nested Case Control,	325 22 years	All morphology (histology or cytology)	Plasma: reverse-phase HPLC	Incidence, invasive & in situ breast	Q5 vs Q1	0.76 (0.55-1.05) Ptrend:0.05	Age at first child, age at menarche,	Superseded by pooled analysis Eliassen, 2012

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 43-70 years, W, Registered nurses				cancer			alcohol, benign breast disease, BMI, family history, fasting condition, HRT use, laboratory variables , other anthropometric index	
Tamimi, 2004 BRE12084 USA	NHS, Nested Case Control, Age: 30-55 years, W, Registered nurses	254/ 235 controls 8 years	Partially histological - over 80%	Plasma: reverse-phase HPLC	Incidence, breast cancer	Q3 vs Q1	0.93 (0.59-1.47)	Age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, duration of HRT use, family history, parity/pregnancies, smoking habits	Superseded by pooled analysis Eliassen, 2012
Sato, 2002 BRE20839 USA	CLUE I, Nested Case Control, Age: 51 years, W, blood donors	244/ 244 controls 20 years	Partially histological - over 80%	Serum: reverse-phase HPLC	Incidence, breast cancer	≥121.6 vs ≤51.4 µg /dl	0.55 (0.29-1.03) Ptrend:0.02		Superseded by pooled analysis Eliassen, 2012
	CLUE II, Nested Case Control, Age: 60 years,	115/ 115 controls 3 years	Partially histological - over 80%		Incidence, breast cancer	≥123.8 vs ≤67 µg /dl	0.61 (0.26-1.43) Ptrend:0.25		Superseded by pooled analysis Eliassen, 2012

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	W, blood donors								
Toniolo, 2001 BRE12399 USA	NYUWHS, Nested Case Control, Age: 35-65 years, W	14 275	Partially histological - over 80%	Serum: HPLC, Steghens et al. method	Incidence, breast cancer	Q4 vs Q1	2.31 (1.35-3.96) Ptrend:0.0008	Age at first child, benign breast disease, biomarkers, family history	Superseded by pooled analysis Eliassen, 2012

Figure 411 RR estimates of breast cancer by levels of total circulating carotenoid concentration

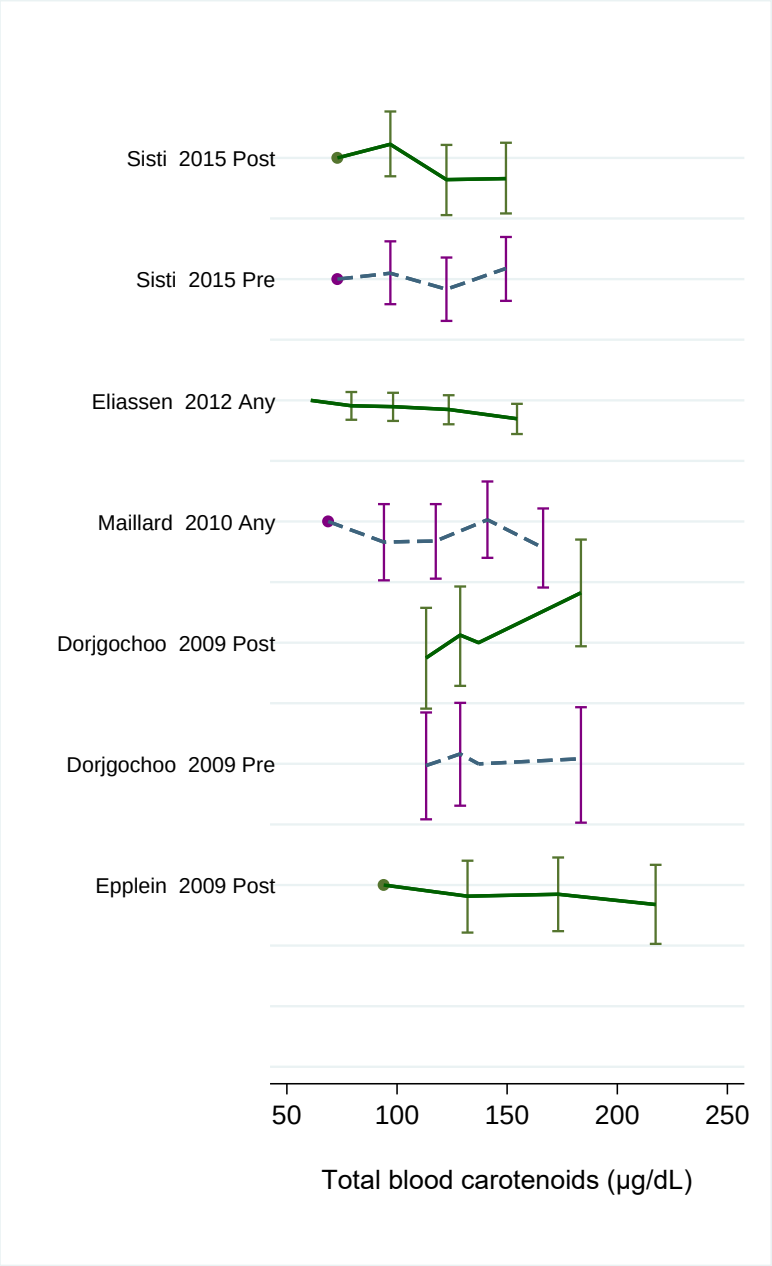


Figure 412 RR (95% CI) of breast cancer for the highest compared with the lowest level of total circulating carotenoid concentration

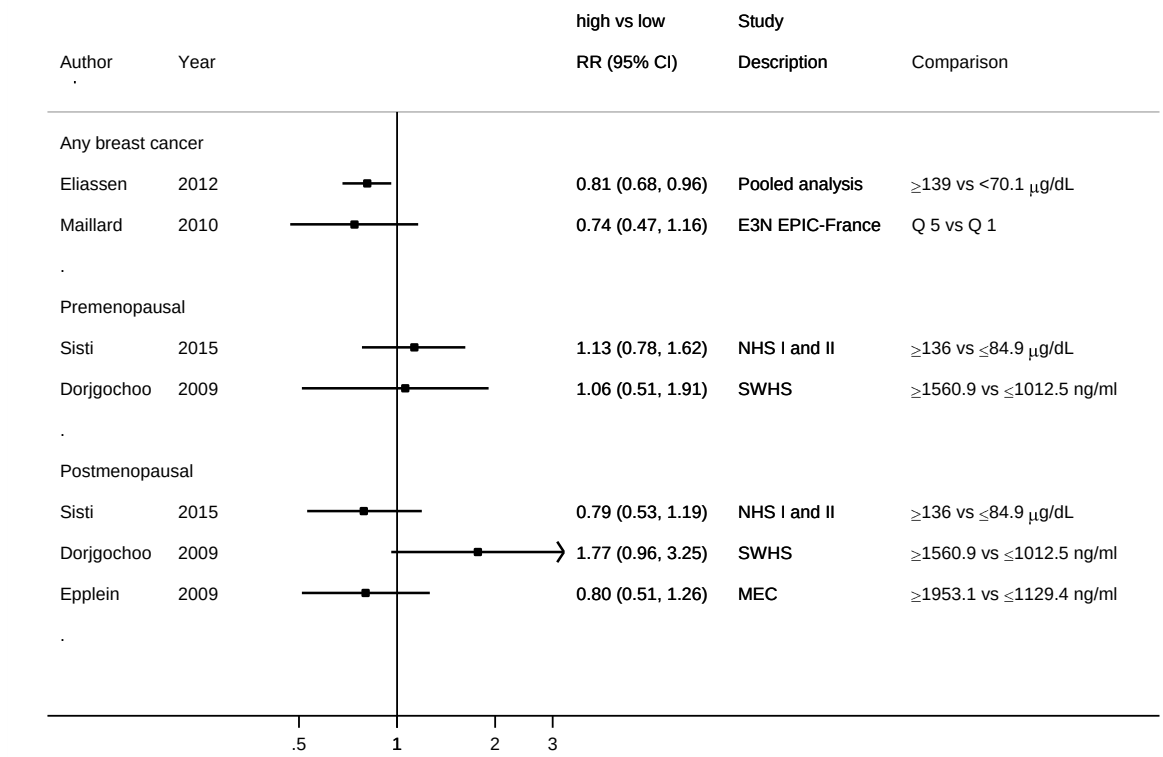


Figure 413 Relative risk of breast cancer (any) for 100 μg/dL increase of total circulating carotenoid concentration

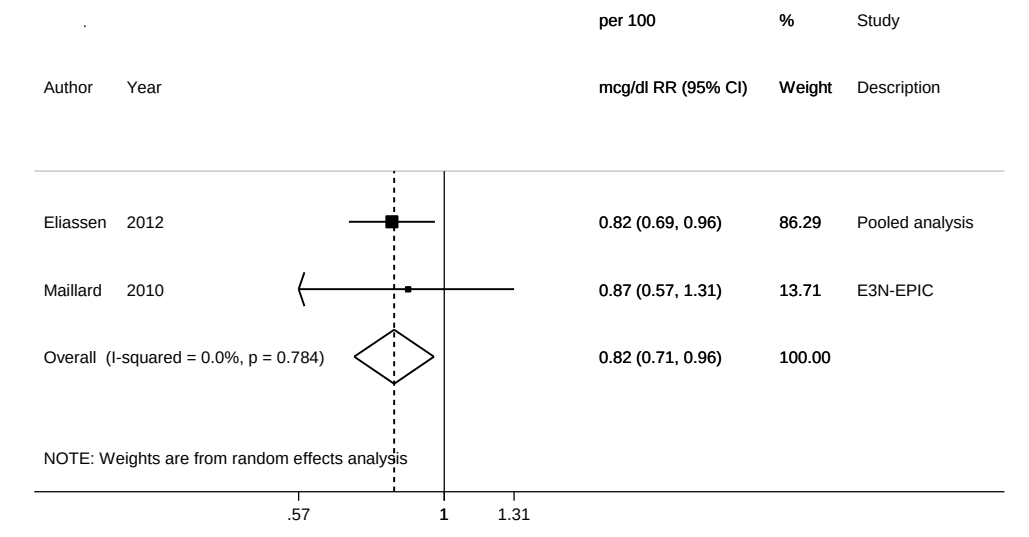


Figure 414 Relative risk of premenopausal breast cancer for 100 µg/dL increase of total circulating carotenoid concentration

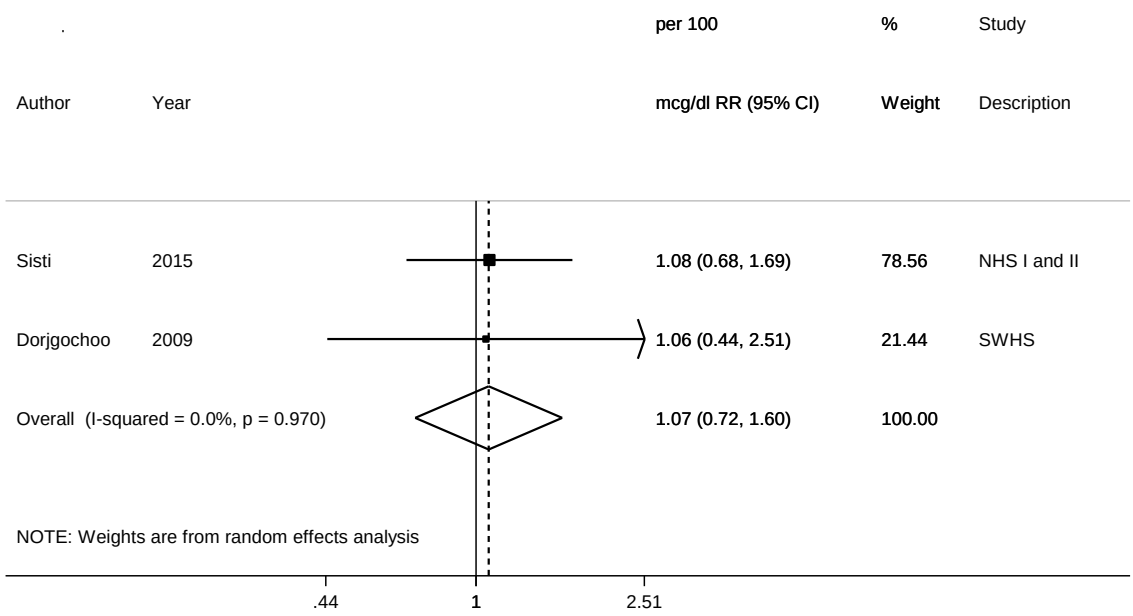
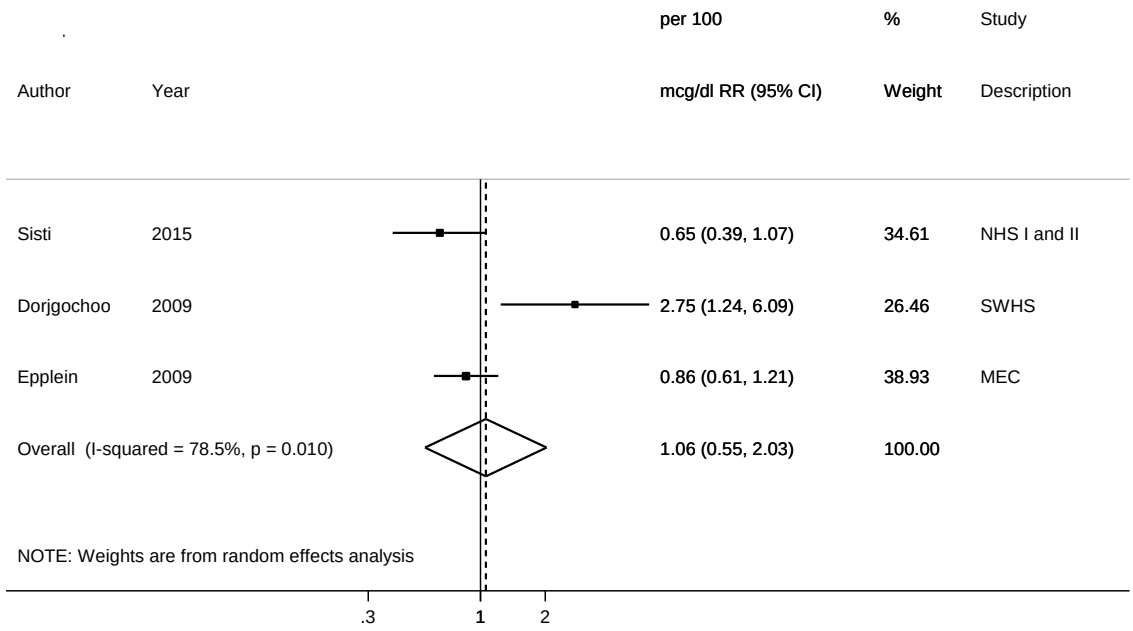


Figure 415 Relative risk of postmenopausal breast cancer for 100 µg/dL increase of total circulating carotenoid concentration



5.5.2.1 Circulating lutein

Breast cancer (any)

Seven cohorts from five publications (Pouchieu, 2014, SU.VI.MAX; Maillard, 2010, E3N French cohort; Sato, 2002, CLUE I and CLUE II; Hulten, 2001, VIP-MONICA, MSP; Toniolo, 2001, NYUWHS) were identified and included in the dose-response meta-analysis. Overall, a significant inverse asociation was observed (summary RR for 25 μg/dL=0.72, 95% CI=0.55-0.93; I^2=0%, Pheterogeneity=0.82).

In a pooled analysis of eight cohorts (Eliassen, 2012) the sum of circulating lutein and zeaxanthin was not significanlty related to breast cancer risk (RR for Q5 vs Q1= 0.84 (95% CI 0.70 - 1.01; ptrend=0.05) [lutein and zeaxanthin were read together in the laboratory assays].

The EPIC study (Bakker, 2016) examined the association of circulating lutein with breast cancer by ER status and age at diagnosis (less or more than 50 years). This study was identified in 2016 after the end date of search and was not included in the meta-analysis.

Hormone receptor status

The association of the sum of lutein and zeaxanthin did not differ by ER status in the pooled analysis (Eliassen, 2012).

In EPIC (Bakker, 2016), circulating lutein was non-significantly associated with ER-negative breast cancer (RR for highest vs lowest concentrations=1.19, 95% CI=0.66-2.13, Ptrend=0.48) and inversely associated with ER-positive breast cancer (RR=0.59, 95% CI=0.35-1.00, Ptrend=0.15) (Pheterogeneity=0.11).

Premenopausal breast cancer

One study (Hulten, 2001) was identified (RR for highest vs lowest concentrations=0.30, 95% CI=0.10-1.40, Ptrend=0.03).

Postmenopausal breast cancer

Two cohorts from one publication (Hulten, 2001) were identified and included in the dose-response meta-analysis. Circulating lutein was non-significantly positively associated with postmenopausal breast cancer (summary RR for 25 μg/dL=1.10, 95% CI=0.38-3.21; I^2=0%, Pheterogeneity=0.98).

Table 326 Circulating lutein and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	7 (5 publications)
Studies included in forest plot of highest compared with lowest intake	Breast cancer: 6 (4 publications) Premenopausal: Not enough studies Postmenopausal: 2 (1 publications)
Studies included in linear dose-response meta-analysis	Breast cancer: 7 (5 publications) Premenopausal: Not enough studies Postmenopausal: 2 (1 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 327 Circulating lutein and breast cancer risk. Summary of the linear dose-response meta-analysis in the CUP

	Breast cancer (any)	**Premenopausal**	**Postmenopausal**
Increment unit used	25 µg/dL		
Studies (n)	7	-	2
Cases (total number)	1 296	-	134
RR (95%CI)	0.72 (0.55-0.93)	-	1.10 (0.38-3.21)
Heterogeneity (I^2, p-value)	0%, p=0.82	-	0%, p=0.98
P value Egger test	0.82	-	-

Table 328 Circulating lutein and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR

Author, Year	**Number of studies**	**Total number of cases**	**Studies country, area**	**Outcome**	**Comparison**	**RR (95%CI)**	**P trend**	**Heterogeneity (I^2, p value)**
Meta-analysis								
Aune et al, 2012	7	1 186	North America, Europe, Asia	Incidence, breast cancer	High vs. low Per 25 µg/dL	0.70 (0.52-0.96) 0.68 (0.52-0.89)	- -	21% 0%

Table 329 Circulating lutein and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Pouchieu, 2014 BRE80565 France	SU.VI.MAX, Nested Case Control, Age: 49.8 years, W	100/ 100 controls 8 years	Self report verified by medical record	Plasma: HPLC	Incidence, breast cancer	per 0.1 µmol/l	1.06 (0.72-1.56)	Age, alcohol intake, BMI, dietary records, educational level, energy intake, family history of breast cancer, fat intake, fruits and vegetables consumption, height, HRT use, intervention group, menopausal status, number of children, physical activity, smoking status	Included, all breast cancer, RR rescaled for an increment used, units converted to µg/dl
		50/ 50 controls			Intervention group	per 0.1 µmol/l	0.82 (0.41-1.68)		
					Placebo-group	per 0.1 µmol/l	1.35 (0.50-3.63)		
Maillard, 2010 BRE80258 France	E3N EPIC-France, Nested Case Control, Age: 40-65 years, W	366/ 720 controls 7 years	Self report verified by medical record	Serum: HPLC	Incidence, breast cancer	Q 5 vs Q 1	0.97 (0.63-1.50) Ptrend:0.64	Age, age at first child birth, alcohol consumption, benign breast disease, blood collection centre, date of	Included, all breast cancer; intakes estimated from mean and standard deviation, midpoints of

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								blood collection, educational level, family history of cancer, fasting condition, height, menopausal hormone use, menopausal status, parity	exposure quantiles
					Alcohol <=10g/day	Q5 vs Q1	1.12 (0.58-2.17) Ptrend:0.79		
					Alcohol 10+ g/day	Q5 vs Q1	2.55 (0.62-10.49) Ptrend:0.08		
Sato, 2002 BRE20839 USA	CLUE I, Nested Case Control, Age: 51 years, W, blood donors	244/ 244 controls 20 years	Partially histological - over 80%	Serum: reverse-phase HPLC	Incidence, breast cancer	≥32.2 vs ≤13.6 µg/dl	0.77 (0.43-1.40) Ptrend:.41	Matched on age (within 1 year), race, menopausal status, and month and year of blood donation; premenopausal women were also matched on date of last menstrual cycle	Included, all breast cancer; midpoints of exposure quantiles
	CLUE II, Nested Case Control, Age: 60 years, W, blood donors	115/ 115 controls 3 years				≥30.9 vs ≤16.4 µg/dl	0.40 (0.17-0.98) Ptrend:0.11		Included, all breast cancer; midpoints of exposure quantiles
Hulten, 2001 BRE04155	VIP-MONICA-MSP,	201/ 390 controls	Partially histological -	Plasma: HPLC	Incidence, breast cancer	Q4 vs Q1	1.00 (0.60-1.70) Ptrend:0.73	Biomarkers, BMI	Included, all breast;

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Sweden	Nested Case Control, W		over 80%						converted units, midpoints
	VIP-MONICA	57/ 93 controls			Premenopausal	>0.51 vs ≤0.33µmol/l	0.30 (0.10-1.40) Ptrend:0.03		Not analysed
	VIP-MONICA	67/ 109 controls			Postmenopausal	>0.51 vs ≤0.33µmol/l	0.90 (0.30-2.60) Ptrend:0.73		Included, postmenopausal breast cancer; converted units, midpoints
	MSP	67/ 127 controls				>0.57 vs ≤0.36µmol/l	0.40 (0.10-1.40) Ptrend:0.28		
Toniolo, 2001 BRE12399 USA	NYUWHS, Nested Case Control, Age: 35-65 years, W	270/ 14 275	Partially histological - over 80%	Serum: HPLC, Steghens et al. method	Incidence, breast cancer	Q 1 vs Q4	2.08 (1.11-3.90) Ptrend: 0.01	Age at first child, benign breast disease, biomarkers, family history	Included, all breast cancer, inverted RR of lowest vs highest

Table 330 Circulating lutein and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Bakker, 2016 Europe	EPIC, Nested Case Control, Mean age: 50 years, W	636/ 632 controls	Linkage to population cancer registries in most countries, a combination of methods in some countries, including health insurance records, cancer and pathology registries, and active follow-up	Plasma, sum of carotenoids, HPLC	Incidence, invasive breast cancer, ER+	≥633.22 vs ≤125.35 nmol/l	0.59 (0.35-1.00) Ptrend:0.15	BMI, height, age at menarche, age at first full-term pregnancy, OC use, HRT use, smoking status, alcohol consumption, educational level, intake of saturated fatty acids, energy intake, season of blood collection Matching factors: study centre, age, menopausal status, use of exogenous hormones, phase of menstrual cycle, fasting status at blood collection, time of blood collection	Excluded, identified after end of search, analysis by tumour hormone receptor status was not conducted
		515/ 514 controls			ER-	≥616.13 vs ≤125.35 nmol/l	1.19 (0.66-2.13) Ptrend:0.48		
					ER+PR+	Q5 vs Q1	0.57 (0.28-1.17)		
					ER-PR-		1.54 (0.75-3.16)		

Figure 416 RR estimates of breast cancer by levels of circulating lutein concentration

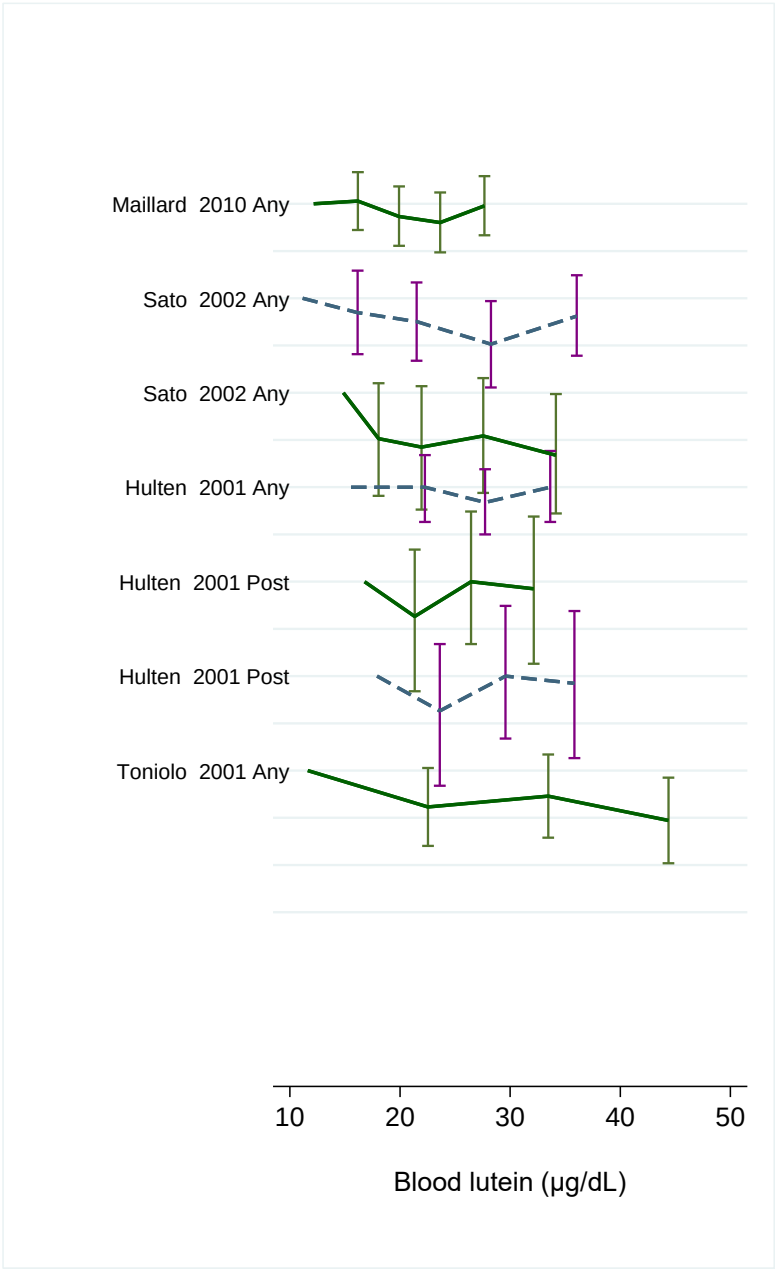


Figure 417 RR (95% CI) of breast cancer for the highest compared with the lowest level of circulating lutein concentration

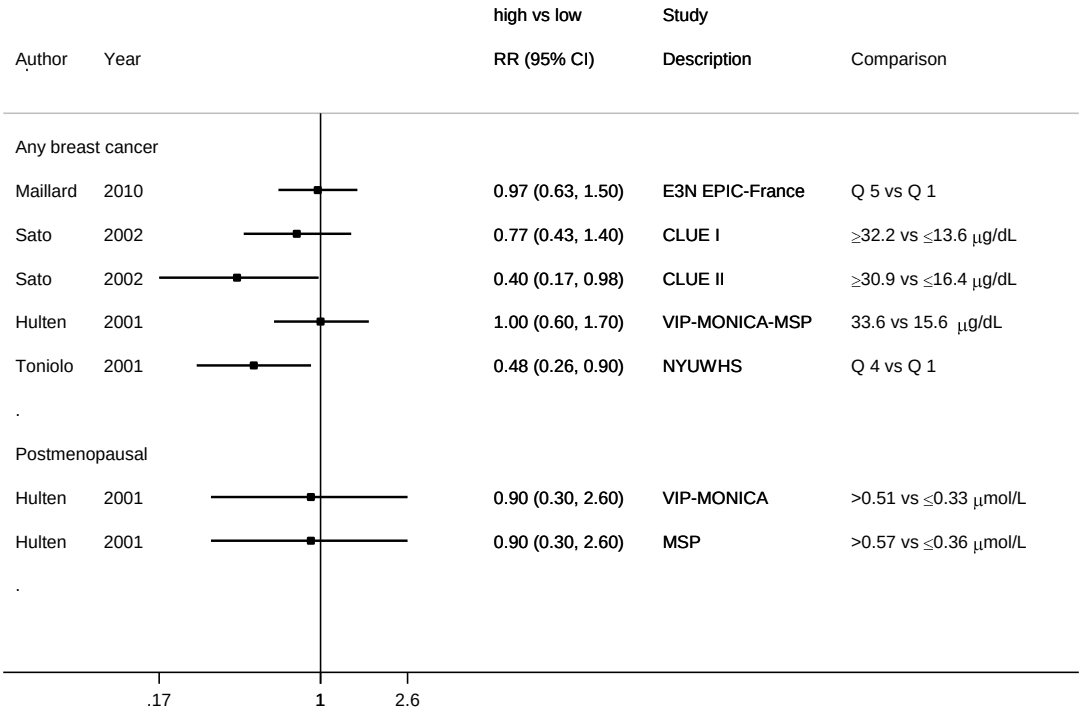


Figure 418 Relative risk of breast cancer (any) for 25 µg/dl increase of circulating lutein concentration

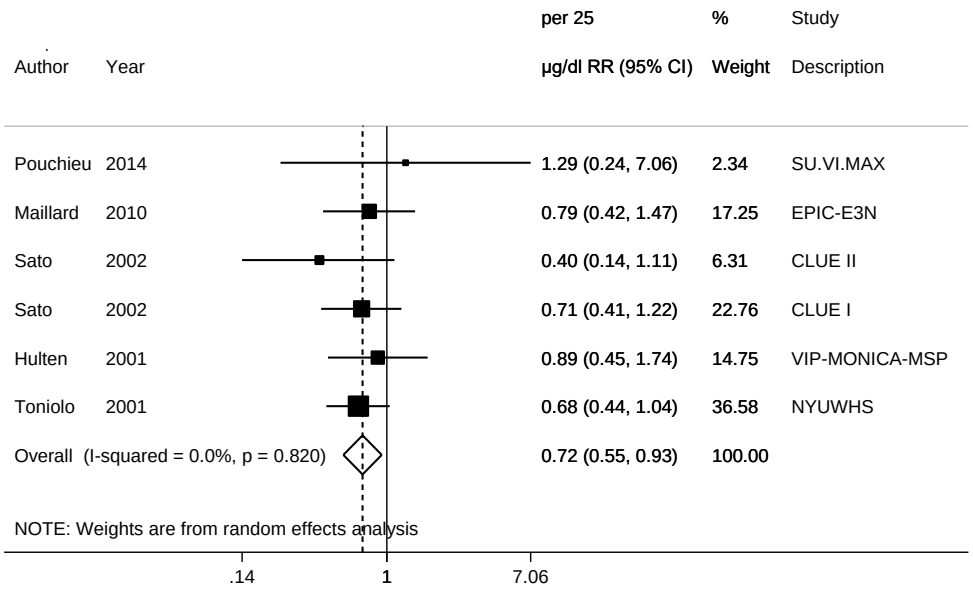


Figure 419 Funnel plot of studies included in the dose response meta-analysis of circulating lutein concentration and breast cancer (any) risk

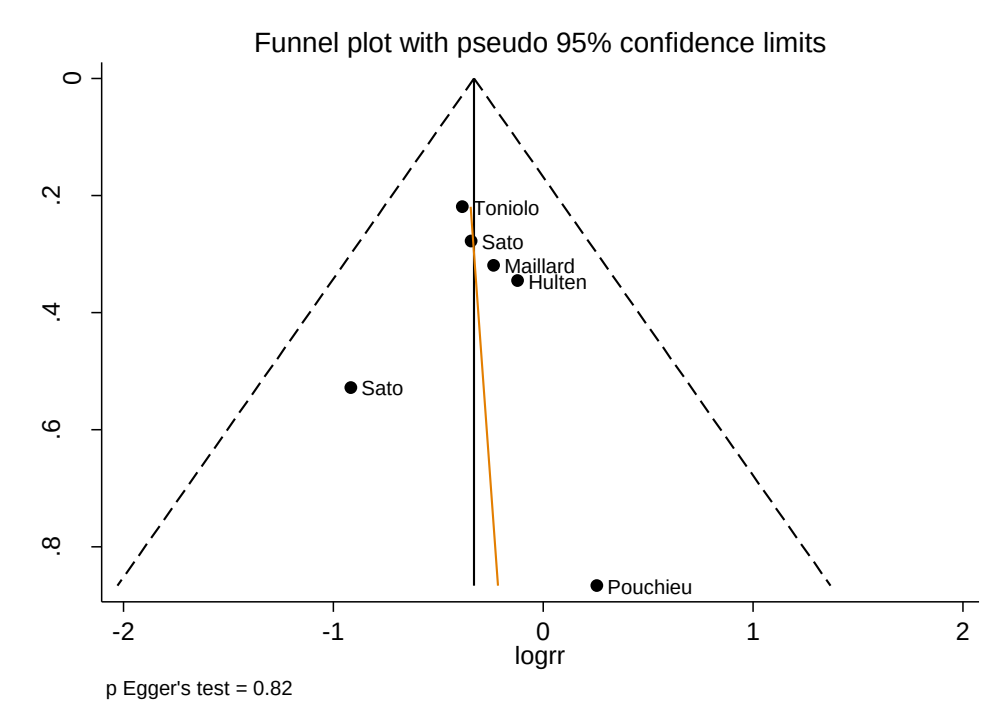
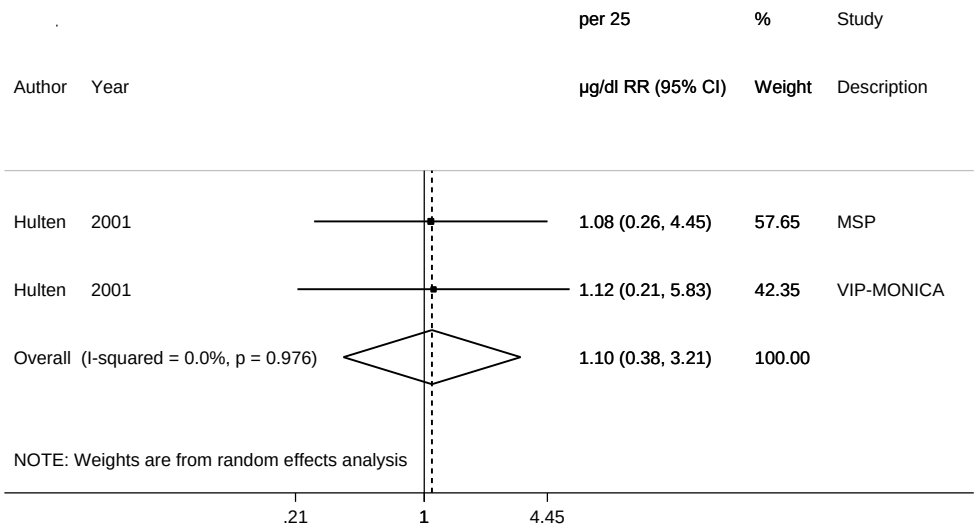


Figure 420 Relative risk of postmenopausal breast cancer for 25 µg/dl increase of circulating lutein concentration



5.5.2.3 Circulating lycopene

Breast cancer (any)

The pooled analysis of eight prospective cohorts (Columbia, MO; Umeå; CLUE I and II; NHS; WHS; NYUWHS; SWHS; MEC) (Eliassen, 2012) and two French cohorts (Pouchieu, 2014, SU.VI.MAX; Maillard, 2010, E3N cohort) were identified and included in the dose-response meta-analysis. Overall, a non-significant inverse association was observed (summary RR for 25 μg/dL=0.90, 95% CI=0.70-1.16), with moderate heterogeneity (I^2=39%, Pheterogeneity=0.19). All other publications were superseded by the pooled analysis.

The EPIC study (Bakker, 2016) examined the association of plasma lycopene with breast cancer by ER status and age at diagnosis (less or more than 50 years). This study was published after the end date of search and was not included in the dose-response meta-analysis.

Hormone receptor status

No heterogeneity by ER status was observed in the pooled analysis (Eliassen, 2012). The RR for the highest vs the lowest quintile of lycopene was 0.83 (95% CI 0.60-1.15; ptrend=0.57) in ER-positive and 0.95 (95% CI 0.66-1.38; ptrend=0.63) in ER- negative.

In EPIC (Bakker, 2016), plasma lycopene was not associated with ER-negative breast cancer (RR for highest vs lowest concentrations=1.07, 95% CI=0.56-2.03, Ptrend=0.38) and ER-positive breast cancer (RR=0.90, 95% CI=0.55-1.48, Ptrend=0.61) (Pheterogeneity=0.26).

Premenopausal breast cancer

Four cohorts from three publications (Sisti, 2015; Dorjgochoo, 2009; Hulten, 2001) were identified and all were included in the dose-response meta-analysis. Circulating lycopene was non-significantly positively associated with premenopausal breast cancer (summary RR for 25 μg/dL=1.06, 95% CI=0.83-1.35), with no evidence of heterogeneity (I2=0%, Pheterogeneity=0.72).

Postmenopausal breast cancer

Seven cohorts from five publications (Sisti, 2015; Dorjgochoo, 2009; Epplein, 2009; Kabat, 2009; Hulten, 2001) were identified and were all included in the dose-response meta-analysis. Circulating lycopene was non-significantly inversely associated with postmenopausal breast cancer (summary RR for 25 μg/dL=0.96, 95% CI=0.73-1.28), with moderate heterogeneity (I^2=44%, Pheterogeneity=0.11).

The association remained not significant in influence analysis. There was no significant evidence of small study or publication bias (P Egger's test=0.21). Visual inspection of the funnel plot showed asymmetry, which may be driven by smaller studies with stronger positive associations (Hulten, 2001).

Table 331 Circulating lycopene and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	11 (16 publications)
Studies included in forest plot of highest compared with lowest intake	Breast cancer: 9 (2 publications) Premenopausal: 4 (3 publications) Postmenopausal: 9 (6 publications)
Studies included in linear dose-response meta-analysis	Breast cancer: 10 (3 publications) Premenopausal: 4 (3 publications) Postmenopausal: 7 (5 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 332 Circulating lycopene and breast cancer risk. Summary of the linear dose-response meta-analysis in the CUP

	Breast cancer (any)	**Premenopausal**	**Postmenopausal**
Increment unit used	25 µg/dL		
Studies (n)	10	4	7
Cases (total number)	3 506	776	1 280
RR (95%CI)	0.90 (0.70-1.16)	1.06 (0.83-1.35)	0.96 (0.73-1.28)
Heterogeneity (I^2, p-value)	39%, p=0.19	0%, p=0.72	44%, p=0.11
P value Egger test	-	-	0.21

Table 333 Circulating lycopene and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR

Author, Year	**Number of studies**	**Total number of cases**	**Studies country, area**	**Outcome**	**Comparison**	**RR (95%CI)**	**P trend**	**Heterogeneity (I^2, p value)**
Meta-analysis								
Aune et al, 2012	13	3 512	North America, Europe, Asia	Incidence, breast cancer	High vs low Per 25 µg/dL	0.90 (0.77-1.06) 0.88 (0.77-1.01)	- -	7% 20%

Table 334 Circulating lycopene and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Sisti, 2015 BRE80597 USA	NHS I and II, Nested Case Control, Age: 25-55 years, W, Premenopausal	535/ 1 179	Biennial follow-up questionnaires and medical records	Blood: participants collected follicular phase blood samples during days 3–5 of their menstrual cycle, and blood and urine samples during the luteal phase, 7–9 days before the anticipated start of their next cycle.	Incidence, breast cancer, premenopausal at diagnosis	≥55 vs ≤32.9 µg/dl	1.00 (0.70-1.42) Ptrend:0.65		Included, premenopausal breast cancer; midpoints of exposure quartiles
		489/			Postmenopausal at diagnosis		0.66 (0.45-0.96) Ptrend:0.02		Included, postmenopausal breast cancer; midpoints of exposure quartiles
		1 130/ 1130 controls					0.80 (0.62-1.02) Ptrend:0.14	Age at menarche, alcohol intake, BMI, family history of breast cancer, history of benign breast disease, matching variables, parity and age at first birth	Superseded by pooled analysis, Eliassen, 2012
		614/			ER+		0.76 (0.57-1.01) Ptrend:0.06		Not analysed
		150/			ER-		0.72 (0.44-1.19) Ptrend:0.44		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Pouchieu, 2014 BRE80565 France	SU.VI.MAX, Nested Case Control, Age: 49.8 years, W	100/ 100 controls 8 years	Self report verified by medical record	Plasma: HPLC	Incidence, breast cancer	per 0.1 µmol/l	1.04 (0.95-1.13)	Age, alcohol intake, BMI, dietary records, educational level, energy intake, family history of breast cancer, fat intake, fruits and vegetables consumption, height, HRT use, intervention group, menopausal status, number of children, physical activity, smoking status	Included, all breast cancer, RR rescaled for an increment used, units converted to µg/dl
		50/ 50 controls			Intervention group	per 0.1 µmol/l	1.16 (0.90-1.50)		
					Placebo-group	per 0.1 µmol/l	1.00 (0.89-1.13)		
Eliassen, 2012 China, Sweden, USA	Pooled analysis of 8 prospective studies*, Mean age ranged from 51.3-66.0 years, W *Columbia,	3,055 cases/ 3,956 controls		Plasma, recalibrated values, reverse-phase HPLC, median time between blood collection and diagnosis was	Incidence, breast cancer	≥45.0 vs <15.7 µg/dl	0.78 (0.62-0.99) Ptrend:0.02	Menopausal status, age at menopause, age at menarche, parous, age at first birth, exogenous hormone use, BMI, current	Included, all breast cancer; midpoints of exposure quintiles

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	MO; Umeå; CLUE I and II; NHS; WHS; NYUWHS; SWHS; MEC			4.3 years				smoking, race, personal history of benign breast disease, family history of breast cancer Matching factors included age at blood collection, date, time, and fasting status at blood collection, menopausal status, date of last menstrual period and/or phase and day of menstrual cycle (premenopausal women), PMH use, race or ethnicity, study centre, smoking status, follow-up time, availability of FFQ, use of antibiotics, number of blood collections within the cohort, diagnosis of benign breast	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								disease	
		1,481			ER+ breast cancer	Q5 vs Q1	0.83 (0.60-1.15) Ptrend:0.57		
		417			ER- breast cancer	Q5 vs Q1	0.72 (0.44-1.17) Ptrend:0.83		
Maillard, 2010 BRE80258 France	E3N EPIC-France, Nested Case Control, Age: 40-65 years, W	366/ 720 controls 7 years	Self report verified by medical record	Serum: HPLC	Incidence, breast cancer	Q5 vs Q1	0.95 (0.58-1.55) Ptrend:0.44	Age, age at first child birth, alcohol consumption, benign breast disease, blood collection centre, date of blood collection, educational level, family history of cancer, fasting condition, height, menopausal hormone use, menopausal status, parity	Included, all breast cancer; intakes estimated from mean and standard deviation, midpoints of exposure quantiles
					Alcohol <=10g/day		1.29 (0.61-2.72) Ptrend:0.93		
					Alcohol 10+ g/day		2.11 (0.59-7.49) Ptrend:0.47		
Dorjgochoo, 2009	SWHS, Nested Case	365/ 726 controls	Cancer registry	Plasma: reverse-phase HPLC	Incidence, breast cancer	Q5 vs Q1	0.83 (0.49-1.39) Ptrend:0.76	Age, age at first child birth, age	Superseded by pooled analysis,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
BRE80289 China	Control, Age: 40-70 years, W	7.5 person-years						at menarche, antioxidant intake, benign breast disease, educational level, energy intake, family history of cancer, fish, fruit intake, laboratory batch, menopausal status, occupation, physical activity, red meat intake, smoking status, tea intake, vegetable intake, waist-hip ratio	Eliassen, 2012
		184/ 358 controls			Premenopausal		0.66 (0.30-1.43) Ptrend:0.69		Included, premenopausal breast cancer; converted units, midpoints of exposure quintiles
		181/ 368 controls			postmenopausal		1.17 (0.54-2.51) Ptrend:0.85		Included, postmenopausal breast cancer; converted units,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
									midpoints of exposure quintiles
Epplein, 2009 BRE80236 USA	MEC, Nested Case Control, Age: 45-75 years, W, Postmenopausal	286/ 535 controls	Cancer registry	Plasma: HPLC with photodiode array detection	Incidence, breast cancer, postmenopausal	≥391.8 vs ≤218.7 ng/ml	0.88 (0.57-1.38) Ptrend:0.50	Age at first child birth, age at interview, age at menarche, age at menopause, alcohol consumption, BMI, date of blood collection, ethnicity, fasting condition, geographic area, HRT use, parity, year of birth	Included, postmenopausal breast cancer; converted units, midpoints of exposure quintiles
Kabat, 2009 BRE80250 USA	WHI - DM, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	190/ 5 450 8 years	Self report, medical record and pathology report reviewed by centrally trained physician	Serum: reverse-phase HPLC	Incidence, invasive & in situ breast cancer	≥0.47 vs ≤0.29 µg/ml	1.34 (0.92-1.94) Ptrend:0.12	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, benign breast disease, BMI, calcium intake, educational level, energy intake, ethnicity, family history of cancer, HRT use, OC use,	Included, postmenopausal breast cancer; converted units, midpoints of exposure quintiles

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								physical activity, randomized treatment assignment	
Hulten, 2001 BRE04155 Sweden	VIP-MONICA-MSP, Nested Case Control, W	201/ 390 controls	Partially histological - over 80%	Plasma: HPLC	Incidence, breast cancer	Q4 vs Q1	1.00 (0.60-1.80) Ptrend:0.54	BMI, total cholesterol, triglycerides, age at menarche, parity, age at first full-term pregnancy, use of hormone replacement therapy, menopausal status, cotinine (a marker of recent exposure to tobacco smoke), and hours of fasting	Superseded by pooled analysis, Eliassen, 2012
	VIP-MONICA	57/ 93 controls			Premenopausal	>0.37 vs ≤0.14 µmol/L	1.20 (0.30-4.80) Ptrend:0.85		Included, premenopausal breast cancer; converted units, midpoints of exposure quintiles
	VIP-MONICA	67/ 109 controls			Postmenopausal		2.40 (0.70-7.90) Ptrend:0.53		Included, postmenopausal breast cancer; converted units, midpoints of exposure quintiles
	MSP	67/ 127 controls			Postmenopausal	>0.40 vs ≤0.16 µmol/L	0.90 (0.30-2.60) Ptrend:0.73		

Table 335 Circulating lycopene and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Bakker, 2016 Europe	EPIC, Nested Case Control, Mean age: 50 years, W	636/ 632 controls	Linkage to population cancer registries in most countries, a combination of methods in some countries, including health insurance records, cancer and pathology registries, and active follow-up	Plasma, sum of carotenoids, HPLC	Incidence, invasive breast cancer, ER+	≥748.86 vs ≤108.91 nmol/l	0.90 (0.55-1.48) Ptrend:0.61	BMI, height, age at menarche, age at first full-term pregnancy, OC use, HRT use, smoking status, alcohol consumption, educational level, intake of saturated fatty acids, energy intake, season of blood collection Matching factors: study centre, age, menopausal status, use of exogenous hormones, phase of menstrual cycle, fasting status at blood collection, time of blood collection	Identified after end of search, analysis by tumour hormone receptor status was not conducted
		515/ 514 controls			ER-	≥742.08 vs ≤113.42 nmol/l	1.07 (0.56-2.03) Ptrend:0.38		
					ER+PR+	Q5 vs Q1	0.99 (0.49-2.01)		
					ER-PR-		1.26 (0.55-2.87)		
Eliassen, 2015 BRE80598 USA	NHS, Nested Case Control, Age: 43-67 years, W	2 147/ 2146 controls 20 years	Biennial follow-up questionnaires and medical records	Blood: first sample collected 1989-1990 second sample collected 2000-2002	Incidence, breast cancer	≥563 vs ≤287.9 µg/dl	0.82 (0.67-1.01) Ptrend:0.02	Age at first child birth, age at menarche, age at menopause, alcohol intake, BMI at age 18 years, family history of breast cancer, history of benign breast disease,	Superseded by pooled analysis, Eliassen, 2012

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								matching variables, parity	
		1 313/			Incidence, breast cancer ER+	≥563 vs ≤287.9 µg/dl	0.80 (0.64-1.01) Ptrend:0.02		Not analysed
		291/			Incidence, breast cancer ER-	≥563 vs ≤287.9 µg/dl	1.09 (0.74-1.62) Ptrend:0.92		
		350/			Incidence, well differentiated breast cancer	≥563 vs ≤287.9 µg/dl	0.56 (0.38-0.83) Ptrend:0.002		
		595/			Incidence, moderate differentiated breast cancer	≥563 vs ≤287.9 µg/dl	0.90 (0.67-1.22) Ptrend:0.26		
		371/			Incidence, poorly differentiated breast cancer	≥563 vs ≤287.9 µg/dl	1.00 (0.70-1.41) Ptrend:0.91		
		645/			Incidence, luminal a breast cancer	≥563 vs ≤287.9 µg/dl	0.75 (0.56-1.01) Ptrend:0.02		
		216/			Incidence, luminal b breast cancer	≥563 vs ≤287.9 µg/dl	0.79 (0.50-1.26) Ptrend:0.31		
		107/			Incidence, triple negative breast cancer	≥563 vs ≤287.9 µg/dl	1.36 (0.75-2.44) Ptrend:0.27		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		1 848/			Incidence, nonrecurrent and nonlethal breast cancer	≥563 vs ≤287.9 µg/dl	0.87 (0.71-1.07) Ptrend:0.08		
		299/			Incidence, recurrent or lethal breast cancer	≥563 vs ≤287.9 µg/dl	0.78 (0.53-1.16) Ptrend:0.11		
		1 118/ 1206 controls			Incidence, breast cancer, BMI <25	≥563 vs ≤287.9 µg/dl	0.72 (0.55-0.94) Ptrend:0.006		
		696/ 640 controls			BMI 25- <30	≥563 vs ≤287.9 µg/dl	1.15 (0.80-1.65) Ptrend:0.56		
		332/ 299 controls			BMI >=30	≥563 vs ≤287.9 µg/dl	1.14 (0.66-1.97) Ptrend:0.64		
		1 876/ 1923 controls			Nonsmokers	≥563 vs ≤287.9 µg/dl	0.91 (0.74-1.11) Ptrend:0.15		
		271/ 223 controls			Current smokers	≥563 vs ≤287.9 µg/dl	0.60 (0.33-1.11) Ptrend:0.12		
		1 823/ 1822 controls			Follow up <10 years	≥563 vs ≤287.9 µg/dl	0.86 (0.70-1.05) Ptrend:0.19		
		893/ 898 controls			Follow up >=10 years	≥563 vs ≤287.9 µg/dl	0.69 (0.50-0.94) Ptrend:0.01		
Tamimi, 2009 BRE80276 USA	NHS, Nested Case Control, W, Postmenopausal	604/ 626 controls 9 years	Self report verified by medical record	Plasma: reverse-phase HPLC	Incidence, breast cancer	Q 5 vs Q1	1.00 (0.70-1.40) Ptrend:0.56	Age, age at first child birth, alcohol, benign breast disease, BMI, family history of cancer, parity,	Superseded by pooled analysis, Eliassen, 2012

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								postmenopausal hormone use	
							0.80 (0.60-1.20) Ptrend:0.26	Mammographic density	
Sesso, 2005 BRE24061 USA	WHS, Nested Case Control, W, Health professionals	480 7 years	Medical records + self-reported	Plasma: reverse-phase HPLC	Incidence, breast cancer	≥13.1 vs ≤7.2 g/dl	0.93 (0.56-1.52) Ptrend:0.86	Age at first child, age at menarche, alcohol, biomarkers, BMI, design , design , design , family history, HRT use, menopausal status, nutrients, nutrients, nutrients, nutrients, OC use, parity/pregnancies, physical activity	Superseded by pooled analysis, Eliassen, 2012
		344/ 344 controls			Incidence, breast cancer ER+/PR+	≥13.1 vs ≤7.2 g/dl	0.90 (0.47-1.71) Ptrend:0.8		
Tamimi, 2005 BRE24274 USA	NHS, Nested Case Control, Age: 43-70 years, W, Registered nurses	325 22 years	All morphology (histology or cytology)	Plasma: reverse-phase HPLC	Incidence, invasive & in situ breast cancer	Q5 vs Q1	1.01 (0.73-1.39) Ptrend:0.53	Age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, family history, fasting condition, HRT use, laboratory variables , other anthropometric index	Superseded by pooled analysis, Eliassen, 2012
Tamimi, 2004 BRE12084 USA	NHS, Nested Case Control,	254/ 235 controls 8 years	Partially histological - over 80%	Plasma: reverse-phase HPLC	Incidence, breast cancer, Val/Val	Q3 vs ≥Q1	1.22 (0.77-1.92)	Age at first child, age at menarche, age at menopause, alcohol,	Superseded by pooled analysis, Eliassen, 2012

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 30-55 years, W, Registered nurses				(MnSOD)			benign breast disease, BMI, body weight, duration of HRT use, family history, parity/pregnancies, smoking habits	
Sato, 2002 BRE20839 USA	CLUE I, Nested Case Control, Age: 51 years, W, blood donors	244/ 244 controls 20 years	Partially histological - over 80%	Serum: reverse-phase HPLC	Incidence, breast cancer	≥49.3 vs ≤20 µg/dl	0.55 (0.29-1.06) Ptrend:0.04	Matched on age (within 1 year), race, menopausal status, and month and year of blood donation; premenopausal women were also matched on date of last menstrual cycle	Superseded by pooled analysis, Eliassen, 2012
	CLUE II, Nested Case Control, Age: 60 years, W, blood donors	115/ 115 controls 3 years	Partially histological - over 80%		Incidence, breast cancer	≥49.1 vs ≤23.6 µg/dl	0.80 (0.34-1.85) Ptrend:0.57		Superseded by pooled analysis, Eliassen, 2012
Toniolo, 2001 BRE12399 USA	NYUWHS, Nested Case Control, Age: 35-65 years, W	14 275	Partially histological - over 80%	Serum: HPLC, Steghens et al. method	Incidence, breast cancer	Q 4 vs Q 1	1.00 Ptrend:0.15	Age at first child, benign breast disease, biomarkers, family history	Superseded by pooled analysis, Eliassen, 2012
Dorgan, 1998 BRE14889 USA	Columbia, MO cohort, Nested Case Control, Age: 41-73 years, W	105/ 209 controls 9.5 years	All histology	Serum	Incidence, invasive breast cancer	0.51-1.75 vs ≤0.22 µmol/l	0.50 (0.20-1.20) Ptrend:0.02	Biomarkers, BMI, smoking habits	Superseded by pooled analysis, Eliassen, 2012

Figure 421 RR estimates of breast cancer by levels of circulating lycopene concentration

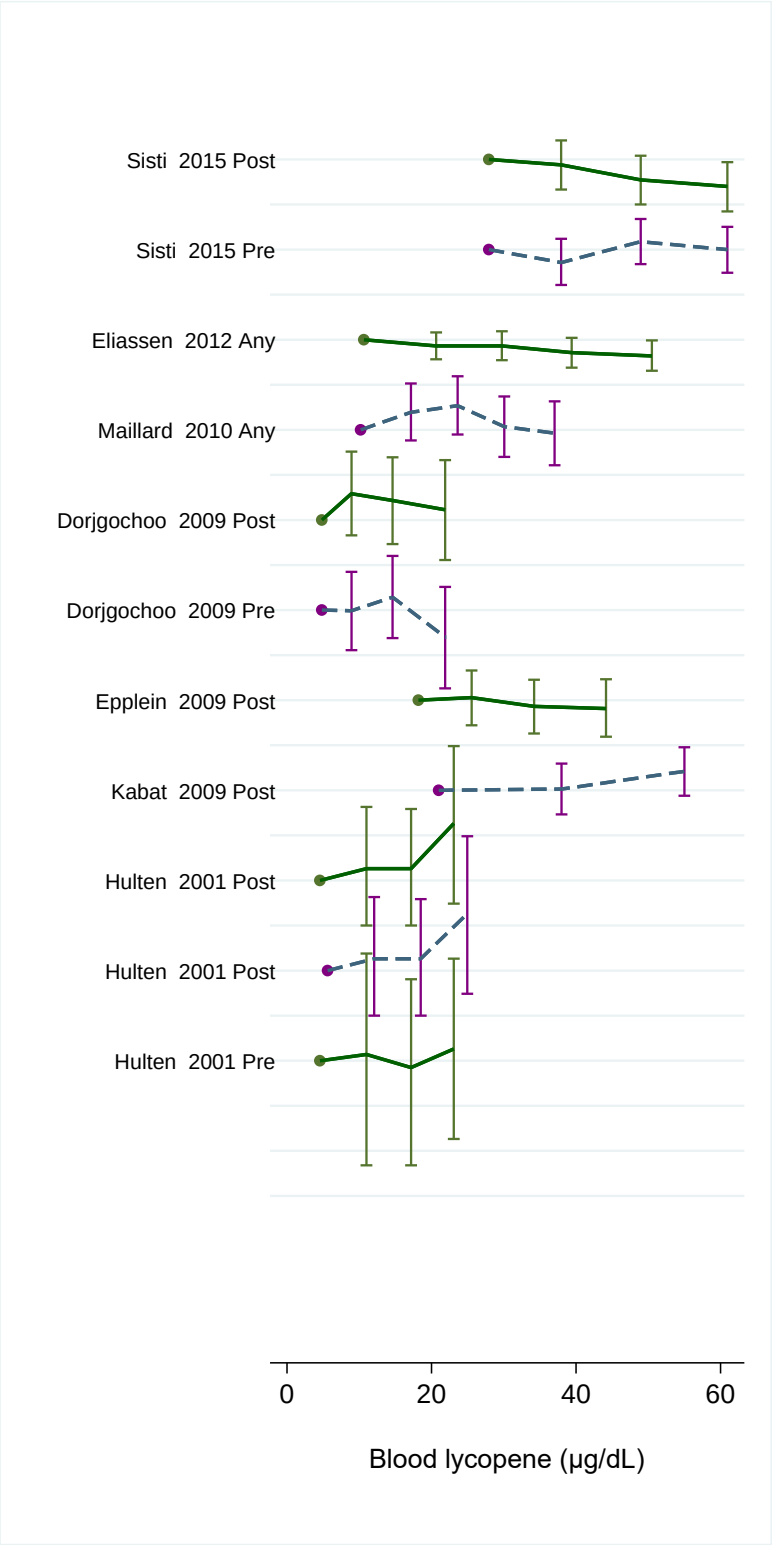


Figure 422 RR (95% CI) of breast cancer for the highest compared with the lowest level of circulating lycopene concentration

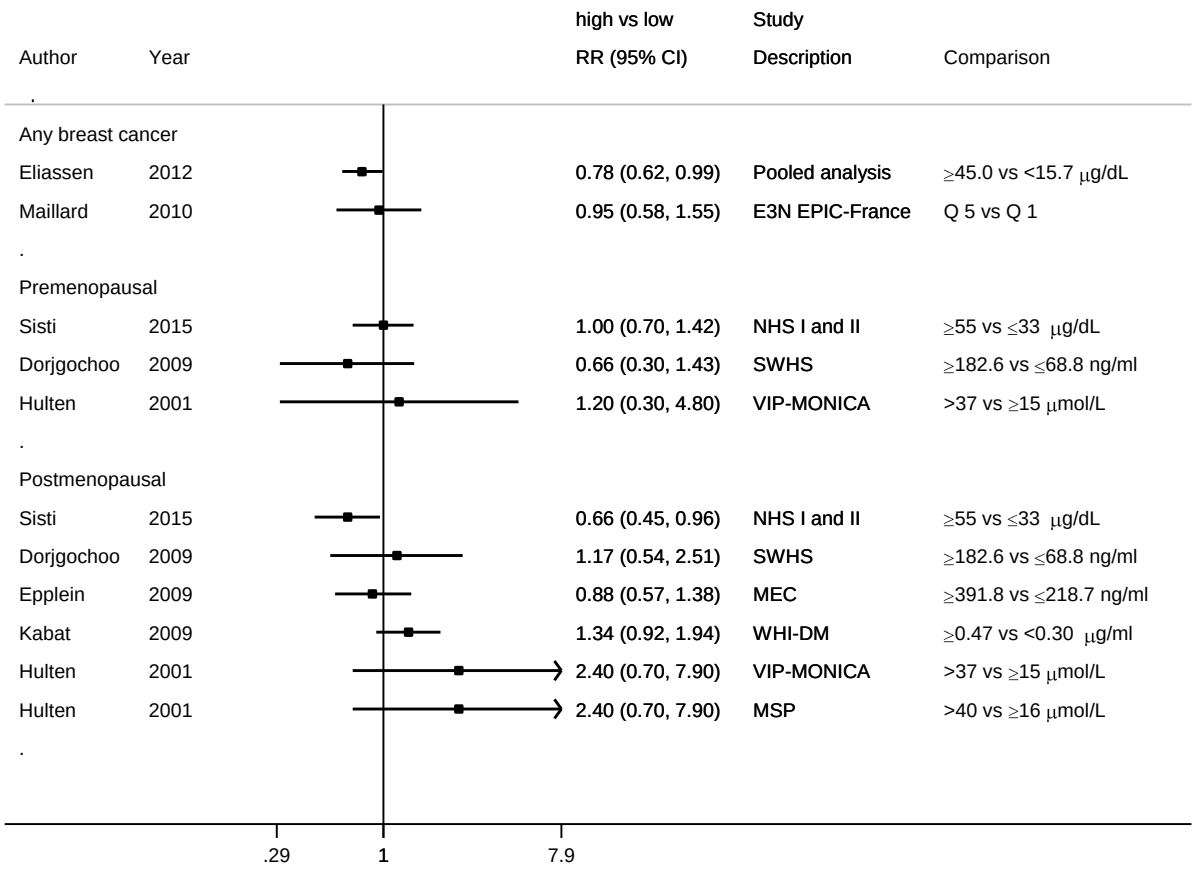


Figure 423 Relative risk of breast cancer (any) for 25 µg/dl increase of circulating lycopene concentration

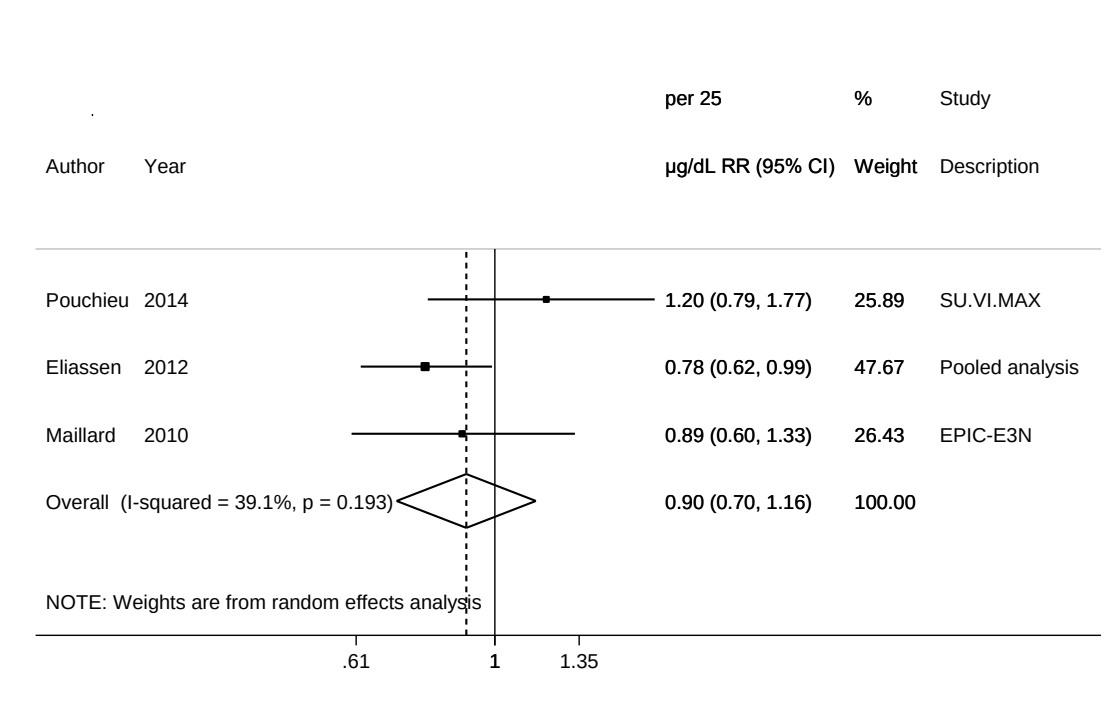


Figure 424 Relative risk of premenopausal breast cancer for 25 µg/dl increase of circulating lycopene concentration

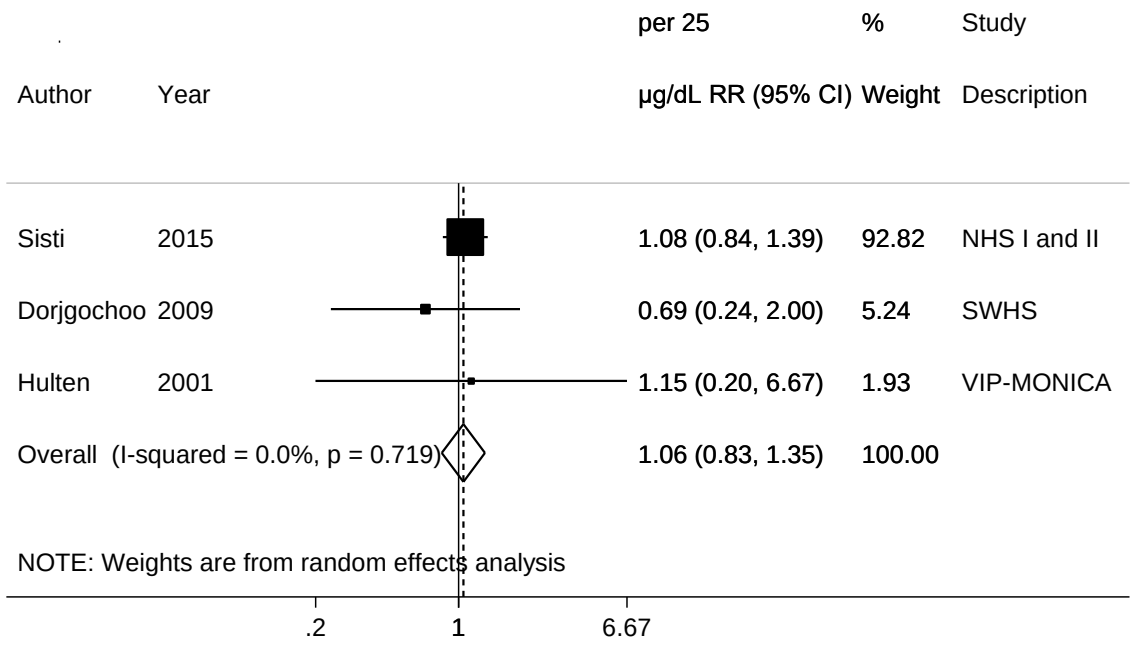


Figure 425 Relative risk of postmenopausal breast cancer for 25 µg/dl increase of circulating lycopene concentration

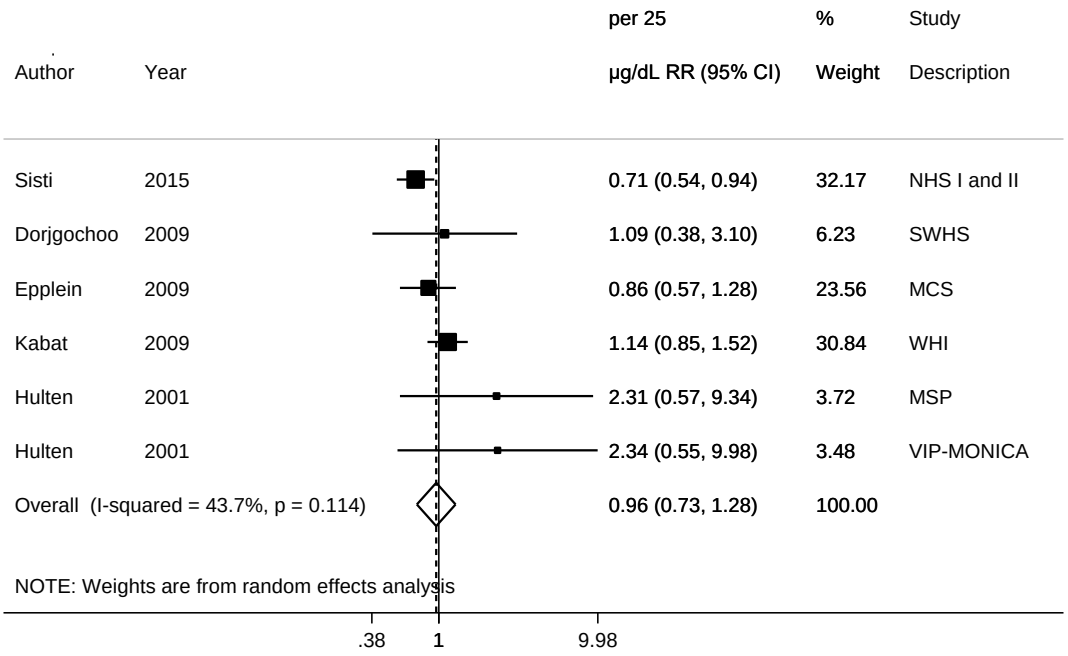
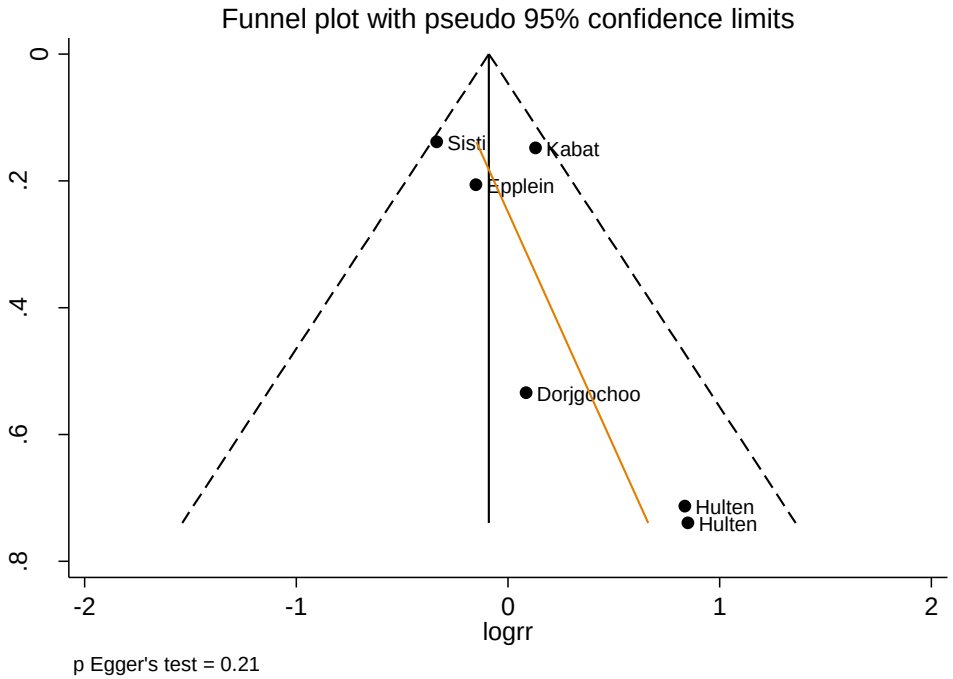


Figure 426 Funnel plot of studies included in the dose response meta-analysis of circulating lycopene concentration and postmenopausal breast cancer



5.5.3 Folates and associated compounds

5.5.3.1 Total folate

Overall summary

18 publications from 17 studies were identified, including one publication of pooled study on breast cancer incidence (Jung, 2015, 13 cohorts). Dose-response meta-analyses were conducted to examine the association of total folate with risk of breast cancer and postmenopausal breast cancer.

The Pooling Project of Prospective Studies on Diet and Cancer was published after the end of the search for this review but was considered for inclusion in the dose-response meta-analysis (Jung, 2015).

Breast cancer (any)

Summary

Main results:

Three studies (6 094 cases) (3 publications) were included in the dose-response meta-analysis. Total folate intake was not associated with breast cancer (any) risk.

Three publications were excluded from the dose-response meta-analysis. The Pooling Project (Jung, 2015) was excluded because of insufficient data for the dose-response meta-analysis. Pooling Project reported no association between total folate intake and risk of breast cancer (any) and types of breast cancer by hormone receptor status. Zhang, 2005 publications from NHS II cohort which was included in the Pooling Project, reported similar results for breast cancer risk by hormone receptor status, apart from significant inverse association with ER- (985 cases) breast cancer. Larsson, 2008 investigated only two categories of folate intake and was excluded from the meta-analysis. In this study, total folate intake was associated with non-significant positive and inverse risk with invasive breast cancer and ER+/PR- breast cancer, respectively.

Influence and stratified analyses were not conducted as the number of studies was low.

Combined effect of folate and alcohol intake:

In the NHS I, significant interaction between folate and alcohol was reported (Zhang, 1999c). Highest intake of folate (≤ 600 μg/day) was associated with significantly lower risk of breast cancer for alcohol intake of ≥ 15 g/day (Zhang, 1999c). However, WHI-OS and the Pooling Project of 13 studies, including the NHS I, reported no significant interaction between alcohol and folate (Duffy, 2009).

Study quality:

All studies reported assessment of total folate intake by FFQ. Case ascertainment was mainly through self-report verified by medical records.

Table 336 Total folate and breast cancer (any) risk. Number of studies in the CUP SLR

	Number
Studies identified	14 (6 publications)
Studies included in forest plot of highest compared with lowest exposure	3 (3 publications)
Studies included in linear dose-response meta-analysis	3 (3 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 337 Total folate and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	-	100 μg/day
Studies (n)	-	3
Cases	-	6 094
RR (95%CI)	-	1.01 (0.96-1.06)
Heterogeneity (I^2, p-value)	-	70%, 0.04

Table 338 Total folate intake and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	I^2
Meta-analysis							
Chen, 2014	11 prospective studies	24 168	USA, Europe, Asia	Breast cancer (female)	Highest vs lowest category	0.97 (0.87-1.08)	67%
	2			ER+		0.99 (0.89-1.11)	0%
	3			ER-		0.86 (0.72-1.02)	0%
Zhang, 2014*	14 prospective studies		USA, Europe, Asia	Breast cancer	Per 100 μg/day increment	0.99 (0.98-1.01)	66%
					Highest vs lowest category	0.97 (0.90-1.05)	56%

*****Includes studies on dietary and total folate and in pre- , postmenopausal or any breast cancer.

Table 339 Total folate and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Duffy, 2009 BRE80288 USA	WHI-OS, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	1 783/ 88 530 5.5 years	Self-report verified by medical records	FFQ	Incidence, breast cancer	per 1 µg/day	1.00 (1.00-1.001)	Age at menarche, age at menopause, BMI, breast biopsies, breastfeeding, educational level, ethnicity, family history, HRT use, income, parity/pregnancies, smoking status	RR rescaled for an increment of 100 µg/day
		1 599/				>642 vs 0-227.6 µg/day	0.97 (0.84-1.12)		
		132 vs 144/				0-227.6 µg/day folate and ≥15 g/day alcohol vs 0-227.6 µg/day folate and no alcohol	1.12 (0.97-1.03)	Smoking, BMI, history of breast biopsy, number of pregnancies, ever breast fed, family history, previous HRT use, age at menarche, age at menopause, weekly METs	
		70 vs 144/				≥642.7 µg/day folate and ≥15 g/day alcohol vs 0-227.6 µg/day folate and no alcohol	1.09 (0.88-1.14)		
Lin, 2008 BRE80186 USA	WHS, Nested Case Control, Age: 45- years	828/ 1653 cases and controls 11 years	Self-report verified by medical records	FFQ	Incidence, breast cancer	>582 vs ≤263.9 µg/day	1.24 (0.88-1.76) Ptrend:0.03	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, benign breast disease, BMI, date of blood collection, ethnicity, family history of cancer, fasting condition, menopausal status, parity,	Mid-points of exposure categories

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								physical activity, postmenopausal hormone use, randomization group, randomized treatment assignment, smoking habits	
Zhang, 1999c BRE13954 USA	NHS I, Prospective Cohort, Age: 30-55 years, W, Registered nurses	3 483/ 88 818 16 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer	≥600 vs 150-299.9	0.91 (0.82-1.01) Ptrend:.11	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, energy Intake , family history, height, HRT use, length of follow-up, parity/ pregnancies	Reference category changed using Hamling's method, mid-points of intake quantiles
		2 953/			<15 g/day ethanol		0.98 (0.88-1.10) $P_{interaction}$:0.02	Age , age at first child, age at menarche, age at menopause, benign breast disease, BMI, body weight, energy intake , family history, height, HRT use, length of follow-up, parity/pregnancies	
		530/			≥15 g/day ethanol		0.55 (0.39-0.76) $P_{interaction}$:0.02		

Table 340 Total folate and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Jung, 2015 North America, Europe, Asia, Australia	12 cohorts: BCDDP CTS CPS II CLUE II IWHS* MEC NYUWHS NIH-AARP* NHS (a) NHS (b) NHS II PLCO* WHS	28 523, 6 to 18 years maximum follow-up	Variable in each cohort	Questionnaires	Incidence, breast cancer	≥15 g/day vs non-drinkers of all alcohol	0.98 (0.94-1.02)	Age, energy intake, ethnicity, education, BMI, height, physical activity, smoking status, age at menarche, menopausal status and HRT, parity and age at first birth, oral contraceptive use, family history of breast cancer, personal history of benign breast disease, alcohol consumption	Excluded, intake ranges for quantiles are not available, used in the highest vs lowest analysis
		17 212			ER+		1.00 (0.95-1.05)		
		3 887			ER-		0.98 (0.87-1.11)		
		14 165			PR+		0.98 (0.93-1.04)		
		6 149			PR-		1.01 (0.93-1.09)		
		13 607			ER+PR+	Q5 vs Q1	0.99 (0.94-1.05)		
		2 805			ER+PR-		1.00 (0.86-1.15)		
		3 262			ER-PR-		1.01 (0.90-1.15)		
	8 cohorts: BCDDP CTS CPS II	435			ER-PR+		0.85 (0.62-1.16)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	IWHS* MEC NIH-AARP* NHS (a) NHS (b) NHS II								
	13 cohorts: BCDDP CTS CPS II CLUE II IWHS* MEC NLCS* NYUWHS NIH-AARP* NHS (a) NHS (b) NHS II PLCO* WHS	2 184			Total breast cancer	<200 µg/day folate µg/day folate, per 10 g/day alcohol increment	1.12 (1.07-1.16) $P_{interaction}$:0.60		
		11 217				200-<400 µg/day folate, per 10 g/day alcohol increment	1.08 (1.06-1.10) $P_{interaction}$:0.60		
		4 825				400-<600 µg/day folate, per 10 g/day alcohol increment	1.08 (1.05-1.12) $P_{interaction}$:0.60		
		9 025				≥600 µg/day folate, per 10 g/day alcohol increment	1.08 (1.06-1.11) $P_{interaction}$:0.60		
Larsson, 2008 BRE80208 Sweden	SMC, Prospective Cohort, Age: 54 years, W	1 008/ 61 433 17.4 years	Cancer registry	FFQ	Incidence, invasive breast cancer	552 vs 192 µg/day	1.06 (0.87-1.28)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, benign breast disease, BMI, educational level, energy Intake, family history of	Excluded, only two levels of exposure, used in the highest vs lowest analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								cancer, height, parity, postmenopausal hormone use, use of oral contraception	
					Incidence, breast cancer ER+/PR-		0.78 (0.53-1.15)		
Zhang, 2005 BRE24752 USA	NHS I, Prospective Cohort, Age: 30-55 years, W, Registered nurses	2 812/ 88 744 20 years	Medical record + pathology report	FFQ-semi-quantitative	ER+	≥534 vs ≤228 µg/day	1.00 (0.89-1.14) Ptrend:0.83	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, duration of HRT use, energy Intake , family history, height, length of follow-up, menopausal status, other anthropometric Index, parity/ pregnancies	Excluded, analysis by hormone receptor status was not conducted, superseded by Jung, 2015 Pooling Project
		2 256/			PR+		0.95 (0.83-1.09) Ptrend:0.24		
		1 361/			PR-		0.97 (0.82-1.16) Ptrend:0.79		
		985/			ER-		0.81 (0.66-0.99) Ptrend:0.03		

*Studies in postmenopausal women only.

Figure 427 RR estimates of breast cancer (any) by levels of total folate intake

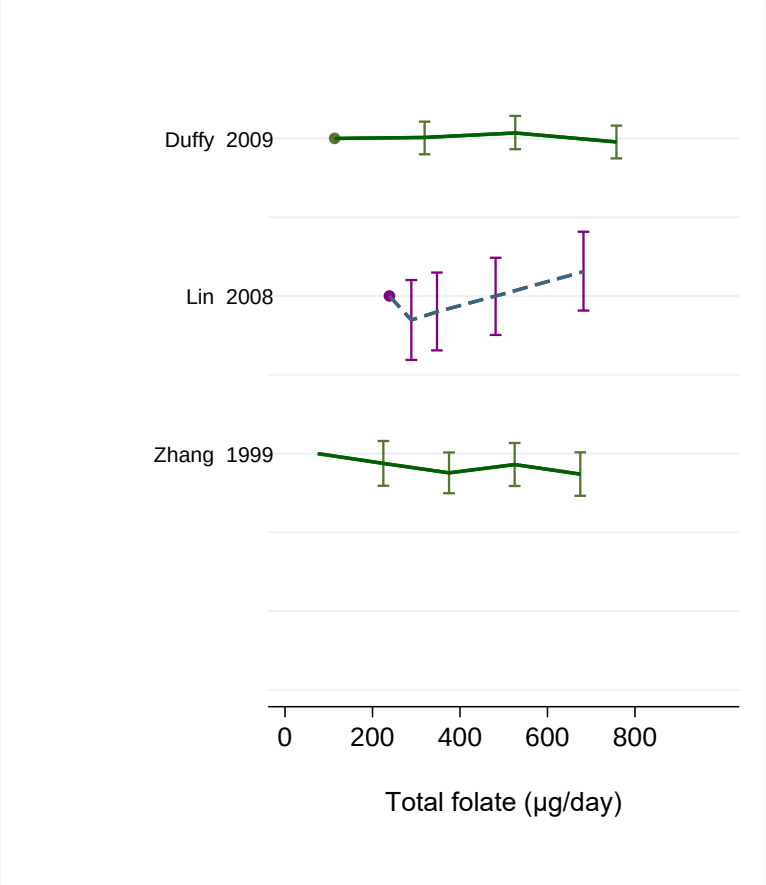


Figure 428 RR (95% CI) of breast cancer (any) for the highest compared with the lowest level of total folate intake

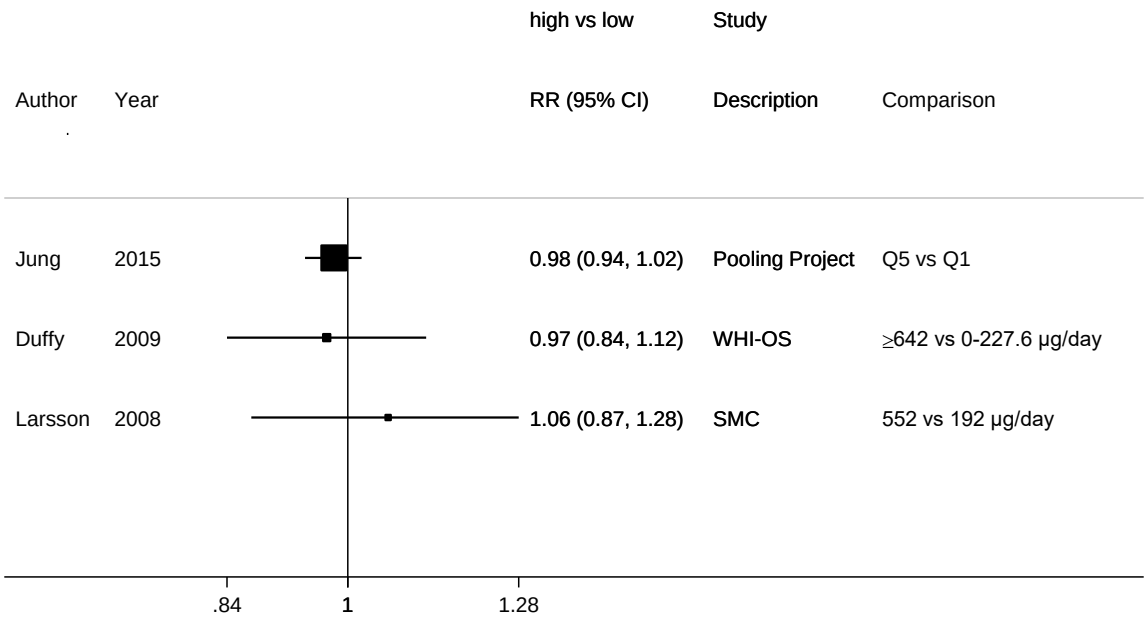
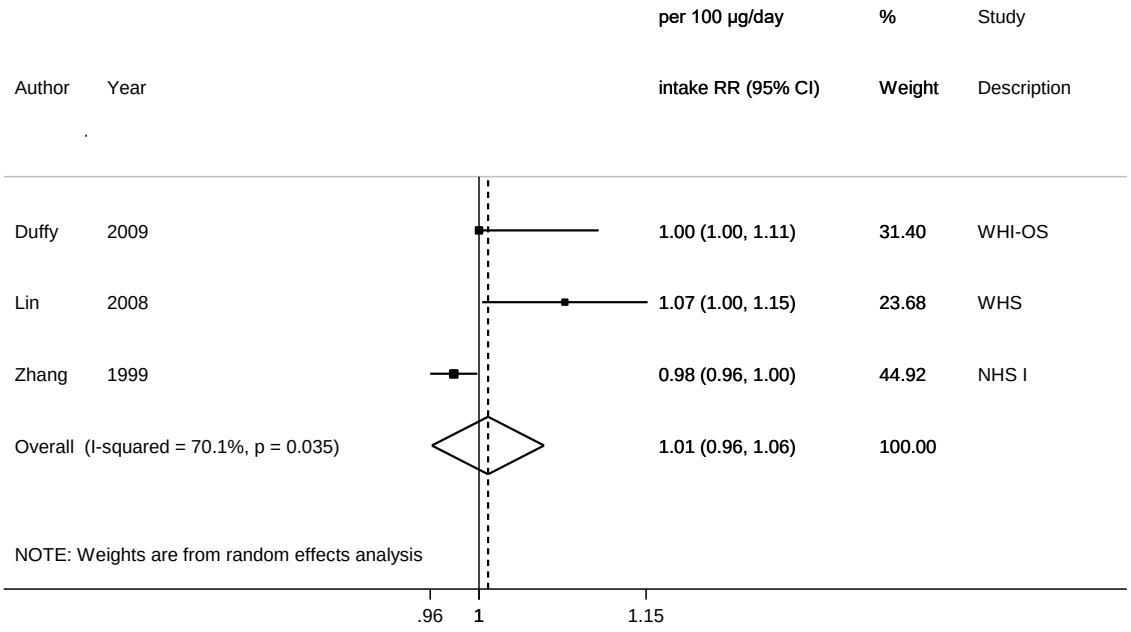


Figure 429 Relative risk of breast cancer for 100 µg/day increase of total folate intake



Premenopausal breast cancer

Summary

Main results:

Only two publications from NHS II study reported on total folate intake and breast cancer (any) risk. In both publications, total folate intake was positively but not significantly associated with invasive breast cancer. Similar association was reported for ER-breast cancer (Cho, 2007).

Table 341 Total folate and premenopausal breast cancer risk. Main characteristics of studies identified

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Cho, 2007 BRE80152 USA	NHS II, Prospective Cohort, Age: 26-46 years, W, Premenopausal	1 032/ 90 663 12 years	Self-report verified by medical record	Semi-quantitative FFQ	Incidence, invasive breast cancer, premenopausal	822 vs 237 µg/day	1.09 (0.88-1.34) Ptrend:0.31	Age, age at first child birth, age at menarche, alcohol Intake, animal fat Intake, benign breast disease, BMI, calendar year, energy Intake, family history of cancer, oral contraceptive use, parity, smoking habits	
		221/			ER-		1.08 (0.70-1.66) Ptrend:0.85		
Cho, 2003c BRE01652 USA	NHS II, Prospective Cohort, Age: 26-46 years, W, Registered nurses	714/ 90 655 8 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, invasive breast cancer, premenopausal	826 vs 228 µg/day	1.03 (0.81-1.32) Ptrend:0.96	Age at first child, age at menarche, alcohol, benign breast disease, BMI, family history, height, menopausal status, nutrients, oral contraceptive use, parity/pregnancies, residual (willet), smoking habits	Superseded by Cho, 2007

Postmenopausal breast cancer

Summary

Main results:

Five studies (7 639cases) (5 publications) were included in the dose-response meta-analysis. Total folate intake was not associated with postmenopausal breast cancer risk.

Two studies were excluded from the dose-response meta-analysis (Maruti, 2009, Mattison, 2004). Mattison, 2004 reported no risk estimates and Maruti, 2009 reported significant inverse association for postmenopausal and ER- but not ER+ breast cancer.

One included study reported results by hormone receptor status (Roswall, 2010). No association was found between total folate intake and postmenopausal ER+PR+, ER-PR-, ER+PR-, and ER-PR+ breast cancers.

Sensitivity and stratified analyses:

In influence analysis, the summary relative risk changed from 0.98 (95% CI, 0.92-1.03) when Stevens, 2010 was excluded to 1.00 (0.98-1.03) when Ericson, 2007 was excluded.

Combined effect of folate and alcohol intake:

Two studies reported risk estimates for combined effect of folate and alcohol (Stolzenberg-Solomon, 2006, Sellers, 2001). High alcohol and low folate intake was associated with significantly higher risk but high alcohol intake and high folate intake was associated with non-significantly higher risk of postmenopausal breast cancer risk in both studies. Roswall, 2010 reported no interaction between total folate and alcohol intake.

Study quality:

All studies reported assessment of total folate intake by FFQ apart from one study where a combination of 7-day food records, questionnaire and an interview was used (Ericson, 2007). Case ascertainment was mainly through self-report verified by medical records cancer and state registries, death certificates.

Table 342 Total folate and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	6 (10 publications)
Studies included in forest plot of highest compared with lowest exposure	6 (6 publications)
Studies included in linear dose-response meta-analysis	5 (5 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 343 Total folate and postmenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	-	100 µg/day
Studies (n)	-	5
Cases	-	7 639
RR (95%CI)	-	1.00 (0.97-1.03)
Heterogeneity (I^2, p-value)	-	70%, 0.01
P value Egger test	-	0.44
Stratified analyses in CUP SLR		
Geographic area	**Europe**	**North America**
Studies (n)	2	3
RR (95%CI)	0.92 (0.76-1.11)	1.00 (0.97-1.04)
Heterogeneity (I^2, p-value)	83%, 0.02	72%, 0.03
Adjustment for age, BMI, alcohol and reproductive factors	**Adjusted**	**Not adjusted***
Studies (n)	3	2
RR (95%CI)	1.00 (0.98-1.02)	0.93 (0.75-1.17)
Heterogeneity (I^2, p-value)	34%, 0.22	87%, 0.01

***One study was unadjusted for reproductive factors (Ericson, 2007) and one for alcohol (Stolzenberg-Solomon, 2006).

Table 344 Total folate intake and postmenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	I^2
Meta-analysis							
Chen, 2014	7 prospective studies		USA, Europe	Breast cancer (female)	Highest vs lowest category	1.00 (0.88-1.14)	63%

Table 345 Total folate and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Roswall, 2010 BRE80338 Denmark	DCH, Prospective Cohort, Age: 50-64 years, Postmenopausal	1 072/ 26 224 10.6 years	Cancer registry	FFQ	Incidence, breast cancer, postmenopausal	>463.9 vs 0-288.2 µg/day	1.23 (0.97-1.56) Ptrend:0.95	Age at first child birth, alcohol, beta-carotene Intake, BMI, educational level, hormone replacement therapy, HRT use, number of childbirths, parity, vitamin c (diet), vitamin c supplement, vitamin e Intake	
						per 100 µg/day	1.00 (0.97-1.03)		None
		269			ER+/PR+		1.01 (0.97-1.05)		
		103/			ER-/PR-		1.01 (0.95-1.07)		
		87/			ER+/PR-		0.85 (0.67-1.08)		
		8/			ER-/PR+		1.03 (0.93-1.13)		
Stevens,	CPS II,	3 898/	Self-report	FFQ	Incidence,	≥918.9 vs <192.2	1.03 (0.93-1.15)	Age, age at first child	Mid-points of

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
2010 BRE80299 USA	Prospective Cohort, Age: 50-74 years, W, Postmenopausal	70 656 13 years	verified by medical records		breast cancer, postmenopausal	µg/day	Ptrend:0.97	birth, age at menarche, age at menopause, alcohol consumption, BMI, breast diseases , educational level, energy Intake, family history of cancer, HRT use, parity, physical activity, race	exposure categories
Ericson, 2007 BRE80128 Sweden	MDCS, Prospective Cohort, Age: 50- years, Postmenopausal	392/ 11 699 9.5 years	Cancer registry	Dietary history questionnaire, interview	Incidence, invasive breast cancer postmenopausal ≥50 years	456 vs 160 µg/day	0.56 (0.34-0.91) Ptrend:0.006	Age, age at menopause, alcohol Intake, body weight, height, household physical activity, HRT use, leisure time physical activity, season of year, smoking habits, socio-economic status, temp, total energy Intake, vitamin b12 Intake, vitamin b6 Intake, vitamins	None
Stolzenberg -Solomon, 2006 BRE80113 USA	PLCO, Prospective Cohort, Age: 55-74 years, W, Postmenopausal	691/ 31 411 4.94 years	Self-report in the annual mail-in survey, state cancer registries, death certificates, physician reports, and (for deceased persons) reports from the next of kin	FFQ	Incidence, breast cancer, postmenopausal	>853 vs ≤335.5 µg/day	1.32 (1.04-1.68) Ptrend:0.03	Age , BMI, educational level, energy intake, HRT use, mammography screening history, birth control pill use, history of benign breast disease, age at menarche, age at menopause, age at first birth, number of live births	Mid-points of exposure categories
		115/				≤335.5 µg/day	2.10 (1.08-4.07)	Age, energy, education,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
						folate: >7.62 g/day alcohol vs ≤0.01 g/day alcohol	$P_{interaction}$:0.05	HRT, BMI	
		576/				>335.5 µg/day: >7.62 g/day alcohol vs ≤0.01 g/day alcohol	1.23 (0.93-1.62) $P_{interaction}$:0.05		
Sellers, 2001 BRE80420 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	1 586/ 34 387 12 years	State Health Registry	Semi-quantitative FFQ	Incidence, breast cancer, postmenopausal	≤186 vs >351 µg/day	1.19 (0.90-1.58)	Age, age at first child birth, age at menarche, age at menopause, alcohol, BMI, BMI at age 18 years, educational level, family history of breast cancer, height, HRT, oral contraceptive use, other B vitamins, parity, physical activity, smoking, total energy intake, waist to hip ratio	Reference category changed using Hamling's method
		814/				>4 vs 0 g/day alcohol in >294 µg/day folate category	1.07 (0.88-1.29)		
		316/				>4 vs 0 g/day alcohol in 240-294 µg/day folate category	1.15 (0.87-1.53)		
		281/				>4 vs 0 g/day alcohol in 173-239 µg/day folate category	0.84 (0.59-1.20)		
		175/				>4 vs 0 g/day alcohol in ≤172 µg/day folate	1.59 (1.05-2.41)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
						category			

NOTE: total folate does not include multivitamin use in CPS II study (Stevens, 2010), total folate is expressed as dietary folate equivalents.

Table 346 Total folate and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Maruti, 2009 BRE80259 USA	VITAL, Prospective Cohort, Age: 50-76 years, W, Postmenopausal	659/ 35 023 5 years	Seer registry	Semi-quantitative FFQ	Incidence, postmenopausal breast cancer	1272 vs 345 DEF/day	0.78 (0.61-0.99) Ptrend:0.05	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, benign breast disease, BMI, energy Intake, family history of cancer, height, mammography, physical activity, postmenopausal hormone use, race	Excluded, intake reported in DEF/day that cannot be converted to µg/day, used in the highest vs lowest analysis
		558/			ER+		0.88 (0.68-1.14) Ptrend:0.43		
		88/			ER-		0.38 (0.18-0.80) Ptrend:0.02		
Tjønneland, 2006 BRE80104	DCH, Nested Case Control,	388/ 388 controls	Cancer registry	FFQ	Incidence, breast cancer, postmenopausal	>400 vs ≤300 µg/day	0.60 (0.35-1.06)	Age at first child, benign breast disease, BMI, educational	Superseded by Roswall, 2010
						Per 100	0.88 (0.71-1.1)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Denmark	Age: 50-64 years, Postmenopausal					µg/day		level, energy Intake , nutrients, parity/pregnancies	
Mattisson, 2004a BRE17807 Sweden	MDCS, Prospective Cohort, Age: 50- years, W, Postmenopausal	342/ 11 726 7.6 years	Partially histological - over 80%	7-day record + questionnaire	Incidence, breast cancer, postmenopausal		(mean exposure)		Excluded, only mean intake
Stolzenberg-Solomon, 2004 BRE18746 USA	PLCO, Prospective Cohort, Age: 55-74 years, W, Postmenopausal	777/ 28 210 4.94 years	Not specified	Questionnaire	Incidence, breast cancer, postmenopausal	5th vs 1st quintile	1.18 (0.90-1.55) Ptrend:.14	Age , benign breast disease, educational level, energy Intake , HRT use, length of follow-up, nutrients, parity/pregnancies, recruitment center	Superseded by Stolzenberg-Solomon, 2006
Feigelson, 2003 BRE02720 USA	CPS II, Prospective Cohort, W	1 303/ 66 561 6 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	≥603.7 vs <209.8 µg/day	1.10 (0.94-1.29)	Age , age at first child, age at menarche, age at menopause, BMI, body weight, educational level, ethnicity, family history, HRT use, mammography, nutrients, other nutritional factors, parity/pregnancies, physical activity , residual (willet), supplements	Superseded by Stevens, 2010

Figure 430 RR estimates of postmenopausal breast cancer by levels of total folate intake

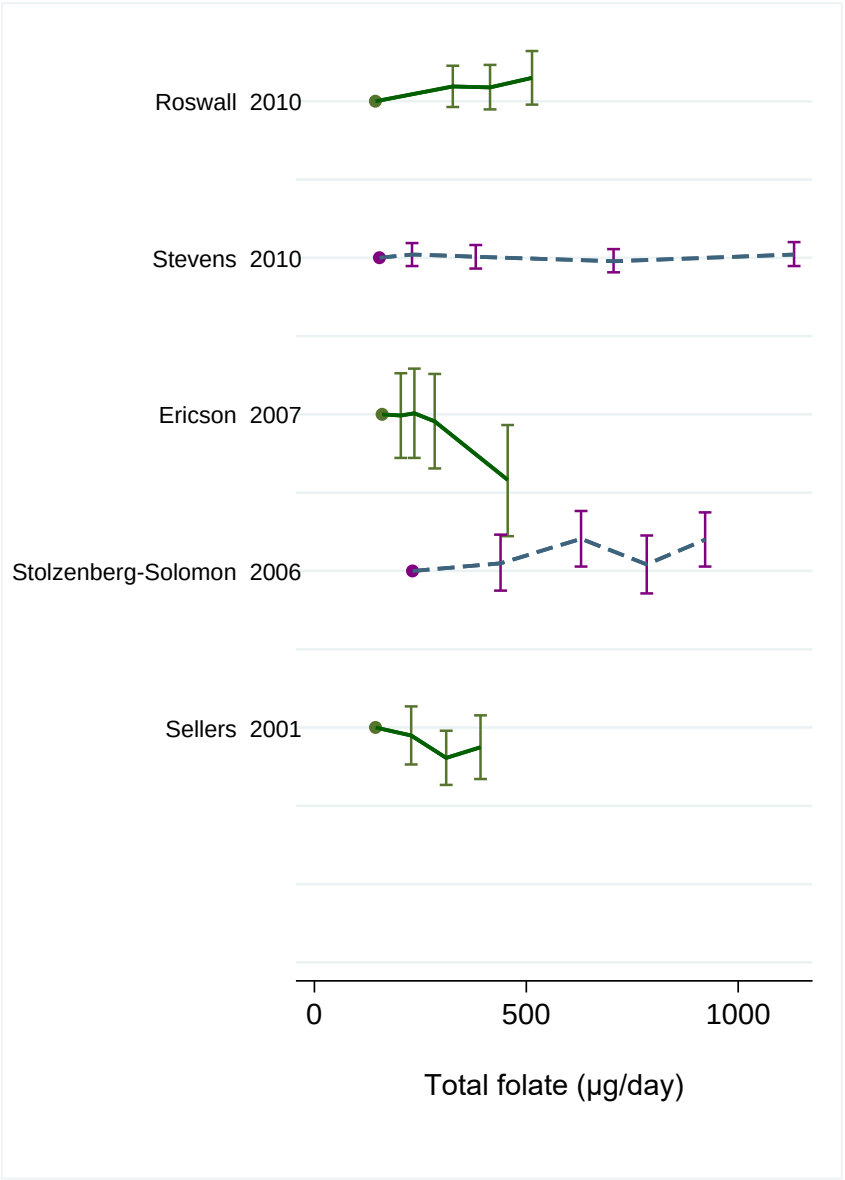


Figure 431 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest level of total folate intake

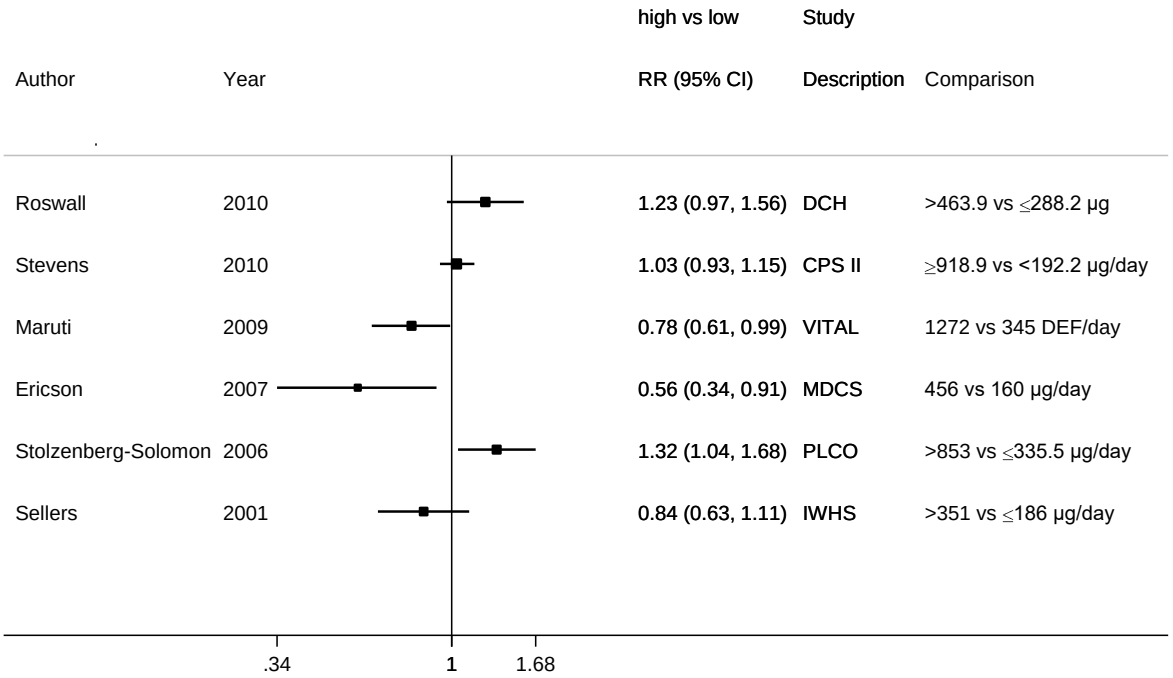


Figure 432 Relative risk of postmenopausal breast cancer for 100 µg/day increase of total folate intake

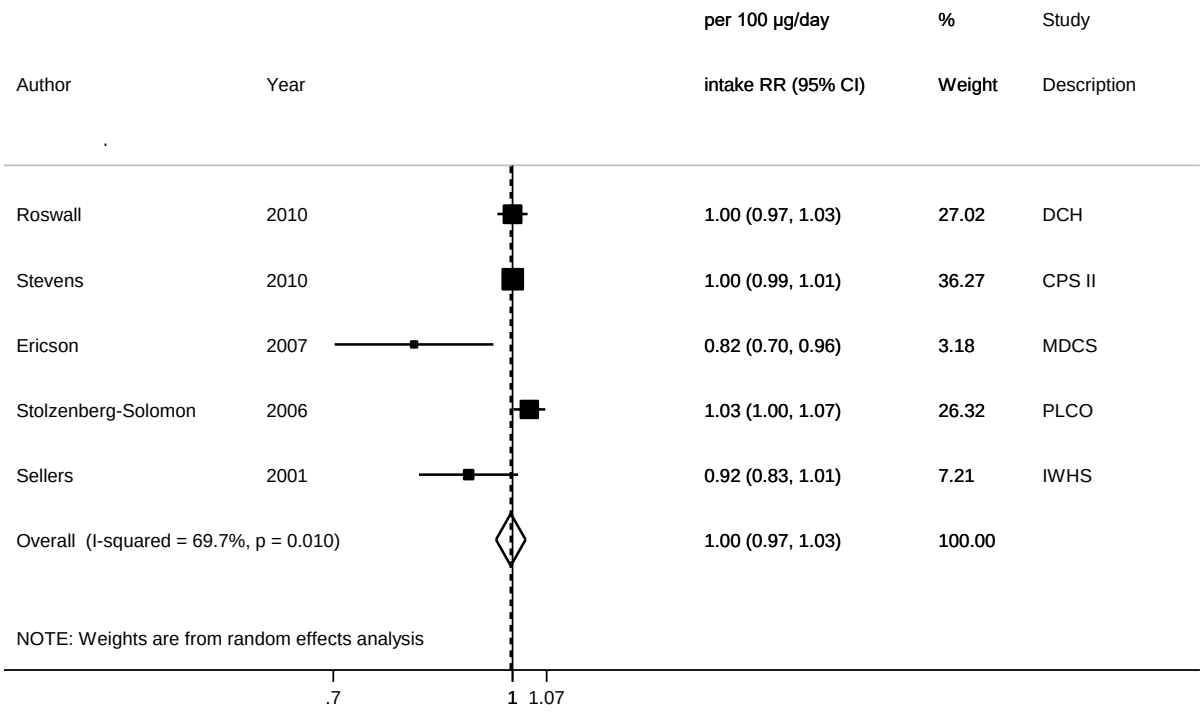


Figure 433 Funnel plot of studies included in the dose response meta-analysis of total folate and postmenopausal breast cancer

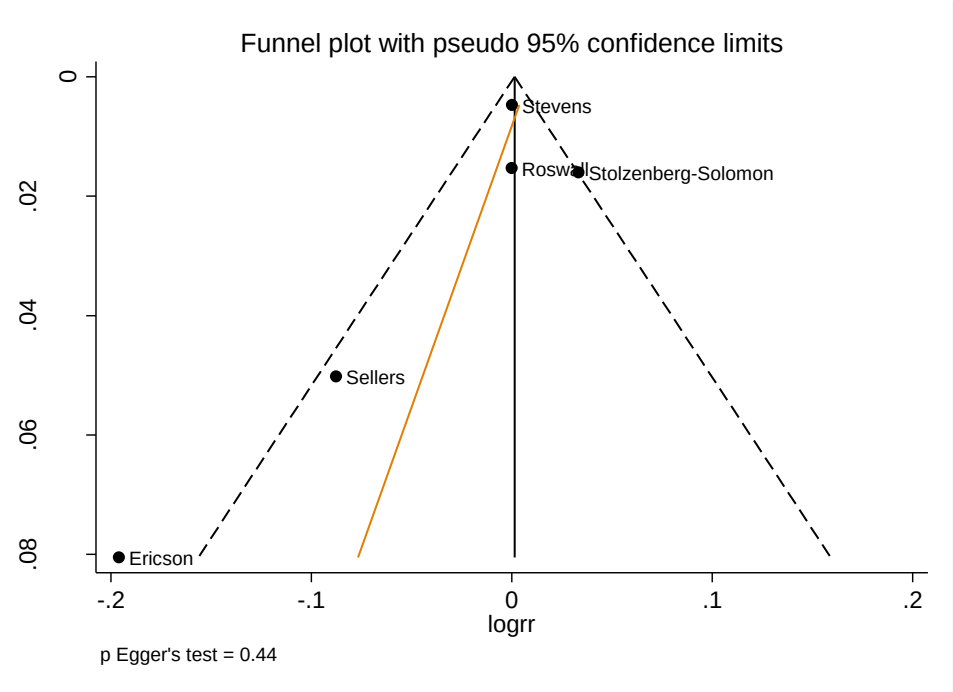
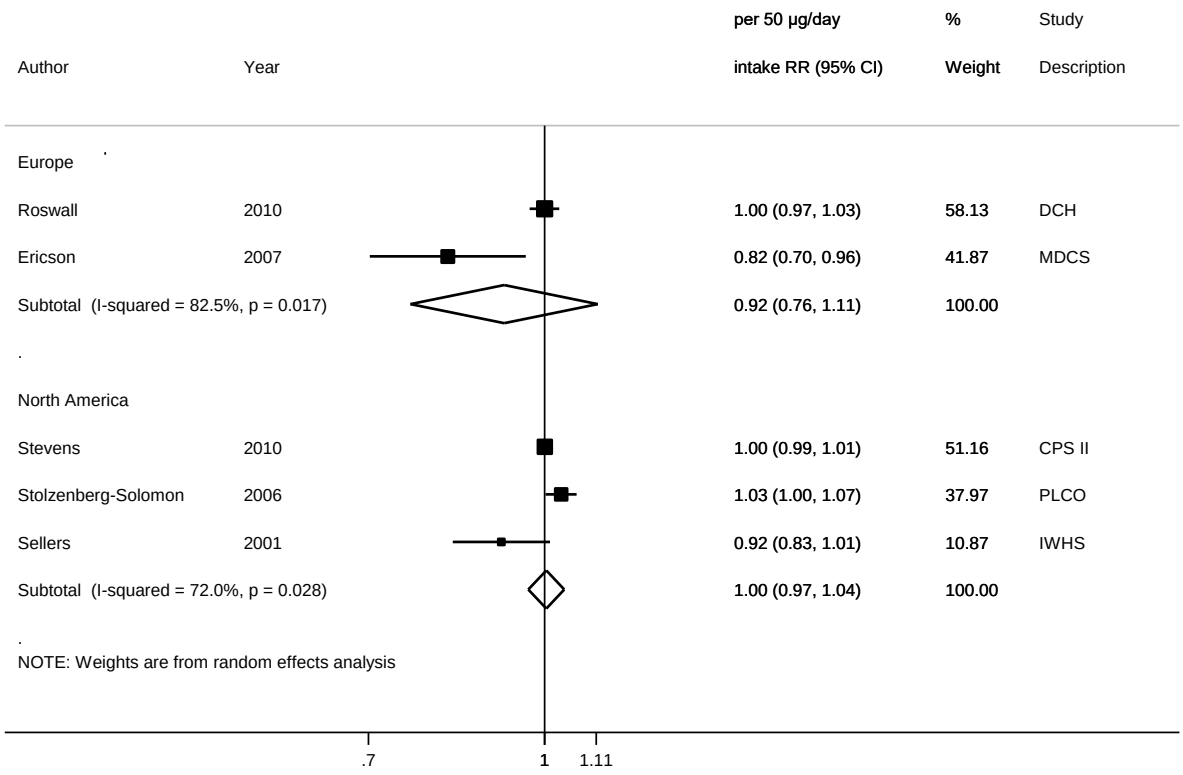


Figure 434 Relative risk of postmenopausal breast cancer incidence for 50 µg/day increase of total folate intake, by geographic location



5.5.3.2 Dietary folate

Overall summary

22 publications from 22 studies were identified, including one publication of pooled study on breast cancer incidence (Jung, 2015, 20 cohorts). Dose-response meta-analyses were conducted to examine the association of dietary folate with risk of breast cancer (any), premenopausal and postmenopausal breast cancer.

The Pooling Project of Prospective Studies on Diet and Cancer was published after the end of the search for this review but was considered for inclusion in the dose-response meta-analysis (Jung, 2015).

Breast cancer (any)

Summary

Main results:

Six studies (19 251cases) (6 publications) were included in the dose-response meta-analysis. Dietary folate intake was not associated with breast cancer (any) risk.

The Pooling Project (Jung, 2015) was excluded because of insufficient data for the dose-response meta-analysis. This publication reported no association between dietary folate intake and risk of total breast cancer.

Breast cancer risk and dietary folate intake by hormone receptor status:

Two studies investigated the association of dietary folate intake and breast cancer risk by tumour hormone receptor status: the Pooling Project of Cohort Studies on Diet and Cancer (Jung, 2015) and SWHS (Shrubsole, 2011).

In the Pooling Project (Jung, 2015) dietary folate intake was not associated with ER+, ER-, PR+, PR- breast cancer risk. The association was inverse but not significant for ER+PR- and ER-PR+ breast cancer (Jung, 2015). Both studies reported non-significant inverse association with ER+PR+ breast cancer. Dietary folate intake was not associated with with ER-PR- cancer type in the Pooling Project (Jung, 2015) but non-significantly inversely associated in the SWHS study (Shrubsole, 2011).

Influence and stratified analyses:

In influence analysis, the summary relative risk remained close to 1.00 after excluding each study in turn.

Combined effect of folate and alcohol intake:

Three studies reported RRs for interaction between alcohol and dietary folate (de Batlle, 2015, Larsson, 2008, Baglietto, 2005). Two studies repored significant interaction between alcohol and folate intake (de Batlle, 2015, Baglietto, 2005). In the EPIC, high folate intake (>326 μg/day) at any level of alcohol intake was significantly inversely associated with breast cancer risk, comparing with low folate (<250 μg/day) and high alcohol intake (>12 drinks/week) (de Batlle, 2015). Similar findings were reported in the CNBSS (Rohan, 2000b). In the MCCS, highest folate intake (400 μg/day) was inversely but not significantly

associated with breast cancer risk for alcohol intakes above 40 g/day. Lowest folate intake (200 μg/day) was associated with significantly higher risk of breast cancer in heavy consumers of alcohol. In the SMC study, highest intake of folate (≥277 μg/day) was not associated with risk of breast cancer in nondrinkers and consumers of 0.1-9.9 alcohol g/day and nonsignificantly positively associated with breast cancer for intakes of ≥10 g/day (Larsson, 2008).

Study quality:

All studies reported assessment of total folate intake by FFQ apart from EPIC (de Batlle, 2015) where country-specific questionnaires were used. Case ascertainment was mainly through cancer and death registries or self-report verified by medical records.

Table 347 Dietary folate and breast cancer (any) risk. Number of studies in the CUP SLR

	Number
Studies identified	22 (10 publications)
Studies included in forest plot of highest compared with lowest exposure	22 (3 publications)
Studies included in linear dose-response meta-analysis	6 (6 publications)
Studies included in non-linear dose-response meta-analysis	

Table 348 Dietary folate and breast cancer risk (any). Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	-	50 μg/day
Studies (n)	-	6
Cases	-	19 251
RR (95%CI)	-	0.99 (0.98-1.01)
Heterogeneity (I^2, p-value)	-	0%, 0.81
P value Egger test		0.90
Stratified analyses in CUP SLR		
Geographic area	**Asia**	**Europe**
Studies (n)	1	2
RR (95%CI)	0.96 (0.90-1.03)	0.99 (0.98-1.00)
Heterogeneity (I^2, p-value)		0%, 0.83
Geographic area	**North America**	**Australia**

Studies (n)	2	1
RR (95%CI)	1.00 (0.97-1.03)	1.01 (0.97-1.05)
Heterogeneity (I^2, p-value)	0%, 0.83	
Adjustment for age, BMI, alcohol and reproductive factors	**Adjusted**	**Not adjusted***
Studies (n)	5	1
RR (95%CI)	0.99 (0.98-1.01)	0.96 (0.90-1.03)
Heterogeneity (I^2, p-value)	0%, 0.85	-

*Shrubsole, 2011did not adjust for alcohol.

Table 349 Dietary folate intake and breast cancer (any) risk. Results of meta-analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	I^2
Meta-analysis							
Chen, 2014	Prospective studies: 15		North America, Europe, China	Breast cancer (female)	Highest vs lowest category	0.95 (0.87-1.03)	66%
	5			ER+		1.07 (0.98-1.17)	0%
	6			ER-		0.95 (0.82-1.09)	0%
Liu, 2014	Prospective studies: 15	24 083	North America, Europe, Australia	Breast cancer	Per 220 µg/day increment	0.96 (0.95-1.05)	54%
	10				Highest vs lowest category	0.98 (0.90-1.05)	68%
	6			Low alcohol intake		1.05 (0.95-1.15)	0%
	6			High alcohol intake		0.92 (0.57-1.27)	84%
	3			ER+PR+		1.05 (0.95-1.50)	0%
	4			ER-/PR-		0.91 (0.80-1.03)	0%

Table 350 Dietary folate and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
de Batlle, 2015 BRE80571 Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, UK	EPIC, Prospective Cohort, Age: 35-70 years, W	11 575/ 334 848 11.5 years	Active follow up and cancer registry	FFQ, diet history, 7-day food diary	Incidence, breast cancer	per 50 µg/day	0.99 (0.98-1.01)	Age, age at first child birth, age at menarche, alcohol Intake, educational attainment, ever use of HT, ever use of oral contraceptive, glycemic index, height, menopausal status, physical activity, smoking status, study center, total dietary fibre, vitamin / mineral supplement use, waist to hip ratio, weight	None
						≥371.1 vs ≤221 µg/day	0.92 (0.83-1.01) Ptrend:0.37		
		606 vs 667				High folate (>326 µg/day), high alcohol (12 drinks/week) vs low folate (<120 µg/day), high alcohol intake	0.86 (0.75-0.98)	Age, age at first child birth, age at menarche,, educational attainment, ever use of HRT, ever use of oral contraceptive use, glycemic index, height, menopausal status, physical activity, smoking status, study center, total dietary fibre, vitamin / mineral supplement use, waist to hip ratio, weight	
		1042 vs 667				High folate, low alcohol (<2 drinks/week) vs low folate, high alcohol intake	0.83 (0.74-0.93)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Bassett, 2013 BRE80473 Australia	MCCS, Prospective Cohort, Age: 27-80 years, W	936/ 20 756 16.3 years	Cancer registry and national health database	FFQ	Incidence, invasive breast cancer	422 vs 224 µg/day	0.99 (0.83-1.19) Ptrend:0.60	Age at menarche, alcohol consumption, BMI, breastfeeding, educational level, ethnicity, HRT use, menopausal status, oral contraceptive use, parity, physical activity, smoking status	
						per 92 µg/day	1.02 (0.95-1.09)		RR rescaled for an increment of 50 µg/day
		690/			Incidence, breast cancer ER+/PR+	422 vs 224 µg/day	1.05 (0.85-1.29) Ptrend:0.30		
						per 92 µg/day	1.04 (0.96-1.13)		
		179/			Incidence, breast cancer ER-/PR-	422 vs 224 µg/day	0.89 (0.59-1.34) Ptrend:0.60		
						per 92 µg/day	0.96 (0.82-1.12)		
Shrubsole, 2011 BRE80357 China	SWHS, Prospective Cohort, Age: 40-70 years, W	718/ 72 861 9.2 years	Record linkages to cancer database and to the national mortality database	FFQ	Incidence, breast cancer	404 vs 194 µg/day	0.79 (0.59-1.06) Ptrend:0.32	Age at baseline, age at first child birth, age at menarche, educational level, energy Intake, fat Intake, height, menopausal status, parity, physical activity, vegetable Intake, vitamin B supplements	None
		291/			Incidence, breast cancer ER+/PR+	393 vs 200 µg/day	1.09 (0.71-1.67) Ptrend:0.55		
		170/			Incidence,	393 vs 200	0.84 (0.50-1.43)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
					breast cancer ER-/PR-	µg/day	Ptrend:0.19		
Kabat, 2008 BRE80194 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	2 491/ 49 654 16.4 years	Cancer registry	FFQ	Incidence, breast cancer	≥374 vs ≤236.9 µg/day	1.02 (0.90-1.17) Ptrend:0.79	Age, age at menarche, alcohol Intake, BMI, breast biopsies, educational level, energy Intake, family history of cancer, hormone use, menopausal status, oral contraceptive use, pack-years of smoking, parity	Mid-points of exposure categories, person-years and cases per quantile
Larsson, 2008 BRE80208 Sweden	SMC, Prospective Cohort, Age: 54 years, W	2 952/ 61 433 17.4 years	Cancer registry	FFQ	Incidence, invasive breast cancer	per 100 ug/day	0.99 (0.92-1.06)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, benign breast disease, BMI, educational level, energy Intake, family history of cancer, height, parity, postmenopausal hormone use, use of oral contraception	RR rescaled for an increment of 50 µg/day
						≥277 vs <200 ug/day	1.01 (0.90-1.13) Ptrend:0.84		
		1 286/			ER+/PR+	per 100 ug/day	1.05 (0.94-1.17)		
						≥277 vs <200 ug/day	1.03 (0.87-1.23) Ptrend:0.35		
		417/			ER+/PR-	≥277 vs <200 ug/day	0.79 (0.59-1.07) Ptrend:0.01		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
						per 100 ug/day	0.78 (0.64-0.95)		
		266/			ER-/PR-	≥277 vs <200 ug/day	0.92 (0.63-1.35) Ptrend:0.27		
						per 100 ug/day	0.95 (0.74-1.21)		
		765/			Incidence, breast cancer, nondrinkers	≥277 vs <200 ug/day	1.01 (0.81-1.27)	Age, education, BMI, height, parity, age at first birth, age at menarche, age at menopause, use of oral contraceptives, use of HRT, family history of breast cancer, history of benign breast disease, total energy intake	
						Per 100 µg/day	1.06 (0.93-1.21)		
		2009/			Incidence, breast cancer, 0.1-9.9 g/day alcohol	≥277 vs <200 ug/day	0.99 (0.86-1.15)		
						Per 100 µg/day	0.97 (0.89-1.06)		
		178/			Incidence, breast cancer, ≥10 g/day alcohol	≥277 vs <200 ug/day	1.18 (0.67-2.07)		
						Per 100 µg/day	1.23 (0.85-1.79)		
Lin, 2008 BRE80186 USA	WHS, Nested Case Control, Age: 45- years	579/ 576 controls 11 years	Self-report verified by medical records	FFQ	Incidence, breast cancer	≥380 vs ≤248 µg/day	0.84 (0.52-1.37) Ptrend:0.97	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, benign breast disease, BMI, date of blood collection, ethnicity, family history of cancer, fasting condition, menopausal status, parity, physical activity, postmenopausal hormone use,	None

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								randomization group, randomized treatment assignment, smoking habits	
Zhang, 2005 BRE24752 USA	NHS I, Prospective Cohort, Age: 30-55 years, W, Registered nurses	2 812/ 88 744 20 years	Medical record + pathology report	FFQ-semi-quantitative	Incidence, breast cancer ER+	>332 vs <206 µg/day	1.15 (1.01-1.30) Ptrend:0.05	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI at the age of 18, duration of HRT use, energy intake , family history, height, length of follow-up, menopausal status, other anthropometric index, parity/pregnancies, weight change since the age of 18	Analysis by hormone receptor status was not conducted
		985/			ER-		0.97 (0.79-1.18) Ptrend:0.34		
		2 256/			PR+		1.09 (0.95-1.26) Ptrend:0.55		
		1 361/			PR-		1.08 (0.91-1.29) Ptrend:0.42		
		438/			ER+, alcohol ≥15 g/day		1.06 (0.77-1.47) Ptrend:0.74		
		129/			ER-, alcohol ≥15 g/day		0.66 (0.36-1.21) Ptrend:0.06		
		2 374/			ER+, alcohol <15 g/day		1.16 (1.02-1.33) Ptrend:0.04		
		856/			ER-, alcohol <15 g/day		1.04 (0.83-1.28) Ptrend:0.85		
		344/			PR+, alcohol ≥15 g/day		0.98 (0.69-1.40) Ptrend:0.63		
		188/			PR-, alcohol ≥15 g/day		0.76 (0.45-1.27) Ptrend:0.29		
		1 912/			PR+, alcohol <15 g/day		1.12 (0.97-1.30) Ptrend:0.37		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
		1 173/			PR-, alcohol <15 g/day		1.14 (0.95-1.38) Ptrend:0.16		

Table 351 Dietary folate and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Jung, 2015 North America, Europe, Asia, Australia	20 cohorts: CARET* BCDDP CTS CNBSS CPS II CLUE II IWHS* JPHC I MCCS MEC NLCS* NYUWHS NIH-AARP* NHS (a) NHS (b) NHS II Prospective Study on Hormones, Diet and Breast Cancer (Italy)	37 191, 6 to 18 years maximum follow-up	Variable in each cohort	Questionnaires	Incidence, breast cancer	≥15 g/day vs non-drinkers of all alcohol	1.00 (0.97-1.04)	Age, energy intake, ethnicity, education, BMI, height, physical activity, smoking status, age at menarche, menopausal status and HRT, parity and age at first birth, oral contraceptive use, family history of breast cancer, personal history of benign breast disease, alcohol	Excluded, intake ranges for quantiles are not available, used in the highest vs lowest analysis
		21 633			ER+		1.02 (0.98-1.06)		
		5 113			ER-		1.00 (0.92-1.10)		
		17 606			PR+		1.03 (0.98-1.08)		
		7 932			PR-		0.98 (0.89-1.07)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	PLCO* SMC WHS SWLHCS							consumption	
		16 783			ER+PR+	Q5 vs Q1	1.03 (0.98-1.08)		
		4 131			ER-PR-		1.01 (0.92-1.12)		
	19 cohorts: CARET excluded	3 674			ER+PR-		0.94 (0.84-1.06)		
	11 cohorts: BCDDP CTS CPS II IWHS* MCCS MEC NIH-AARP* NHS (a) NHS (b) NHS II SMC SWLHCS	612			ER-PR+		0.95 (0.71-1.28)		
Baglietto, 2005 BRE21669 Australia	MCCS, Prospective Cohort, Age: 7-75 years,	537/ 17 447 13 years	Cancer registry	121-item FFQ	Incidence, breast cancer	per 100 µg/day	1.01 (0.93-1.10)	Energy intake. Other potential confounders examined	Superseded by Bassett, 2013

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	W							included education, BMI, age at menarche, hormone replacement therapy, parity, and use of multivitamins	
						≥40 g/day alcohol vs abstainers, 200 µg/day folate	2.00 (1.14-3.49), $P_{interaction}$=0.04	Age, energy intake	
						≥40 g/day alcohol vs abstainers, 330 µg/day folate	1.08 (0.60-1.93) $P_{interaction}$=0.04		
						≥40 g/day alcohol vs abstainers, 400 µg/day folate	0.77 (0.33-1.80) $P_{interaction}$=0.04		
Rohan, 2000b BRE17968 Canada	CNBSS, Case Cohort, W	1 336/ 56 837 13 years	Partially histological - over 80%	FFQ-quantitative	Incidence, invasive breast cancer	≥354.28 vs ≤224.77 µg/day	0.99 (0.79-1.25) Ptrend:0.88	Age , age at menarche, alcohol, design , energy Intake , family history, menopausal status, other specified factor, parity/	Superseded by Kabat, 2008
		797/				Consumers of ≤14 g/day alcohol	1.22 (0.94-1.58) Ptrend:0.34		
		254/				Consumers of >14 g/day	0.34 (0.18-0.61) Ptrend:0.004		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
						alcohol		pregnancies, recruitment center	

Figure 435 RR estimates of breast cancer by levels of dietary folate intake

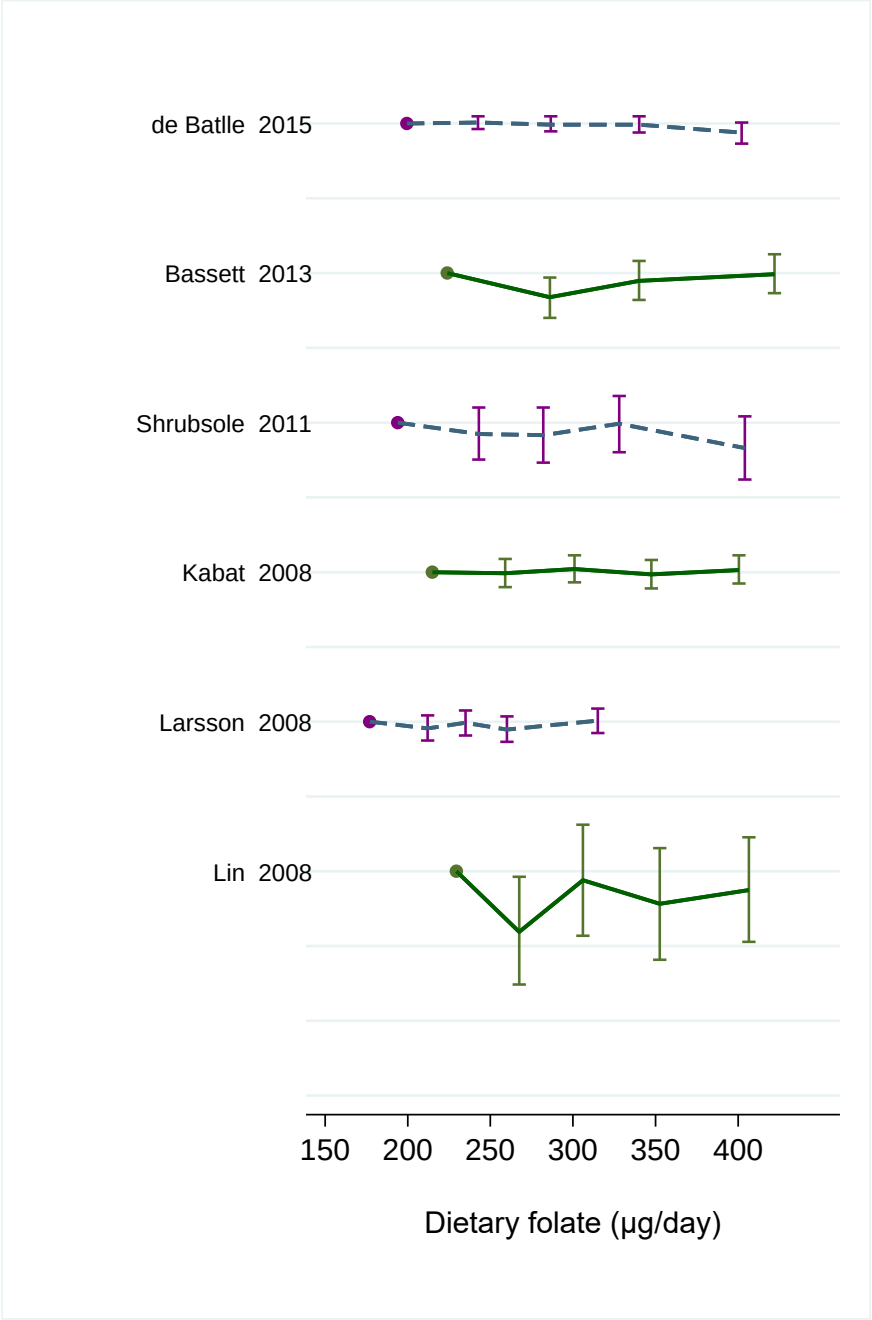


Figure 436 RR (95% CI) of breast cancer (any) for the highest compared with the lowest level of dietary folate intake

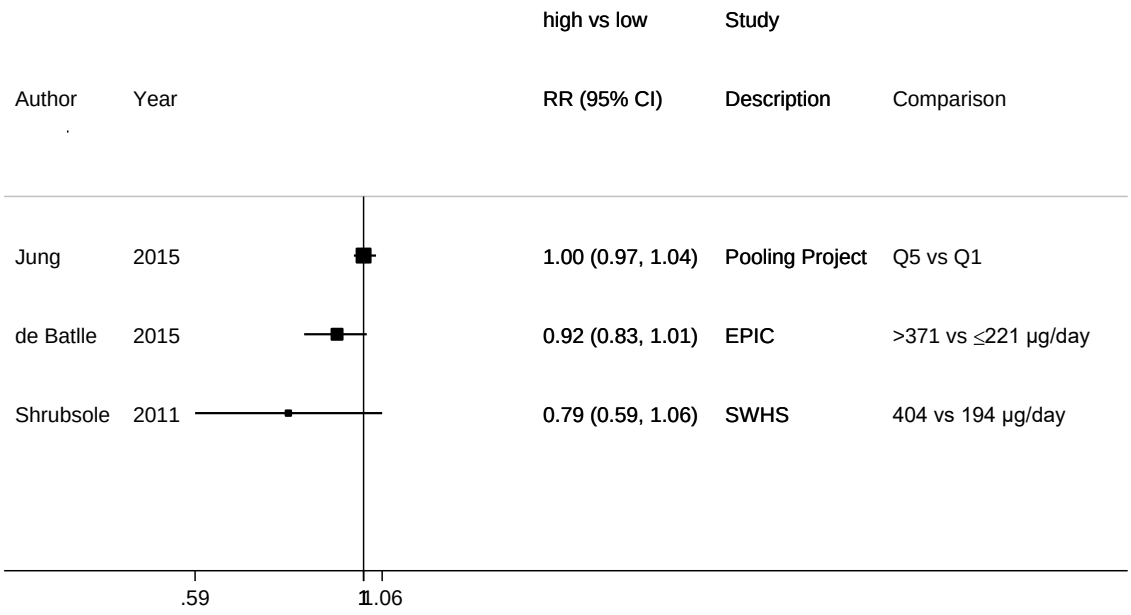


Figure 437 Relative risk of breast cancer for 50 µg/day increase of dietary folate intake

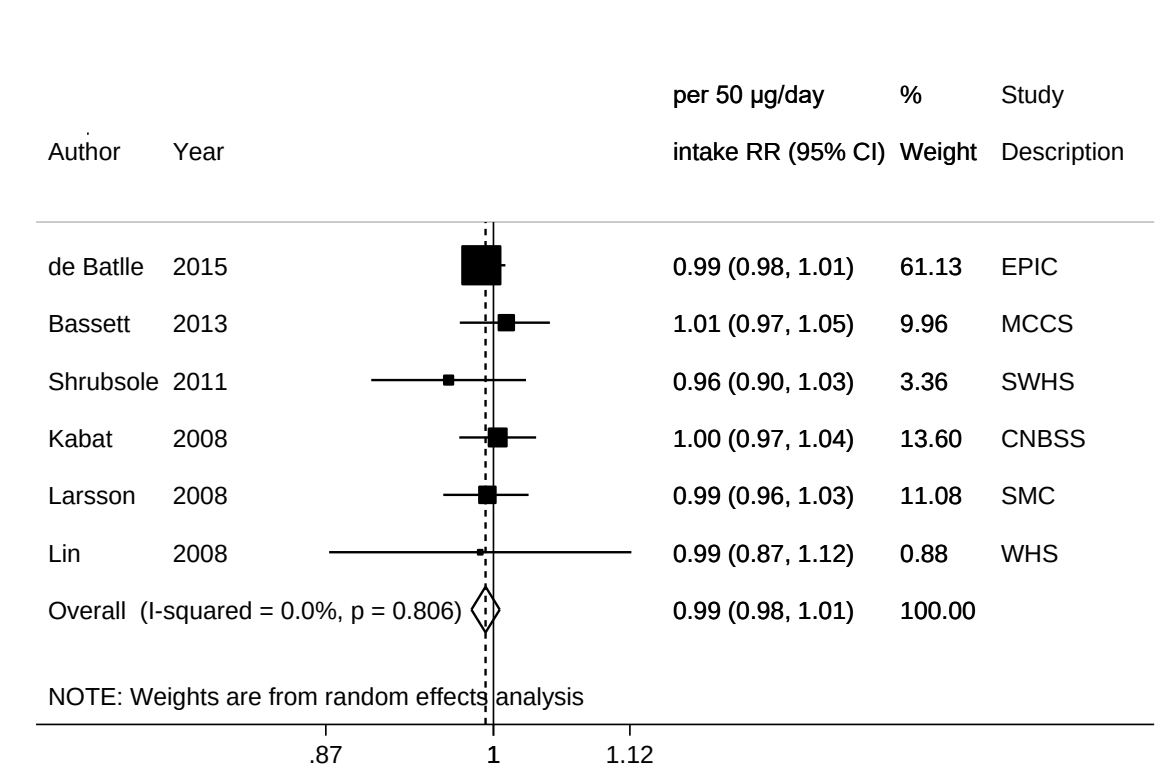


Figure 438 Funnel plot of studies included in the dose response meta-analysis of dietary folate and breast cancer

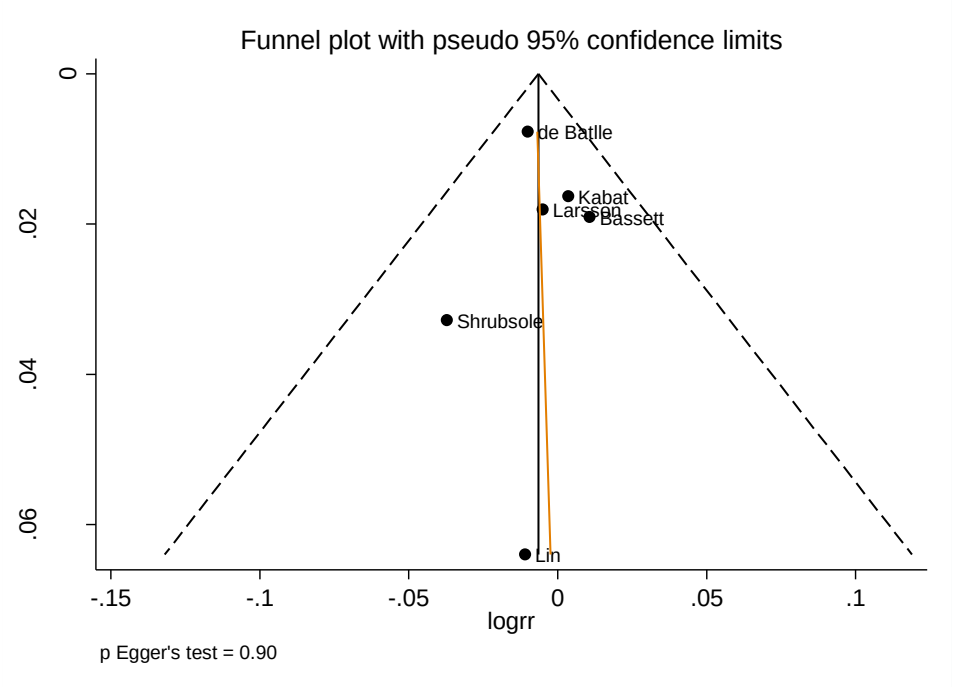


Figure 439 Relative risk of breast cancer incidence for 50 μg/day increase of dietary folate intake, by geographic location

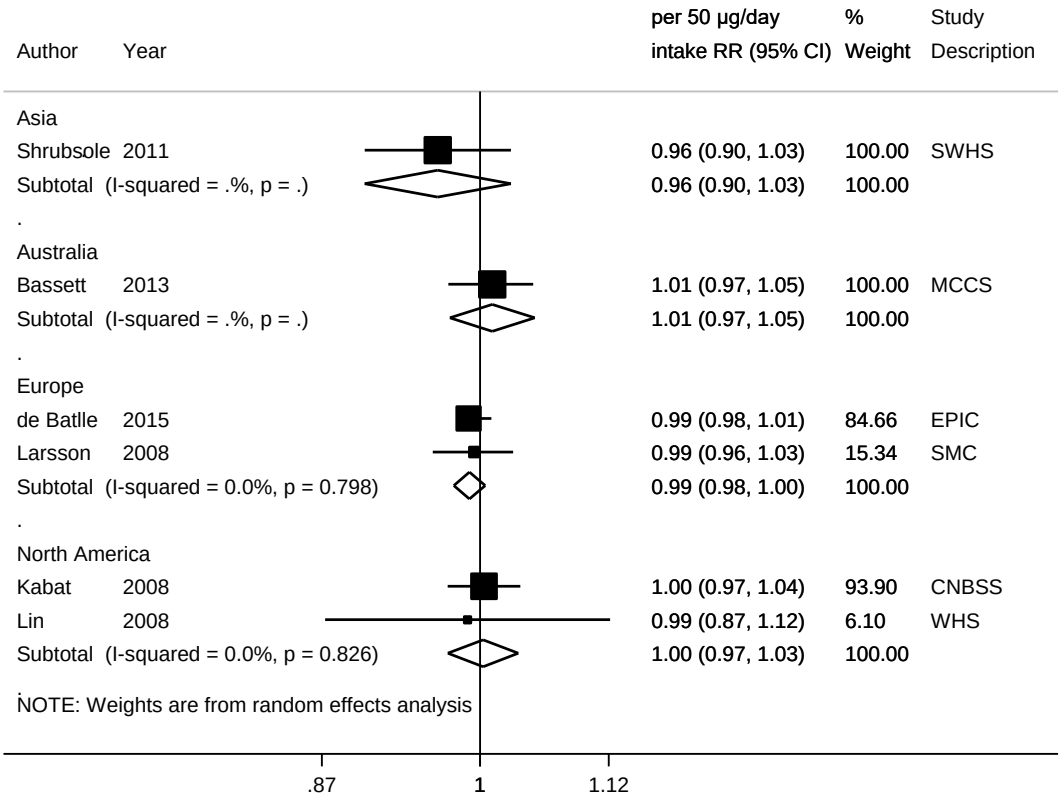
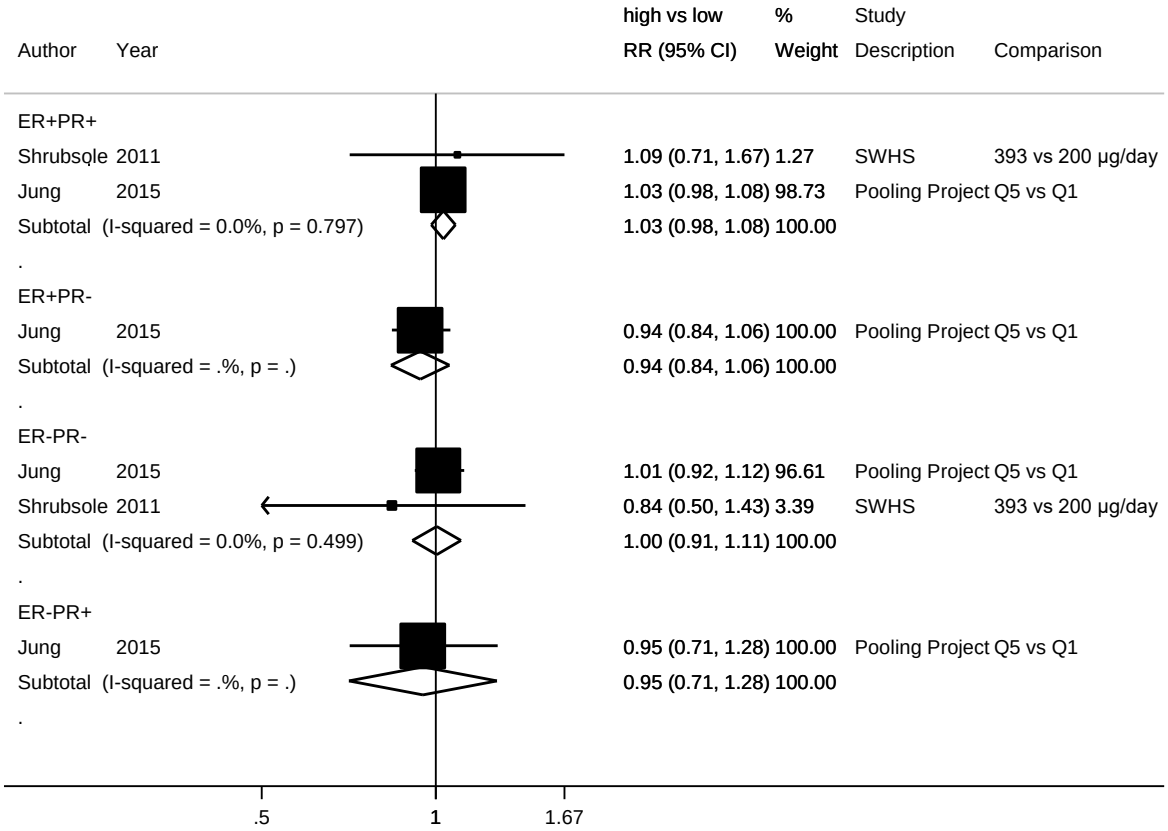


Figure 440 RR of breast cancer (any) for the highest compared with the lowest level of dietary folate intake, by hormone receptor status



Premenopausal breast cancer

Summary

Main results:

Five studies (8 150cases) (5 publications) were included in the dose-response meta-analysis. Dietary folate intake was not associated with premenopausal breast cancer risk.

None of the identified studies were excluded from the dose-response meta-analysis.

Influence and stratified analyses:

In influence analysis, the summary relative risk remained close to 1.00 after excluding each study in turn.

Study quality:

All studies reported assessment of dietary folate intake by FFQ; EPIC study used country-specific questionnaires (de Batlle, 2015). Case ascertainment was mainly through cancer registries and self-report verified by medical records. The population of SWHS are mainly non-consumers of alcohol. Alcohol intake was also low in the NHS II (highest category ≥5 g/day) (Cho, 2007).

Combined effect of folate and alcohol intake:

Only one study (CNBSS) investigated the association between folate intake and risk of premenopausal breast cancer by levels of alcohol intake in two categories: ≤14g/day and >14 g/day (Rohan, 2000b). In this study, high folate intake (Q4) was associated with marginally significantly lower risk if premenopausal breast cancer for alcohol intakes of ≤14 g/day. The number of cases consuming ≥14 g/day of alcohol was low and inverse associations at all levels of folate intake were not significant.

Highest intake of folate was inversely but not significantly associated with premenopausal breast cancer for alcohol intake above 14 g/day (12 cases in Q5).

Table 352 Dietary folate and premenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	5 (6 publications)
Studies included in forest plot of highest compared with lowest exposure	4 (4 publications)
Studies included in linear dose-response meta-analysis	5 (5 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 353 Dietary folate and premenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR	**CUP SLR**	
Increment unit used	-	50 μg/day	
Studies (n)	-	5	
Cases	-	8 150	
RR (95%CI)	-	1.00 (0.96-1.03)	
Heterogeneity (I^2, p-value)	-	52%, 0.08	
P value Egger test	-	0.69	
Stratified analyses in CUP SLR			
Geographic area	**Asia**	**Europe**	**North America**
Studies (n)	1	2	2
RR (95%CI)	0.89 (0.79-1.00)	0.99 (0.96-1.03)	1.04 (0.95-1.13)
Heterogeneity (I^2, p-value)		35%, 0.21	41%, 0.19
Adjustment for age, BMI,	**Adjusted**	**Not adjusted***	

alcohol and reproductive factors			
Studies (n)	3	2	
RR (95%CI)	0.99 (0.97-1.02)	0.99 (0.79-1.25)	
Heterogeneity (I^2, p-value)	11%, 0.32	83%, 0.02	

*****Shrubsole, 2011 unadjusted for alcohol (very few women were regular consumers of alcohol), Rohan, 2000b unadjusted for BMI.

Table 354 Dietary folate intake and premenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	I^2
Meta-analysis							
Chen, 2014	3 prospective studies			Breast cancer (female)	Highest vs lowest category	1.02 (0.62-1.67)	74%
Liu, 2014	4 prospective studies			Breast cancer	Highest vs lowest category	1.06 (0.96-1.16)	0%

Table 355 Dietary folate and premenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
de Batlle, 2015 BRE80571 Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain,	EPIC, Prospective Cohort, Age: 35-70 years, W	5 374/ 334 848 11.5 years	Active follow up and cancer registry	FFQ, diet history, 7-day food diary	Incidence, breast cancer premenopausal at baseline	per 50 µg/day	0.98 (0.96-1.01)	Age, age at first child birth, age at menarche, alcohol Intake, educational attainment, ever use of HT, ever use of, oral contraceptive use, glycaemic index, height, menopausal status,	None
						≥371.1 vs ≤221 µg/day	0.88 (0.77-1.02) Ptrend:0.041		
		2 649/			ER+	per 50 µg/day	0.98 (0.95-1.01)		
						≥371.1 vs ≤221 µg/day	0.94 (0.77-1.15) Ptrend:0.346		
		1 966/			PR+	≥371.1 vs ≤221 µg/day	1.06 (0.83-1.34) Ptrend:0.75		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Sweden, UK						per 50 µg/day	1.01 (0.97-1.05)	physical activity, smoking status, study center, total dietary fibre, vitamin / mineral supplement use, waist to hip ratio, weight	
		1 816/			ER+PR+	≥371.1 vs ≤221 µg/day	1.06 (0.83-1.36) Ptrend:0.753		
						per 50 µg/day	1.00 (0.96-1.05)		
		1 043/			PR-	per 50 µg/day	0.92 (0.86-0.98)		
						≥371.1 vs ≤221 µg/day	0.70 (0.51-0.97) Ptrend:0.021		
		981/			HER-2-	per 50 µg/day	0.99 (0.93-1.05)		
		891/				≥371.1 vs ≤221 µg/day	0.96 (0.67-1.36) Ptrend:0.589		
		748/			ER-	per 50 µg/day	0.95 (0.89-1.02)		
						≥371.1 vs ≤221 µg/day	0.66 (0.45-0.96) Ptrend:0.042		
		534/			ER-PR-	per 50 µg/day	0.94 (0.87-1.02)		
						≥371.1 vs ≤221 µg/day	0.66 (0.42-1.04) Ptrend:0.073		
		304/			HER-2+	per 50 µg/day	0.90 (0.81-1.01)		
						≥371.1 vs ≤221 µg/day	0.80 (0.44-1.47) Ptrend:0.396		
Shrubsole, 2011 BRE80357 China	SWHS, Prospective Cohort, Age: 40-70 years, W	213/ 72 861 9.2 years	Record linkages to cancer database and to the national mortality database	FFQ	Incidence, breast cancer, premenopausal	404 vs 194 µg/day	0.58 (0.34-0.99) Ptrend:0.22	Age at baseline, age at first child birth, age at menarche, educational level, energy Intake, fat Intake, height,	None

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								parity, physical activity, vegetable Intake, vitamin b supplements	
Larsson, 2008 BRE80208 Sweden	SMC, Prospective Cohort, Age: 54 years, W	1 244/ 61 433 17.4 years	Cancer registry	FFQ	Incidence, Invasive breast cancer, premenopausal	per 100 ug/day	1.04 (0.93-1.17)	Age, age at first child birth, age at menarche, alcohol Intake, benign breast disease, BMI, educational level, energy Intake, family history of cancer, height, parity, use of oral contraception	RR rescaled for an increment of 50 µg/day
Cho, 2007 BRE80152 USA	NHS II, Prospective Cohort, Age: 26-46 years, W, Premenopausal	1 032/ 90 663 12 years	Self-report verified by medical record	Semi-quantitative FFQ	Incidence, invasive breast cancer, premenopausal	436 vs 217 µg/day	1.08 (0.86-1.35) Ptrend:0.77	Age, age at first child birth, age at menarche, alcohol Intake, animal fat Intake, benign breast disease, BMI, calendar year, energy Intake, family history of cancer, oral contraceptive use, parity, smoking habits	Person-years per quantile
		221/			ER-	436 vs 217 µg/day	1.16 (0.73-1.85) Ptrend:0.53		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Rohan, 2000b BRE17968 Canada	CNBSS, Case Cohort, W	287/ 56 837 13 years	Partially histological - over 80%	FFQ-quantitative	Incidence, invasive breast cancer, premenopausal	≥354.28 vs ≤224.77 µg/day	1.72 (0.97-3.06) Ptrend:0.32	Age , age at menarche, alcohol, design , energy intake , family history, menopausal status, other specified factor, parity/pregnancies, recruitment center	Mid-points of exposure categories
		166/				Consumers of ≤14 g/day alcohol	0.47 (0.22-1.00)		
		57/				Consumers of <14 g/day alcohol	0.90 (0.14-5.80)		

Table 356 Dietary folate and premenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Cho, 2003c BRE01652 USA	NHS II, Prospective Cohort, Age: 26-46 years, W, Registered nurses	714/ 90 655 8 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, Invasive breast cancer, premenopausal	429 vs 210 µg/day	1.07 (0.82-1.38) Ptrend:0.94	Age at first child, age at menarche, alcohol, benign breast disease, BMI, family history, height, menopausal status, nutrients, oral contraceptive use, parity/pregnancies, residual (willet), smoking habits	Superseded by Cho, 2007

Figure 441 RR estimates of premenopausal breast cancer by levels of dietary folate intake

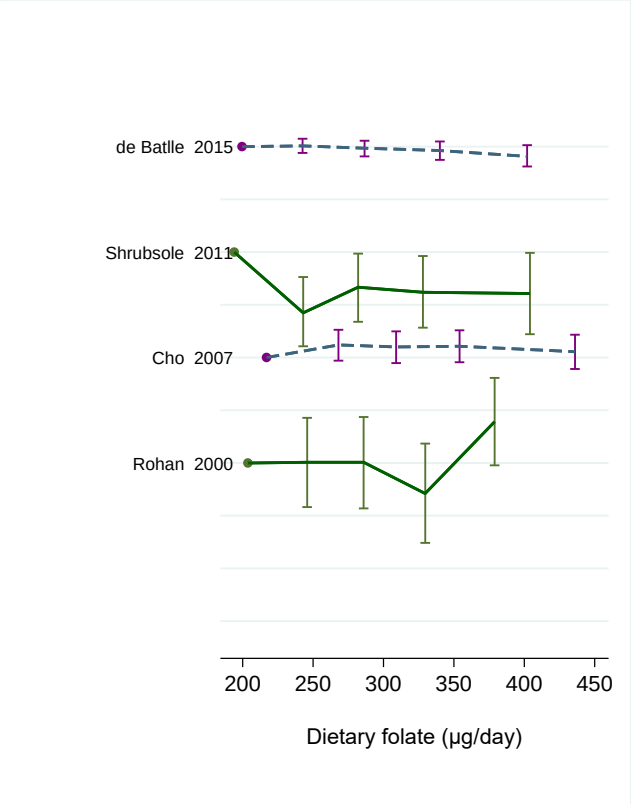


Figure 442 RR (95% CI) of premenopausal breast cancer for the highest compared with the lowest level of dietary folate intake

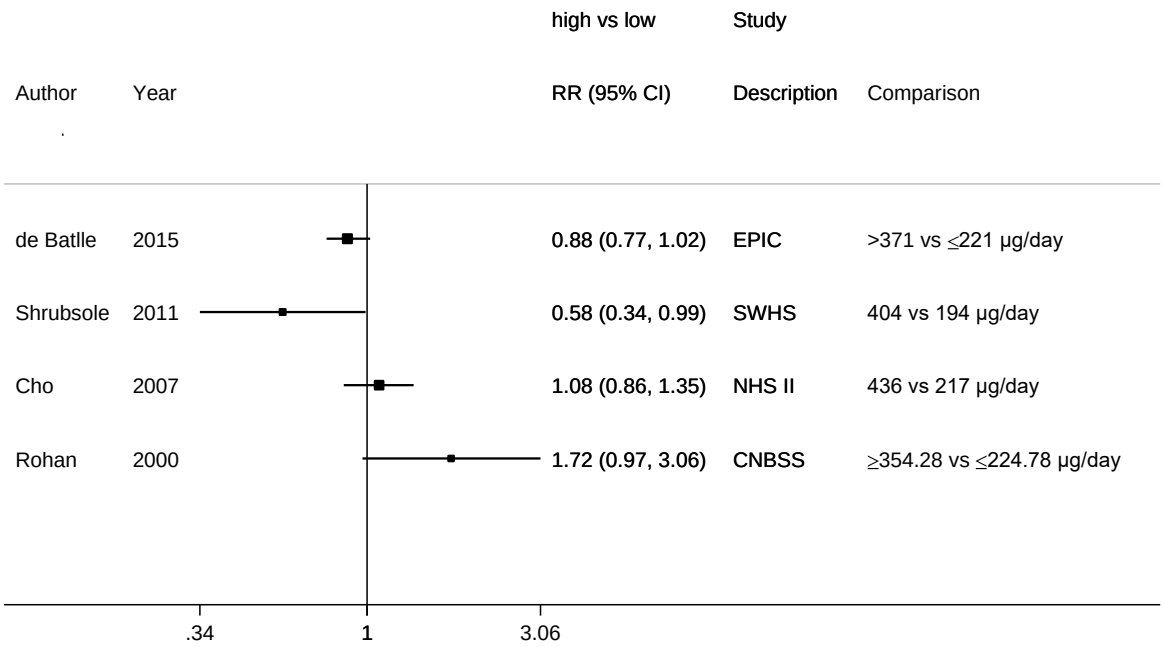


Figure 443 Relative risk of premenopausal breast cancer for 50 µg/day increase of dietary folate intake

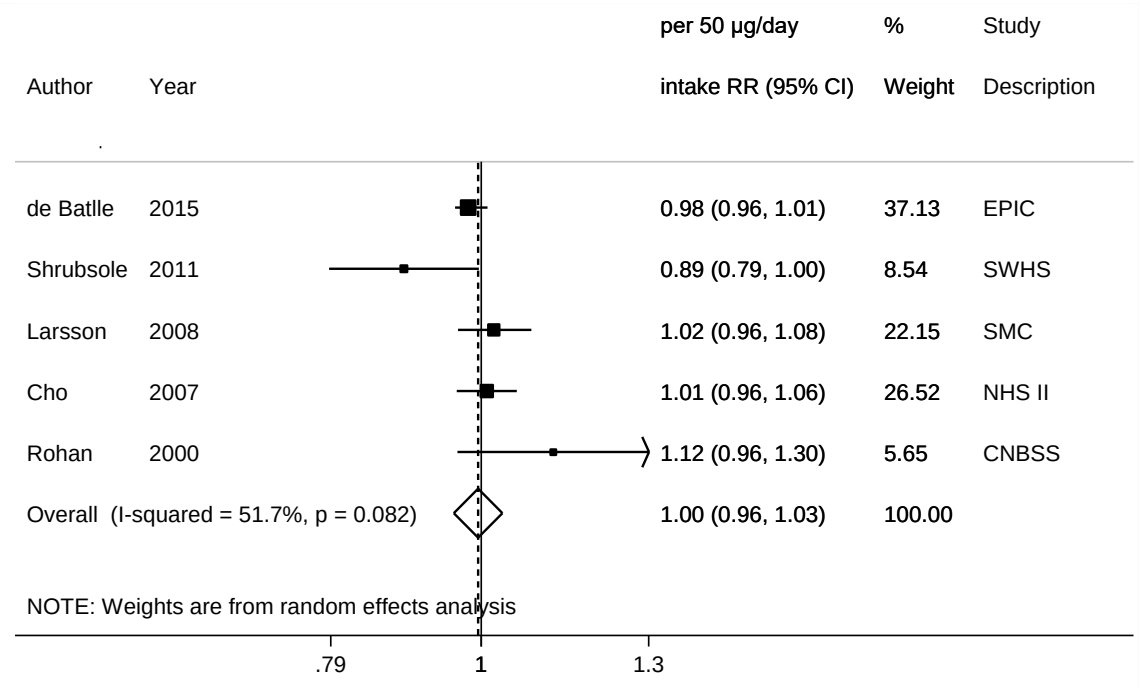


Figure 444 Funnel plot of studies included in the dose response meta-analysis of dietary folate and premenopausal breast cancer

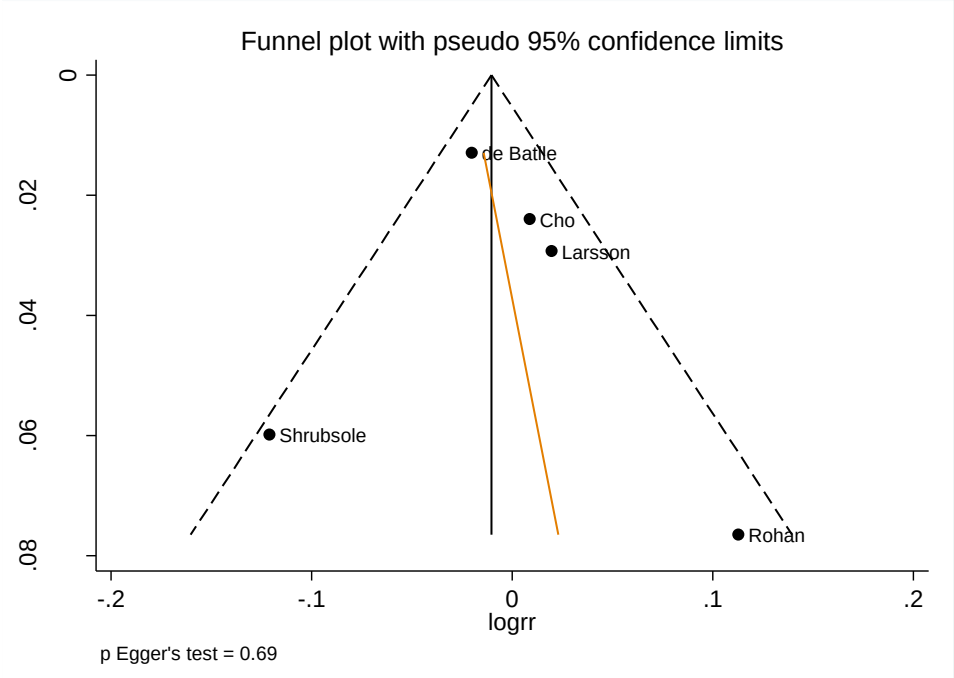
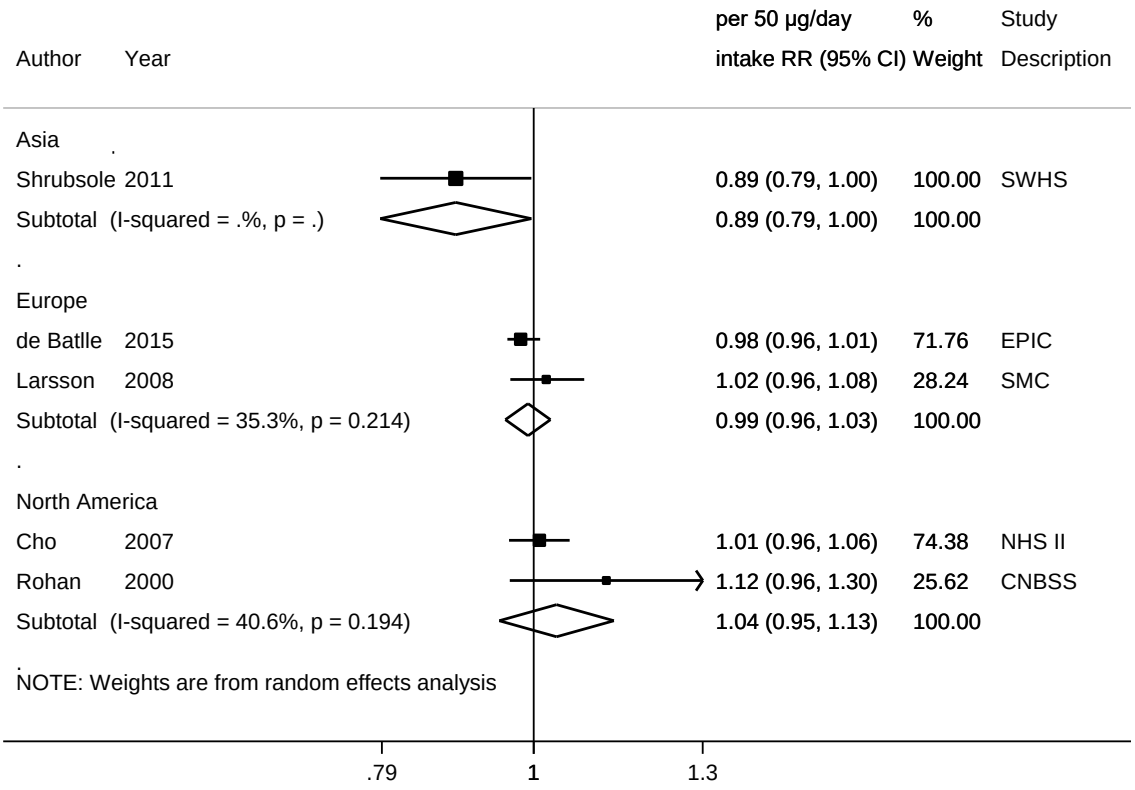


Figure 445 Relative risk of premenopausal breast cancer incidence for 50 µg/day increase of dietary folate intake, by geographic location



Postmenopausal breast cancer

Summary

Main results:

Ten studies (19 360 cases) (10 publications) were included in the dose-response meta-analysis. Dietary folate intake was not associated with postmenopausal breast cancer risk.

None of the identified studies were excluded from the dose-response meta-analysis.

Influence and stratified analyses:

In influence analysis, the summary relative risk remained close to 1.00 after excluding each study in turn.

Breast cancer risk and dietary folate intake by hormone receptor status:

Three studies investigated the association of dietary folate intake and breast cancer risk by tumour hormone receptor status: EPIC (de Batlle, 2015), DCH (Roswall, 2010) and NHS I (Zhang, 2005).

In EPIC study, no association was found between dietary folate intake and risk of ER-, ER+, PR-, PR+, HER2- , ER-PR-, and ER+PR+ postmenopausal breast cancer with RRs close to 1.00, per increment of 50 µg/day. The association was positive but not statistically significant for HER2+ breast cancer.

In the DCH study, dietary folate intake was significantly positively associated with ER+PR+ postmenopausal breast cancer. Non-significant positive association was reported for ER+PR- and ER-PR- and non-significant inverse association for ER-PR+ postmenopausal breast cancer.

In the NHS I study, dietary folate intake was significantly positively associated with risk of ER+ postmenopausal breast cancer and non-significantly positively with PR+ and PR- breast cancer, comparing highest versus lowest intake categories. Dietary folate intake was associated with non-significantly lower risk of ER- breast cancer.

Study quality:

All studies reported assessment of dietary folate intake by FFQ apart from MDCS where a combination of 7-day food records, questionnaire and an interview was used (Ericson, 2007) and EPIC study where country-specific questions were used (de Batlle, 2015). Case ascertainment was mainly through cancer registries, death registries and self-report verified by medical records.

Combined effect of folate and alcohol intake:

Three studies reported risk estimates of folate and alcohol intake on risk of postmenopausal breast cancer (Stevens, 2010, Sellers, 2004, Rohan, 2000b). In the CPS II, the risk of breast cancer was not attenuated at higher intakes of folate and no significant interaction between alcohol and folate was found (Stevens, 2010). Interactions were not significant in the DCH (Roswall, 2010) and PLCO (and Stolzenberg-Solomon, 2006) but no data was shown. In the IWHS study, folate intake was not associated with breast cancer risk in non-drinkers but there was a significant positive association between the lowest intake of folate and risk of postmenopausal breast cancer in drinkers (Sellers, 2004). In the CNBSS, similar association was reported for alcohol intakes above 14 g/day.

Table 357 Dietary folate and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	11 (13 publications)
Studies included in forest plot of highest compared with lowest exposure	9 (9 publications)
Studies included in linear dose-response meta-analysis	10 (10 publications)
Studies included in non-linear dose-response meta-analysis	

Table 358 Dietary folate and postmenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	1 mg/day	50 μg/day
Studies (n)	4	10
Cases	N/A	19 360
RR (95%CI)	0.90 (0.59-1.39)	1.00 (0.98-1.01)
Heterogeneity (I^2, p-value)	0%	40%, 0.09
P value Egger test	-	0.16

Stratified analyses in CUP SLR			
Geographic area	**Asia**	**Europe**	**North America**
Studies (n)	1	4	5
RR (95%CI)	1.00 (0.91-1.10)	1.00 (0.96-1.03)	0.99 (0.96-1.02)
Heterogeneity (I^2, p-value)		56%, 0.08	51%, 0.09
Adjustment for age, BMI, alcohol and reproductive factors	**Adjusted**	**Not adjusted***	
Studies (n)	5	5	
RR (95%CI)	1.01 (0.99-1.02)	0.97 (0.94-1.01)	
Heterogeneity (I^2, p-value)	0%, 0.42	30%, 0.22	

*****Three studies were unadjusted for alcohol (Shrubsole, 2011, Stolzenberg-Solomon, 2006, Sellers, 2004), two for BMI (Stolzenberg-Solomon, 2006, Rohan, 2000b) and one for reproductive factors (Ericson, 2007).

Table 359 Dietary folate intake and postmenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	I^2
Meta-analysis							
Chen, 2014	9 prospective studies			Breast cancer	Highest vs lowest category	0.94 (0.81-1.08)	69%
Liu, 2014	10 prospective studies			Breast cancer	Highest vs lowest category	0.98 (0.89-1.07)	57%

Table 360 Dietary folate and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
de Batlle, 2015 BRE80571 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden, UK	EPIC, Prospective Cohort, Age: 35-70 years, W	6 201/ 334 848 11.5 years	Active follow up and cancer registry	FFQ, diet history, 7-day food diary	Incidence, breast cancer, postmenopausal	per 50 µg/day	1.00 (0.98-1.02)	Age, age at first child birth, age at menarche, alcohol Intake, educational attainment, ever use of HRT, ever use of oral contraceptive, glycaemic index, height, menopausal	None
						≥371.1 vs ≤221 µg/day	0.95 (0.83-1.08) Ptrend:0.35		
		3 181/			ER+	per 50 µg/day	0.99 (0.96-1.03)		
						≥371.1 vs ≤221 µg/day	0.94 (0.78-1.13) Ptrend:0.43		
		1 912/			PR+	per 50 µg/day	1.00 (0.96-1.05)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
						≥371.1 vs ≤221 µg/day	0.98 (0.78-1.25) Ptrend:0.88	status, physical activity, smoking status, study center, total dietary fibre, vitamin / mineral supplement use, waist to hip ratio, weight	
		1 837/			ER+PR+	per 50 µg/day	0.99 (0.94-1.03)		
						≥371.1 vs ≤221 µg/day	0.96 (0.75-1.23) Ptrend:0.68		
		1 147/			PR-	per 50 µg/day	1.00 (0.95-1.06)		
						≥371.1 vs ≤221 µg/day	1.02 (0.75-1.39) Ptrend:0.80		
		873/			PR+	per 50 µg/day	1.00 (0.94-1.07)		
						≥371.1 vs ≤221 µg/day	1.04 (0.72-1.49) Ptrend:0.76		
		690/			ER-	per 50 µg/day	1.08 (0.92-1.26)		
						≥371.1 vs ≤221 µg/day	0.95 (0.64-1.41) Ptrend:0.73		
		516/			ER-PR-	per 50 µg/day	0.98 (0.91-1.07)		
						≥371.1 vs ≤221 µg/day	1.02 (0.65-1.60) Ptrend:0.96		
		266/			HER-2+	per 50 µg/day	1.06 (0.95-1.17)		
						≥371.1 vs ≤221 µg/day	0.97 (0.51-1.86) Ptrend:0.91		
		981/			HER-2-	per 50 µg/day	1.00 (0.94-1.07)		
						≥371.1 vs ≤221 µg/day	1.04 (0.72-1.49) Ptrend:0.76		
Shrubsole, 2011	SWHS,	346/	Record linkages	FFQ	Incidence,	404 vs 194	0.97 (0.63-1.49)	Age at baseline, age	None

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
BRE80357 China	Prospective Cohort, Age: 40-70 years, W	72 861 9.2 years	to cancer database and to the national mortality database		breast cancer, postmenopausal	µg/day	Ptrend:0.98	at first child birth, age at menarche, educational level, energy Intake, fat Intake, height, parity, physical activity, vegetable Intake, vitamin b supplements	
Roswall, 2010 BRE80338 Denmark	DCH, Prospective Cohort, Age: 50-64 years, Postmenopausal	1 072/ 26 224 10.6 years	Cancer registry	FFQ	Incidence, breast cancer	per 100 µg	1.08 (0.97-1.19)	Age at first child birth, alcohol, beta-carotene Intake, BMI, educational level, folate supplementation, hormone replacement therapy, HRT use, number of childbirths, parity, vitamin C (diet), vitamin C supplement, vitamin E Intake	RR rescaled for an increment of 50 µg/day
						≥389 vs 0-258.2 µg	1.22 (0.95-1.57) Ptrend:0.16		
		269/			ER+PR+	per 100 µg	1.27 (1.03-1.95)		
		103/			ER-PR-		1.17 (0.84-1.63)		
					ER+PR-		1.04 (0.74-1.47)		
		8/			ER-PR+		0.94 (0.28-3.17)		
Stevens, 2010 BRE80299 USA	CPS II, Prospective Cohort, Age: 50-74 years, W, Postmenopausal	3 898/ 70 656 13 years	Self-report verified by medical records	FFQ	Incidence, breast cancer	≥312.1 vs <166.9 µg/day	1.12 (1.01-1.24) Ptrend:0.15	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, breast diseases , educational level, energy Intake, family	None
		336 vs 363				≥312.1 vs <166.9 µg/day folate in nondrinkers	1.05 (0.90-1.22) $P_{interaction}$:0.83		
		23 vs 336				≥312.1 µg/day	1.30 (0.85-2.00)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
						folate and ≥2 drinks/day alcohol vs <166.9 µg/day folate in nondrinkers	$P_{interaction}$:0.83	history of cancer, HRT use, multivitamin supplement Intake, parity, physical activity, race	
Maruti, 2009 BRE80259 USA	VITAL, Prospective Cohort, Age: 50-76 years, W, Postmenopausal	663/ 35 023 5 years	SEER registry	Semi-quantitative FFQ, folate – natural and synthetic from foods	Incidence, breast cancer	450-1483 vs 37-259 µg/day	0.91 (0.68-1.22) Ptrend:0.76	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, benign breast disease, BMI, energy Intake, family history of cancer, height, mammography, physical activity, postmenopausal hormone use, race	Person-years per quantile
Larsson, 2008 BRE80208 Sweden	SMC, Prospective Cohort, Age: 54 years, W	1 584/ 61 433 17.4 years	Cancer registry	FFQ	Incidence, Invasive breast cancer, postmenopausal	per 100 ug/day	0.97 (0.88-1.07)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, benign breast disease, BMI, educational level, energy Intake, family history of cancer, height, parity, postmenopausal hormone use, use of oral contraception	RR rescaled for an increment of 50 µg/day

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Ericson, 2007 BRE80128 Sweden	MDCS, Prospective Cohort, Age: 50- years, Postmenopausal	392/ 11 699 9.5 years	Cancer registry	Dietary history questionnaire, interview	Incidence, Invasive breast cancer, 50 years and older	582 vs 160 µg/day	0.59 (0.36-0.97) Ptrend:0.01	Age, age at menopause, alcohol intake, body weight, height, household physical activity, HRT use, leisure time physical activity, season of year, smoking habits, socio-economic status, temp, total energy intake, vitamin B12 intake, vitamin B6 intake, vitamins	None
Stolzenberg-Solomon, 2006 BRE80113 USA	PLCO, Prospective Cohort, Age: 55-74 years, W, Postmenopausal	700/ 31 411 4.94 years	Self-report in the annual mail-in survey, state cancer registries, death certificates, physician reports, and (for deceased persons) reports from the next of kin	FFQ	Incidence, breast cancer	≥412 vs ≤261.3 mg/day	1.01 (0.80-1.27) Ptrend:0.72	Age , age at first child, age at menarche, age at menopause, benign breast disease, educational level, energy intake , family history, HRT use, mammography, oral contraceptive use, parity/pregnancies	Mid-points of exposure categories

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Sellers, 2004 BRE18027 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	1 875/ 33 552 14 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	≤172 vs >294 µg/day	1.19 (0.98-1.45) Ptrend:0.20	Age , age at first child, age at menarche, age at menopause, BMI, educational level, energy Intake , height, HRT use, oral contraceptive use, parity/ pregnancies, physical activity , smoking habits, folate supplements	Reference category changed using Hamling's method, mid-points of exposure categories
	No family history of breast cancer					≤172 vs >294 µg/day in non-drinkers	0.96 (0.73-1.26)		
						≤172 vs >294 µg/day in drinkers	1.40 (1.05-1.86)		
	With family history of breast cancer					≤172 vs >294 µg/day in non-drinkers	2.21 (1.43-3.41)		
						≤172 vs >294 µg/day in drinkers	2.39 (1.36-4.20)		
Rohan, 2000b BRE17968 Canada	CNBSS, Case Cohort, W	817/ 56 837 13 years	Partially histological - over 80%	FFQ-quantitative	Incidence, invasive breast cancer, postmenopausal	≥354.28 vs ≤224.77 µg/day	0.92 (0.71-1.20) Ptrend:0.57	Age , age at menarche, alcohol, design, energy intake, family	Mid-points of exposure categories
		639/				Consumers of	1.15 (0.86-1.54)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
						≤14 g/day alcohol		history, other specified factor, parity/pregnancies, recruitment center	
		178/				Consumers of <14 g/day alcohol	0.28 (0.14-0.55)		

Table 361 Dietary folate and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Lajous, 2006 BRE80135 France	E3N EPIC-France, Prospective Cohort, Age: 0 years, W, Postmenopausal	1 812/ 62 739 9 years	Patient records/direct contact/health Insurance records	FFQ	Incidence, invasive & in situ breast cancer	522 vs 296 µg/day	0.78 (0.67-0.90) Ptrend:0.001	Age, age at menarche, age at menopause, alcohol Intake, benign breast disease, BMI, breastfeeding, educational level, family history of breast cancer, height, HRT use, mammography, oral contraceptive use, parity, physical activity, residence, supplement use, time period, vitamin use	Superseded by de Batlle, 2015

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Tjønneland, 2006 BRE80104 Denmark	DCH, Nested Case Control, Age: 50-64 years, Postmenopausal	388/ 388 controls	Cancer registry	FFQ	Incidence, breast cancer	>400 vs ≤250 µg/day	0.80 (0.37-1.69)	Age at first child, benign breast disease, BMI, educational level, energy intake , nutrients, parity/pregnancies, supplements	Superseded by Roswall, 2010
						per 100 µg/day	0.82 (0.62-1.07)		
Feigelson, 2003 BRE02720 USA	CPS II, Prospective Cohort, W	1 303/ 66 561 6 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	≥294.3 vs ≤178.7 µg/day	1.07 (0.91-1.27)	Age , age at first child, age at menarche, age at menopause, BMI, body weight, educational level, ethnicity, family history, HRT use, mammography, nutrients, other nutritional factors, parity/pregnancies, physical activity , residual (willet), supplements	Superseded by Stevens, 2010

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Sellers, 2001 BRE80420 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	1 586/ 34 387 12 years	State health registry	Semi-quantitative FFQ	Incidence, postmenopausal breast cancer	≤172 vs >294 µg/day	1.21 (0.91-1.61)	Age at first child birth, age at menarche, age at menopause, alcohol, BMI, BMI at age 18 years, educational level, family history of breast cancer, height, hormone replacement therapy, oral contraceptive use, other b vitamins, parity, physical activity, smoking, waist to hip ratio	Superseded by Sellers, 2004

Figure 446 RR estimates of postmenopausal breast cancer by levels of dietary folate intake

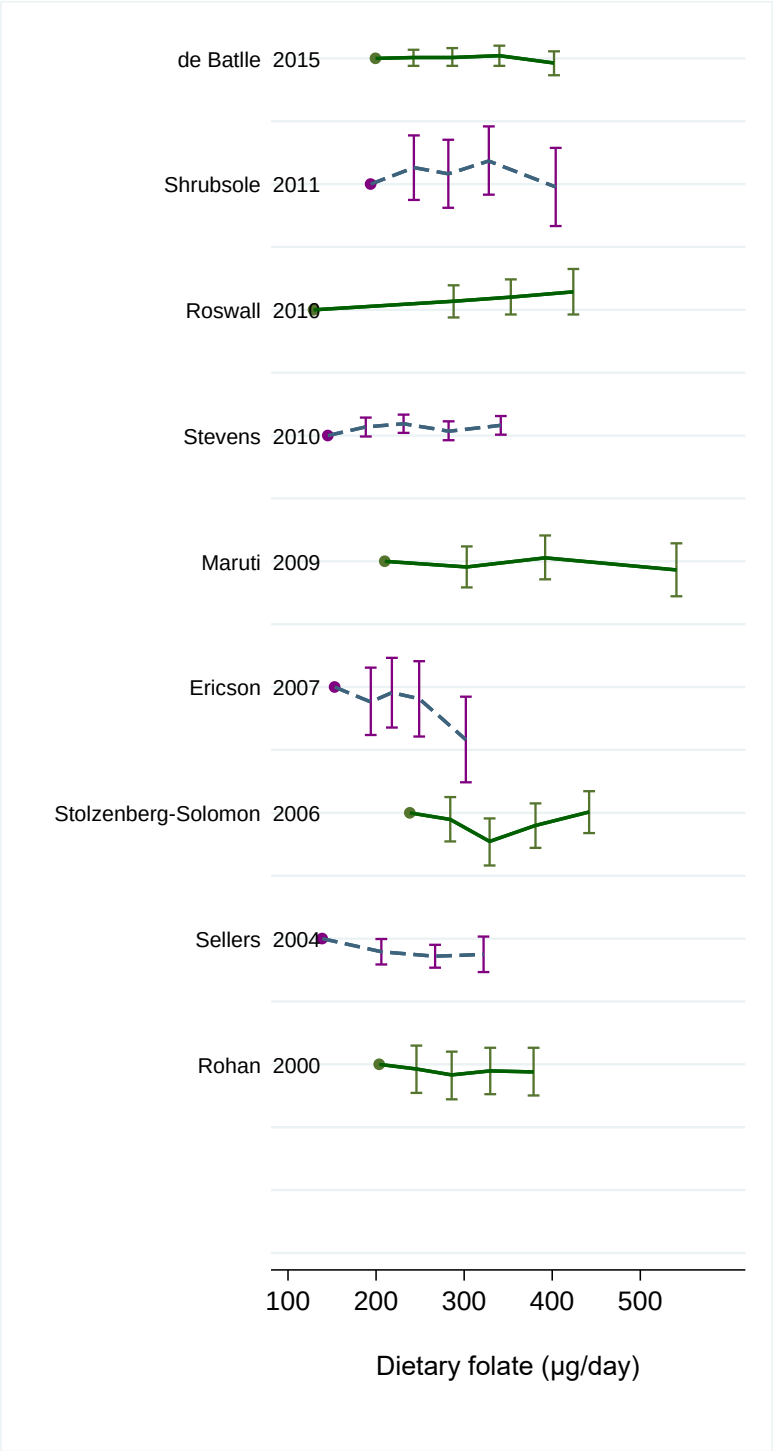


Figure 447 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest level of dietary folate intake

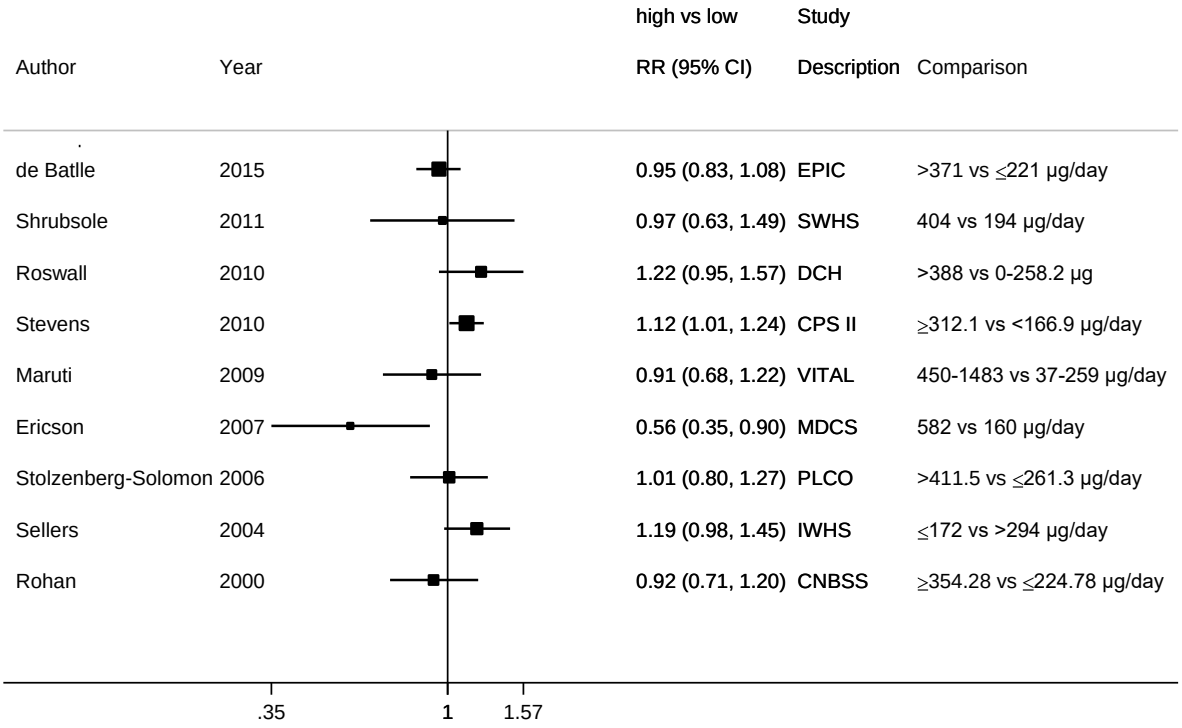


Figure 448 Relative risk of postmenopausal breast cancer for 50 µg/day increase of dietary folate intake

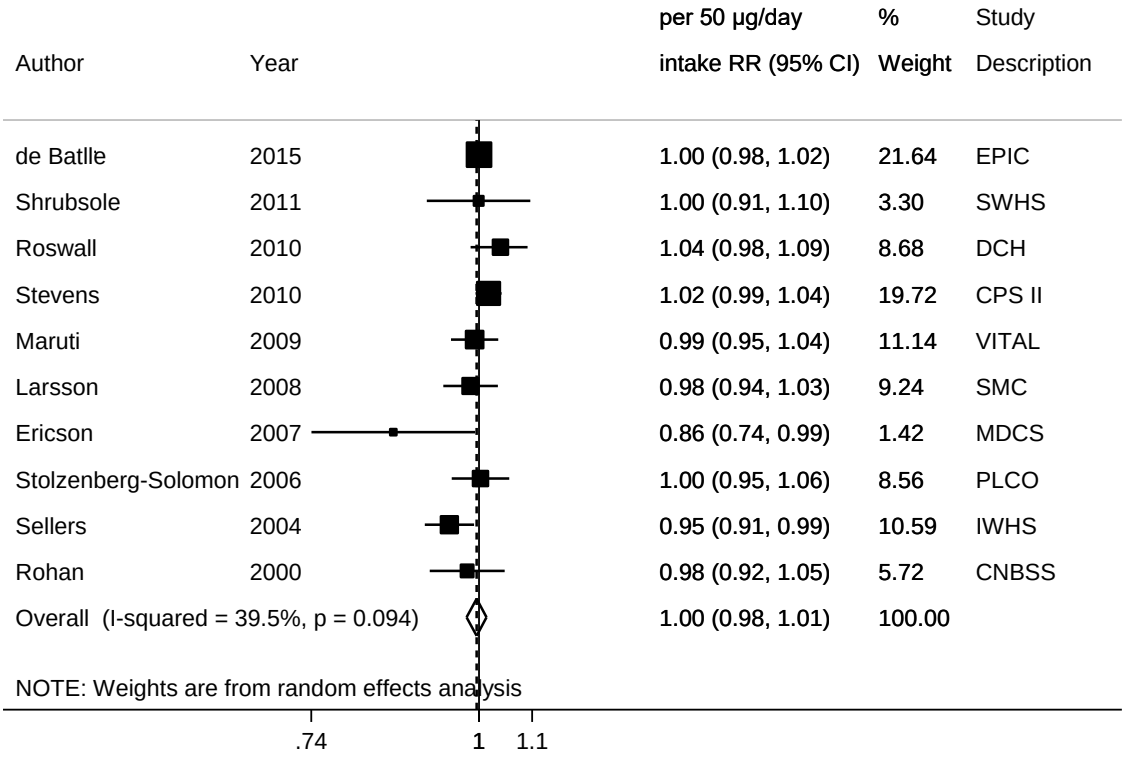


Figure 449 Funnel plot of studies included in the dose response meta-analysis of dietary folate and postmenopausal breast cancer

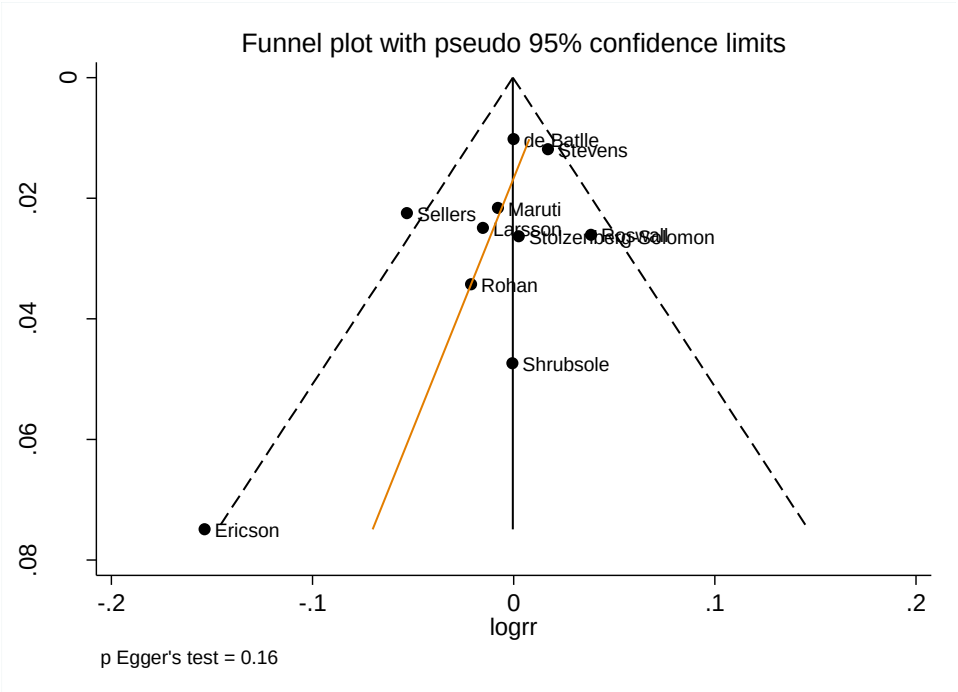
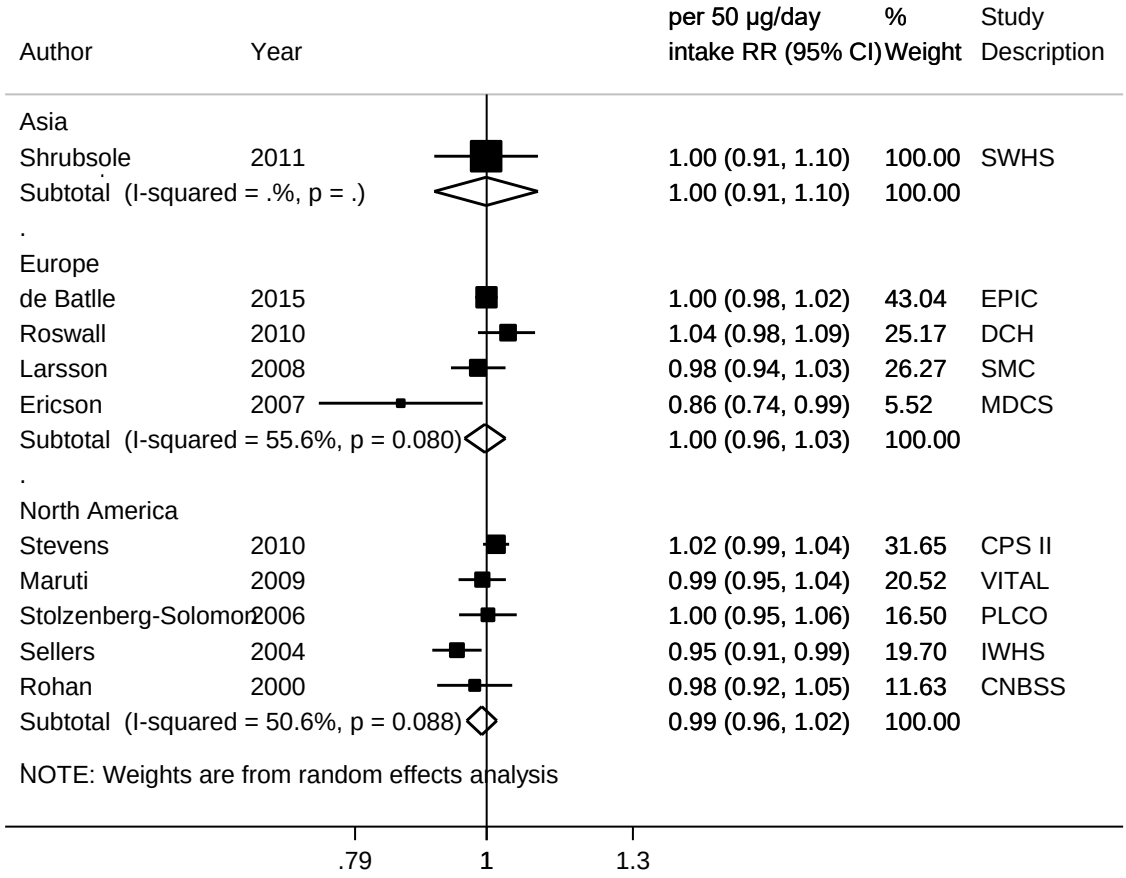


Figure 450 Relative risk of postmenopausal breast cancer incidence for 50 µg/day increase of dietary folate intake, by geographic location



5.5.10 Total vitamin D (from food and supplements)

Cohort studies

Overall summary

Six studies and two meta-analyses were identified.

Dose response meta-analysis was not conducted due to inadequate number of studies.

Breast cancer

Two studies were identified.

The NOWAC study examined the association between breast cancer and dietary vitamin D including cod liver oil supplements, in a large Norwegian population-based cohort. It did not find an association between vitamin D and breast cancer for the highest compared to the lowest intake (Edvardsen, 2011).

The NHANES I showed an inverse non-significant association between breast cancer and intake of 200 I.U or more or daily supplements of vitamin D compared to less than 100 I.U. without daily supplements of vitamin D (John, 1999).

Table 362 Main characteristics of prospective studies on total vitamin D and risk of breast cancer.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Edvardsen, 2011 BRE80294 Norway	NOWAC, Prospective Cohort, Age: 40-70 years, W	844/ 41 811 8.5 years	Cancer registry	FFQ	Incidence, breast cancer	20.8 vs 2.7 mcg/day	1.06 (0.86-1.31) Ptrend:0.69	Age, alcohol consumption, BMI, family history of cancer, height, HRT use, mammography, menopausal status, OC use, parity and age at first birth combined
John, 1999 BRE04433 USA	NHANES I, Prospective Cohort, Age: 25-74 years, W	177/ 4 747 17.3 years	Medical records + self-reported +death certificate	24h recall	Incidence, breast cancer	≥200 I.U./day or daily supplements vs <100 I.U./day without daily supplements	0.86 (0.61-1.20) Ptrend:0.37	Age , age at menarche, age at menopause, alcohol, BMI, calcium intake, educational level, physical activity

Table 363 Total vitamin D intake and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Chen, 2009*	11studies (7 cohort and 4 case-control studies)	Not reported	USA	Breast cancer	Highest vs lowest dietary Fixed-effect Random effect	 0.91 (0.85-0.97) 0.91 (0.83-1.00)	-	 24.3%, -
Gissel, 2008*	6 prospective studies	9 144	USA, Canada	Breast cancer	Non-linear dose response	0.98 (0.93-1.03)	-	-, <0.01

*All cohort studies identified were included in the present review.

Premenopausal breast cancer

Two studies were identified.

The WHS study showed an inverse borderline association between highest total vitamin D intake and premenopausal breast cancer compared to the lowest (Lin, 2007). Stratified analysis by hormone receptor showed that among women with ER+ and PR+ premenopausal breast cancer there was an inverse significant association for the highest compared to the lowest total vitamin D intake. Among ER- premenopausal breast cancers a positive non-significant association was found, while there was no association for PR- premenopausal breast cancers for the same comparison.

The NHS study showed an inverse significant association for the highest versus the lowest total vitamin D intake and premenopausal breast cancer (Shin, 2002).

Table 364 Main characteristics of prospective studies on total vitamin D and risk of premenopausal breast cancer.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Lin, 2007 BRE80165 USA	WHS, Prospective Cohort, Age: 54-56 years, W	276/ 31 487 10 years	Medical records	FFQ	Incidence, Invasive breast cancer, premenopausal	≥548 vs ≤162 I.U./day	0.65 (0.42-1.00) Ptrend:0.07	Age, age at first child birth, age at menarche, alcohol consumption, BMI, family history of cancer, history of breast cyst, multivitamin supplement intake, parity, physical activity, randomised treatment assignment, smoking status, total energy intake
		206/			ER+		0.64 (0.40-1.03) Ptrend:0.14	
		58/			ER-		0.68 (0.26-1.77) Ptrend:0.41	
		186/			PR+		0.62 (0.38-1.02) Ptrend:0.09	
		74/			PR-		0.83 (0.36-1.92) Ptrend:0.81	
Shin, 2002 BRE16658 USA	NHS, Prospective Cohort, Age: 47 years, W, Registered nurses	827/ 88 691 16 years	Medical records	FFQ	Incidence, Invasive breast cancer, premenopausal	>500 vs ≤150 I.U./day	0.72 (0.55-0.94)	Age, age at first child, age at menarche, alcohol, beta-carotene intake, BMI, breast diseases, energy intake , family history, glycaemic index, height, other design issue, fat intake, parity, physical activity, time period, vitamin E intake, weight change since 18y old

Table 365 Total vitamin D intake and premenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Chen, 2009*	6 studies (3 cohort and 3 case-control studies)	Not reported	USA, Germany, Italy	Premenopausla breast cancer	Highest vs lowest dietary	0.83 (0.73-0.95)	-	34.5%, -

*All cohort studies identified were included in the present review.

Postmenopausal breast cancer

Four studies were identified.

The WHS study (Lin, 2007) found a positive non-significant association for postmenopausal breast cancer and the highest total vitamin D intake compared to the lowest. Similarly, positive non-significant associations were found among ER+, PR+ and PR- postmenopausal breast cancer for the highest versus the lowest total vitamin D intake, while no association was found for ER- postmenopausal breast cancer.

The IWHS study (Robien, 2007) reported no association for the highest versus the lowest total vitamin D intake and postmenopausal breast cancer. Furthermore, no association was found among ER+/PR+ postmenopausal breast cancers, while an inverse non-significant association was found among ER+/PR- and ER-/PR- postmenopausal breast cancers.

The CPS II study (McCullough, 2005) did not find an association between postmenopausal breast cancer and total vitamin D for the highest versus the lowest intake. For the same comparison an inverse non-significant association was found among ER+ postmenopausal breast cancers, while a positive non-significant association was found for ER- cases.

No association was found in the NHS study (Shin, 2002) between postmenopausal breast cancer and the highest total vitamin D intake compared to the lowest.

Table 366 Main characteristics of prospective studies on total vitamin D and risk of postmenopausal breast cancer.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95% CI) Ptrend	Adjustment factors
Lin, 2007 BRE80165 USA	WHS, Prospective Cohort, Age: 54-56 years, W	743/ 31 487 10 years	Medical records	FFQ	Incidence, Invasive breast cancer, postmenopausal	≥548 vs ≤162 I.U./day	1.30 (0.97-1.73) Ptrend:0.52	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, family history of cancer, history of breast cyst, multivitamin supplement intake, parity, physical activity, postmenopausal hormone therapy at baseline, randomised treatment assignment, smoking status, total energy intake
		602/			ER+		1.23 (0.94-1.61) Ptrend:0.17	
		109/			ER-		0.94 (0.45-1.98) Ptrend:0.78	
		522/			PR+		1.17 (0.89-1.56) Ptrend:0.30	
		179/			PR-		1.22 (0.69-2.15) Ptrend:0.64	
Robien, 2007 BRE80130 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	2 440/ 34 321	State health registry	FFQ	Incidence, Invasive breast cancer	800-3468 vs 2-399 I.U./day	0.89 (0.77-1.03) Ptrend:0.12	Age, age at first child birth, age at menarche, age at menopause, BMI, educational level, estrogen use, family history of cancer, mammography, parity, physical activity, place of residence, smoking status, total alcohol drinking, total energy intake, total fat
		1 221/			ER+/PR+		0.96 (0.78-1.18) Ptrend:0.69	
		230/			ER+/PR-		0.85 (0.53-1.36) Ptrend:0.5	
		224/			ER-/PR-		0.77 (0.48-1.25) Ptrend:0.29	
McCullough, 2005 BRE23368 USA	CPS II, Prospective Cohort, Age: 50-74 years, W, Postmenopausal	2 855/ 68 567 9 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	≥701 vs ≤100 I.U./day	0.95 (0.81-1.13) Ptrend:0.98	Age , age at first child, age at menopause, alcohol, breast diseases , educational level, energy Intake , ethnicity, family history, height, HRT use, mammography, other anthropometric Index, parity/pregnancies
		1 283/	All histology		ER+		0.84 (0.65-1.09) Ptrend:0.57	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95% CI) Ptrend	Adjustment factors
		227/	All histology		ER-		1.35 (0.79-2.33) Ptrend:0.82	
Shin, 2002 BRE16658 USA	NHS, Prospective Cohort, Age: 47 years, W, Registered nurses	2 345/ 88 691 16 years	Medical records	FFQ	Incidence, Invasive breast cancer, postmenopausal	>500 vs ≤150 I.U./day	0.94 (0.80-1.10)	Age, age at first child, age at menarche, age at menopause, alcohol, beta-carotene intake, BMI, breast diseases, energy intake , family history, glycaemic index, height, HRT use, other design issue, fat intake, parity, physical activity, time period, vitamin E intake, weight change since 18y old

Table 367 Total vitamin D intake and postmenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Chen, 2009*	5 studies (4 cohort and 1 case-control studies)	Not reported	USA, Italy	Postmenopausla breast cancer	Highest vs lowest dietary	0.94 (0.83-1.07)	-	51.9%, -

*All cohort studies identified were included in the present review

5.5.10 Dietary vitamin D

Cohort studies

Overall summary

Ten publications from nine different cohorts that examined dietary vitamin D intake were identified.

Dose response meta-analysis on dietary vitamin D intake with risk of postmenopausal breast cancer was conducted. There was not enough data to do dose-response meta-analysis on premenopausal breast cancer.

Table 368 Summary of results of the dose-response meta-analysis in the 2016 CUP SLR

	Postmenopausal breast cancer
Dietary vitamin D Increment unit used	 100 I.U./day
Studies (n)	5
Cases	11 864
RR (95%CI)	1.00 (0.97-1.04)
Heterogeneity (I^2, p-value)	51.5%, 0.083
P value Egger test	0.134

Note: Not enough data on breast cancer (any) and premenopausal breast cancer

Breast cancer (any)

Three studies and one component of one cohort consortium from five publications were identified. None of the studies reported significant associations: EPIC study (Abbas, 2013) and the EPIC French component E3N (Engel 2011), a Norwegian study (Yang L, 2011; Kuper, 2009), the NHANES I study (John, 1999).

In another publication in the NHS II, dietary vitamin D intake during adolescence was not related to breast cancer risk during adulthood (Frazier, 2004).

Premenopausal breast cancer

Three studies from four publications were identified. None of the studies reported significant association of dietary vitamin D and premenopausal breast cancer risk: the EPIC study (Abbas, 2013) and the E3N cohort participating in EPIC (Engel, 2011), the WHS study (Lin, 2007) and the NHS (Shin, 2002)

Table 369 Main characteristics of prospective studies on dietary vitamin D and risk of breast cancer.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data estimated for analysis
Abbas, 2013 BRE80460 Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, UK	EPIC, Prospective Cohort, W	7 760/ 319 985 8.8 years	Cancer and pathology registry, active follow up, health Insurance record, mortality registry and contact of participants or next-of-kin	FFQ, diet history depending on the country	Incidence, Invasive breast cancer	≥5.46 vs ≤1.85 mcg/day	1.04 (0.94-1.14) Ptrend:0.92	Age, age at menarche, alcohol, centre location, contraception, educational level, fat, height, hormone use, menopausal status, non-alcohol energy, non-fat energy, physical activity, smoking, weight	
						per 1 mcg/day	1.02 (0.99-1.06)		
		1 802/			Premenopausal	≥5.46 vs <1.85 mcg/day	1.07 (0.87-1.32) Ptrend:0.78		
		4259/			Postmenopausal		1.02 (0.90-1.16) Ptrend:0.21		
Yang L, 2011 BRE80378 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	1 053/ 49 559 15 years	Cancer registry	Semi-quantitative FFQ	Incidence, breast cancer	≥5.11 vs ≤2.91 mcg/day	0.95 (0.80-1.13) Ptrend:0.24	Age, age at first child birth, age at menarche, alcohol drinking, BMI, breastfeeding, contraception, educational level, family history of breast cancer, parity, physical activity, smoking	
Lin, 2007 BRE80165 USA	WHS, Follow-up RCT, Age: 54-56 years, W	276/ 31 487 10 years	Medical records	FFQ	Incidence, Invasive breast cancer, premenopausal	≥319 vs ≤141.9 I.U./day	1.02 (0.69-1.53) Ptrend:0.4	Age, age at first child birth, age at menarche, alcohol consumption, BMI, family history of cancer, history of breast cyst, multivitamin supplement intake, parity, physical activity, randomised treatment	
		743/			Postmenopausal		1.22 (0.95-1.55) Ptrend:0.09		
		602/			ER+		1.23 (0.94-1.61) Ptrend:0.17		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data estimated for analysis
		109/			ER-		0.94 (0.45-1.98) Ptrend:0.78	assignment, smoking status, total energy intake	
Robien, 2007 BRE80130 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	2 440/ 34 321 18 years	State health registry	FFQ	Incidence, Invasive breast cancer	802-3301 vs 2-399 I.U./day	0.55 (0.24-1.22) Ptrend:0.14	Age, age at first child birth, age at menarche, age at menopause, BMI, educational level, estrogen use, family history of cancer, mammography, parity, physical activity, place of residence, smoking status, total alcohol drinking, total energy intake, total fat	
McCullough, 2005 BRE23368 USA	CPS II, Prospective Cohort, Age: 50-74 years, W, Postmenopausal	2 855/ 68 567 9 years	Active follow-up	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	>300 vs ≤100 I.U./day	0.89 (0.76-1.03) Ptrend:0.21	Age, age at first child, age at menopause, alcohol, breast diseases , educational level, energy intake, ethnicity, family history, height, HRT use, mammography, other anthropometric index, parity/pregnancies, supplements	
		1 283/			ER+		0.74 (0.59-0.93) Ptrend:0.006		
		227/			ER-		1.03 (0.61-1.73) Ptrend:0.84		
Shin, 2002 BRE16658 USA	NHS, Prospective Cohort, Age: 47 years, W, Registered	827/ 88 691 16 years	Medical records	Repeated FFQ	Incidence, Invasive breast cancer, premenopausal	>300 vs ≤75 I.U./day	0.66 (0.43-1.00)	Age, age at first child, age at menarche, alcohol, beta-carotene intake, BMI, breast diseases, energy intake , family history,	
					Postmenopausal		1.06 (0.85-1.34)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data estimated for analysis
	nurses	1 567/						glycaemic index, height, other design issue, fat intake, parity, physical activity, time period, vitamin E intake, weight change since 18y old	
John, 1999 BRE04433 USA	NHANES I, Prospective Cohort, Age: 25-74 years, W	177/ 4 747 17.3 years	Medical records, self-reported and death certificate	24h recall	Incidence, breast cancer	≥200 vs ≤99 I.U./day	0.85 (0.59-1.24) Ptrend:0.48	Age , age at menarche, age at menopause, alcohol, BMI, educational level, other nutritional factors, physical activity	

Table 370 Dietary vitamin D intake and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reason for exclusion
Engel, 2011 BRE80308 France	E3N EPIC-France, Prospective Cohort, Age: 40-65	2 761/ 67 721 10.4 years	Follow up questionnaires (self-report), medical record and pathology	FFQ	Incidence, Invasive breast cancer	≥113.1 vs ≤79.9 I.U./day	0.94 (0.86-1.03) Ptrend:0.13	Age at menarche, age at menopause, alcohol intake, BMI, bone mineral densitometry exams, calcium supplement,	Superseded from Abbas 2013

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reason for exclusion
	years, W, teachers	614/	reports		Premenopausal		1.03 (0.85-1.25) Ptrend:0.9	diabetes & thyroid disease, dietary calcium, family history of breast cancer, history of breast cyst, menopausal status, number of full-term pregnancies, physical activity, skin complexion, smoking status, sun burn resistance, total energy intake without alcohol, university, use of HRT, use of oral contraception	
		2 147/			Postmenopausal		0.92 (0.83-1.02) Ptrend:0.08		
Kuper, 2009 BRE80246 Sweden	WLHS, Prospective Cohort, Age: 30-50 years	840/ 41 889 12.9 years	Cancer registry	FFQ	Incidence, Invasive breast cancer	Q4 vs Q1	0.90 (0.80-1.10)	Age, age at first child birth, age at menarche, alcohol Intake, BMI, breastfeeding, educational level, family history of cancer, OC use, parity, physical activity, smoking habits	Superseded by Yang L, 2011
Frazier, 2004 USA	NHS II, Retrospective cohort, Age: 34-51 years, W	361/ 47 355	Medical records	High school FFQ (adolescent diet)	Incidence, Invasive breast cancer as adults	591 vs 159.6 I.U./day	0.97 (0.70-1.34) Ptrend:0.78	Age, time period, height, parity and age at first birth, BMI at age 18, age at menarche, family history of breast cancer, history of BBD, menopausal status, alcohol intake, energy, oral contraceptive use, weight gain since age 18	Adolescent diet

Table 371 Dietary vitamin D intake and breast cancer risk. Results of recent meta-analyses of prospective studies SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Kim, 2014b*	10 prospective cohort studies	22 341 breast cancer	Europe, USA	Breast cancer	Highest vs lowest analysis	0.95 (0.88-1.01)	-	38.3%, 0.086
Hong, 2012*	13 studies (6 cohorts and 7 case-control studies)	20 343 breast cancer	Europe, USA, Japan, Canada, Taiwan, Mexico	Breast cancer	Non-linear dose-response 50 I.U./day 100 I.U./day 150 I.U./day 200 I.U./day 250 I.U./day 300 I.U./day 350 I.U./day 500 I.U./day	 0.98 (0.95-1.00) 0.95 (0.92-0.99) 0.93 (0.89-0.98) 0.92 (0.88-0.96) 0.91 (0.87-0.96) 0.91 (0.87-	-	-

					600 I.U./day	0.85) 0.90 (0.86-0.95) 0.90 (0.85-0.95) 0.90 (0.85-0.95)		

*All cohort studies identified were included in the present review. Include studies in pre- and post-menopausal breast cancers

Postmenopausal breast cancer

Summary

Main results:

Five studies (11 864) out of six publications identified could be included in the dose-response meta-analysis. There was one European (Abbas, 2013) and four American studies (Lin, 2007; Robien, 2007; McCullough, 2005; Shin, 2002).

No association was found for postmenopausal breast cancer and dietary vitamin D intake (per 100 I.U./ day). High heterogeneity was found between the studies. There was no statistical evidence of significant publication or small study bias but the number of studies was low and the funnel plot is asymmetric, suggesting the presence of small study bias. Subgroup analysis was not conducted due to the low number of studies in each stratum.

Sensitivity analyses:

The summary RR did not change materially when studies were omitted in turn in influence analysis.

Non-linear dose response meta-analysis:

Non-linear dose-response meta-analysis was not performed due to the low number of studies with adequate data.

Study quality:

All studies used FFQ to assess diet and derived dietary vitamin D intake from food composition tables, except NHANES I (John, 1999) in which one 24 hour recall was applied. Food histories were collected in some EPIC centres (Abbas, 2013).

All studies had a follow up of at least 8.8 years. Loss to follow-up was low in the cohorts that reported such information. Case identification was through cancer registries and when identified through active follow-up, the cancer diagnosis was verified using medical records.

All studies were adjusted for main risk factors.

Table 372 Dietary vitamin D intake and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	5 (6 publications)
Studies included in forest plot of highest compared with lowest exposure	5 (6 publications)
Studies included in linear dose-response meta-analysis	5 (6 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 373 Dietary vitamin D intake and postmenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005/2008 SLR and 2016 CUP

	2005 SLR*	**2016 CUP**
Dietary calcium intake **Increment unit used**	-	100 I.U./day
Studies (n)	-	5
Cases	-	11 864
RR (95%CI)	-	1.00 (0.97-1.04)
Heterogeneity (I^2, p-value)	-	51.5%, 0.083
P value Egger test	-	0.134

*No meta-analysis in the past report

Figure 451 RR estimates of postmenopausal breast cancer by levels of dietary vitamin D intake

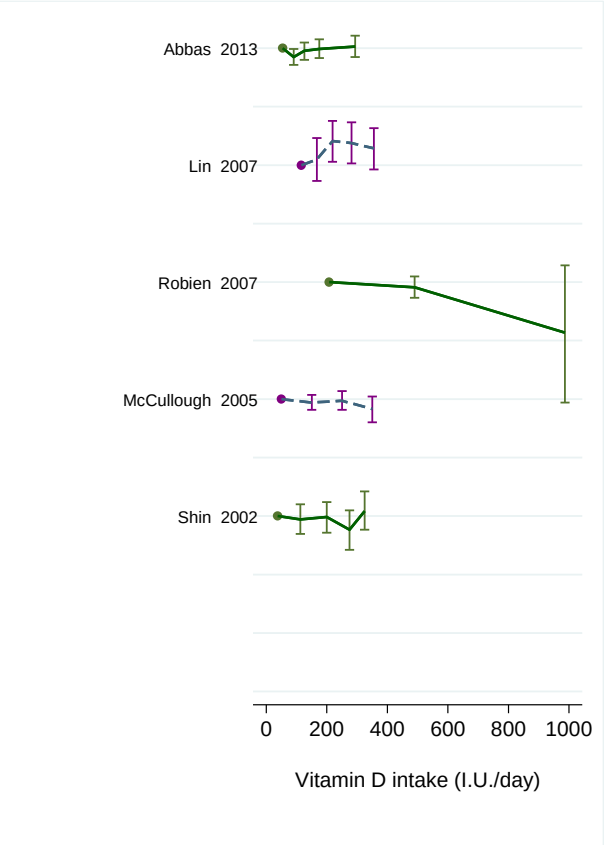


Figure 452 RR (95% CI) of postmenopausal breast cancer for the highest dietary vitamin D intake compared with reference category

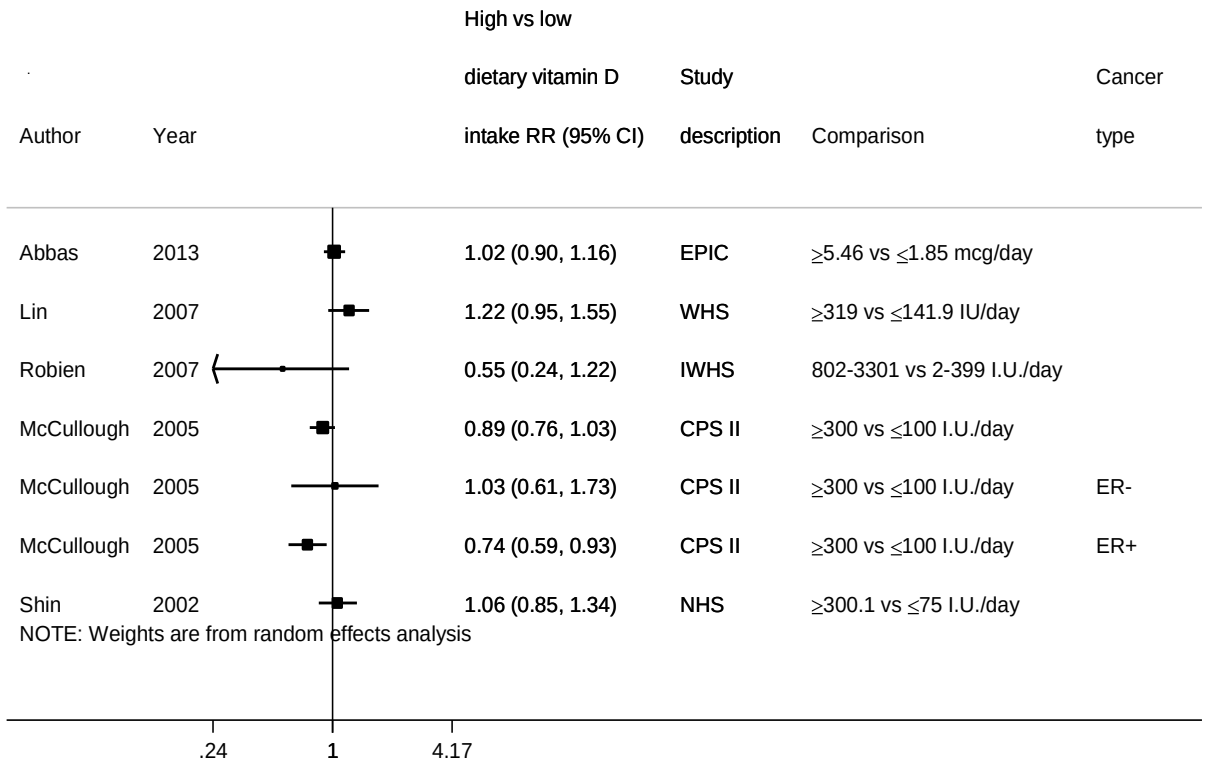


Figure 453 Relative risk of postmenopausal breast cancer for 100 I.U./day increase of dietary vitamin D intake

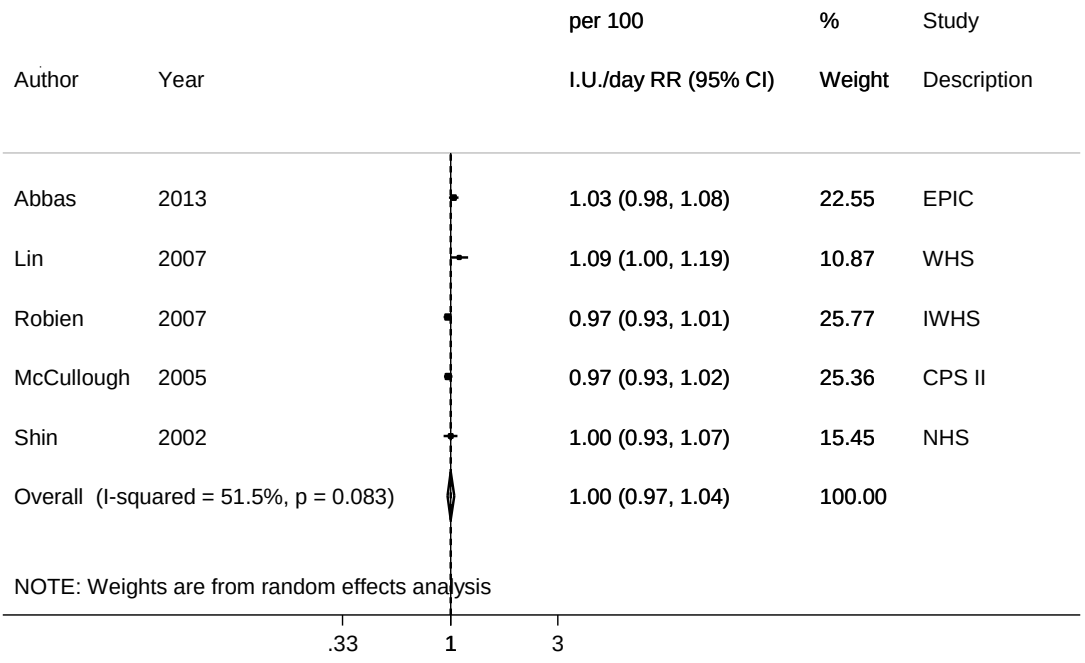
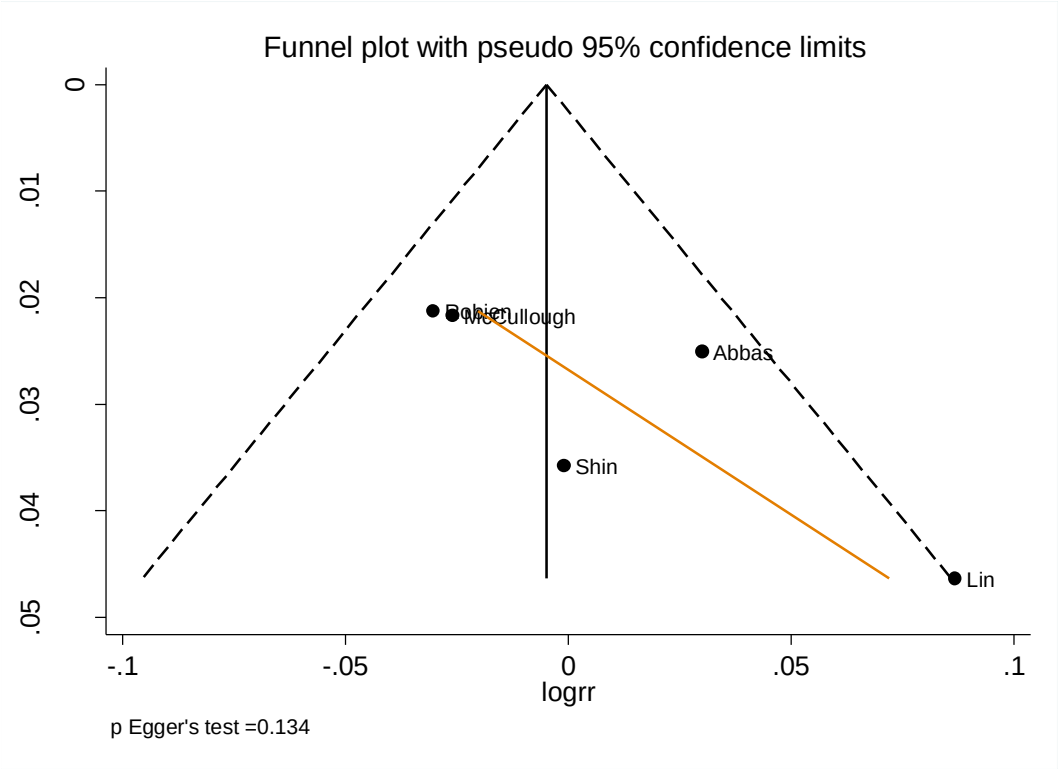


Figure 454 Funnel plot of studies included in the dose response meta-analysis of dietary vitamin D intake and postmenopausal breast cancer



5.5.10 Vitamin D from supplements

Randomised controlled trials

Overall summary

Two meta-analysis of RCTs were identified (Bjelakovic, 2014; Sperati, 2013), reporting no association between supplemental vitamin D (alone or with calcium) intake and risk of breast cancer. From the studies that were included in the two meta-analyses, one was designed to investigate cancer risk and mortality as primary outcome (WHI; Brunner, 2011). The WHI study used calcium and vitamin D supplementation as the intervention arm (CaD) and placebo as the control (PLA). Hence, the results are reported in the Calcium (and Vitamin D) chapter. Another study, with primary outcomes all-cause mortality, vascular disease mortality and cancer mortality and incidence did not report HRs for breast cancer (RECORD trial; Avenell, 2012). Of the rest five studies, two had as primary outcome blood pressure reduction (Witham, 2013; Larsen, 2012), one the number of upper respiratory tract infection episodes (Murdoch, 2012), on changes on biomarkers of CVD (Wood, 2012) and one fracture incidence (Lappe, 2007). Vitamin D (VitD) was administered singly in four studies (Witham, 2013; VitD: 0 cases vs PLA: 1 case; Larsen, 2012; VitD: 1 case vs PLA: 0 cases; Murdoch, 2012; VitD: 3 cases vs PLA: 1 case; Wood, 2012; VitD:1 case vs PLA: 1 case) or combined with calcium (Ca) in two studies (Brunner, 2011: CaD: 505cases vs PLA: 523 cases; Lappe, 2007: CaD: 5 cases vs PLA and Ca: 14 cases). One trial tested singly or/and combined with calcium (Avenell, 2012: VitD and CaD: 43 cases vs PLA and Ca: 37 cases). One study (Witham, 2013) does not report number of breast cancer cases. It is unclear how Bjelakovic (2014) retrieved this information.

Table 374 Supplemental vitamin D intake and breast cancer risk. Results of meta-analyses of randomized controlled trials published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Bjelakovic, 2014	7 studies	558(VitD arm) 577 (No VitD arm)	USA, UK, Denmark, New Zealand	Breast cancer incidence	Vitamin D or Vitamin D plus Calcium vs Placebo or no intervention	0.79 (0.86-1.09)	-	0.0%
Sperati, 2013	2 studies	25 (VitD arm) 27 (No VitD arm)	UK, USA	Breast cancer incidence	Vitamin D or Vitamin D plus Calcium vs No vitamin D	0.93 (0.54-1.60)		0.0%

Cohort studies

Overall summary

Five studies were identified.

Dose response meta-analysis was not conducted due to the low number of studies with the required information.

Breast cancer (any)

Two studies (E3N-EPIC; Engel, 2011; NHANES I; John, 1999) were identified. The E3N cohort, which included French women who were mainly teachers did not find any association between breast cancer and vitamin D supplementation when comparing Vitamin D supplement users with women with less than 80 I.U./day of dietary vitamin D intake (Engel, 2011). Women living in areas with higher exposure to UV had reduced risk of breast cancer. In the NHANES I, daily use of vitamin D supplements (single or from multivitamins) was related to a non significant breast cancer risk reduction. The risk reductions were highest for women who lived in United States regions of high solar radiation. No reductions in risk were found for women who lived in regions of low solar radiation. Vitamin D intake was in general low in the study population. Only 28% of women exceeded the recommended dietary intake of 200 IU. The study was limited by the low sample size (190 cases) .

Premenopausal breast cancer

Two studies were identified (E3N-EPIC; Engel, 2011; WHS; Lin, 2007).

The E3N-EPIC study found an inverse non-significant association between premenopausal breast cancer among women who were using vitamin D supplementation compared to women who had less than 80 I.U./day of dietary vitamin D intake (Engel, 2011). The WHS study revealed an inverse non-significant association for the highest versus the lowest vitamin D supplementation (≥400 I.U./day vs none) and premenopausal breast cancer (Lin, 2007).

Postmenopausal breast cancer

Four studies were identified (E3N-EPIC; Engel, 2011; WHS; Lin, 2007; IWHS; Robien, 2007; WHI; Prentice, 2013b). None of the studies reported an association.

The WHI Observational study (Prentice, 2013b) did not find an association of vitamin D supplements use and postmenopausal breast cancer.The E3N-EPIC study (Engel, 2011) did not find an association of postmenopausal breast cancer risk and vitamin D supplementation use compared to less than 80 I.U./day dietary vitamin D intake. The WHS and IWHS (Lin, 2007; Robien, 2007) reported no association between the highest vitamin D supplement intake (≥400 I.U./day and ≥800 I.U./day, respectively) compared to nonusers.

Table 375 Main characteristics of prospective studies on vitamin D from supplements and risk of breast cancer (any).

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Prentice, 2013b BRE80438 USA	WHI, Observational Study, Age: 50-79 years, W, Postmenopausal	60/ 46 892 7 years	Self-reported verified by local and central physician adjudicators	FFQ and interview	Incidence, Invasive breast cancer, postmenopausal	Yes vs No	1.01 (0.75-1.34)	Age, BMI, calcium Intake, ethnicity, hormone use, smoking, time of recruitment
Engel, 2011 BRE80308 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W, teachers	1 037/ 67 721 10.4 years	Follow up questionnaires (self-report), medical record and pathology reports	Questionnaire	Incidence, Invasive breast cancer	Supplemented vs non supplement with <80 I.U./day from diet	0.90 (0.72-1.12)	Age at menarche, age at menopause, alcohol Intake, BMI, calcium supplement, diabetes & thyroid disease, dietary calcium, family history of breast cancer, history of breast cyst, mammographic exam, menopausal status, number of full-term pregnancies, physical activity, skin complexion, smoking status, sun burn resistance, total energy intake without alcohol, university degree, use of HRT, use of oral contraception
		931/			Premenopausal		0.68 (0.25-1.87)	
		821/			Postmenopausal		0.91 (0.73-1.14)	
Lin, 2007 BRE80165	WHS, Prospective	276/ 31 487	Medical records	FFQ	Incidence, Invasive breast cancer,	≥400 vs ≤0 I.U./day	0.76 (0.50-1.17) Ptrend:0.41	Age, age at first child birth, age at menarche,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
USA	Cohort, Age: 54-56 years, W	10 years			premenopausal			alcohol consumption, BMI, family history of cancer, history of breast cyst, multivitamin supplement intake, parity, physical activity, randomised treatment assignment, smoking status, total energy intake
		743/			Postmenopausal		0.87 (0.68-1.12) Ptrend:0.31	
Robien, 2007 BRE80130 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	2 440/ 34 321 0	State health registry	FFQ	Incidence, Invasive breast cancer, postmenopausal	800-3200 vs ≤0 I.U./day	0.89 (0.74-1.08) Ptrend:0.33	Age, age at first child birth, age at menarche, age at menopause, BMI, educational level, estrogen use, family history of cancer, mammography, parity, physical activity, place of residence, postmenopausal hormone therapy at baseline, smoking status, total alcohol drinking, total energy intake, total fat
John, 1999 BRE04433 USA	NHANES I, Prospective Cohort, Age: 25-74 years, W	177/ 4 747 17.3 years	Medical records + self-reported +death certificate	24h recall	Incidence, breast cancer	daily vs never	0.89 (0.60-1.32) Ptrend:0.52	Age , age at menarche, age at menopause, alcohol, BMI, educational level, calcium intake, physical

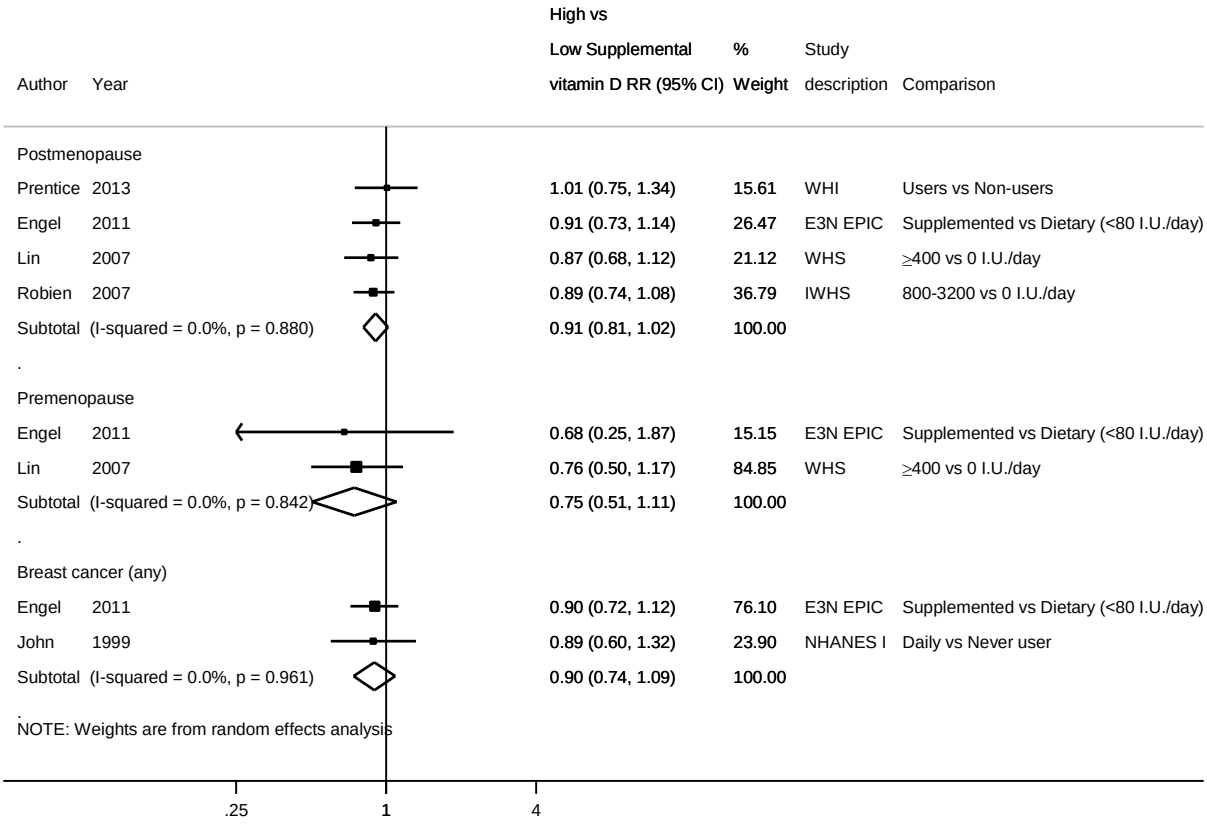
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								activity

Table 376 Vitamin D intake from supplements and breast cancer risk. Results of recent meta-analyses of prospective studies

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Chen, 2009*	3 cohort studies	Not reported	USA	Breast cancer	Highest vs lowest dietary	0.87 (0.76-0.99)	-	0%, -

*All cohort studies identified were included in the present review.

Figure 455 RR (95% CI) of breast cancer for the highest vitamin D intake from supplements compared with the reference category, by menopausal status



5.5.10 Blood 25-hydroxy vitamin D

Cohort studies

Overall summary

Sixteen studies from twenty publications that examined blood 25-hydroxy vitamin D were identified. Seven meta-analyses and no pooled-analysis were identified.

Dose response meta-analyses were conducted to examine association of blood 25-hydroxy vitamin D with risk of breast premenopausal and postmenopausal breast cancer.

Table 377 Summary of results of the dose-response meta-analysis in the 2016 CUP SLR

	Breast cancer (any)	Premenopausal breast cancer	Postmenopausal breast cancer
Blood 25-hydroxy vitamin D Increment unit used	30 nmol/l	30nmol/l	30 nmol/l
Studies (n)	6	5	8
Cases	3 640	1 177	5 269
RR (95%CI)	0.99 (0.89-1.09)	1.04 (0.91-1.18)	0.96 (0.89-1.03)
Heterogeneity (I^2, p-value)	31.5%, 0.195	26.2%, 0.238	4.1%, 0.406
P value Egger test	0.005	0.272	0.112

Breast cancer (any)

Summary

Main results:

Six out of ten cohort studies (12 publications) identified could be included in the dose-response meta-analysis of blood 25-hydroxy vitamin D (3 640 cases). There was on European (Kühn, 2013), two American (Mohr, 2013; Eliassen, 2011), two Danish (Skaaby, 2014; Rejnmark, 2009) and one Swedish (Almquist, 2010) study.

No association was found for breast cancer and blood 25-hydroxy vitamin D (per 30nmol/l). There was moderate heterogeneity. There was evidence of significant publication bias. Furthermore there was an outlier (Rejnmark, 2009).

Six studies on breast cancer incidence were excluded from the dose-response meta-analysis. Two of them found a positive non-significant association (NHS II; Wang, 2014; ESTHER; Ordonez-Mena, 2013), two found an increased association (E3N-EPIC; Engel, 2010; NHS; Bertone-Jonson, 2005) but only one of them found a significant association (Engel, 2010) and two found no association (NYUWHS and NSMSC; Scarmo, 2013; NSABP-P1; Amir, 2012) between breast cancer and the highest blood 25-hydroxy vitamin D levels compared to the lowest. Significant p-trend was found for Engel (2010) and Bertone-Jonson (2005).

One study (two publications) on breast cancer mortality was further excluded from the analysis (NHANES III; Freedman, 2010; Freedman, 2007). The former publication reported an inverse non-significant association, while the latter showed inverse significant association between breast cancer mortality and the highest blood 25-hydroxy vitamin D compared to the lowest.

Subgroup analysis was not contacted due to the low number of studies in the strata.

Sensitivity analysis:

The summary RR did not change materially when studies were omitted in turn in influence analysis.

Non-linear dose-response meta-analysis:

Non-linear dose-response meta-analysis was not conducted due to insufficient number of studies.

Study quality:

All studies were nested case-control studies except one (Skaaby, 2014). One of the studies in the dose-response analysis was adjusted for age, alcohol intake, BMI and reproductive factors (Almquist, 2010). The rest of the studies were adjusted or matched for several factors including some of the aforementioned variables.

Table 378 Blood 25-hydroxy vitamin D and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	10 (12 publications)
Studies included in forest plot of highest compared with lowest exposure	10 (12 publications)
Studies included in linear dose-response meta-analysis	6 (8 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 379 Blood 25-hydroxy vitamin D and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005SLR and 2016 CUP

	2005SLR*	**2016 CUP**
Dietary calcium intake Increment unit used	-	30nmol/l
Studies (n)	-	6
Cases	-	3 640
RR (95%CI)	-	0.99 (0.89-1.09)
Heterogeneity (I^2, p-value)	-	31.5%, 0.195
P value Egger test	-	0.005

*No meta-analysis in the past reports.

Table 380 Blood 25-hydroxy vitamin D and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Kim, 2014b[1]	14 cohort studies	9 526 breast cancer	USA, Europe, Canada	Breast cancer incidence	Highest vs lowest	0.92 (0.83-1.02)	-	27.3%, 0.162
	4 cohort studies	4 556 breast cancer	Norway, Belgium, USA, Germany	Breast cancer mortality		0.58 (0.40-0.85)		26.7%, 0.251
Bauer, 2013[2]	9 cohort studies	5 206 breast cancer	USA, Denmark, Finland, Sweden, France	Breast cancer incidence	Per 5ng/ml	0.99 (0.97-1.00)	-	-
							-	-
Hong, 2012[2,3]	11 studies (7 cohort and 4 case-control studies)	8 716 breast cancer	USA, Sweden, Mexico, Germany, France	Breast cancer	Non-linear dose-response		-	-
					5ng/ml	0.97 (0.93-1.02)		
					10 ng/ml	0.95 (0.088-1.03)		
					15 ng/ml	0.92 (0.84-1.02)		
					20 ng/ml	0.87 (0.79-0.96)		
					25 ng/ml	0.82 (0.75-0.89)		
					30 ng/ml	0.78 (0.71-0.85)		
					35 ng/ml	0.77 (0.71-0.84)		
					40 ng/ml	0.80 (0.75-0.85)		

Chung, 2011[2]	4 cohort studies	2 363 breast cancer	USA, Sweden	Breast cancer incidence	Per 10nmol/l	0.99 (0.97-1.01)	-	-
Gandini, 2011[2]	10 studies (5 cohort and 5 case-control studies)	6 175 breast cancer	USA, UK, Germany, Denmark	Breast cancer All studies Cohort studies	 Per 10ng/ml 	 0.89 (0.81-0.98) 0.97 (0.92-1.03)	 - -	 88%, <0.001 54%, 0.07
Yin, 2010[2]	10 studies (5 cohort and 5 case-control studies)	6175 breast cancer	USA, UK, Germany, Denmark	Breast cancer Fixed effect Random effect	 Per 20ng/ml	 0.74 (0.69-0.80) 0.73 (0.6-0.88)	 <0.001 0.001	83.9%, 0.01
Chen, 2009[2]	7 studies (3 cohort and 4 case-control studies)	5 489breast cancer	UK, Germany, USA	Breast cancer Fixed effect Random effect	Highest vs lowest	 0.58 (0.50-0.66) 0.55 (0.38-0.80)	-	-
Garland, 2007[2]	2 studies (1 cohort and 1 case-control)	880 breast cancer	USA, UK	Breast cancer	Dose-response gradient (52ng/ml)	0.50	<0.001	

[1]Studies on breast cancer mortality were not included in the present review because there were not fulfilling the inclusion criteria (exposure was a biomarker taken after cancer diagnosis, or the population was on cancer survivors)

[2]All cohort studies identified were included in the present review.

[3]Study reports results for blood 1,25-dihydroxy and 25-hydroxy vitamin D.

Table 381 Blood 25-hydroxy vitamin D and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Skaaby, 2014 BRE80520 Denmark	Monica10, Inter99, Health2006, Prospective Cohort, Age: 18-71 years, W	159/ 12 204 11.3 years	Cancer registry		Incidence, breast cancer	Q4 vs Q1	1.11 (0.71-1.71) Ptrend:0.821	Alcohol, BMI, educational level, fish, gender, physical activity, season, smoking, study. Continuous results were further adjusted for age
						per 10 nmol/l	1.02 (0.96-1.09) Ptrend:0.53	
		Not reported/			BMI >25 kg/m^2	per 10 nmol/l	1.04 (0.95-1.13) Ptrend:0.460	
		Not reported/			BMI: ≤25 kg/m^2	per 10 nmol/l	0.98 (0.90-1.08) Ptrend:0.699	
Kühn, 2013 BRE80467 multi-national	EPIC, Nested Case Control, Age: 35-70 years, W	1 391/ 1391 controls	Cancer registries, Health insurance records, pathology records & active follow up		Incidence, breast cancer	>63.0 vs ≤39.3 nmol/l	1.07 (0.85-1.36) Ptrend:0.67	Age at first child birth, age at first menses, alcohol consumption, BMI, breastfeeding, educational level, number of childbirths, physical activity, smoking status
						per 200 %	1.01 (0.86-1.19)	
		643/ 643 controls			ER+	≥63.1 vs ≤39.3 nmol/l	0.97 (0.67-1.38) Ptrend:0.90	
						per 200 %	0.99 (0.77-1.28)	
					ER-	≥63.1 vs ≤39.3 nmol/l	0.97 (0.66-1.42) Ptrend:0.98	
		547/ 547 controls				per 200 %	0.90 (0.68-1.18)	
		801/ 801 controls			BMI <25	per 200 %	0.83 (0.67-1.03)	
		590/ 590 controls			BMI ≥25		1.30 (1.00-1.69)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Mohr, 2013 USA	US military screening 2002-2008 Nested case-control	600/ 600 controls	Hospitalisation or ≥ 3 outpatient medical care visits		Incidence, breast cancer	≤14.9 vs ≥35.2 ng/ml	1.19 (0.80-1.80) Ptrend:0.72	Age, date of blood sample, length of service, race
Eliassen, 2011 BRE80376 USA	NHS II, Nested Case Control, Age: 25-42 years, W, Registered nurses	613/ 1218 controls	Questionnaire/medical records/death record		Incidence, breast cancer	≥30.6 vs ≤18.4 ng/ml	1.20 (0.88-1.63) Ptrend:0.32	Age at first child birth, age at menarche, benign breast disease, blood draw visit, BMI, BMI at age 18 years, date of blood collection, family history of breast cancer, fasting status at time of blood collection, luteal day, parity, race, time
		415/ 1218 controls			Incidence, Invasive breast cancer		1.29 (0.92-1.81) Ptrend:0.14	
		321/ 1218 controls			ER+		1.21 (0.84-1.75) Ptrend:0.29	
		77/ 1218 controls			ER-		1.31 (0.63-2.74) Ptrend:0.47	
		275/ 1218 controls			ER+/PR+		1.16 (0.79-1.71) Ptrend:0.43	
		70/ 1218 controls			ER-/PR-		1.18 (0.54-2.60) Ptrend:0.64	
		358/ 678 controls			BMI <25		0.90 (0.60-1.33) Ptrend:0.45	
		255/ 540 controls			BMI ≥25		1.90 (1.19-3.03) Ptrend:0.005	
Almquist, 2010 BRE80293 Sweden	MDCS, Nested Case Control, Age: 57 years, W	735/ 735 controls 15 years	Cancer registry		Incidence, Invasive & In situ breast cancer	≥107 vs ≤71 nmol/l	0.96 (0.68-1.37) Ptrend:0.78	Age, age at menarche, albumin, alcohol consumption, biomarkers, BMI, calendar year, country of birth, creatinine,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								educational level, hormonal variables, HRT use, marital status, menopausal status, OC use, parity, phosphate, PTH and calcium, quartiles of 25OHD, smoking status, socio-economic status
		Not reported			BMI ≥25	≥107 vs ≤71 nmol/l	0.99 (0.61-1.62) Ptrend:0.88	Age at baseline, menopausal status, screening month and year, BMI (continuous)
		Not reported			BMI < 25		0.90 (0.57-1.43) Ptrend:0.85	
Rejnmark, 2009 BRE80365 Denmark	Danish mammography exam participants study, Nested Case Control, Age: 58 years, W	142/ 420 controls	Pathology		Incidence, breast cancer	≥84 vs ≤60 nmol/l	0.52 (0.32-0.85)	Age, menopausal status, season

Table 382 Blood 25-hydroxy vitamin D and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reason for exclusion
Wang, 2014 BRE80596 USA	NHS II, Nested Case Control, Age: 25-42 years, W	584/ 584 controls 11 years	Self-report verified by medical record		Incidence, breast cancer	≥25.5 vs ≤13.2 pmol/l	1.21 (0.83-1.77) Ptrend:0.5	Age at menarche, alcohol consumption, benign breast disease, BMI at age 18 years, BMI at blood draw, family history of breast cancer, parity and age at first birth	Same as Eliassen, 2011
		398/ 584 controls			Incidence, Invasive breast cancer		1.15 (0.77-1.72) Ptrend:0.69	Further adjusted for: age at blood collection, date of blood collection, fasting condition, luteal day, menopausal status, race, time of blood collection	
		260/ 584 controls			Incidence, breast cancer ER+/PR+		1.31 (0.82-2.09) Ptrend:0.32		
		66/ 584 controls			Incidence, breast cancer ER-/PR-		0.85 (0.37-1.93) Ptrend:0.35		
		Not reported			Incidence, breast cancer, BMI≥25	Q4 vs Q1	2.11 (1.21-3.70) Ptrend:0.01	Not reported	
Ordonez-Mena, 2013 BRE80463 Germany	ESTHER, Prospective Cohort, Age: 50-74 years, W	137/ 5 261 8 years	Self-report verified by medical records or by linkage with state cancer registries		Incidence, breast cancer	Q4 vs Q2+3	1.39 (0.89-2.18)	Age, BMI, educational level, family history of cancer, fish, fruits and vegetables consumption, multivitamin supplement intake, physical activity, red meat, smoking	Quartile cut-point was different between batches
Scarmo, 2013 BRE80461 US, Sweden	NYUWHS and NSMSC, Nested Case Control,	1 585/ 2940 controls	Self-report, death report, national death Index, medical records		Incidence, Invasive breast cancer	82.6 vs 30.7 mmol/l	0.94 (0.76-1.16) Ptrend:0.27	Age at first child birth, age at menarche, alcohol, BMI, family history of breast cancer, HRT use,	Exposure ranges not clearly defined
						per 2 times	0.95 (0.84-1.07)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reason for exclusion
	Age: 54 years, W		reviewed by physicians					multivitamin, parity, physical activity, season	
		848/ 1767 controls			ER+	Q5 vs Q1	1.10 (0.83-1.44) Ptrend:0.79	Age at first child birth, age at menarche, alcohol, BMI, family history of breast cancer, HRT use, parity	
		272/ 497 controls			ER-		1.08 (0.64-1.85) Ptrend:0.85		
		819/ 1644 controls			Incidence, breast cancer, BMI<25.0		0.97 (0.73-1.29) Ptrend:0.99	Age at sampling, age at first child birth, age at menarche, alcohol, BMI, cohort, family history of breast cancer, HRT use, parity	
		735/ 1244 controls			Incidence, breast cancer, BMI≥25		0.93 (0.68-1.27) Ptrend:0.16		
Amir, 2012 US	NSABP-P1 Nested case-control Age:53.6 years	231/ 856 controls			Incidence, Invasive breast cancer	<72 vs ≥72 nmol/l	1.07 (0.74-1.54)	BMI, cigarette smoking, history of osteoporosis, hormone use, tamoxifen treatment,	Two categories
Engel, 2010 BRE80373 France	E3N EPIC-France, Nested Case Control	615/ 1218 controls 10 years	Pathology reports		Incidence, breast cancer	≥27 vs 0-19.8 ng/ml	0.73 (0.55-0.96) Ptrend:0.02	Age, age at menarche, age at menopause, alcohol consumption, benign breast disease, blood draw visit, BMI, calcium Intake, calcium level, contraception, estradiol, oestrogen replacement therapy, family history of breast cancer, hormonal contraceptive at 31y, HRT use, mammography, menopausal status, non-alcohol energy, number of	Superseded by Kühn, 2013

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reason for exclusion
								children, physical activity, progesterone, PTH hormone, smoking status, study centre, supplement use, vitamin d Intake	
Freedman, 2010 BRE80505 USA	NHANES III, Prospective Cohort, Age: 17- years, W	53/ 8 914 13.4 years	National death Index		Mortality, breast cancer	80-99.9 vs ≤49.9nmol/l	0.65 (0.18-2.38) Ptrend:0.56	Age, BMI, ethnicity, smoking	Results on mortality
Freedman, 2007 BRE80506 USA	NHANES III, Prospective Cohort, Age: 17- years, W	28/	National death Index		Mortality, breast cancer	50-79.9 vs ≤49.9nmol/l	0.28 (0.08-0.93)	Age, race, smoking history	Results on mortality
Bertone-Johnson, 2005 BRE21759 USA	NHS, Nested Case Control, Age: 43-69 years, W, Registered nurses	701/ 701 controls 6 years	Medical records and self-reported		Incidence, breast cancer	Q5 vs Q1	0.73 (0.49-1.07) Ptrend:0.06	Age at first child, age at menarche, age at menopause, alcohol, benign breast disease, biomarkers, BMI, family history, HRT use, parity/pregnancies	Quintile cut-point was different between batches

Figure 456 RR estimates of breast cancer by levels of blood 25-hydroxy vitamin D

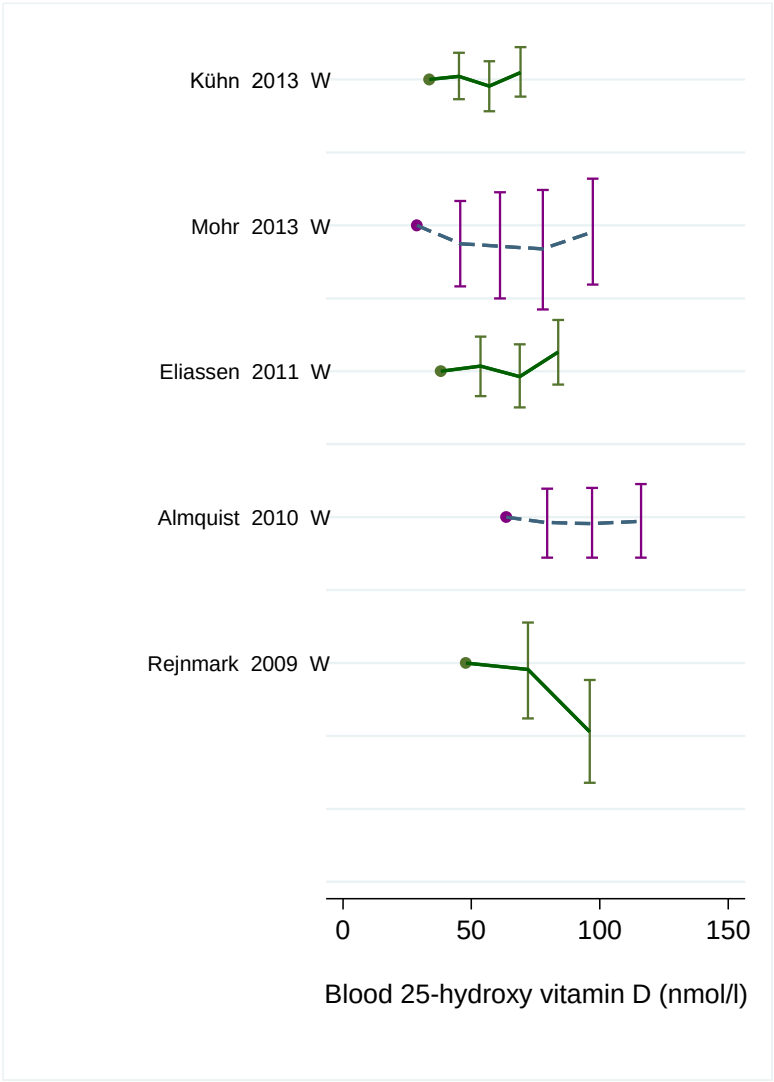
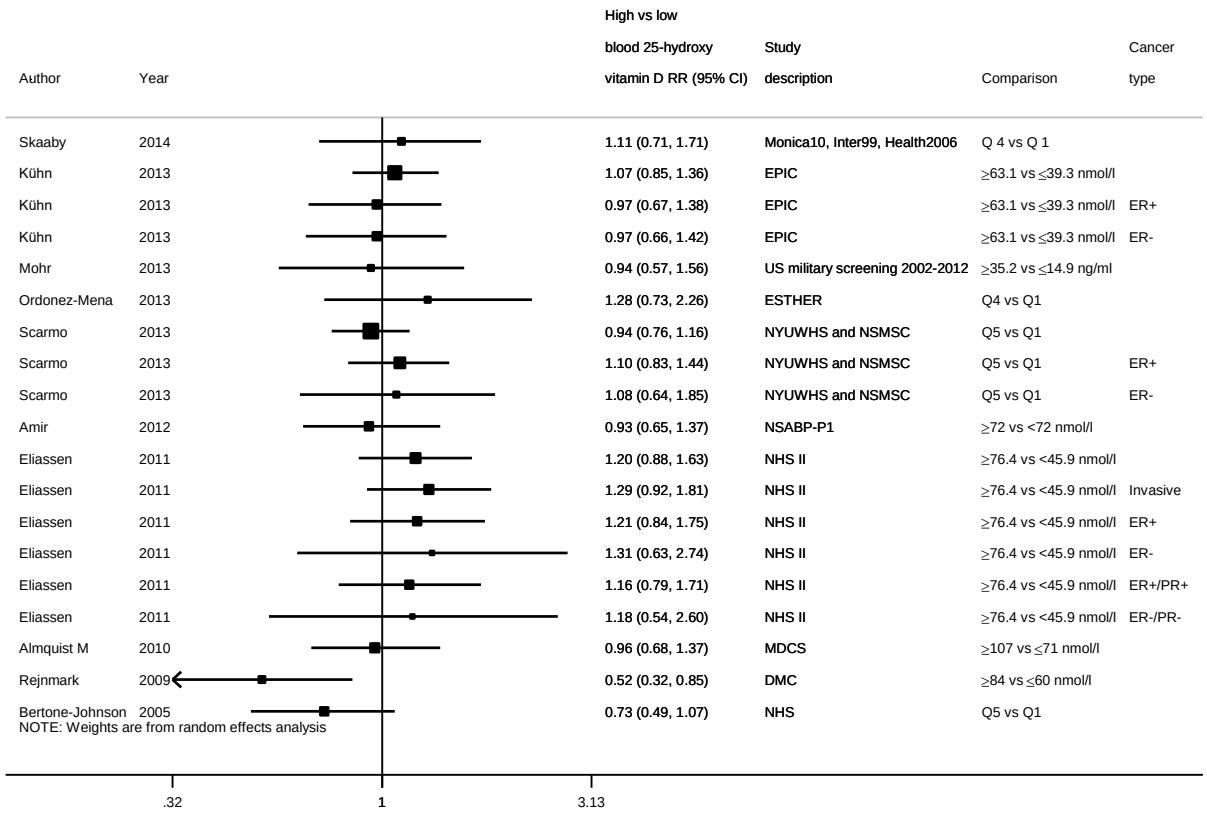


Figure 457 RR (95% CI) of breast cancer for the highest blood 25-hydroxy vitamin D intake compared with reference category



Note: HRs for Skaaby (2014) and ORs for Mohr (2013) and Amir (2012) were recalculated using the Hamling method.

Figure 458 Relative risk of breast cancer for 30nmol/l increase of blood 25-hydroxy vitamin D

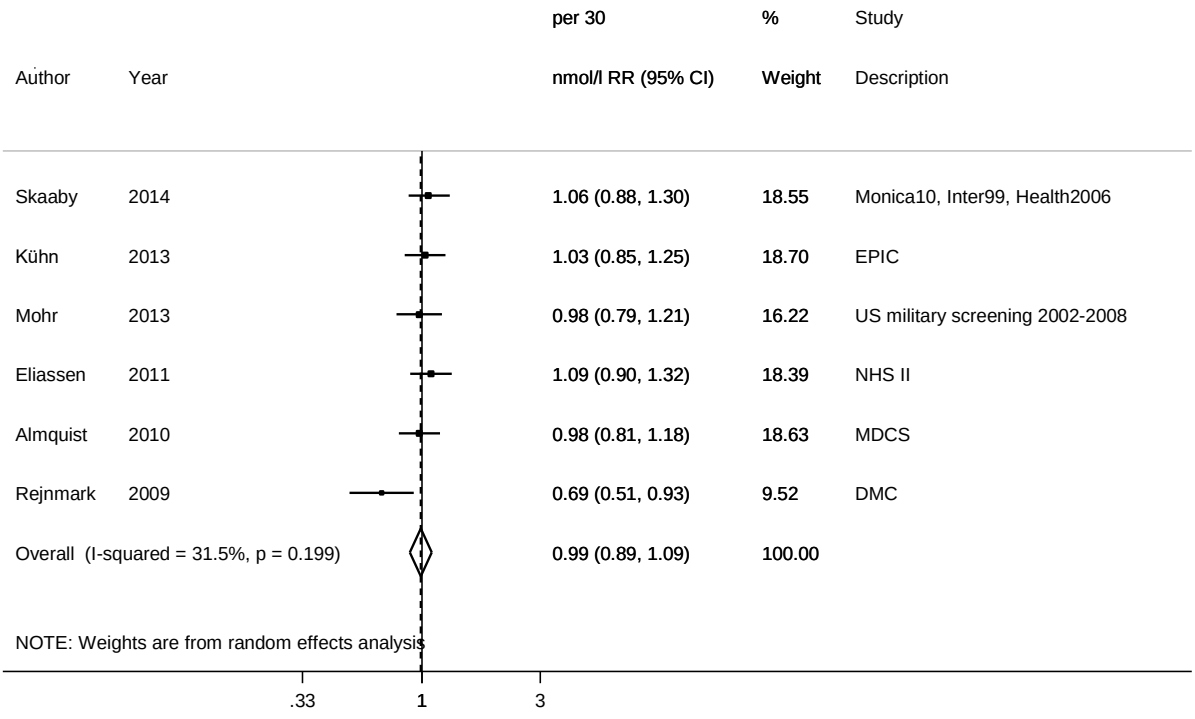
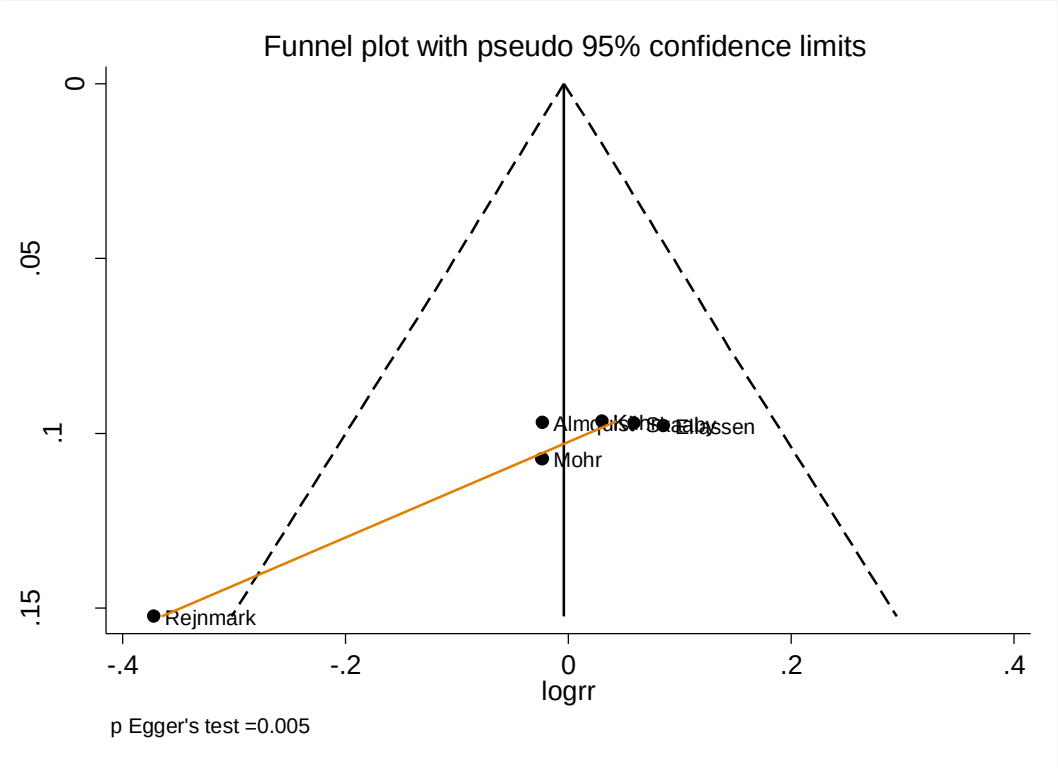


Figure 459 Funnel plot of studies included in the dose response meta-analysis of blood 25-hydroxy vitamin D and breast cancer



Premenopausal breast cancer

Summary

Main results:

Five out of seven studies (1 177 cases) (8 publications) identified could be included in the dose-response meta-analysis. There were two American studies (Eliassen, 2011; Bertone-Johnson, 2005), one Swedish (Almquist, 2010), one French (Engel, 2010) and one Danish (Rejmark, 2009) study.

No association was found for premenopausal breast cancer and blood 25-hydroxy vitamin D (per 30nmol/l). No heterogeneity was observed between studies. There was no evidence of significant or small study bias.

Three cohort studies were excluded from the dose-response meta-analysis. One of them (EPIC) reported no association between premenopausal cancer and season-standardised 25-hydroxy vitamin D on the log2 scale (Kühn, 2013). The NYUWHS and NSMSC studies (Scarmo, 2013) reported an inverse significant association for the highest versus the lowest comparison. Finally, a Finnish study reported an increased non-significant association for the lowest versus the highest comparison between blood 25-hydroxy vitamin D and pregnancy associated breast cancer (Agborsangaya, 2010). There was no significant trend.

Subgroup analysis was not conducted due to the low number of studies in the strata.

Sensitivity analysis:

The summary RR did not change materially when studies were omitted in turn in influence analysis.

Non-linear dose-response meta-analysis:

Non-linear dose-response meta-analysis was not conducted due to insufficient number of studies.

Study quality:

All studies were nested-case control studies. All of the studies included in the dose-response analysis were adjusted for alcohol intake, BMI and reproductive factors, except Rejnmark (2009).

The originally published Rejnmark study had a mean follow-up of three months. Data used for the dose-response analysis were taken from the meta-analysis Bauer (2013), which provided data restricted to cases diagnosed more than one year after blood samples were collected (personal communication). Bauer (2013) reported only continuous results, hence for the HvsL analysis and the independent dose-response analysis data for the original paper were used.

The original paper Bertone-Jonson (2005) reported different cut points of blood 25-hydroxy vitamin D between three different batches. Furthremore, the original paper reported RRs by quintile of plasma 25-hydroxy vitamin D for total cancer only. Hence, the NHS study could not be included in the HvsL and independent dose-response analysis. However, continuous results of the three different batched were taken from Bauer (2013), which was provided with additional information via personal communication. Cases and controls belonged to only one of these batches. Similar procedure was followed for Eliassen (2011).

Figure 460 Blood 25-hydroxy vitamin D and premenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	7 (8 publications)
Studies included in forest plot of highest compared with lowest exposure	4 (5 publications)
Studies included in linear dose-response meta-analysis	5 (6 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 383 Blood 25-hydroxy vitamin D and premenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005SLR and 2016 CUP

	2005SLR*	**2016 CUP**
Dietary calcium intake Increment unit used	-	30nmol/l
Studies (n)	-	5
Cases	-	1 177
RR (95%CI)	-	1.04 (0.91-1.18)
Heterogeneity (I^2, p-value)	-	26.2%, 0.238
P value Egger test	-	0.272

*No meta-analysis in the past reports.

Table 384 Blood 25-hydroxy vitamin D and premenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Bauer, 2013*	6 cohort studies	1 278	USA, Denmark, Finland, Sweden, France	Premenopausal breast cancer inicidence	Per 5ng/ml Linear dose response	0.99 (0.97-1.04)	-	-
Chen, 2009*	3 studies (1 cohort and 2 case-control studies)	Not reported	Germany, USA	Peri/premenopausal breast cancer	Highest vs lowest	0.69 (0.42-1.11)	-	-

*All cohort studies identified were included in the present review.

Table 385 Blood 25-hydroxy vitamin D and premenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Eliassen, 2011 BRE80376 USA	NHS II, Nested Case Control, Age: 25-42 years Registered nurses	613/ 1218 controls	Questionnaire/medical records/death record		Incidence, breast cancer	Per 5ng/ml*	0.99 (0.97-1.04)	Age at first child birth, age at menarche, benign breast disease, blood draw visit, BMI, BMI at age 18 years, date of blood collection, family history of breast cancer, fasting status at time of blood collection, luteal day, parity, race, time
Almquist, 2010 BRE80293 Sweden	MDCS, Nested Case Control, Age: 57 years	196/ 196 controls 15 years	Cancer registry		Incidence, invasive & in situ breast cancer	≥107 vs ≤71 nmol/l	1.74 (0.84-3.60) Ptrend:0.14	Age, age at menarche, alcohol consumption, biomarkers, BMI, calendar year, country of birth, educational level, hormonal variables, HRT use, marital status, menopausal status, OC use, other specified factor, parity, smoking status, socio-economic status
Engel, 2010 BRE80373 France	E3N EPIC-France, Nested Case Control	54cases/ 90 controls 89cases/ 180 controls 10 years	Pathology reports		Incidence, breast cancer Pre/Pre Pre/Post	≥27 vs 0-19.8 ng/ml	0.37 (0.12-1.15) Ptrend:0.11 0.72 (0.35-1.45) Ptrend:0.40	Age, age at menarche, age at menopause, alcohol consumption, benign breast disease, blood draw visit, BMI, calcium Intake, calcium level, contraception, estradiol, oestrogen replacement therapy, family history of breast cancer, hormonal contraceptive at 31y, HRT use,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								mammography, menopausal status, non-alcohol energy, number of children, physical activity, progesterone, PTH hormone, smoking status, study centre, supplement use, vitamin D intake
Rejnmark, 2009 BRE80365 Denmark	Danish mammography exam participants study, Nested Case Control, Age: 58 years	3/	Pathology		Incidence, breast cancer, premenopausal	Per 5ng/ml*	0.94 (0.65-1.36)	Age, menopausal status, season
Bertone-Johnson, 2005 BRE21759 USA	NHS, Nested Case Control, Age: 43-69 years, W, Registered nurses	222/ 235 controls 6 years	Medical records and self-reported		Incidence, breast cancer	Per 5ng/ml*	1.04 (0.96-1.13)	Age at first child, age at menarche, age at menopause, alcohol, benign breast disease, biomarkers, BMI, family history, HRT use, parity/pregnancies

Note: Pre/Pre: premenopausal ta blood collection and premenopausal at diagnosis. Pre/Post: premenopausal at blood collection and postmenopausal at diagnosis.
*Results were taken from Bauer (2013)

Table 386 Blood 25-hydroxy vitamin D and premenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reason for exclusion
Kühn, 2013 BRE80467 multi-national	EPIC, Nested Case Control, Age: 35-70 years	538/ 538 controls	Cancer registries, health insurance records, pathology rec & active follow up	Dietary recall	Incidence, Invasive breast cancer	per 200 %	1.11 (0.84-1.46)	Age at first child birth, age at first menses, alcohol consumption, BMI, breastfeeding, educational level, number of childbirths, physical activity, smoking status	ORs on the log2 scale
Scarmo, 2013 BRE80461	NYUWHS and NSMSC, Nested Case Control, Age: 54 years	637/ 1134 controls	Self-report, death report, national death Index, medical records reviewed by physicians		Incidence, Invasive breast cancer	Q5 vs Q1	0.67 (0.48-0.92) Ptrend:0.03	Age at first child birth, age at menarche, alcohol, BMI, family history of breast cancer, HRT use, multivitamin, parity, physical activity, season	Exposure ranges not clearly defined
Agborsangaya, 2010 BRE80229 Finland	Finnish Maternity Cohort, Nested Case Control, Age: 33 years	100 cases/ 100 controls (for both comparisons) 10 years	Cancer registry		Incidence, breast cancer 1st pregnancy 2nd pregnancy	≥61.6 vs ≤27.5 nmol/l	1.40 (0.50-4.20) Ptrend:0.4 2.10 (0.80-5.10) Ptrend:0.5	Age, gestational age, parity, season of interview, year of recruitment	Not comparable

Figure 461 RR estimates of premenopausal breast cancer by levels of blood 25-hydroxy vitamin D

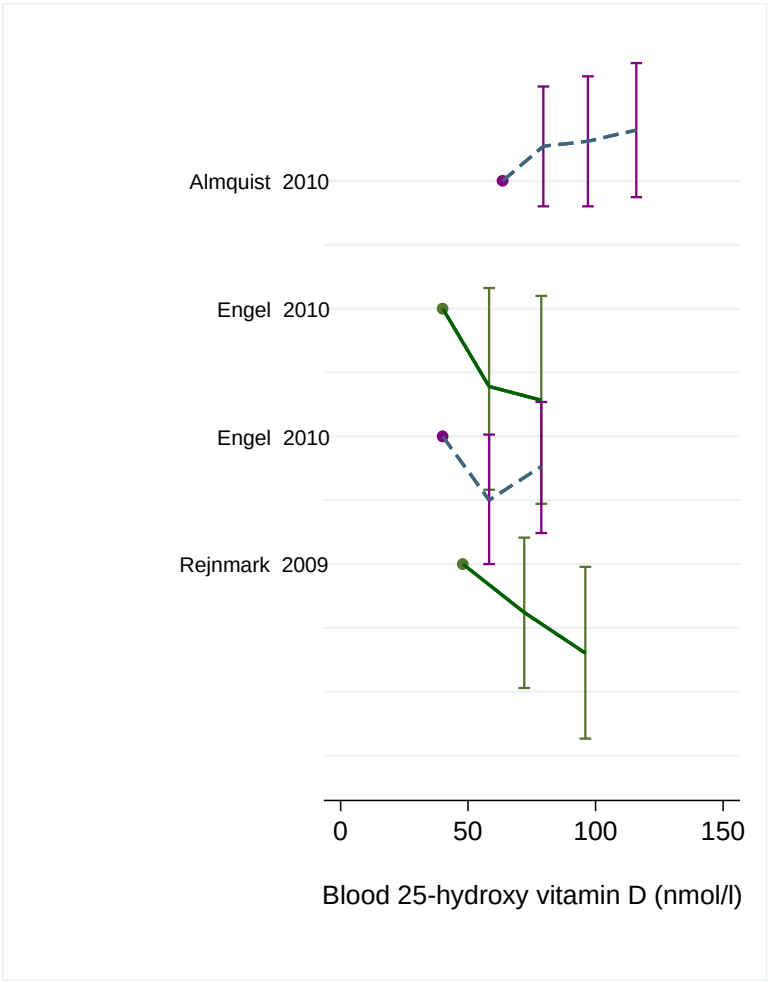
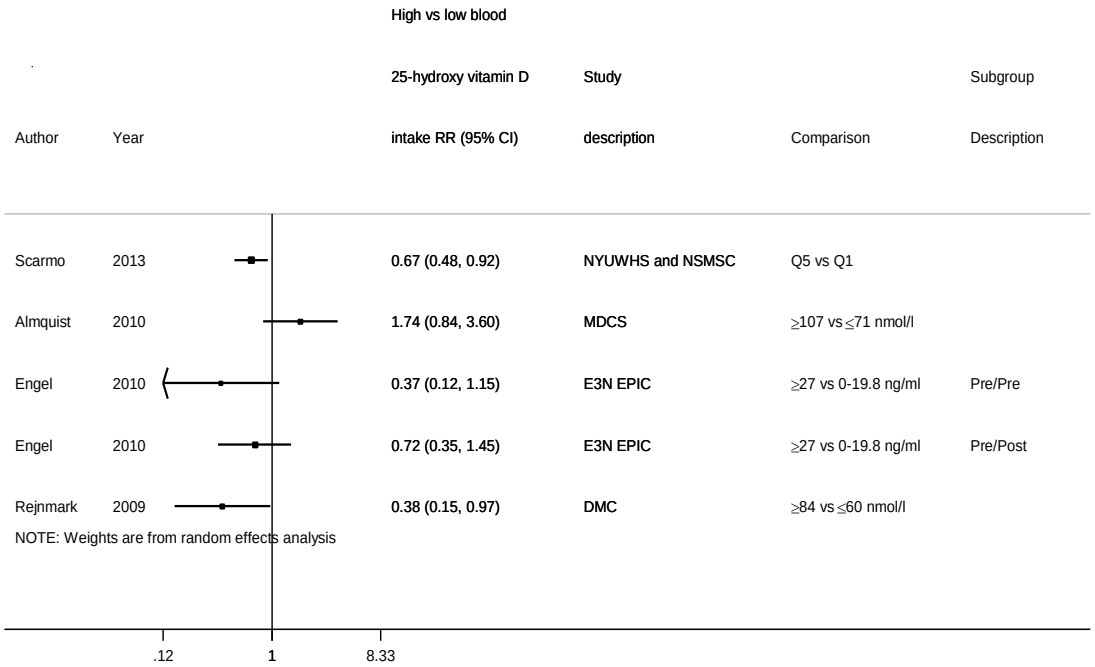
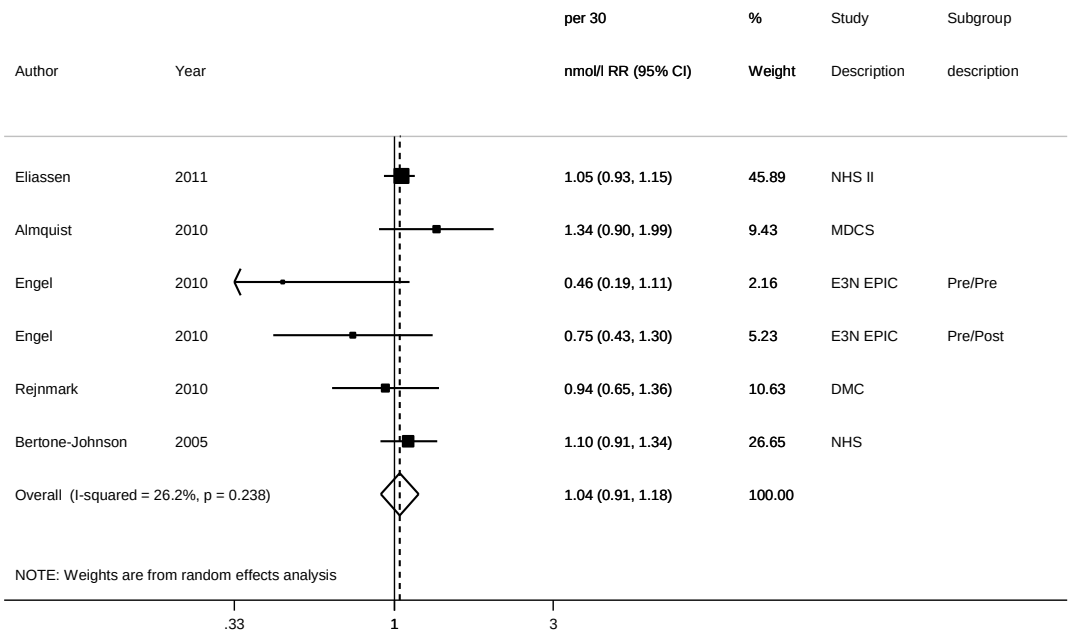


Figure 462 RR (95% CI) of premenopausal breast cancer for the highest blood 25-hydroxy vitamin D intake compared with reference category



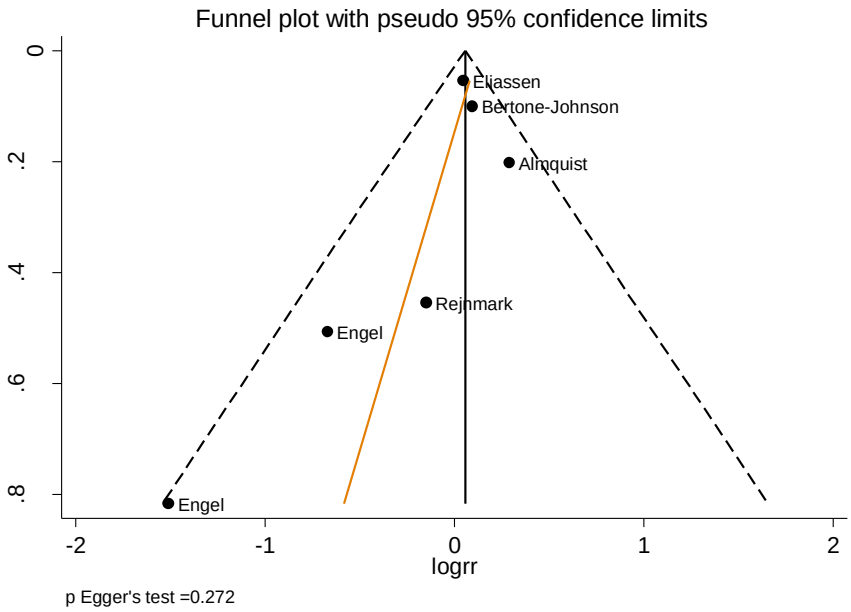
Note: Pre/Pre: premenopausal ta blood collection and premenopausal at diagnosis. Pre/Post: premenopausal at blood collection and postmenopausal at diagnosis.

Figure 463 Relative risk of premenopausal breast cancer for 30nmol/l increase of blood 25-hydroxy vitamin D



Note: Pre/Pre: premenopausal ta blood collection and premenopausal at diagnosis. Pre/Post: premenopausal at blood collection and postmenopausal at diagnosis.

Figure 464 Funnel plot of studies included in the dose response meta-analysis of blood 25-hydroxy vitamin D and premenopausal breast cancer



Postmenopausal breast cancer

Summary

Main results:

Eight out of nine studies (5 269 cases) (11 publications) identified could be included in the dose-response meta-analysis. There were four American studies (Neuhouser, 2012; McCullough, 2009; Freedman, 2008; Bertone-Jonson, 2005), one multi-ethnic study from Hawai and Los Angeles (Kim, 2014a), one Swedish (Almquist, 2010), one French (Engel, 2010) and one Danish (Rejmark, 2009) study.

No association was found for postmenopausal breast cancer and blood 25-hydroxy vitamin D (per 30nmol/l). No heterogeneity was observed between studies. There was no evidence of significant or small study bias.

Three cohort studies were excluded from the dose-response meta-analysis. One of them (EPIC) reported no association between postmenopausal cancer and season-standardised 25-hydroxy vitamin D on the log2 scale (Kühn, 2013). The NYUWHS and NSMSC studies (Scarmo, 2013) reported an increased non-significant association for the highest versus the lowest comparison, while the WHI study (Chlebowski, 2008) reported an increased non-significant association for the lowest versus the highest comparison. There was no significant trend for the last two studies.

Subgroup analysis was not conducted due to the low number of studies in the strata.

Sensitivity analysis:

The summary RR did not change materially when studies were omitted in turn in influence analysis.

Non-linear dose-response meta-analysis:

Non-linear dose-response meta-analysis was not conducted due to insufficient number of studies.

Study quality:

All studies were nested-case control studies. From the studies included in the dose-response analysis, three were adjusted for age, alcohol intake, BMI and reproductive factors (Almquist, 2010; Engel, 2010; Bertone-Jonson, 2005). The rest were adjusted for several factors including some of the aforementioned variables. One study included peri/postmenopausal women (Almquist, 2010).

The originally published Rejnmark study had a mean follow-up of three months. Data used for the dose-response analysis were taken from the meta-analysis Bauer (2013), which provided data restricted to cases diagnosed more than one year after blood samples were collected (personal communication). Bauer (2013) reported only continuous results, hence for the HvsL analysis and the independent dose-response analysis data for the original paper were used.

The original paper Bertone-Jonson (2005) reported different cut points of blood 25-hydroxy vitamin D between three different batches. Furthremore, the original paper reported RRs by quintile of plasma 25-hydroxy vitamin D for total cancer only. Hence, the NHS study could not be included in the HvsL and independent dose-response analysis. However, continuous results of the three different batched were taken from Bauer (2013), which was provided with additional information via personal communication. Cases and controls belonged to only one of these batches.

Table 387 Blood 25-hydroxy vitamin D and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	9 (11 publications)
Studies included in forest plot of highest compared with lowest exposure	7 (9 publications)
Studies included in linear dose-response meta-analysis	8 (10 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 388 Blood 25-hydroxy vitamin D and postmenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005SLR and 2016 CUP

	2005SLR*	**2016 CUP**
Dietary calcium intake Increment unit used	-	30nmol/l
Studies (n)	-	8
Cases	-	5 269
RR (95%CI)	-	0.96 (0.89-1.03)
Heterogeneity (I^2, p-value)	-	4.1%, 0.406
P value Egger test	-	0.112

*No meta-analysis in the past reports.

Table 389 Blood 25-hydroxy vitamin D and postmenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Bauer, 2013*	7 cohort studies	3 928	USA, Denmark, Sweden, France	Postmenopausal breast cancer inicidence	Per 5ng/ml Linear dose response Nonlinear dose response	0.97 (0.93-1.00) 0.88 (0.79-0.97)	- -	- -
Chen, 2009*	5 studies (3 cohort and 2 case-control studies)	Not reported	Germany, USA	Postmenopausal breast cancer	Highest vs lowest	0.60 (0.35-1.03)	-	88.8%

*All cohort studies identified were included in the present review.

Table 390 Blood 25-hydroxy vitamin D and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Kim, 2014a BRE80510 USA	MEC, Nested Case Control, Age: 45-75 years	229/ 147/ 132/ 106/ 68	Seer registry		Incidence, Invasive breast cancer, Japanese White Latinos African-American Native Hawaiian	per 10 ng/ml	0.92 (0.75-1.12) 0.53 (0.37-0.75) 1.29 (0.87-1.89) 1.27 (0.91-1.76) 0.89 (0.59-1.34)	BMI, calcium supplement, family history of breast cancer, multivitamin supplement intake, number of childbirths, season of year, strenuous exercise, sunburn history
Neuhouser, 2012 BRE80410 USA	Women's Health Initiative, Nested Case Control, Age: 50-79 years	1 080/ 1080 controls	Self-report verified by medical record		Incidence, Invasive breast cancer	<36.7 vs ≥64.9 nmol/l	1.06 (0.78-1.43) Ptrend:0.60	Alcohol intake, BMI, Gail model risk, HRT use, intervention arm, mammogram in the past 2 years, matching variables, physical activity, smoking
					BMI(kg/m^2) <25.0 25.0-29.9 ≥30.0		 0.81 (0.44-1.50) 1.02 (0.64-1.61) 1.18 (0.71-1.97)	
Almquist, 2010 BRE80293 Sweden	MDCS, Nested Case Control, Age: 57 years	568/ 568 controls 15 years	Cancer registry		Incidence, Invasive & In situ breast cancer, peri/postmenopausal	≥107 vs ≤71 nmol/l	0.88 (0.60-1.29) Ptrend:0.64	Age, age at menarche, alcohol consumption, biomarkers, BMI, calendar year, continuous values of albumin, creatinine and phosphate, country of birth, educational level, hormonal variables, HRT use, marital status, menopausal status, OC use, PTH and calcium, parity, smoking status, socio-economic status

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Engel, 2010 BRE80373 France	E3N EPIC-France, Nested Case Control	472/ 948 controls 10 years	Pathology reports		Incidence, Invasive breast cancer	>27 vs <19.8 ng/ml	0.80 (0.60-1.07) Ptrend:0.12	Age, age at menarche, age at menopause, alcohol consumption, benign breast disease, blood draw visit, BMI, calcium Intake, calcium level, contraception, estradiol, oestrogen replacement therapy, family history of breast cancer, hormonal contraceptive at 31y, HRT use, mammography, menopausal status, non-alcohol energy, number of children, physical activity, progesterone, PTH hormone, smoking status, study centre, supplement use, vitamin D intake
McCullough, 2009 BRE80260 USA	CPS II-Nutrition Cohort, Nested Case Control, Age: 47-85 years	516/ 516 controls 7 years	Cancer registry and national death Index		Incidence, breast cancer	≥73.2 vs <36.7 nmol/l	1.09 (0.70-1.68) Ptrend:0.60	Age at first child birth, birth year, BMI, date of blood collection, parity, race, season of year, weight change
		342/			ER+	≥64.2 vs <45.9 nmol/l per 10 nmol/l	1.15 (0.80-1.65) Ptrend:0.5 1.02 (0.96-1.09)	
		49/			ER-		0.95 (0.43-2.06) Ptrend:0.9 0.91 (0.78-1.06)	
		103/			In situ breast cancer		0.87 (0.49-1.55) Ptrend:0.7 0.99 (0.90-1.09)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Rejnmark, 2009 BRE80365 Denmark	Danish mammography exam participants study, Nested Case Control, Age: 58 years	142/ 420 controls	Pathology		Incidence, invasive and in situ breast cancer	≥84 vs ≤60 nmol/l per 5ng/ml*	0.71 (0.38-1.30) 0.88 (0.67-1.15)	Age, menopausal status, season
Freedman, 2008 BRE80183 USA	PLCO, Nested Case Control, Age: 55-74 years	1 005/ 1005 controls	Questionnaire/medical records/death record	FFQ	Incidence, breast cancer	≥33.7 vs ≤18.2 ng/ml	1.04 (0.75-1.45) Ptrend:0.81	Age, age at first child birth, age at menarche, age at menopause, alcohol intake, benign breast disease, BMI, calcium Intake, family history of cancer, HRT use, laboratory batch, parity, smoking status
Bertone-Johnson, 2005 BRE21759 USA	NHS, Nested Case Control, Age: 43-69 years, Registered nurses	701/ 701 controls 6 years	Medical records and self-reported		Incidence, breast cancer Batch1 Batch2 Batch3	per 5ng/ml*	1.03 (0.93-1.15) 0.96 (0.90-1.02) 0.99 (0.90-1.08)	Age at first child, age at menarche, age at menopause, alcohol, benign breast disease, biomarkers, BMI, family history, HRT use, parity/pregnancies

*Results were taken from Bauer (2013)

Table 391 Blood 25-hydroxy vitamin D and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Kühn, 2013 BRE80467 multi-national	EPIC, Nested Case Control, Age: 35-70 years	632/ 632 controls	Cancer registries, health Insurance records, pathology rec & active follow up	Dietary recall	Incidence, breast cancer, postmenopausal	per 200 %	0.93 (0.74-1.17)	Age at first child birth, age at first menses, alcohol consumption, BMI, breastfeeding, educational level, number of childbirths, physical activity, smoking status	ORs on the log2 scale
Scarmo, 2013 BRE80461	NYUWHS and NSMSC, Nested Case Control, Age: 54 years	948/ 1806 controls	Self-report, death report, national death Index, medical records reviewed by physicians		Incidence, Invasive breast cancer	Q5 vs Q1	1.21 (0.92-1.58) Ptrend:0.67	Age at first child birth, age at menarche, alcohol, BMI, family history of breast cancer, HRT use, multivitamin, parity, physical activity, season	Exposure ranges not clearly defined
Chlebowski, 2008 BRE80223 USA	Women's Health Initiative, Nested Case Control, Age: 50-79 years	895/ 898 controls 7 years	Self-report verified by medical record	FFQ	Incidence, Invasive breast cancer	≤32.3 vs ≥67.6 nmol/l	1.22 (0.89-1.67) Ptrend:0.2	Age, BMI, breast biopsies, date of blood collection, oestrogen use, family history of breast cancer, laxative use, physical activity, progestin and oestrogen use, race/ethnicity, randomisation	Superseded by Newhouser 2012

Figure 465 RR estimates of postmenopausal breast cancer by levels of blood 25-hydroxy vitamin D

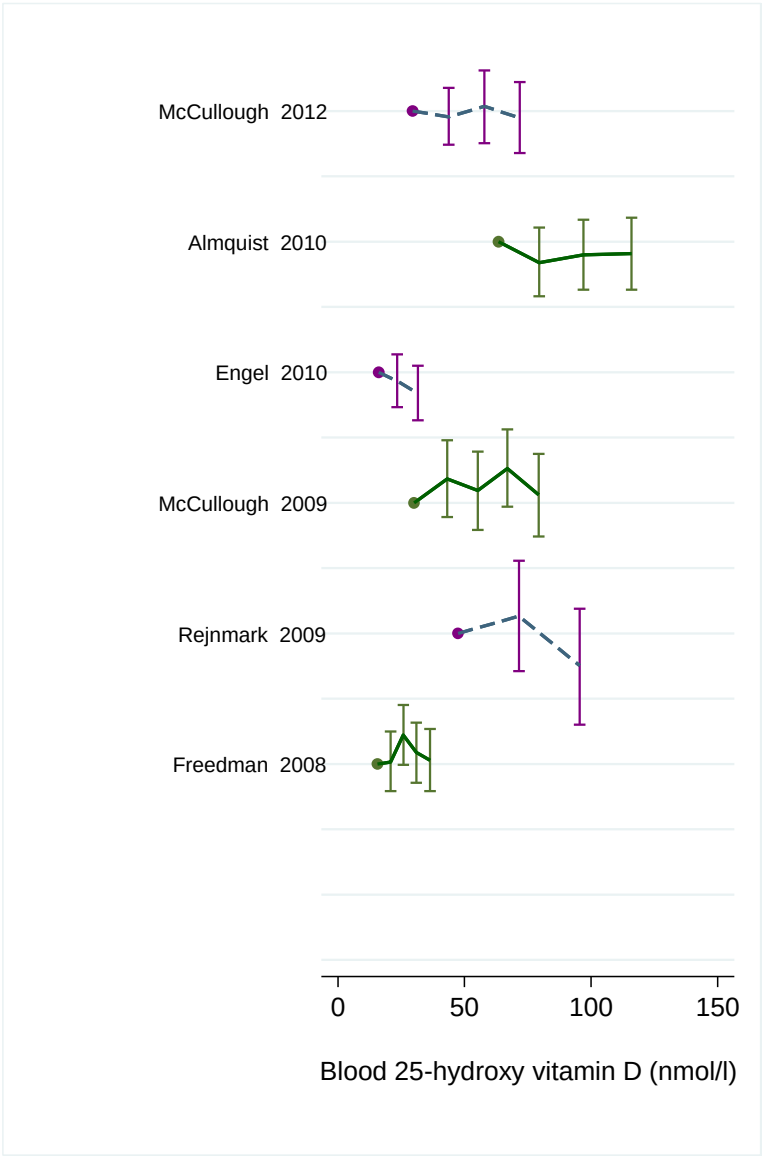
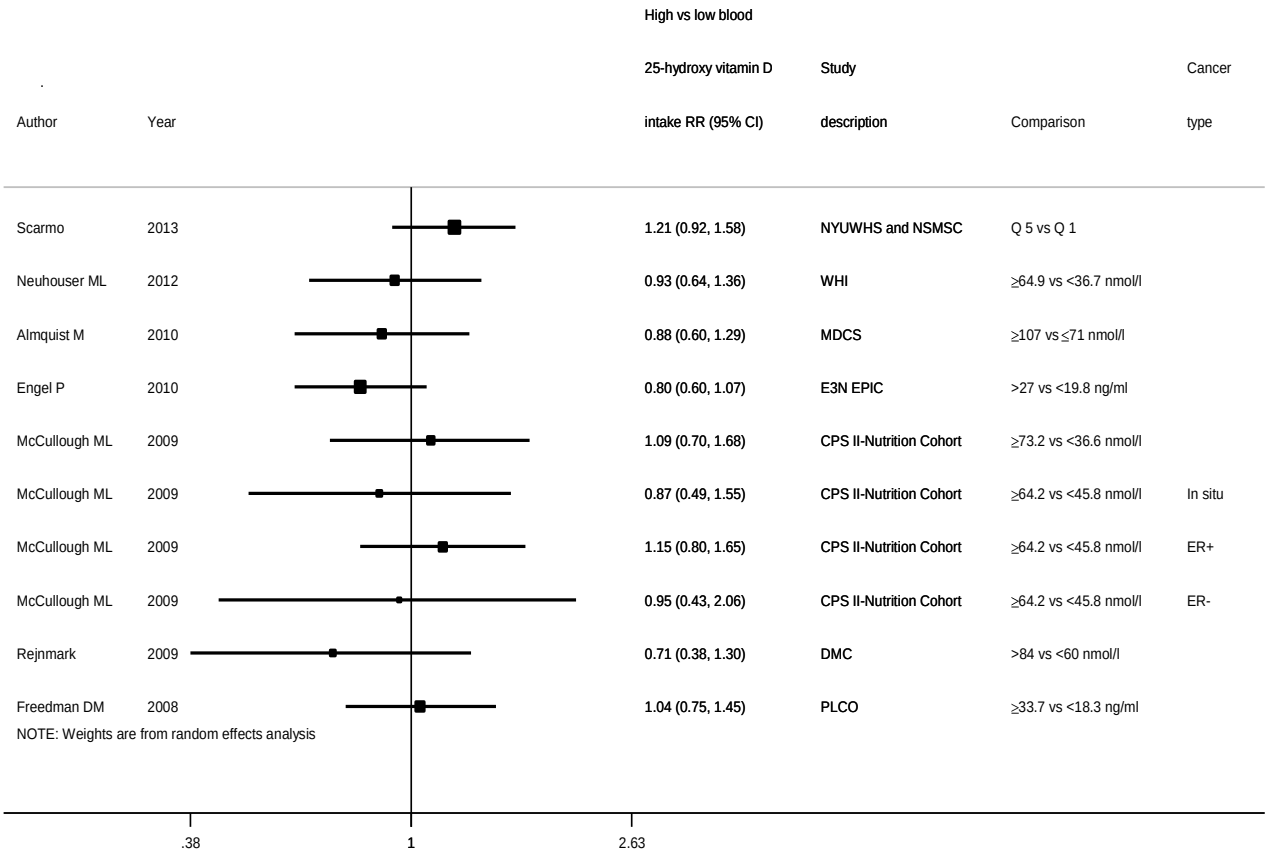


Figure 466 RR (95% CI) of postmenopausal breast cancer for the highest blood 25-hydroxy vitamin D intake compared with reference category



Note: ORs for Neuhouser (2012) were recalculated using the Hamling method.

Figure 467 Relative risk of postmenopausal breast cancer for 30nmol/l increase of blood 25-hydroxy vitamin D

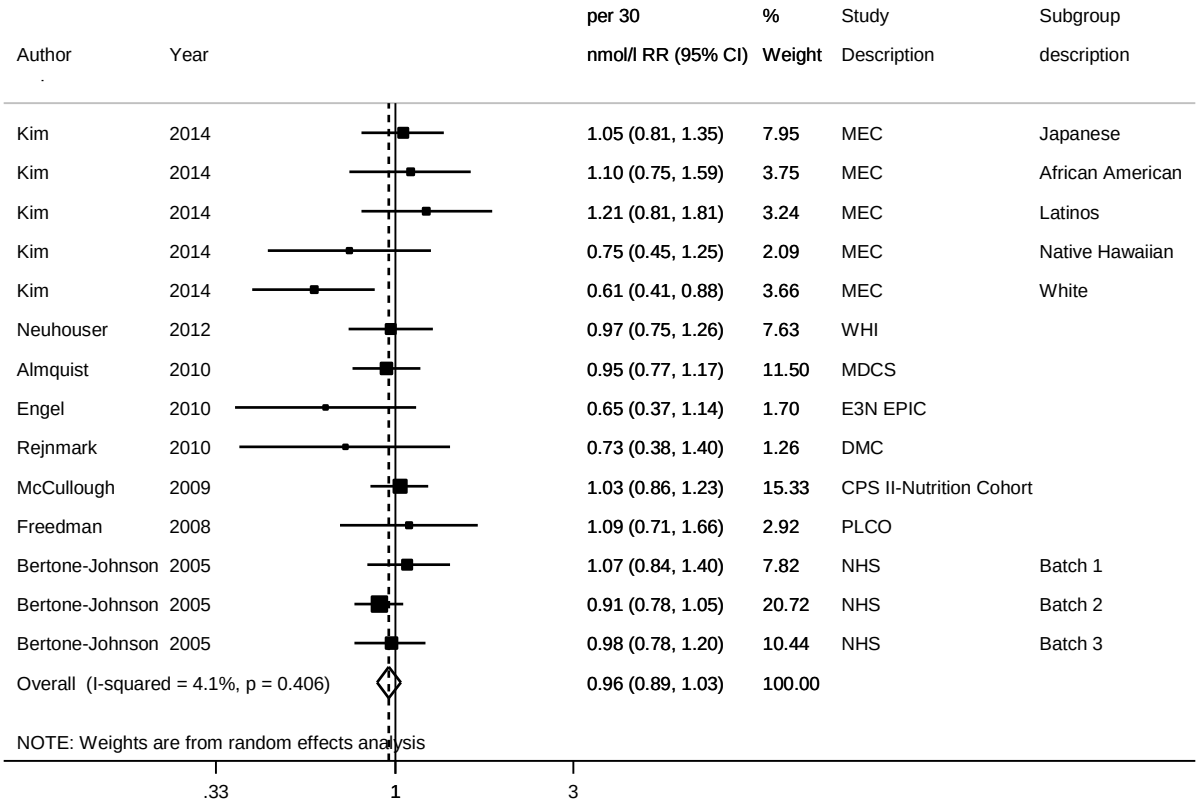
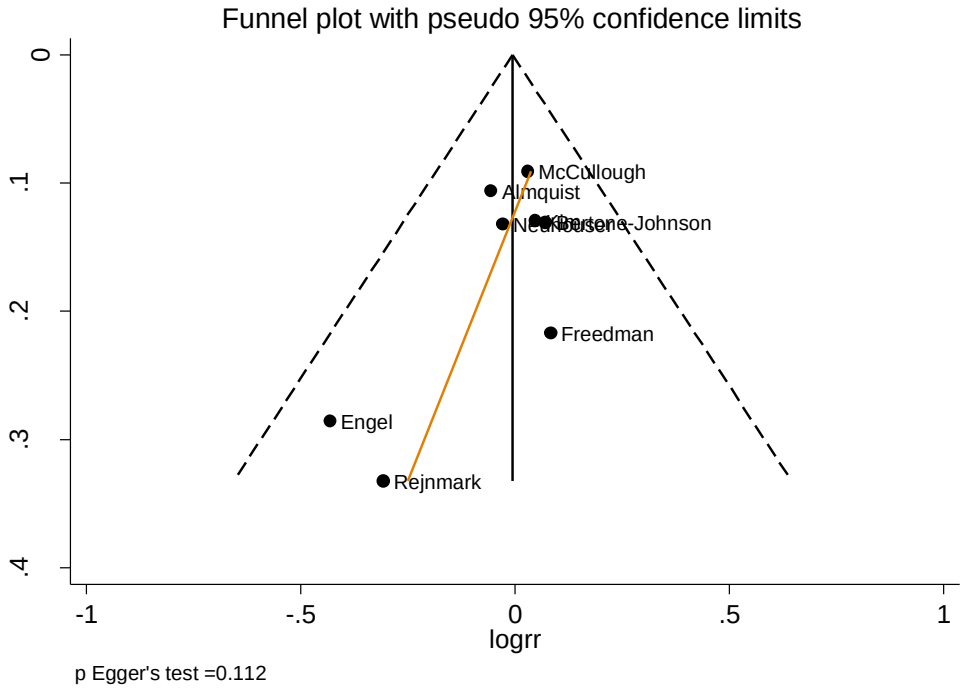


Figure 468 Funnel plot of studies included in the dose response meta-analysis of blood 25-hydroxy vitamin D and postmenopausal breast cancer



p Egger's test =0.112

Note: Pooled results were used for Kim (2014) and Bertone-Johnson (2005).

5.5.10 Blood 1,25-dihydroxy vitamin D

Cohort studies

Overall summary

Three studies that examined blood 1,25-dihydroxy vitamin D were identified (one on breast cancer and two on postmenopausal breast cancer). One meta-analysis and no pooled-analysis were identified.

Dose response meta-analyses were not conducted due to insufficient number of studies.

The NHS study (Bertone-Johnson, 2005) reported an inverse non-significant association between breast cancer and the highest level of 1,25-dihydroxy vitamin D compared to the lowest (443cases/618 controls).

The PLCO study (Freedman, 2008) found a positive non-significant association for the highest versus the lowest comparison of 1,25-dihydroxy vitamin D and postmenopausal breast cancer (1 005 cases/1 005 controls). The KPMCP (Hiatt, 1998b) reported no difference in the mean prediagnostic levels of 1,25-dihydroxy vitamin D between postmenopausal breast cancer cases and their matched controls (96cases/96controls).

Table 392 Blood 1,25-dihydroxy vitamin D and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Chen, 2009*	3 cohort studies	1 802	USA	Breast cancer	Highest vs lowest Fixed effect Random effect	 1.02 (0.80-1.29) 0.99 (0.68-1.44)	-	46.6%

*All cohort studies identified were included in the present review

5.6.3 Calcium (and Vitamin D)

Randomised controlled trials

Overall summary

Five publications from one study were identified (Cauley, 2013; Prentice, 2013b; Bolland, 2011; Brunner, 2011; Chlebowski, 2008).

The WHI double-blind, placebo-controlled trial, revealed an inverse non-significant association between the concurrent supplementation of calcium and vitamin D and breast cancer in postmenopausal women. Analysis in a subset of women who did not receive personal supplementation, an inverse significant association was found (Prentice, 2013b).

Another study using the same population (Cauley, 2013), which followed the participants for 4.9 years after the intervention was stopped, showed that postintervention invasive breast cancer incidence increased non-significantly in the supplementation group compared to the placebo group. Similar results were found for the overall follow-up period. However, in situ breast cancer incidence decreased significantly for postintervention and overall follow-up in the supplementation group compared to the placebo group.

Cohort studies

Overall summary

Two publications from one study were identified (Prentice, 2013b; Chlebowski, 2008). No pooled analysis or meta-analysis was identified.

Postmenopausal breast cancer

The WHI prospective observational study (Prentice, 2013b) showed that postmenopausal women who were using supplements of calcium and vitamin D had an increased non-significant risk of breast cancer incidence compared to women who were not.

A nested case-control study using the same population (Chlebowski, 2008) showed similar results when the baseline 25-hydroxyvitamin D of the participants belonged to the second or third quintile. A reduced non-significant risk of invasive breast cancer incidence was observed among women in the intervention group and who belonged in the first, fourth or fifth quintile of baseline 25-hydroxyvitamin D compared to the placebo group.

5.6.3 Dietary calcium

Cohort studies

Overall summary

Thirteen publications from eleven cohorts that examined dietary calcium intake were identified. No pooled analysis was identified but two meta-analyses were identified.

Dose response meta-analyses were conducted to examine the association of dietary calcium intake with risk of breast, premenopausal and postmenopausal breast cancer.

Table 393 Summary of results of the dose-response meta-analysis in the CUP SLR

	Breast cancer (any)	Premenopausal breast cancer	Postmenopausal breast cancer
Dietary calcium			
Increment unit used	300 mg/day	300 mg/day	300 mg/day
Studies (n)	5	5	6
Cases	17 483	2 980	10 137
RR (95%CI)	0.97 (0.94-1.00)	0.87 (0.76-0.95)	0.96 (0.94-0.99)
Heterogeneity (I^2, p-value)	22.0%, 0.275	66.9%, 0.017	0.0%, 0.675
P value Egger test	0.061	0.013	0.790

Breast cancer (any)

Summary

Main results:

Five out of seven cohort studies (nine publications) identified could be included in the dose-response meta-analysis of dietary calcium intake (17 483 cases). There was one European (Abbas, 2013), one Swedish (Larsson, 2009d), one American (Park, 2009b), one French study (Kesse-Guyot, 2007) and one study in Singapore Chinese participants (Li, 2013).

No significant association was observed for breast cancer and dietary calcium intake (per 300mg/day). There was low heterogeneity. Although Egger's test was not significant, the funnel plot shows an asymmetry suggesting a possible small study bias. One small study reported an inverse association stronger the expected (Kesse-Guyot, 2007).

Two cohort studies (four publications) were excluded from the dose-response meta-analysis. One (vanderPols, 2007) was a study of childhood diet and no association with adult female breast cancer risk was observed. The other excluded study in Finnish women (88 breast cancer cases) reported a significant lower breast cancer in women in the highest tertile of dietary calcium intake compared with those in the lowest. There was no significant trend.

Subgroup analysis was not conducted due to the low number of studies in the strata.

Sensitivity analyses:

The summary RR did not change materially when studies were omitted in turn in influence analysis.

Non-linear dose-response meta-analysis:

There was no evidence of significant non-linearity (P for non-linearity= 0.35)

Study quality:

All studies used validated FFQ or structure questionnaire to derive dietary calcium intake, except the SU.VI.MAX study (Kesse-Guyot, 2007), which used 24h records every 2 months (used 5 randomly selected dietary records collected during the first 18 months of the study). The SMC investigated long term dietary intake by using 2 FFQ, on at baseline and another about 10 years later. One of the excluded studies (vanderPols, 2007) was on childhood diet.

All studies were cohort studies and most participants were selected from the general population except the SU.VI.MAX study that was a randomized double-blind placebo controlled trial of antioxidant supplementation.

All studies had a follow-up of at least seven years.

All studies included in the dose-response analysis adjusted for age, alcohol intake, BMI and reproductive factors, except the Singaporean study (Li, 2013) that did not adjust for alcohol intake.

Table 394 Dietary calcium intake and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	7 (9 publications)
Studies included in forest plot of highest compared with lowest exposure	6 (6 publications)
Studies included in linear dose-response meta-analysis	5 (6 publications)
Studies included in non-linear dose-response meta-analysis	5 (6 publicaions)

Table 395 Dietary calcium intake and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR*	**CUP SLR**
Dietary calcium intake **Increment unit used**	-	300mg/day
Studies (n)	-	5
Cases	-	17 483
RR (95%CI)	-	0.97 (0.94-1.00)
Heterogeneity (I^2, p-value)	-	22.0%, 0.275
P value Egger test	-	0.061

*No meta-analysis in the past reports.

Table 396 Dietary calcium intake and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Hong, 2012[a]	10 studies (5 cohorts and 5 case-control studies)	14 450 breast cancer	China, USA, Japan, Canada, Sweden, Germany	Breast cancer	Non-linear dose-response 250 mg/day 350 mg/day 450 mg/day 550 mg/day 650 mg/day 750 mg/day 850 mg/day 950 mg/day 1100 mg/day	 0.96 (0.93-0.99) 0.95 (0.91-0.99) 0.93 (0.89-0.98) 0.92 (0.87-0.98) 0.91 (0.86-0.97) 0.91 (0.86-0.96) 0.91 (0.86-0.96) 0.91 (0.86-0.96) 0.91 (0.86-0.96)	-	-
Chen, 2010*	15 studies (6 cohorts and 9 case-control studies)	16 010 breast cancer	France, Finland, Spain, Germany, USA, Switzerland, Sweden, China, Italy, Greece	Breast cancer	Highest vs lowest dietary calcium intake.	0.79 (0.70-0.89)	-	-

[a]One cohort study was not in included in the present review (Adams, 2012). This was a study on cadmium and breast cancer risk in the Vital cohort. It is unclear where the authors of the meta-analysis obtained the data from dietary calcium and breast cancer risk in this cohort.

*All cohort studies identified were included in the present review.

Table 397 Dietary calcium intake and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) P-trend	Adjustment factors
Abbas, 2013 BRE80460 Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, UK	EPIC, Prospective Cohort, W	7 760/ 319 985 8.8 years	Cancer and pathology registry, active follow up, health Insurance record, mortality registry and contact of participants or next-of-kin	Questionnaire	Incidence, breast cancer	≥1231 vs ≤635 mg/day	0.91 (0.83-1.01) Ptrend:0.06	Age, age at menarche, alcohol, centre location, contraception, educational level, fat, height, hormone use, menopausal status, non-alcohol energy, non-fat energy, physical activity, smoking, weight
						per 100 mg/day	0.99 (0.97-1.00)	
Li, 2013 BRE80445 Singapore	SCHS, Prospective Cohort, W	823/ 34 028 14.2	Cancer registry and death registry	Validated questionnaire 165 food and beverage items during the past 12 months	Incidence, breast cancer	≥593.8 vs ≤360.9 mg/day	1.01 (0.82-1.24) Ptrend:0.57	Age at Interview, age at menarche, BMI, dialect group, educational level, family history, Interview year, number of childbirths
Larsson, 2009d BRE80210 Sweden	SMC, Prospective Cohort, Age: 54 years, W	2 952/ 61 433 17.4 years	Cancer registry	Long term dietary calcium FFQ 9 67 and 96 food items at baseline and in 1997)	Incidence, Invasive breast cancer	≥1125 vs ≤726 mg/day	0.97 (0.87-1.09) Ptrend:0.49	Age at first child birth, age at menarche, age at menopause, alcohol, benign breast disease, BMI, educational level, family history of cancer, fibre, height, parity, postmenopausal hormone use, total energy, use of oral contraception
		1 286/			Incidence, breast cancer ER+/PR+	≥1125 vs ≤726 mg/day	1.01 (0.85-1.21) Ptrend:0.90	
		417/			Incidence, breast cancer ER+/PR-	≥1125 vs ≤726 mg/day	0.97 (0.70-1.34) Ptrend:0.80	
		266/			Incidence, breast cancer ER-/PR-	≥1125 vs ≤726 mg/day	0.66 (0.44-0.99) Ptrend:0.02	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) P-trend	Adjustment factors
Park, 2009b BRE80464 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W, Retired	5 856/ 492 810 7 years	Cancer registry	Validated FFQ	Incidence, breast cancer	1101 vs 409 mg/day	0.94 (0.86-1.03) Ptrend:0.28	Age at first child birth, age at menopause, alcohol consumption, BMI, calcium supplement, educational level, family history of cancer, fat Intake, marital status, menopausal oestrogen use, number of children, race/ethnicity, red meat Intake, smoking, total energy, vigorous physical activity
Kesse-Guyot, 2007 BRE11112 France	SU.VI.MAX, Prospective Cohort, Age: 35-60 years, W, SU.VI.MAX participants	92/ 3 627 7.7 years	Medical records	Five 24h recall	Incidence, breast cancer, Total dietary calcium	≥1145 vs ≤806 mg/day	0.50 (0.27-0.91) Ptrend:0.04	Alcohol, BMI, educational level, energy from fat, energy from non-fat sources, family history, group supplementation, HRT use, marital status, parity/pregnancies, physical activity , smoking habits
		92/			Dairy calcium	≥734 vs ≤421 mg/day	0.58 (0.32-1.04) Ptrend:0.21	
		92/			Non-dairy calcium	≥452 vs ≤307 mg/day	0.76 (0.42-1.36) Ptrend:0.06	

Table 398 Dietary calcium intake and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Li, 2011 BRE80384 Germany	EPIC-Heidelberg, Prospective Cohort, Age: 35-64 years, W	415/ 12 902 11 years	Medical record	FFQ	Incidence, breast cancer	per 100 mg	1.02 (0.97-1.06)	Age, sex, BMI, calcium supplement, educational level, fibre, lifetime alcohol consumption, meat Intake, physical activity, smoking, total energy, vitamin d, vitamin d, vitamin k2, waist hip ratio	Superseded from Abbas 2013
						1102 vs 515 mg/day	0.98 (0.71-1.35) Ptrend:0.93		
van der Pols JC, 2007 BRE80154 UK	BOCS, Historical Cohort, Age: 8 years	98/ 4 374 57 years	National health records	7-day food records	Incidence, breast cancer	743 vs 406 mg/day		Age, sex, energy Intake	Inadequate results given
Jarvinen, 1997 BRE04383 Finland	Finland, 1966, Prospective Cohort, Age: 15- years, W	4 697 24 years	Partially histological - over 80%	Dietary history questionnaire	Incidence, breast cancer	Q3 vs Q1	0.44 Ptrend:0.09	Age	Inadequate results given
Knekt, 1996 BRE04900 Finland	Finland, 1966, Prospective Cohort, Age: 15-90 years	88/ 40697 25 years	Cancer registry and death certification	Dietary history questionnaire	Incidence, breast cancer	Q3 vs Q1	0.44 (0.24-0.80)	Age	Inadequate results given Included in HvsL analysis

Figure 469 RR estimates of breast cancer by levels of dietary calcium intake

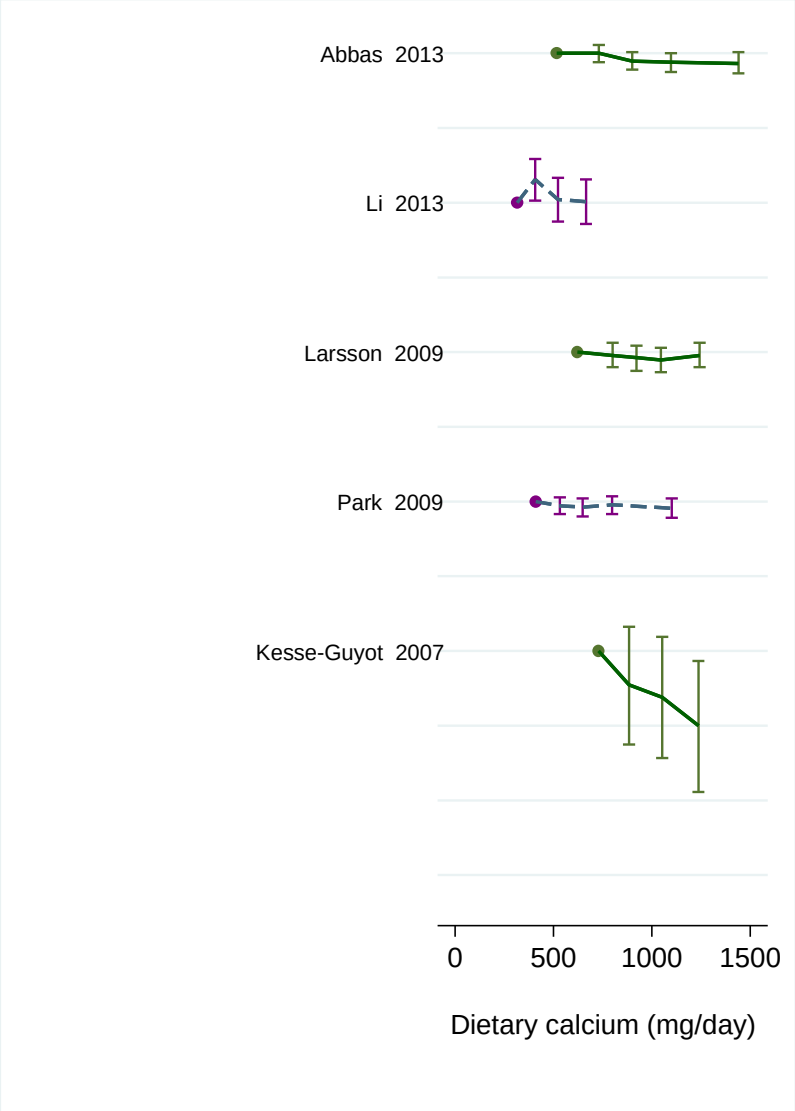


Figure 470 RR (95% CI) of breast cancer for the highest dietary calcium intake compared with reference category

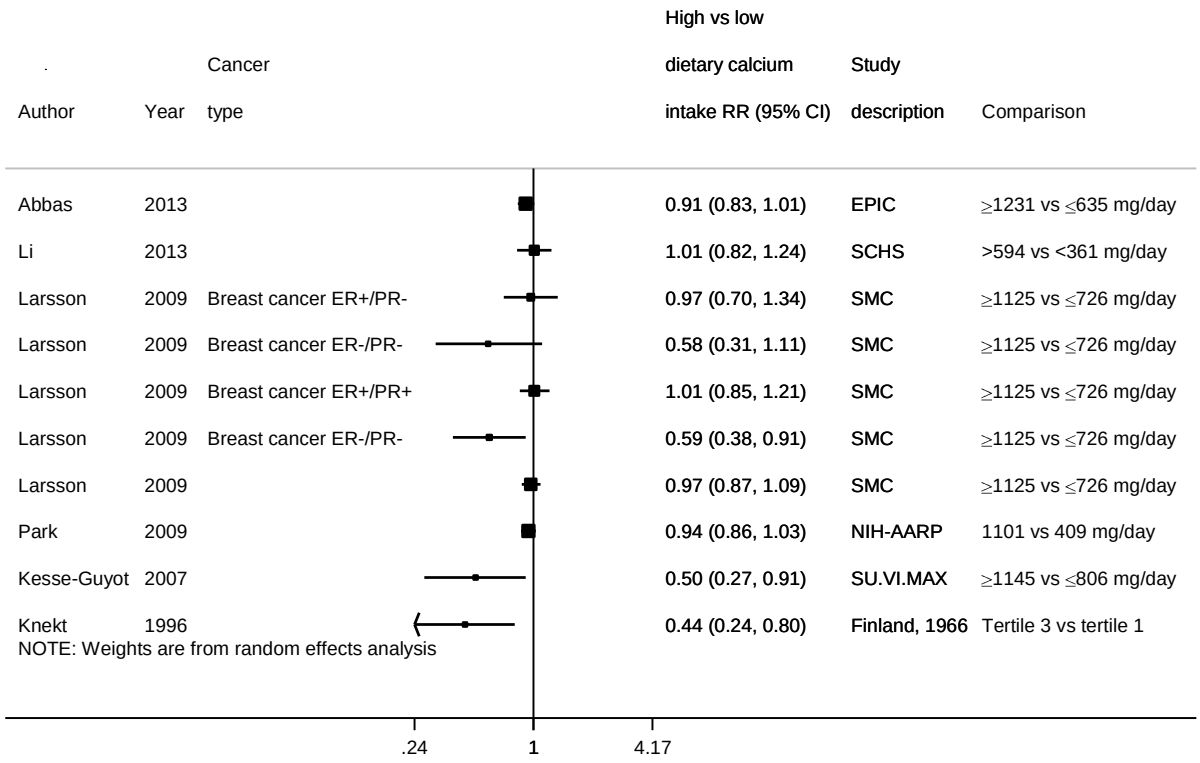


Figure 471 Relative risk of breast cancer for 300mg/day increase of dietary calcium intake

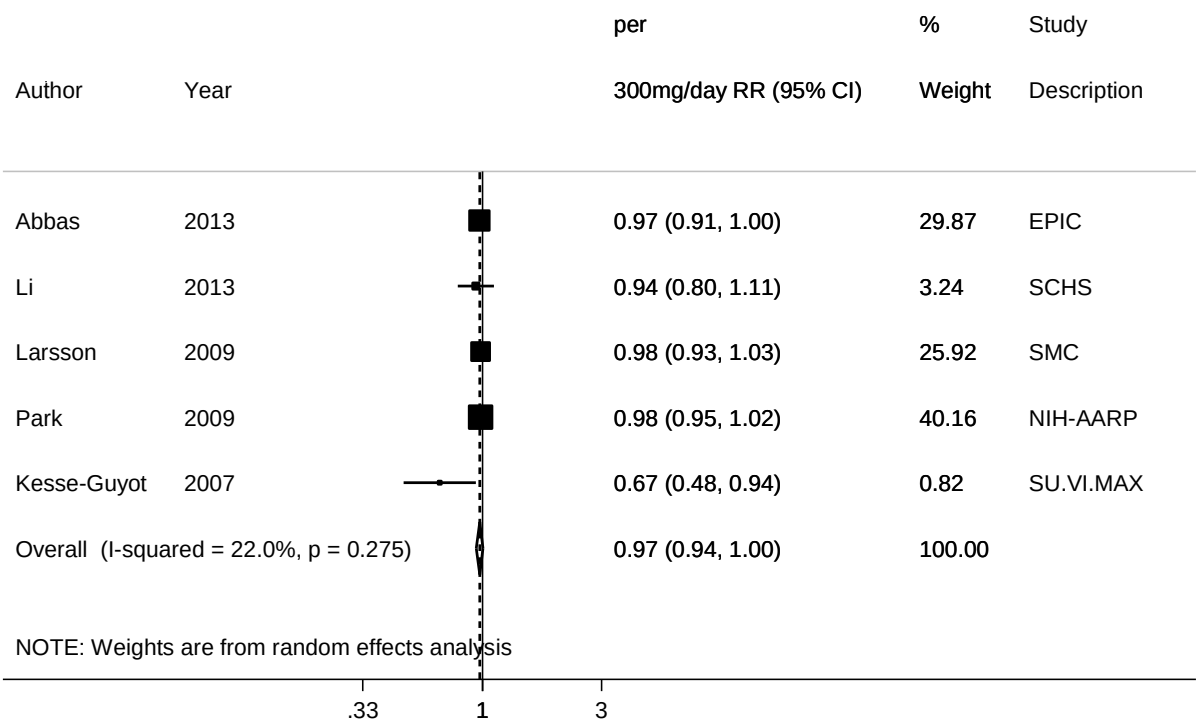
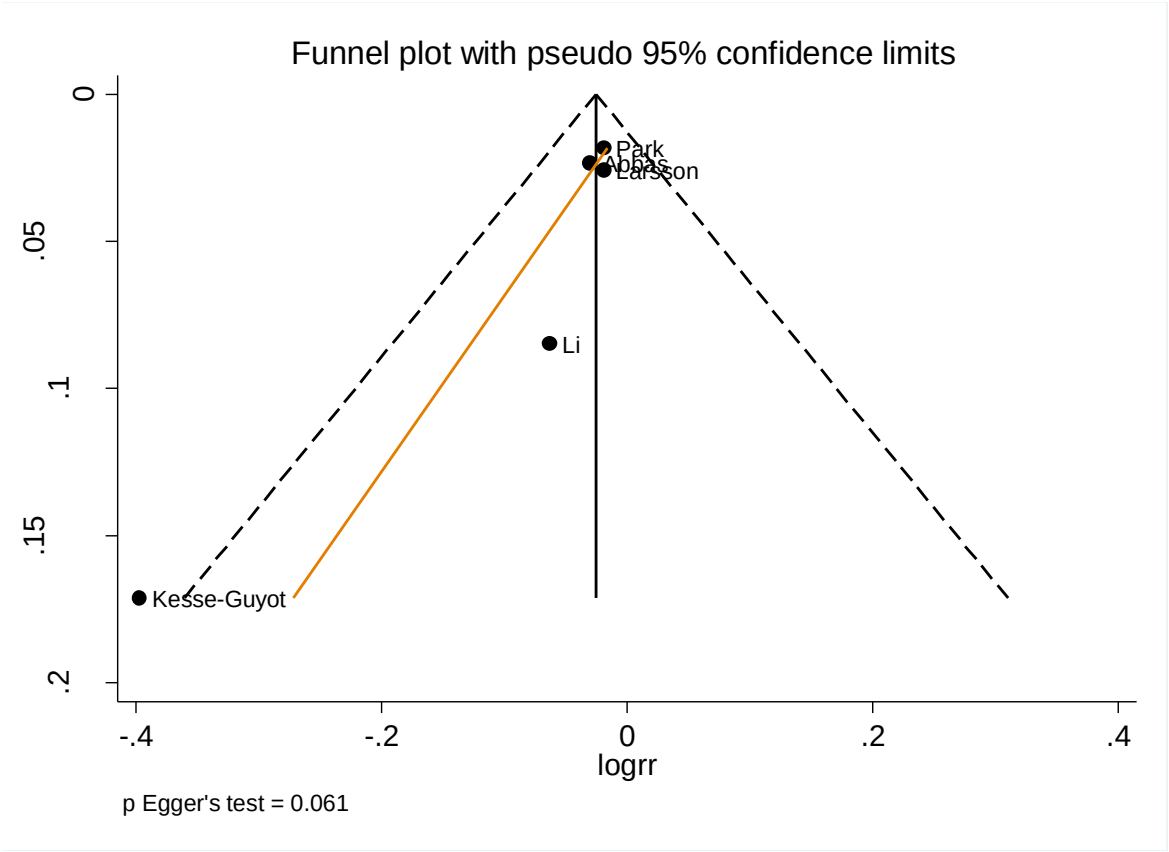


Figure 472 Funnel plot of studies included in the dose response meta-analysis of dietary calcium intake and breast cancer



Premenopausal breast cancer

Summary

Main results:

Five out of six studies (2 980 cases) (six publications) identified could be included in the dose-response meta-analysis of dietary calcium intake and premenopausal breast cancer.

Three of the studies identified on any breast cancer did not report for premenopausal breast cancer and dietary calcium: the Singaporean study (Li, 2013), the NIH-AARP, Park, 2009b) and the Swedish mammography Cohort (Larsson, 2009d). None of these studies reported significant association with risk of any breast cancer or by menopausal status. The Singaporean study reported that the results on dietary calcium were not modified by menopausal status (Li, 2013). Premenopausal breast was not associated with long term dietary calcium intake in an analysis including 1244 premenopausal breast cancers in the SMC (Larsson, 2009d). No data by menopausal status was reported in the NIH-AARP (Park, 2009b) cohort study in which most women were postmenopausal.

A significant inverse significant association was observed (per 300mg/day). However, high heterogeneity was observed. The funnel plot shows asymmetric towards an inverse association, suggesting small study bias. Furthermore, there was one outlier (Kesse-Guyot,

2007). There were one European (Abbas, 2013), one Norwegian (Hjartaker, 2010), two American (Lin, 2007; Shin, 2002) and one French studies (Kesse-Guyot, 2007).

Subgroup analysis was not conducted due to the low number of studies in the strata.

Sensitivity analyses:

In influence analysis, the dose-response was no longer significant when either the NOWAC (Hjatker, 2010), the SU.VI.MAX (Kesse-Guyot, 2007) or the NHS (Shin, 2002) were excluded from the analysis. These studies had 9.7%, 5.6% and 27.9% weight in the analysis, respectively.Non-linear dose-response meta-analysis:

There was no evidence of significant non-linearity (P for non-linearity= 0.778)

Study quality:

All studies used validated FFQ or structure questionnaire to derive dietary calcium intake, except the SU.VI.MAX study (Kesse-Guyot, 2007), which used 24h records every 2 months (used 5 randomly selected dietary records collected during the first 18 months of the study). The SMC investigated long term dietary intake by using 2 FFQ, on at baseline and another about 10 years later. All studies were cohort studies and most participants were selected from the general population except the SU.VI.MAX study that was a randomized double-blind placebo controlled trial of antioxidant supplementation.

All studies had a follow-up of at least eight years.

All studies included in the dose-response analysis adjusted for age, alcohol intake, BMI and reproductive factors.

Table 399 Dietary calcium intake and premenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	6 (6 publications)
Studies included in forest plot of highest compared with lowest exposure	6 (6 publications)
Studies included in linear dose-response meta-analysis	5 (5 publications)
Studies included in non-linear dose-response meta-analysis	5 (5 publications)

Table 400 Dietary calcium intake and premenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005/2008 SLR and CUP SLR

	2005 SLR*	**CUP SLR**
Dietary calcium intake Increment unit used	-	300mg/day
Studies (n)	-	5
Cases	-	2 980
RR (95%CI)	-	0.87 (0.76-0.99)
Heterogeneity (I^2, p-value)	-	66.9%, 0.017
P value Egger test	-	0.013

*No meta-analysis in the past reports.

Table 401 Dietary calcium intake and premenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Abbas, 2013 BRE80460 Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, UK	EPIC, Prospective Cohort, W	1 802/ 319 985 8.8 years	Cancer and pathology registry, active follow up, health Insurance record, mortality registry and contact of participants or next-of-kin	Questionnaire	Incidence, breast cancer, premenopausal	≥1231 vs ≤635 mg/day	0.98 (0.80-1.19) Ptrend:0.85	Age, age at menarche, alcohol, centre location, contraception, educational level, fat, height, hormone use, menopausal status, non-alcohol energy, non-fat energy, physical activity, smoking, weight
Hjartaker, 2010 BRE80327 Norway	NOWAC, Prospective Cohort, W, Premenopausal+ postmenopausal	151/ 64 904 8.6 years	Cancer registry, histology and death certificate	FFQ	Incidence, Invasive breast cancer, premenopausal	≥814.2 vs ≤552.6 mg/day	0.65 (0.39-1.08) Ptrend:0.07	Age at first child birth, age at menarche, alcohol, contraception, educational level, energy Intake, family history of breast cancer, height, mammography, number of children, physical activity, weight
Kesse-Guyot, 2007 BRE11112 France	SU.VI.MAX, Prospective Cohort, Age: 35-60 years, W, SU.VI.MAX participants	44/ 3 627 7.7 years	Medical records	Five 24h recalls	Incidence, breast cancer, premenopausal Total dietary calcium intake	≥1145 vs ≤806 mg/day	0.26 (0.10-0.71) Ptrend:0.01	Alcohol, BMI, educational level, energy from fat, energy from non-fat sources, family history, group supplementation, HRT use, marital status, parity/pregnancies, physical activity , smoking habits
		44/			Dairy calcium intake	≥734 vs ≤421 mg/day	0.32 (0.12-0.82) Ptrend:0.05	
		44/			Non-dairy calcium intake	≥452 vs ≤307 mg/day	0.76 (0.34–1.67) Ptrend:0.11	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Lin, 2007 BRE80165 USA	WHS, Prospective Cohort, Age: 54-56 years, W	276/ 31 487 10 years	Medical records	FFQ	Incidence, Invasive breast cancer, premenopausal	≥998 vs ≤556.9 mg/day	0.84 (0.57-1.22) Ptrend:0.24	Age, age at first child birth, age at menarche, alcohol consumption, BMI, family history of cancer, history of breast cyst, multivitamin supplement Intake, parity, physical activity, randomized treatment assignment, smoking status, total energy Intake
Shin, 2002 BRE16658 USA	NHS, Prospective Cohort, Age: 47 years, W, Registered nurses	640/ 88 691 16 years	Medical records	FFQ	Incidence, Invasive breast cancer, premenopausal Total dietary calcium intake	≥1000.1 vs ≤500 mg/day	0.67 (0.49-0.92) Ptrend:0.02	Age , age at first child, age at menarche, age at menopause, alcohol, BMI, body weight, breast diseases , energy Intake , family history, height, HRT use, other design Issue, other nutritional factors, parity/pregnancies, physical activity
		640/			Dairy calcium	>800 vs ≤200 mg/day	0.69 (0.48-0.98)	

Table 402 Dietary calcium intake and premenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Larsson, 2009d BRE80210 Sweden	SMC, Prospective Cohort, Age: 54 years, W	1 244/ 61 433 17.4 years	Cancer registry	FFQ	Incidence, Invasive breast cancer, premenopausal	≥1125 vs ≤726 mg/day	0.94 (0.79-1.13)	Age at first child birth, age at menarche, age at menopause, alcohol, benign breast disease, BMI, educational level, family history of cancer, fibre, height, parity, postmenopausal hormone use, total energy, use of oral contraception	Inadequate results given. Included in HvsL analysis

Figure 473 RR estimates of premenopausal breast cancer by levels of dietary calcium intake

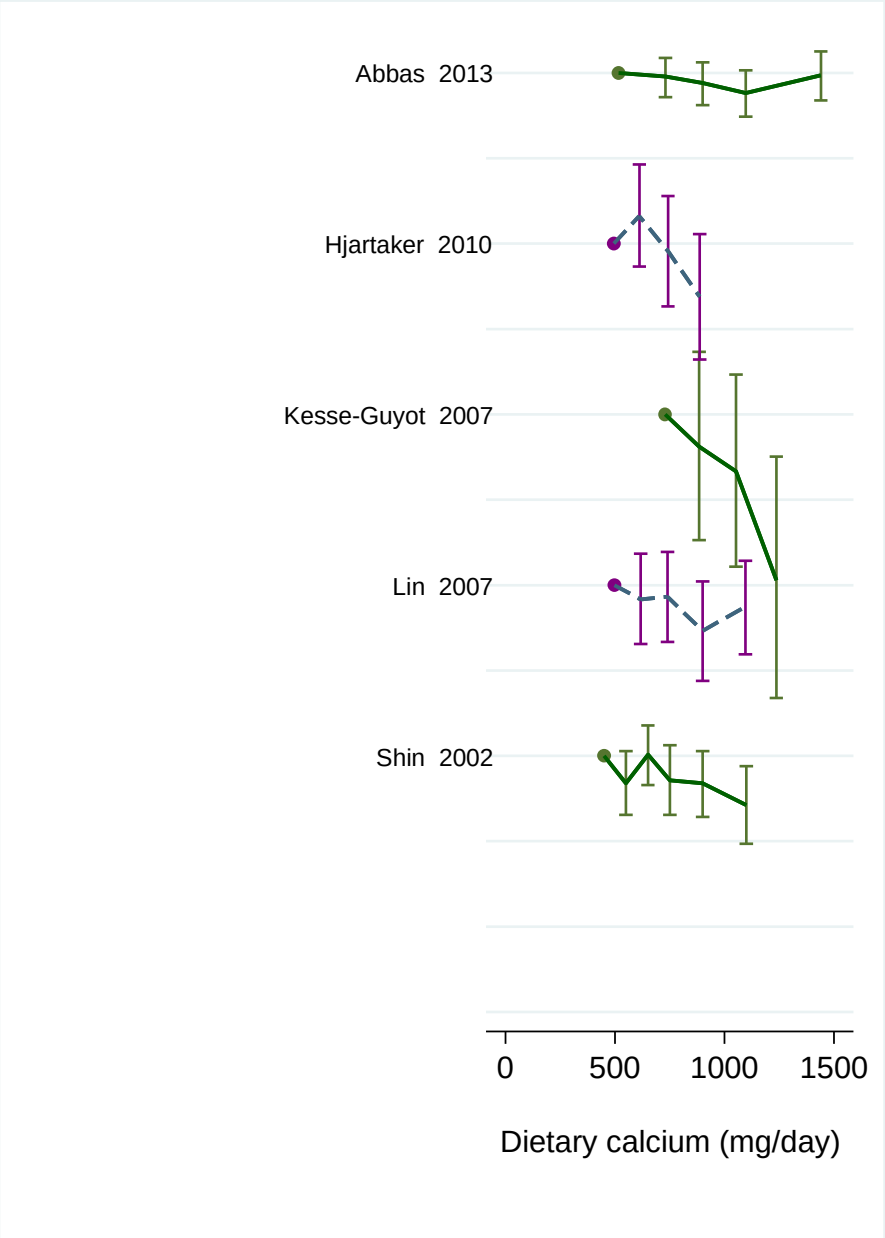


Figure 474 RR (95% CI) of premenopausal breast cancer for the highest dietary calcium intake compared with reference category

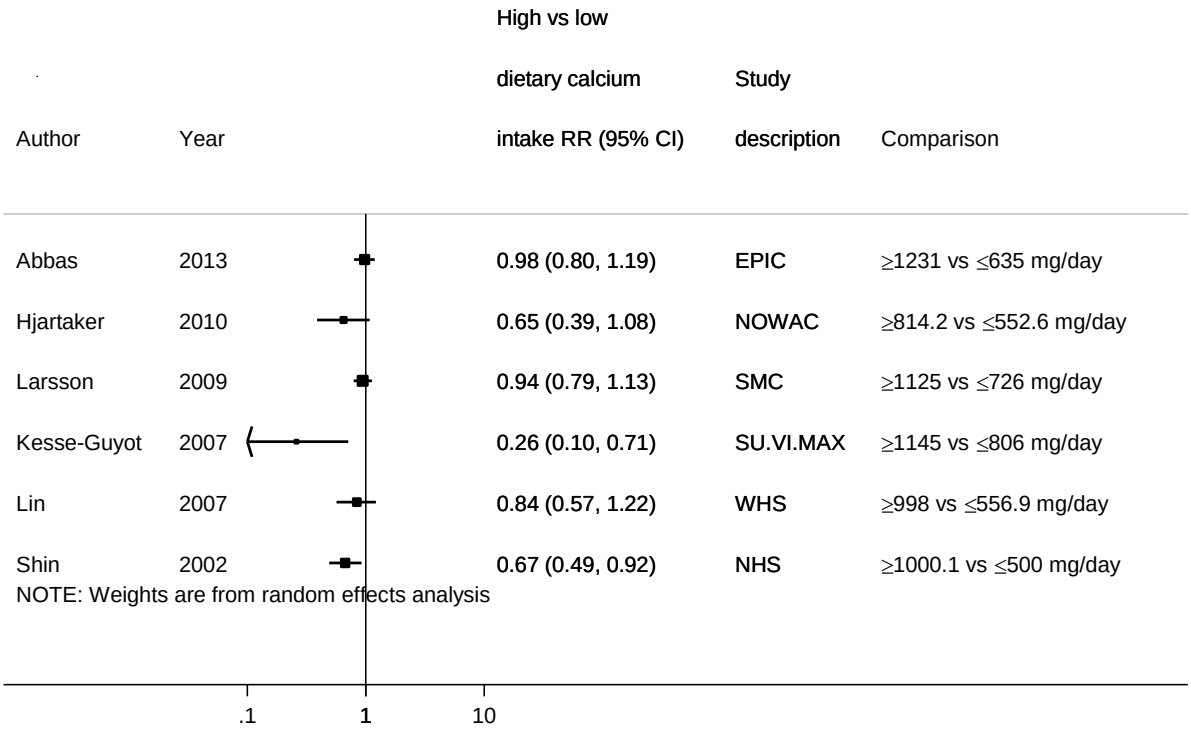


Figure 475 Relative risk of premenopausal breast cancer for 300mg/day increase of dietary calcium intake

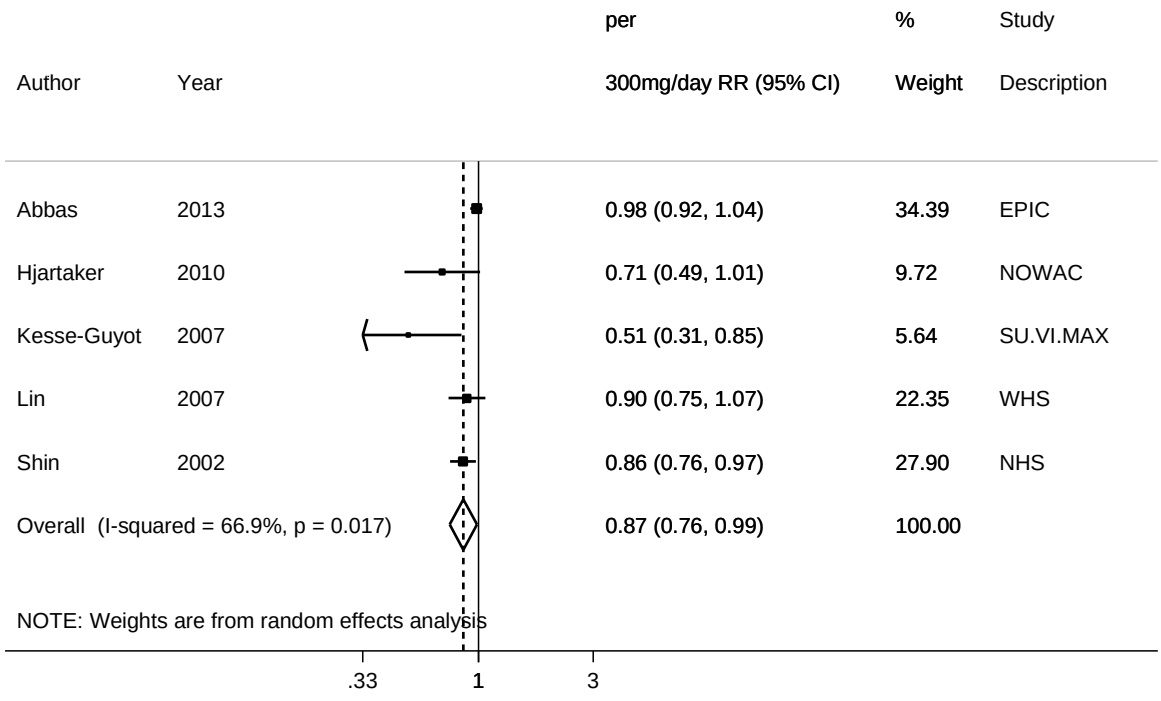
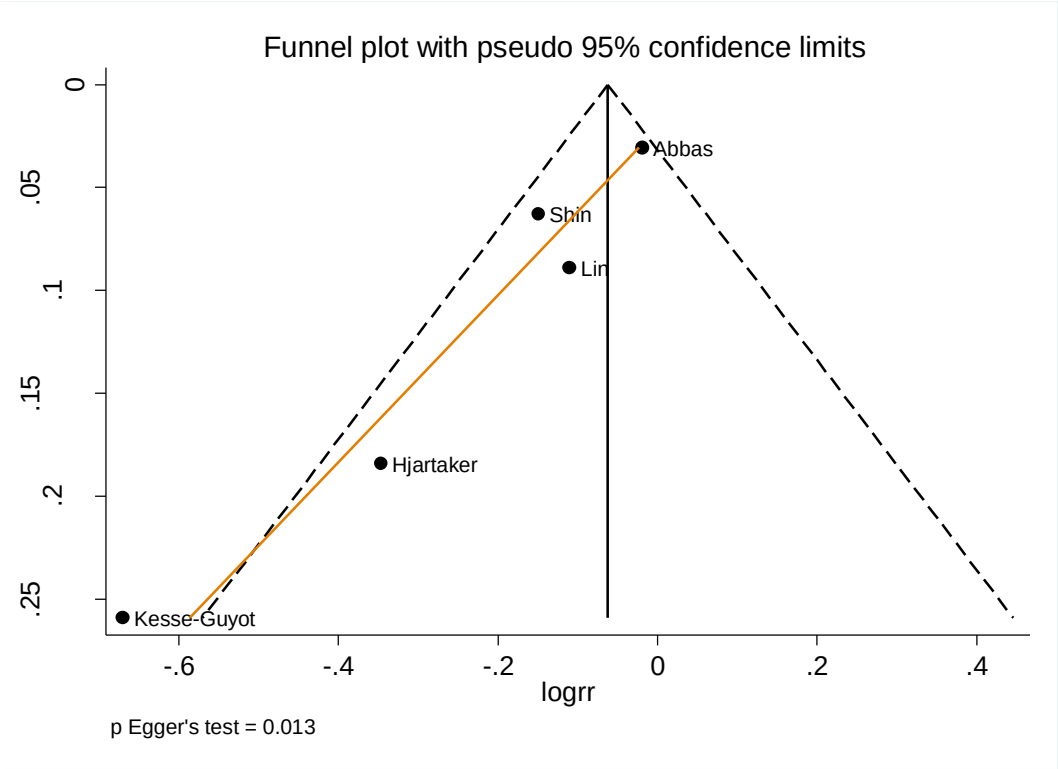


Figure 476 Funnel plot of studies included in the dose response meta-analysis of dietary calcium intake and premenopausal breast cancer



Postmenopausal breast cancer

Summary

Main results:

Six out of seven studies (10 137 cases) (seven publications) identified could be included in the dose-response meta-analysis. There was one European (Abbas, 2013), one Norwegian (Hjartaker, 2010), one French (Kesse-Guyot, 2007) and three American studies (Lin, 2007; McCullough, 2005; Shin, 2002).

A significant inverse association was observed for postmenopausal breast cancer and dietary calcium intake (per 300mg/day). No heterogeneity was observed between studies. There was no evidence of significant publication or small study bias.

Three of the studies identified on any breast cancer did not report for premenopausal breast cancer and dietary calcium: the Singaporean study (Li, 2013), the NIH-AARP (Park, 2009b) and the Swedish Mammography Cohort (Larsson, 2009d). None of these studies reported significant association with risk of any breast cancer or by menopausal status. The Singaporean study reported that the results on dietary calcium were not modified by menopausal status (Li, 2013). Postmenopausal breast was not associated with long term dietary calcium intake in an analysis including 1584 postmenopausal breast cancers in the SMC (Larsson, 2009d). No data by menopausal status was reported in the NIH-AARP (Park, 2009b) cohort study but most women were postmenopausal.

Subgroup analysis was not conducted due to the low number of studies

Sensitivity analyses:

The inverse significant association did not change materially when studies were omitted in turn in influence analysis. Nevertheless, EPIC (Abbas, 2013) and the CPS II (McCullough, 2005) has 42% and 39% of weight in the overall analysis.

Non-linear dose-response meta-analysis:

There was no evidence of significant non-linearity (P for non-linearity= 0.450)

Study quality:

All of the studies used a FFQ to assess dietary calcium intake, except the SU.VI.MAX study (Kesse-Guyot, 2007) which used five 24h record (every 2 months in the first 18 months of follow-up) . The SMC study (Larsson, 2009d) investigated long term calcium intake using questionnaires about ten years apart.

All studies had a follow-up of at least eight years.

All studies were adjusted for main risk factors.

Table 403 Dietary calcium intake and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	7 (7 publications)
Studies included in forest plot of highest compared with lowest exposure	7 (7 publications)
Studies included in linear dose-response meta-analysis	6 (6 publications)
Studies included in non-linear dose-response meta-analysis	6 (6 publications)

Table 404 Dietary calcium intake and postmenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005/2008 SLR and CUP SLR

	2005 SLR*	**CUP SLR**
Dietary calcium intake Increment unit used	300mg/day	300mg/day
Studies (n)	2	6
Cases	4 291	10 137
RR (95%CI)	0.98 (0.96-1.01)	0.96 (0.94-0.99)
Heterogeneity (I^2, p-value)	-	0.0%, 0.675
P value Egger test	-	0.790

Table 405 Dietary calcium intake and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Abbas, 2013 BRE80460 Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, UK	EPIC, Prospective Cohort, W	4 259/ 319 985 8.8 years	Cancer and pathology registry, active follow up, health Insurance record, mortality registry and contact of participants or next-of-kin	Questionnaire	Incidence, breast cancer, postmenopausal	≥1231 vs ≤635 mg/day	0.90 (0.79-1.02) Ptrend:0.05	Age, age at menarche, alcohol, centre location, contraception, educational level, fat, height, hormone use, menopausal status, non-alcohol energy, non-fat energy, physical activity, smoking, weight
Hjartaker, 2010 BRE80327 Norway	NOWAC, Prospective Cohort, W, Premenopausal+ postmenopausal	796/ 64 904 8.6 years	Cancer registry, histology and death certificate	FFQ	Incidence, Invasive breast cancer, postmenopausal	≥814.2 vs ≤552.6 mg/day	0.85 (0.70-1.04) Ptrend:0.14	Age, age at first child birth, age at menarche, alcohol, contraception, educational level, energy Intake, family history of breast cancer, height, mammography, number of children, physical activity, weight
Kesse-Guyot, 2007 BRE11112 France	SU.VI.MAX, Prospective Cohort, Age: 35-60 years, W, SU.VI.MAX participants	48/ 3 627 7.7 years	Medical records	Five 24h recalls	Incidence, breast cancer, postmenopausal Total dietary calcium intake	≥1145 vs ≤806 mg/day	0.76 (0.34-1.70) Ptrend:0.64	Alcohol, BMI, educational level, energy from fat, energy from non-fat sources, family history, group supplementation, HRT use, marital status, parity/pregnancies, physical activity , smoking habits
					Dairy calcium intake	≥734 vs ≤421 mg/day	0.87 (0.40-1.92) Ptrend:0.99	
					Non-dairy calcium intake	≥452 vs ≤307 mg/day	0.84 (0.35-1.98) Ptrend:0.31	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Lin, 2007 BRE80165 USA	WHS, Prospective Cohort, Age: 54-56 years, W	743/ 31 487 10 years	Medical records	FFQ	Incidence, Invasive breast cancer, postmenopausal	≥998 vs ≤556.9 mg/day	1.10 (0.86-1.39) Ptrend:0.56	Age, age at first child birth, age at menarche, alcohol consumption, BMI, family history of cancer, history of breast cyst, multivitamin supplement Intake, parity, physical activity, randomized treatment assignment, smoking status, total energy Intake, randomized treatment assignment, age at menopause, baseline postmenopausal hormone therapy
McCullough, 2005 BRE23368 USA	CPS II, Prospective Cohort, Age: 50-74 years, W, Postmenopausal	2 855/ 68 567 9 years	Active follow-up	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	≥1251 vs ≤500 mg/day	0.80 (0.67-0.95) Ptrend:0.02	Age , age at first child, age at menopause, alcohol, breast diseases , educational level, energy Intake , ethnicity, family history, height, HRT use, mammography, other anthropometric Index, parity/pregnancies, supplements
		1 283/			ER+		0.67 (0.51-0.88)	
		227/			ER-		0.77 (0.40-1.47)	
Shin, 2002 BRE16658 USA	NHS, Prospective Cohort, Age: 47 years, W, Registered	1 436/ 88 691 16 years	Medical records	FFQ	Incidence, Invasive breast cancer, postmenopausal Total dietary calcium intake	≥1001 vs ≤500 mg/day	0.99 (0.81-1.21) Ptrend:0.46	Age , age at first child, age at menarche, age at menopause, alcohol, BMI, body weight, breast diseases , energy Intake , family history, height, HRT use, other design Issue, other

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	nurses				Dairy calcium intake	≥800.1 vs ≤200 mg/day	1.11 (0.88-1.40) Ptrend:0.90	nutritional factors, other nutritional factors, other nutritional factors, other nutritional factors, parity/pregnancies, physical activity

Table 406 Dietary calcium intake and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Larsson, 2009d BRE80210 Sweden	SMC, Prospective Cohort, Age: 54 years, W	1 584/ 61 433 17.4 years	Cancer registry	FFQ	Incidence, Invasive breast cancer, postmenopausal	≥1125 vs ≤726 mg/day	0.92 (0.78-1.09)	Age, age at first child birth, age at menarche, age at menopause, alcohol, benign breast disease, BMI, educational level, family history of cancer, fibre, height, parity, postmenopausal hormone use, total energy, use of oral contraception	Inadequate results given. Included in HvsL analysis

Figure 477 RR estimates of postmenopausal breast cancer by levels of dietary calcium intake

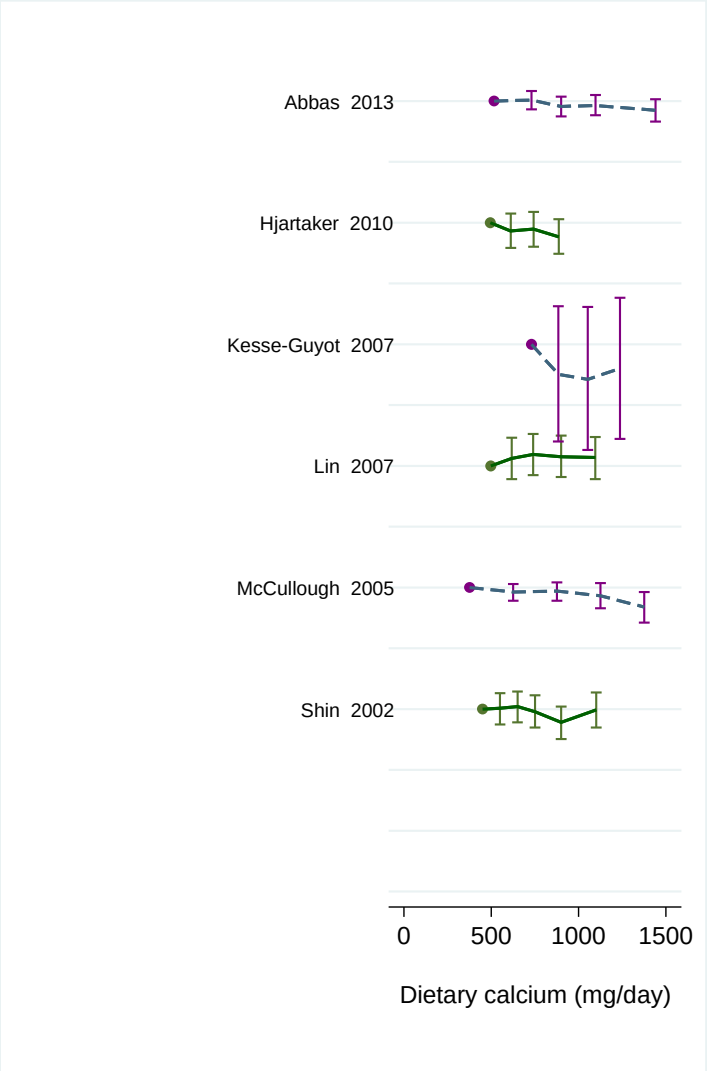


Figure 478 RR (95% CI) of postmenopausal breast cancer for the highest dietary calcium intake compared with reference category

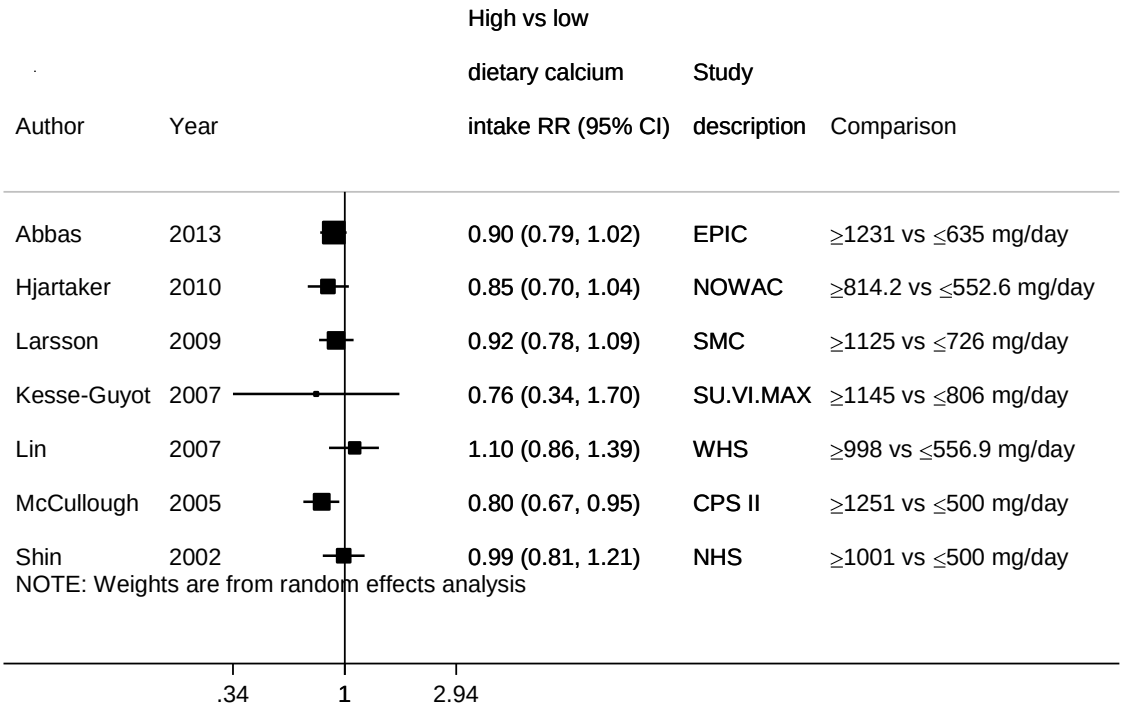


Figure 479 Relative risk of postmenopausal breast cancer for 300mg/day increase of dietary calcium intake

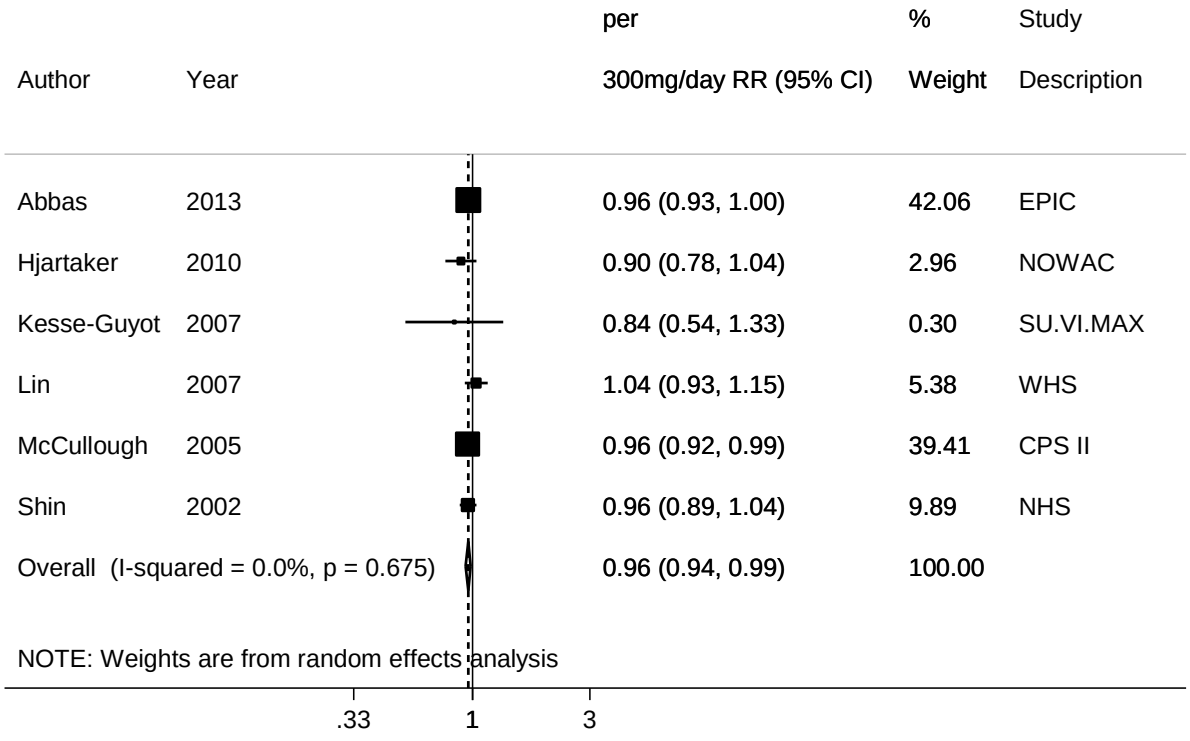
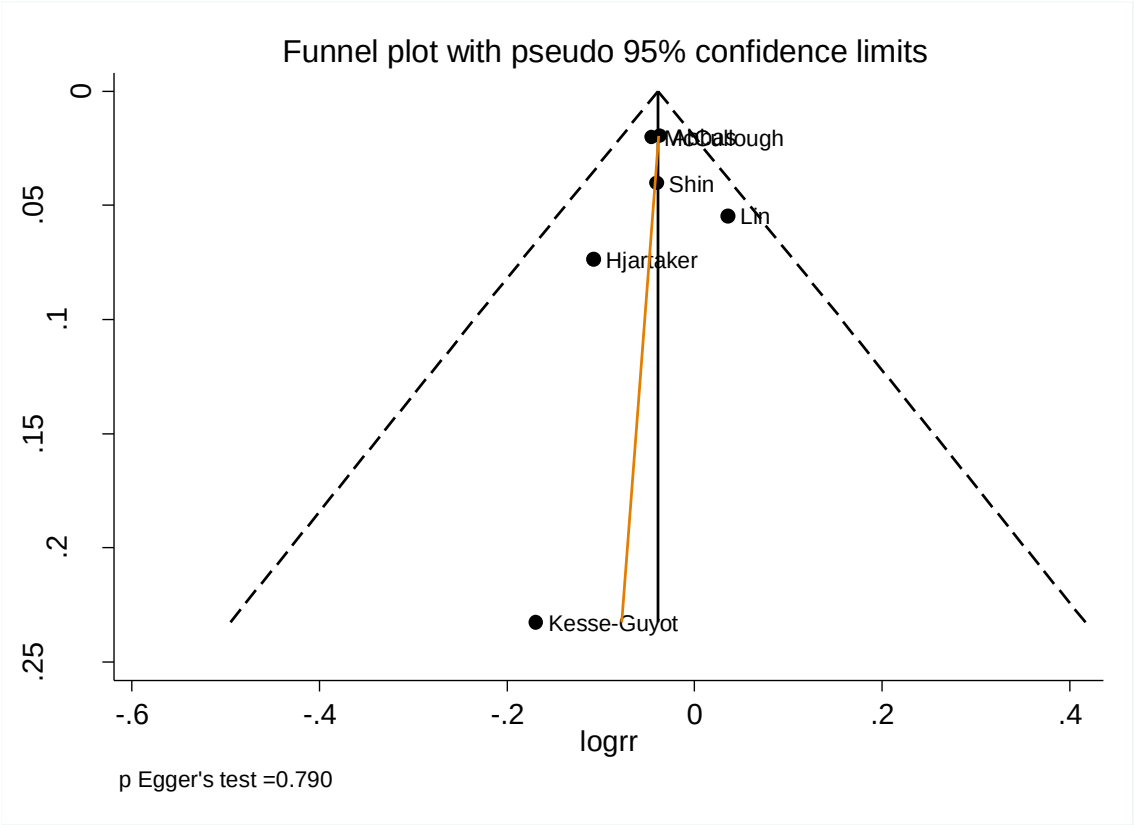


Figure 480 Funnel plot of studies included in the dose response meta-analysis of dietary calcium intake and postmenopausal breast cancer



5.6.3 Calcium from supplements

Randomised controlled trials

Overall summary

One meta-analysis of six RCTs was identified (49 cases in the treatment group and 49 cases in the control group) reporting no association between supplemental calcium intake and risk of breast cancer (Overall RR 1.01; 95% CI 0.64-1.59; P for overall significance=0.97) (Bristow, 2013). None of the studies was designed to investigate cancer risk as primary outcome.

Cohort studies

Overall summary

Six publications from five studies were identified. One meta-analysis was identified.

Dose response meta-analysis was not conducted due to low number of studies with the required information to do it.

Breast cancer (any)

Three publications (from two studies) and one meta-analysis were identified.

A Swedish study (SMC; Larsson 2010) investigating the association between multivitamin use and invasive breast cancer incidence, showed an inverse significant risk of breast cancer

in women that used calcium supplements compared to nonusers of calcium supplements. Another study using the same cohort (Larsson, 2009d), which investigated the association between dietary calcium and breast cancer, revealed an inverse non-significant association of calcium supplement use of breast cancer and ER-/PR- tumours.

An American study (NIH-AARP; Park, 2009b) reported an inverse non-significant association for the highest versus the lowest calcium supplement intake.

Table 407 Main characteristics of prospective studies on calcium from supplements and risk of breast cancer.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Larsson, 2010	SMC, Prospective Cohort, Age: 54 years, W	974/ 35329 9.5 years	Cancer registry	Calcium supplement from 2nd questionnaire	Incidence, Invasive breast cancer	Ca supplement use vs non use	0.74 (0.56-0.97).	Age, education, family history of breast cancer, history of benign breast disease, parity, age at first birth, age at menarche, age at menopause, oral contraceptive use, BMI, physical activity, smoking, and alcohol intake
Larsson, 2009d BRE80210 Sweden	SMC, Prospective Cohort, Age: 54 years, W	2 952/ 61 433 17.4 years	Cancer registry	Calcium supplement from 2nd questionnaire	Incidence, Invasive breast cancer	Highest vs lowest quartile	0.78 (0.60- 1.03)	Age at first child birth, age at menarche, age at menopause, alcohol, benign breast disease, BMI, educational level, family history of cancer, fibre, height, parity, postmenopausal hormone use, total energy, use of oral contraception
		266/			Incidence, breast cancer ER-/PR-	Highest vs lowest quartile	0.51 (0.19-1.39)	
Park, 2009b BRE80464 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W, Retired	5 856/ 492 810 7 years	Cancer registry	Validated FFQ	Incidence, breast cancer	Highest vs lowest quartile	0.98 (0.91-1.06) Ptrend:0.91	Age at first child birth, age at menopause, alcohol consumption, BMI, calcium supplement, educational level, family history of cancer, fat Intake, marital status, menopausal oestrogen use, number of children, race/ethnicity, red meat Intake, smoking, total energy, vigorous physical activity

Table 408 Calcium intake from supplements and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Chen, 2010*	2 prospective cohort studies	3 874 breast cancer	USA	Breast cancer	Highest vs lowest dietary calcium intake.	0.97 (0.87-1.08)	-	-

*All cohort studies identified were included in the present review.

Premenopausal breast cancer

One study was identified.

The WHS (Lin, 2007) reported an inverse non-significant association for the highest compared to the lowest calcium supplements intake in premenopausal women. The RR for the comparison of 500 mg/day of more calcium supplement to none was 0.71 (0.47-1.07), p trend 0.11, 276 premenopausal incident breast cancers during 10 years of follow-up.

Postmenopausal breast cancer

Three studies, all in US were identified. None of the studies reported significant associations. No meta-analysis was conducted.

In the WHI – Observational Study (Prentice, 2013b) the RR for comparing calcium supplement use (210 breast cancer cases) to non supplement use (665 breast cancer cases) was 1.10 (95% CI 0.98- 1.22).

In the WHS (Lin, 2007), the RR for the comparison of 500 mg/day of more of calcium supplement to none was 1.05 (95% CI 0.86-1.30), p trend 0.63, 743 incident postmenopausal breast cancers during 10 years of follow-up.

In the CPS II (McCullough, 2005) the RR for the comparison of 1000 mg/day of more of calcium supplement to none was 0.98 (95% CI 0.86-1.12), p trend 0.23, 2855 incident postmenopausal breast cancers.

Total calcium (calcium from food and supplements)

Cohort studies

Overall summary

Four studies were identified. One meta-analysis was identified.

Dose response meta-analysis was not conducted due to low number of studies.

Breast cancer

Two studies were identified (Li, 2013; Lin, 2007). Meta-analysis was not conducted.

One study from Singapore (SCHS) showed a positive non-significant association between highest total calcium intake and breast cancer risk compared to the lowest (Li, 2013). Similar results were found among women with BMI≥ 23.2 kg/m^2 and among women with vitamin D intake ≥ 83.2 IU/day. Inverse non-significant associations were found among women with BMI<23.2 kg/m^2 and among women with Vitamin D intake< 83.2 IU/day.

One American study (NIH-AARP) reported an inverse non-significant association for the highest versus the lowest total calcium intake and breast cancer incidence (Lin, 2007)..

Table 409 Total calcium intake and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Chen, 2010*	15 studies (6 cohorts, 9 case-control studies)	16 010 breast cancer	France, Finland, Spain, Germany, USA, Switzerland, Sweden, China, Italy, Greece	Breast cancer Fixed effect model Random effects model	Highest vs lowest total calcium intake in women of any menopausal status (15 studies)	 0.87 (0.82-0.93) 0.81 (0.72-0.90	-	-
				Using trim and fill method: Fixed effect model Random effects model		 0.91 (0.85-0.97) 0.89 (0.78-1.01)		
				Cohort studies Case-control studies		0.87 (0.75-1.00) 0.77 (0.68-0.88)		

*All cohort studies identified were included in the present review

Premenopausal breast cancer

Two studies were identified. Meta-analysis was not conducted.

One study from Singapore (SCHS) showed an inverse non-significant association between highest total calcium intake and premenopausal breast cancer risk compared to the lowest (Li, 2013).

One American study (WHS) reported an inverse significant association for the highest total calcium intake and premenopausal breast cancer compared to the lowest. Inverse non-significant associations were reported for ER+, ER-, PR+, and PR- premenopausal breast cancer and total calcium intake (Lin, 2007).

Table 410 Total calcium intake and peri-/premenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Chen, 2010*	5 studies (3 cohort studies and 2 case-control studies)	1 483 premenopausal breast cancer	USA, France, Germany, Russian	Premenopausal breast cancer	Highest vs lowest dietary calcium intake.	0.72 (0.55-0.95)	-	-

*All cohort studies identified were included in the present review.

Postmenopausal breast cancer

Three studies were identified. Meta-analysis was not conducted.

One study from Singapore (SCHS) showed a positive non-significant association between highest total calcium intake and postmenopausal breast cancer risk compared to the lowest (Li, 2013).

One American study (WHS) reported a positive non-significant association for the highest total calcium intake and postmenopausal breast cancer compared to the lowest. Positive non-significant associations were reported for ER+, PR+, and PR- postmenopausal breast cancer and total calcium intake, while an inverse non-significant association was found for ER- postmenopausal breast cancer (Lin, 2007).

Another American study (CPS II) reported an inverse non-significant association for the highest compared to the lowest total calcium intake and postmenopausal breast cancer. Similar results were reported for ER+ postmenopausal breast cancer, whereas a positive non-significant association was found for ER- postmenopausal breast cancer for the highest total calcium intake compared to the lowest (McCullough, 2005).

Table 411 Total calcium intake and postmenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Chen, 2010*	5 studies (4 cohort studies and 1 case-control studies)	5 999 postmenopausal breast cancer	USA, France, Russia,	Postmenopausal breast cancer	Highest vs lowest dietary calcium intake.	0.95 (0.79-1.14)	-	-

*All cohort studies identified were included in the present review.

5.7.5 Phytoestrogens

Summary

One study, reporting results on phytoestrogens and breast cancer, was identified (Ward, 2008). The EPIC-Norfolk study showed a positive non-significant association between breast cancer and total phytoestrogens.

5.7.5 Isoflavones

Cohort studies

Overall summary

Twelve publications from seven cohorts that examined dietary isoflavone intake were identified. No pooled analysis was identified but three meta-analyses were identified.

Dose response meta-analyses were conducted to examine the association of dietary isoflavone intake with risk of postmenopausal breast cancer.

Table 412 Summary of results of the dose-response meta-analysis in the CUP SLR

	Breast cancer (any)	**Premenopausal breast cancer**	**Postmenopausal breast cancer**
Dietary isoflavones Increment unit used	-	-	3 mg/day
Studies (n)	-	-	6
Cases	-	-	12 962
RR (95%CI)	-	-	0.99 (0.98-1.00)
Heterogeneity (I^2, p-value)	-	-	85.4%, 0.243
P value Egger test	-	-	0.498

Breast cancer (any)

Nine publications from six cohorts were identified. Dose-response meta-analysis was not conducted due to insufficient data.

For the two cohorts (MEC and EPIC) on dietary isoflavones and breast cancer risk, inconsistent results were reported (Morimoto, 2014; Zamora-Ros, 2013). Morimoto (2014) reported inverse non-significant associations with invasive only, invasive and in situ, and ER+ breast cancer cases for the highest compared to the lowest quintile of dietary isoflavones, whereas a positive non-significant association was found for ER- cases (Morimoto, 2014). The EPIC study reported no association between breast cancer and isoflavone intake (Zamora-Ros, 2013). Stratified analysis by breast cancer phenotype showed inverse non-significant associations for ER-/PR-, ER-/PR+ and ER+/PR+, while positive

non-significant association was reported for ER+/PR- breast cancer (data are log2 transformed). Two publications reporting results from the EPIC-Norfolk (Ward, 2008) and EPIC-Oxford (Travis, 2008) cohorts showed positive non-significant association between isoflavone intake and breast cancer risk. The Prospect-EPIC cohort reported inverse non-significant association with breast cancer risk for the highest quintile of isoflavone intake compared to the lowest (Keinan-Boker, 2004).

Three studies on isoflavone intake from soy products and breast cancer risk (Wada, 2013; Lee, 2009; Wu, 2008), inverse associations, one being significant (Wu, 2008), were reported.

One study on Swedish women (Hedelin, 2008), reported an inverse non-significant association with the highest intake of isoflavonoids compared to the lowest. Similar results were found among women with ER-/PR- tumours.

Table 413 Total dietary isoflavone intake and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	6 (9 publications)
Studies included in forest plot of highest compared with lowest exposure	6 (9 publications)
Studies included in linear dose-response meta-analysis	Not enough studies
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 414 Dietary isoflavone intake and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Xie, 2013	22 studies (7 prospective cohort studies, 15 case-control studies)	15 927 breast cancer (cases from one study are not reported)	Asian and Western women	Incidence	Soy protein and isoflavone intake Asian women Highest vs Lowest (12 studies) >25mg/day (8 studies) Per 10mg/day (9 studies) Western women Highest vs Lowest (10 studies) >1000µg/day (4 studies)	 0.70 (0.57-0.86) 0.68 (0.52-0.89) 0.99 (0.96-1.03) 0.97 (0.89-1.06) 0.98 (0.87, 1.11)	-	 60.1%, 0.004 0.002 0.018 4.5%, 0.399 0.114
Dong, 2011	14 prospective studies	5 828 breast cancer	Europe, Asia, North America	Incidence	Soy isoflavone consumption (urinary, plasma, serum, dietary) Highest vs Lowest	 0.89 (0.79-0.99)	-	 62.4%, 0.001

Table 415 Dietary isoflavone intake and breast cancer risk. Main characteristics of studies included in the highest versus lowest forest plot.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) P-trend	Adjustment factors
Morimoto, 2014 BRE80547 USA	MEC, Prospective Cohort, Age: 45-75 years, W	4 769/ 84 550 12.5 years	Record linkage to cancer registries and cancer surveillance programmes and seer	FFQ	Incidence, Invasive & In situ breast cancer	20.3-178.7 vs 0-3.1 mg/day	0.96 (0.85-1.08)	Age at baseline, age at first child birth, age at menarche, alcohol consumption, BMI, diabetes, education years, ethnicity, family history of breast cancer, hypertension, menopausal hormone use, menopause status, oral contraceptive use, parity, smoking status, total energy Intake
		3 873/ 84 550 12.5 years			Incidence, Invasive breast cancer	20.3-178.7 vs 0-3.1 mg/day	0.92 (0.81-1.05)	
		2 393/ 84 550 12.5 years			Incidence, breast cancer ER+	20.3-178.7 vs 0-3.1 mg/day	0.94 (0.80-1.12)	
		1 547/ 84 550 12.5 years			Incidence, Invasive & In situ breast cancer, Japanese American	28-160.8 vs 0.1-7 mg/day	0.86 (0.70-1.05)	
		1 245/ 84 550 12.5 years			Incidence, Invasive & In situ breast cancer, white	11.8-114.1 vs 0-1.7 mg/day	1.06 (0.86-1.30)	
		857/ 84 550 12.5 years			Incidence, Invasive & In situ breast cancer, African American	11.3-112.3 vs 0-1.9 mg/day	0.87 (0.68-1.12)	
		675/ 84 550 12.5 years			Incidence, Invasive & In situ breast cancer, Latina	24-178.7 vs 0-3.1 mg/day	0.89 (0.65-1.21)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) P-trend	Adjustment factors
		625/ 84 550 12.5 years			Incidence, breast cancer ER-	20.3-178.7 vs 0-3.1 mg/day	1.06 (0.76-1.47)	
		445/ 84 550 12.5 years			Incidence, Invasive & In situ breast cancer, native Hawaiian	23.7-165.8 vs 0.1-5.1 mg/day	1.45 (1.02-2.07)	
		44/ 84 550 12.5 years			Incidence, breast cancer ER-, native Hawaiian	upper Q4 vs Q1	3.06 (1.15-8.13)	
		44/ 84 550 12.5 years			Incidence, breast cancer ER-, native Hawaiian	23.7-165.8 vs 0.1-5.1 mg/day	3.87 (1.30-11.54)	
Wada, 2013 BRE80455 Japan	TCCJ, Prospective Cohort, Age: 35- years	172/ 15 607 16 years	Cancer registry	FFQ	Incidence, breast cancer	70.6 vs 18.6 mg/day	0.67 (0.44-1.03)	Age, age at first child birth, age at menarche, alcohol, BMI, educational level, energy, HRT use, menopausal status, parity, physical activity, smoking
Zamora-Ros, 2013 BRE80468 Denmark,France,Germany,Greece,Italy,Net	EPIC, Prospective Cohort, Age: 35-70 years, W	11 576/ 334 850 11.5 years	Cancer and pathology registry, active follow up, health Insurance record, mortality registry and	Dietary recall	Incidence, breast cancer	≥1.37 vs ≤0.21 mg/day	1.00 (0.91-1.10)	Age, age at first child birth, age at menarche, age at menopause, alcohol, educational level, energy Intake, fibre, height, hormone use, menopausal
		11 576/ 334 850 11.5 years			Incidence, breast cancer	per 200 %	1.00 (0.98-1.02)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) P-trend	Adjustment factors
herlands,Norway,Spain,Sweden,UK		3 653/ 334 850 11.5 years	contact of participants or next-of-kin		Incidence, breast cancer ER+/PR+	per 200 %	0.99 (0.96-1.03)	status, OC use, physical activity, smoking status, study centre, weight
		1 133/ 334 850 11.5 years			Incidence, breast cancer ER+/PR-	per 200 %	1.03 (0.96-1.11)	
		1 050/ 334 850 11.5 years			Incidence, breast cancer ER-/PR-	per 200 %	0.98 (0.92-1.06)	
		217/ 334 850 11.5 years			Incidence, breast cancer ER-/PR+	per 200 %	0.94 (0.80-1.10)	
Lee, 2009 BRE80254 China	SWHS, Prospective Cohort, Age: 40-70 years, W	594/ 73 223 7.4 years	Cancer registry and death certificates	FFQ	Incidence, breast cancer	≥44.24 vs ≤15.93 mg/day	0.81 (0.61-1.07)	Age, age at first child birth, BMI, educational level, family history of cancer, physical activity, season of Interview, total caloric Intake
Hedelin, 2008 BRE80162 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	1 014/ 45 448 13 years	Cancer registry	FFQ	Incidence, Invasive breast cancer	Q 4 vs Q 1	0.98 (0.83-1.17)	Age, age at first child, age at menarche, alcohol Intake, BMI, energy Intake, family history of cancer, OC use, parity, saturated fat
					Invasive breast cancer ER-/PR-		0.9 (0.5-1.5)	
Wu, 2008	SCHS,	629/	Cancer registry	Semi-	Incidence, breast	≥10.6 vs <10.6	0.82 (0.70-0.97)	Age, age at menarche, BMI,

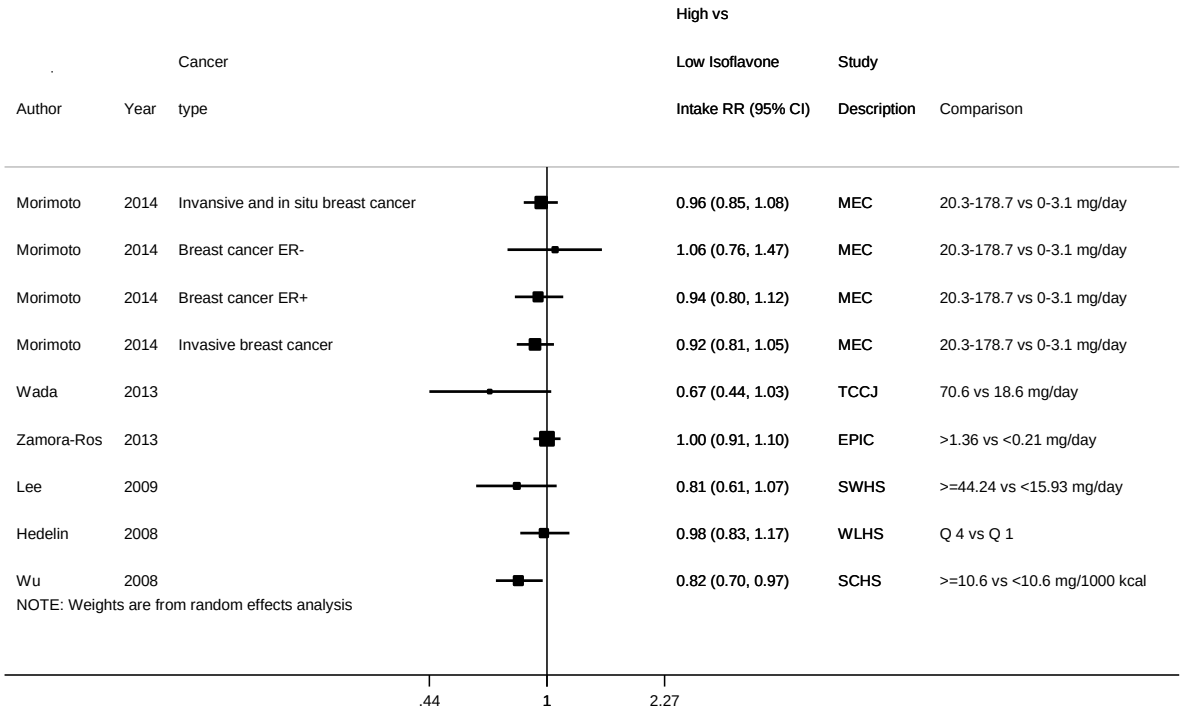
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) P-trend	Adjustment factors
BRE80199 Singapore	Prospective Cohort, Age: 45-74 years, W	35 303 12 years		quantitative FFQ	cancer	mg/1000 kcal		educational level, ethnicity, family history of cancer, menopausal status, omega3 PUFA, parity, year of Interview
		556/ 35 303 12 years			Incidence, breast cancer, 1-9 yrs. of follow-up	≥10.6 vs <10.6 mg/1000 kcal	0.88 (0.74-1.05)	
		73/ 35 303 12 years			Incidence, breast cancer, follow-up 10+yrs	≥10.6 vs <10.6 mg/1000 kcal	0.48 (0.29-0.78)	

Table 416 Dietary isoflavones and breast cancer risk. Main characteristics of studies excluded from the highest versus lowest forest plot.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) P-trend	Adjustment factors	Reason for exclusion
Ward, 2010 BRE80280 UK	EPIC-Norfolk, Nested Case Control, Age: 40-79 years, W	244/ 938 controls 9 years	Cancer registry	7-day food records	Incidence, breast cancer Total isoflavones	per 200 %	1.05 (0.90-1.21)	Age, breastfeeding, energy Intake, family history of cancer, fat Intake, HRT use, OC use, oophorectomy/hysterectomy, parity, social class, weight	Superseded by Zamora-Ros 2013
Travis, 2008 BRE80141 UK	EPIC-Oxford, Prospective Cohort, Age: 20-89 years, W	585/ 36 489 7.4 years	National health records	FFQ	Incidence, Invasive & In situ breast cancer	≥20 vs ≤9.9 mg/day	1.17 (0.79-1.71)	Age, age at first child birth, age at menarche, alcohol consumption, BMI, energy Intake, height, HRT use, menopausal status, method of recruitment, parity	Superseded by Zamora-Ros 2013
		433/ 36 489 7.4 years			Incidence, Invasive & In situ breast cancer HRT - no	≥10 vs ≤9.9 mg/day	1.16 (0.92-1.48)		
		556/ 35 303 12 years			Incidence, breast cancer, 1-9 yrs. of follow-up	≥10.6 vs ≤10.5 mg/1000 kcal	0.88 (0.74-1.05)		
		73/ 35 303 12 years			Incidence, breast cancer, follow-up 10+yrs	≥10.6 vs ≤10.5 mg/1000 kcal	0.48 (0.29-0.78)		
Keinan-Boker, 2004 BRE04713 Netherlands	Prospect-EPIC, Prospective Cohort, Age: 50-69	280/ 15 555 5.2 years	Partially histological - over 80%	FFQ	Incidence, breast cancer,	0.77 vs 0.19 mg/day	0.98 (0.65-1.48)	Age , age at first child, body weight, educational level, energy Intake ,	Superseded by Zamora-Ros 2013

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) P-trend	Adjustment factors	Reason for exclusion
	years, W, Screening Program							height, HRT use, marital status, OC use, parity/pregnancies, physical activity	

Figure 481 RR (95% CI) of breast cancer for the highest isoflavone intake compared with reference category



Note: Isoflavones from soy products only are reported for Wada (2013), Lee (2009) and Wu (2008). Zamora-Ross (2013) and Hedelin (2008) reported invasive breast cancer cases only. Wada (2013) reported cancer cases with invasive breast cancer and one case with in situ breast cancer.

Genistein

Four studies were identified, reporting results on dietary genistein and breast cancer risk. Studies are not tabulated.

Two studies reported inverse associations between breast cancer risk and the highest genistein intake compared to the lowest (Iwasaki, 2008; Yamamoto, 2003), one being significant (Yamamoto, 2003).

EPIC-Norfolk (Ward, 2010) observed a positive non-significant association between genistein intake and breast cancer, while Horn-Ross *et al.* (2002) did not report any association (Horn-Ross, 2002).

Lignans

Five studies from three cohorts were identified. Studies are not tabulated.

For the two cohorts (EPIC and WLHS) positive non-significant associations were reported between breast cancer and the highest lignans intake compare to the lowest (Zamora-Ros, 2013; Hedelin, 2008), whereas the SU.VI.MAX cohort showed an inverse non-significant association (Touvier, 2013).

EPIC-Norfolk (Ward, 2010) reported a positive non-significant association between lignans intake and breast cancer, while Prospect-EPIC (Keinan-Boker, 2004) showed an inverse non-significant association for the highest lignan intake compared to the lowest.

Premenopausal breast cancer

Seven publications from five cohorts were identified. Dose-response meta-analysis was not conducted due to insufficient data.

The EPIC study (Zamora-Ros, 2013) reported an inverse non-significant association with premenopausal breast cancer for the highest compared to the lowest quintile of dietary isoflavones. In contrast, EPIC-Oxford (Travis, 2008) and E3N-EPIC (Touillaud, 2006) revealed a positive non-significant association and no association, respectively.

Three studies on isoflavone intake from soy products and premenopausal breast cancer risk, reported positive non-significant associations (Wada, 2013; Wu, 2008) and inverse significant association (Lee, 2009).

One study on Swedish women (Hedelin, 2008), reported a positive non-significant association with the highest intake of isoflavonoids compared to the lowest in Swedish women aged less than 50 years old, which is the mean age at menopause in Sweden.

Table 417 Total dietary isoflavone intake and premenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	5 (7 publications)
Studies included in forest plot of highest compared with lowest exposure	5 (7 publications)
Studies included in linear dose-response meta-analysis	Not enough studies
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 418 Dietary isoflavone intake and premenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Chen, 2014	22 studies (8 prospective studies, 14 case-control studies)	6 710 premenopausal breast cancer	Asian and Western countries	Incidence	Soy isoflavone/protein intake and isoflavone levels (urine, plasma) Highest vs Lowest	 0.76 (0.62-0.89)	- 	 73.6%, 0.001
Xie, 2013	11 studies (4 prospective studies, 7 case-control studies)	Not reported	Asian and Western women	Incidence	Soy protein and isoflavone intake Asian women >25mg/day (6 studies) Western women Pooled risk (5 studies)	 0.63 (0.50-0.80) 1.00 (0.98, 1.02)	- 	 0.089 0.521
Dong, 2011	7 prospective studies	Not reported	Europe, Asia, North America	Incidence	Soy isoflavone consumption (urinary, plasma, serum, dietary) Highest vs Lowest	 0.90 (0.64-1.15)	- 	 71.6%, 0.002

Table 419 Dietary isoflavone intake and premenopausal breast cancer risk. Main characteristics of studies included in the highest versus lowest forest plot.

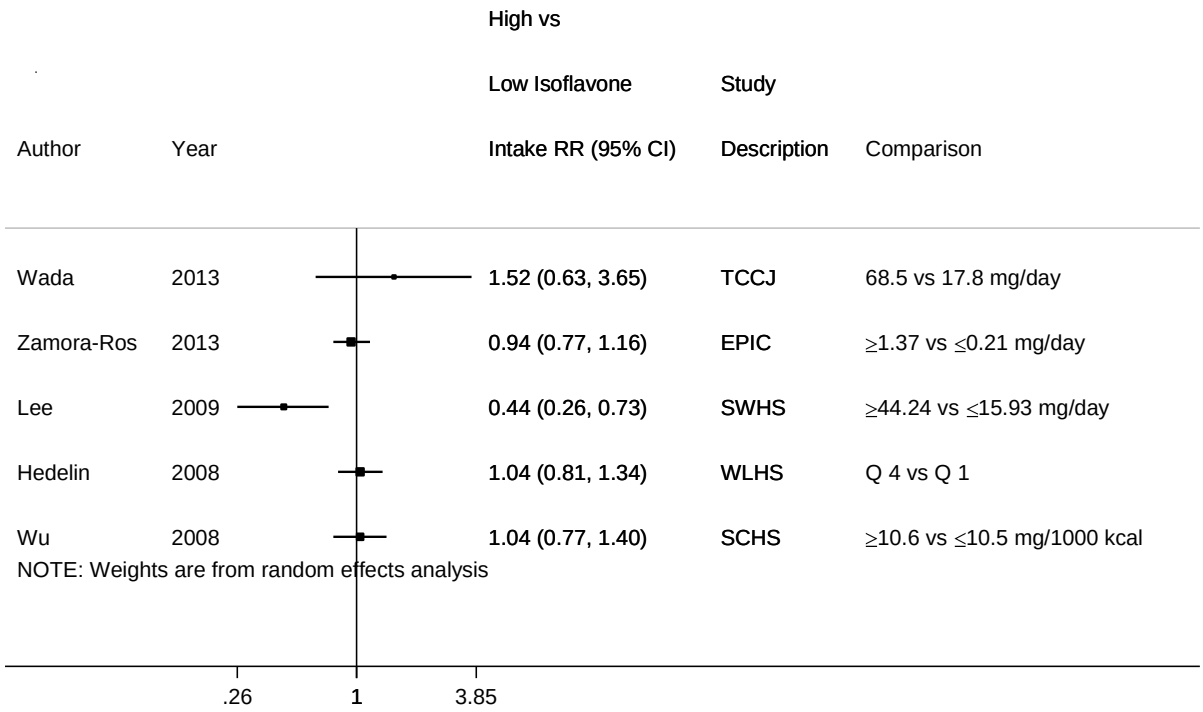
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) P-trend	Adjustment factors
Wada, 2013 BRE80455 Japan	TCCJ, Prospective Cohort, Age: 35- years	48/ 15 607 16 years	Cancer registry	FFQ	Incidence, premenopausal breast cancer	68.5 vs 17.8 mg/day	1.52 (0.63-3.65)	Age, age at first child birth, age at menarche, alcohol, BMI, educational level, energy, HRT use, menopausal status, parity, physical activity, smoking
Zamora-Ros, 2013 BRE80468 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	2 827/ 334 850 11.5 years	Cancer and pathology registry, active follow up, health Insurance record, mortality registry and contact of participants or next-of-kin	Dietary recall	Incidence, premenopausal breast cancer	≥1.37 vs ≤0.21 mg/day	0.94 (0.77-1.16)	Age, age at first child birth, age at menarche, age at menopause, alcohol, educational level, energy Intake, fibre, height, hormone use, menopausal status, OC use, physical activity, smoking status, study centre, weight
Lee, 2009 BRE80254 China	SWHS, Prospective Cohort, Age: 40-70 years, W	305/ 73 223 7.4 years	Cancer registry and death certificates	FFQ	Incidence, premenopausal breast cancer	≥44.24 vs ≤15.93 mg/day	0.44 (0.26-0.73)	Age, age at first child birth, BMI, educational level, family history of cancer, physical activity, season of Interview, total caloric Intake
Hedelin, 2008 BRE80162 Sweden	WLHS, Prospective Cohort, Age: 30-49	494/ 45 448 13 years	Cancer registry	FFQ	Incidence, Invasive premenopausal breast cancer	Q 4 vs Q 1	1.04 (0.81-1.34)	Age, age at first child, age at menarche, alcohol Intake, BMI, energy Intake, family history of cancer, OC use,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) P-trend	Adjustment factors
	years, W							parity, saturated fat
Wu, 2008 BRE80199 Singapore	SCHS, Prospective Cohort, Age: 45-74 years, W	190/ 35 303 12 years	Cancer registry	Semi-quantitative FFQ	Incidence, premenopausal breast cancer	≥10.6 vs <10.5 mg/1000 kcal	1.04 (0.77-1.40)	Age, age at menarche, BMI, educational level, ethnicity, family history of cancer, menopausal status, omega3 PUFA, parity, year of Interview

Table 420 Dietary isoflavones and premenopausal breast cancer risk. Main characteristics of studies excluded from the highest versus lowest forest plot.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) P-trend	Adjustment factors	Reason for exclusion
Travis, 2008 BRE80141 UK	EPIC-Oxford, Prospective Cohort, Age: 20-89 years, W	585/ 36 489 7.4 years	National health records	FFQ	Incidence, Invasive & In situ breast cancer	≥10 vs <10 mg/day	1.31 (0.95-1.81)	Age, age at first child birth, age at menarche, alcohol consumption, BMI, energy Intake, height, HRT use, menopausal status, method of recruitment, parity	Superseded by Zamora-Ros 2013
Touillaud, 2006 BRE80111 France	E3N-EPIC, Prospective Cohort, W	402/ 74 5245 4.2 years	Patient records, direct contact, health insurance records	FFQ	Incidence, Invasive premenopausal breast cancer,	36-112 vs 1-21 mg/day	1.00 (0.76-1.31)	Educational level, height, BMI, age at menarche, benign breast disease, family history, OC use, age at first child, parity/pregnancies, recruitment centre, alcohol, energy intake	Superseded by Zamora-Ros 2013

Figure 482 RR (95% CI) of premenopausal breast cancer for the highest isoflavone intake compared with reference category



Note: Isoflavones from soy products only are reported for Wada (2013), Lee (2009) and Wu (2008). Hedelin (2008) based the effect of menopausal status on the mean age at menopause in Sweden, which is 50 years old. Zamora-Ross (2013) and Hedelin (2008) reported invasive breast cancer cases only. Wada (2013) reported cancer cases with invasive breast cancer and one case with in situ breast cancer.

Postmenopausal breast cancer

Summary

Main results:

Six out of seven studies (12 962cases) (nine publications) identified could be included in the dose-response meta-analysis of dietary isoflavones.

No association was observed for postmenopausal breast cancer and isoflavone intake (per 3mg/day). Low heterogeneity was observed between studies. There was no evidence of significant publication or small study bias.

Subgroup analysis was not conducted due to low number of studies in the strata. There was one multi-ethnic study, one American study, one Japanese, one Europe and two Chinese studies, from which one included participants located in Singapore.

Three studies were excluded from the dose-response analysis (Hedelin, 2008, WLHS; Travis, 2008, EPIC-Oxford; Wu, 2008, SCHS). For those studies, inverse associations, one being significant (Wu, 2008), were reported.

Sensitivity analyses:

The summary RR did not change materially when studies were omitted in turn in influence analysis.

Non-linear dose-response meta-analysis:

Non-linear dose-response meta-analysis was not conducted due to insufficient data.

Study quality:

All studies used FFQ to assess isoflavone intake, except EPIC which used country-specific validated questionnaires.

TCCJ, SCHS and SWHS are cohorts on Japanese, Singapore Chinese and Chinese women, which estimated isoflavone intake only from soy products (Wada, 2013; Butler, 2010; Lee, 2009). CPS II and EPIC included invasive breast cancer only (Wang, 2014; Zamora-Ros, 2013); MEC and TCCJ used invasive and in situ breast cancer (TCCJ reported also unknown breast cancers cases) (Morimoto, 2014; Wada, 2013) and SCHS and SWHS do not report type of breast cancer (Butler, 2010; Lee, 2009).

Most of the studies were adjusted for major confounding factors (age, alcohol and reproductive factors) except the SCHS cohort (Butler, 2010) which was not adjusted for alcohol consumption and the SWHS cohort (Lee, 2009) which was not adjusted for alcohol intake and reproductive factors.

Influence analysis shows that the inverse non-significant association remained when each study was excluded in turn from the meta-analysis.

Table 421 Total dietary isoflavone intake and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	7 (9 publications)
Studies included in forest plot of highest compared with lowest exposure	7 (9 publications)
Studies included in linear dose-response meta-analysis	6 (8 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 422 Total dietary isoflavone intake and postmenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR*	CUP SLR
Increment unit used	-	3 mg/day
Studies (n)	-	6
Cases	-	12 962
RR (95%CI)	-	0.99 (0.98-1.00)
Heterogeneity (I^2, p-value)	-	25.4%, 0.243
P value Egger test	-	0.498

*No meta-analysis in the past reports

Table 423 Dietary isoflavone intake and postmenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Chen, 2014	21 studies (8 prospective studies, 13 case-control studies)	9 341 postmenopausal breast cancer	Asian and Western countries	Incidence	Soy isoflavone/protein intake and isoflavone levels (urine, plasma) Highest vs Lowest	0.73 (0.58-0.88)	- 	87.8%, 0.001
Xie, 2013	11 studies (4 prospective studies, 7 case-control studies)	Not reported	Asian and Western women	Incidence	Soy protein and isoflavone intake Asian women >25mg/day (6 studies) Western women Pooled risk (5 studies)	0.46 (0.28-0.78) 0.99 (0.87, 1.12)	- 	0.004 0.926
Dong, 2011	8 prospective studies	Not reported	Europe, Asia, North America	Incidence	Soy isoflavone consumption (urinary, plasma, serum, dietary) Highest vs Lowest	0.78 (0.63-0.93)	- 	57.1%, 0.022

Table 424 Dietary isoflavone intake and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) P-trend	Adjustment factors
Morimoto, 2014 BRE80547 USA	MEC, Prospective Cohort, Age: 45-75 years, W	4 112/ 84 550 12.5 years	Record linkage to cancer registries and cancer surveillance programmes and seer	FFQ	Incidence, Invasive & In situ breast cancer, postmenopausal	20.3-178.7 vs 0-3.1 mg/day	0.98 (0.86-1.12) Ptrend:0.56	Age at baseline, age at first child birth, age at menarche, alcohol consumption, BMI, diabetes, education years, ethnicity, family history of breast cancer, hypertension, menopausal hormone use, menopause status, oral contraceptive use, parity, smoking status, total energy Intake
Wang, 2014 BRE80603 USA	CPS II, Prospective Cohort, Age: 68.6 years, W, Postmenopausal	2 116/ 56 630 8.5 years	Self-report and linkages with states tumour registries, verified by medical records	Semi-quantitative FFQ	Incidence, Invasive postmenopausal breast cancer	0.09-45 vs ≤0.03 mg/day	1.04 (0.91-1.20) Ptrend:0.64	Age, age at menopause, educational level, ethanol Intake, family history of breast cancer, history of breast cyst, hormone replacement therapy, parity and age at first birth, smoking history, total energy Intake, weight gain since 18
						per 3 mg/day	0.97 (0.92-1.02)	
		1 498/			Incidence, postmenopausal breast cancer ER+	0.09-45 vs ≤0.03 mg/day	1.06 (0.90-1.24) Ptrend:0.68	
						per 3 mg/day	0.98 (0.93-1.03)	
		218/			Incidence, postmenopausal breast cancer ER-	0.09-45 vs ≤0.03 mg/day	0.91 (0.60-1.39) Ptrend:0.84	
						per 3 mg/day	0.95 (0.81-1.11)	
Wada, 2013	TCCJ,	134/	Cancer registry	FFQ	Incidence,	70.6 vs 18.7	0.52 (0.32-0.85)	Age, age at first child birth, age

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) P-trend	Adjustment factors
BRE80455 Japan	Prospective Cohort, Age: 35- years	15 607 16 years			postmenopausal breast cancer	mg/day	Ptrend:0.046	at menarche, alcohol, BMI, educational level, energy, HRT use, menopausal status, parity, physical activity, smoking
		111/			Incidence, postmenopausal breast cancer, BMI <= 25		0.52 (0.31-0.88) Ptrend:0.038	
		106/			Incidence, postmenopausal breast cancer, never smoked		0.48 (0.28-0.85) Ptrend:0.011	
		95/			Incidence, postmenopausal breast cancer, physical activity score <=2		0.67 (0.38-1.16) Ptrend:0.49	
		86/			Incidence, postmenopausal breast cancer, drinker		0.41 (0.22-0.78) Ptrend:0.021	
		48/			Incidence, postmenopausal breast cancer, no alcohol Intake		0.75 (0.34-1.68) Ptrend:0.73	
		39/			Incidence, postmenopausal		0.21 (0.07-0.62) Ptrend:0.002	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) P-trend	Adjustment factors
					breast cancer, physical activity score >2			
		23/			Incidence, postmenopausal breast cancer, BMI > 25		0.59 (0.13-2.62) Ptrend:0.94	
		16/			Incidence, postmenopausal breast cancer, ever smoker		0.42 (0.08-2.22) Ptrend:0.65	
Zamora-Ros, 2013 BRE80468 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	5 872/ 334 850 11.5 years	Cancer and pathology registry, active follow up, health Insurance record, mortality registry and contact of participants or next-of-kin	Dietary recall	Incidence, breast cancer, postmenopausal	≥1.37 vs ≤0.21 mg/day	1.00 (0.87-1.14) Ptrend:0.702	Age, age at first child birth, age at menarche, age at menopause, alcohol, educational level, energy Intake, fibre, height, hormone use, menopausal status, oc use, phyisical activity, smoking status, study center, weight
						per 200 %	0.99 (0.96-1.02)	
Butler, 2010 BRE80295 Singapore	SCHS, Prospective Cohort, Age: 45-74 years, W	439/ 34 028 10.7 years	Cancer registry	FFQ	Incidence, breast cancer, postmenopausal	33.9 vs 4.6 mg/day	0.86 (0.64-1.16) Ptrend:0.15	Age, BMI, dialect group, educational level, energy Intake, family history of cancer, parity, year of Interview
Lee, 2009	SWHS,	289/	Cancer registry and death	FFQ	Incidence, breast	≥44.24 vs	1.09 (0.78-1.52)	Age, age at first child birth, BMI,

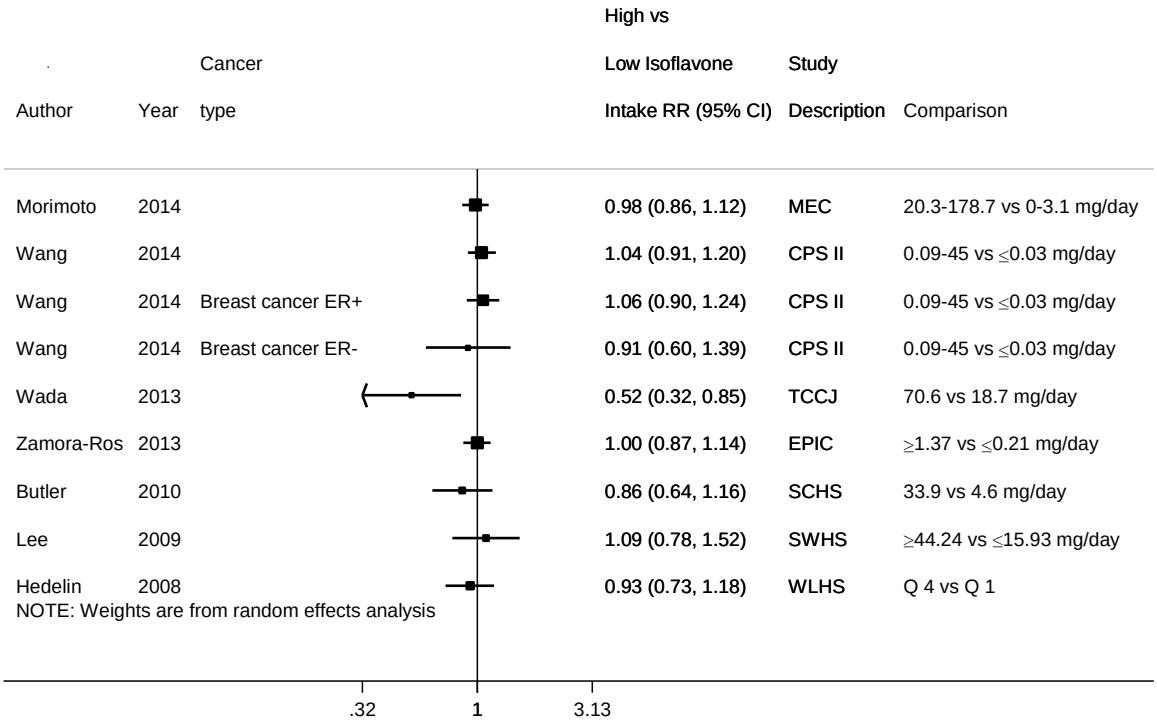
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) P-trend	Adjustment factors
BRE80254 China	Prospective Cohort, Age: 40-70 years, W	73 223 7.4 years	certificates		cancer, postmenopausal	≤15.93 mg/day	Ptrend:0.800	educational level, family history of cancer, physical activity, season of Interview, total caloric Intake

Table 425 Dietary isoflavones and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) P-trend	Adjustment factors	Reason for exclusion
Hedelin, 2008 BRE80162 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	520/ 45 448 13 years	Cancer registry	FFQ	Incidence, Invasive postmenopausal breast cancer	Q 4 vs Q 1	0.93 (0.73-1.18)	Age, age at first child, age at menarche, alcohol Intake, BMI, energy Intake, family history of cancer, OC use, parity, saturated fat	Paper does not report dose ranges
Travis, 2008 BRE80141 UK	EPIC-Oxford, Prospective Cohort, Age: 20-89 years, W	290/ 36 489 7.4 years	National health records	FFQ	Incidence, Invasive & In situ breast cancer, postmenopausal	≥20 vs ≤9.9 mg/day	0.95 (0.66-1.38)	Age, age at first child birth, age at menarche, alcohol consumption, BMI, energy Intake, height, HRT use, menopausal status, method of recruitment, parity	Superseded by Zamora-Ros 2013
Wu, 2008 BRE80199 Singapore	SCHS, Prospective Cohort, Age: 45-74 years, W	439/ 35 303 12 years	Cancer registry	Semi-quantitative FFQ	Incidence, postmenopausal breast cancer	≥10.6 vs <10.6 mg/1000 kcal	0.74 (0.61-0.90)	Age, age at menarche, BMI, educational level, ethnicity, family history of cancer, menopausal status, omega3 PUFA, parity, year of Interview	Superseded by Butler 2010

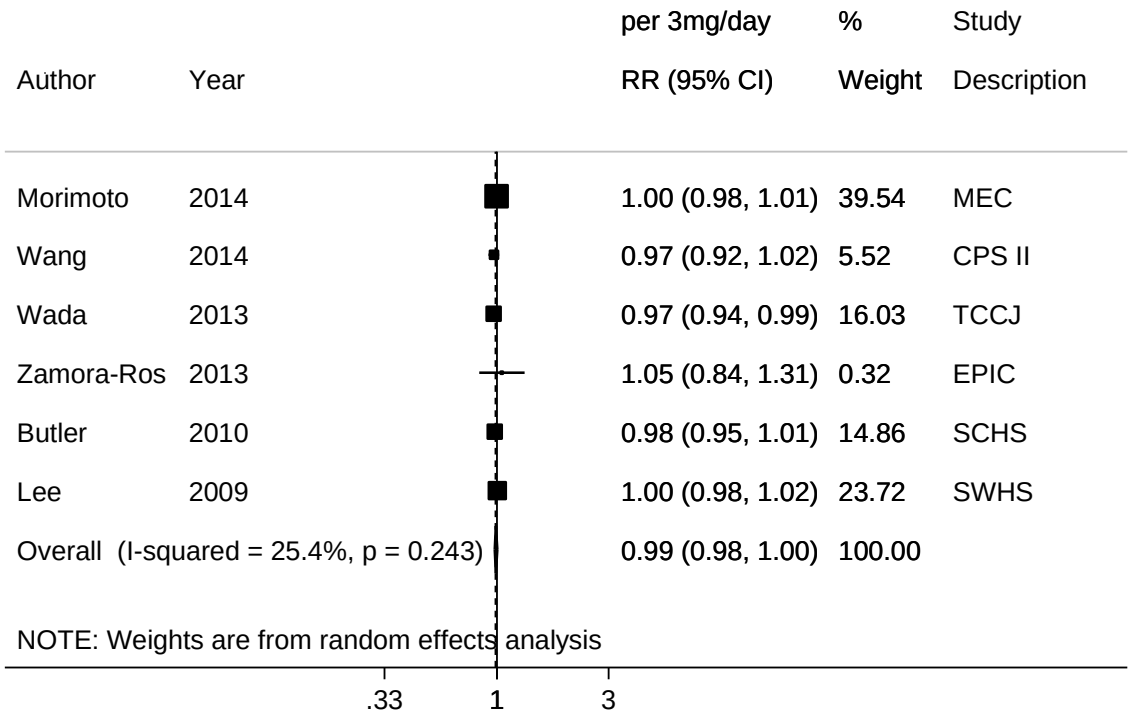
Figure 483 RR estimates of postmenopausal breast cancer by levels of dietary isoflavone intake

Figure 484 RR (95% CI) of postmenopausal breast cancer for the highest isoflavone intake compared with reference category



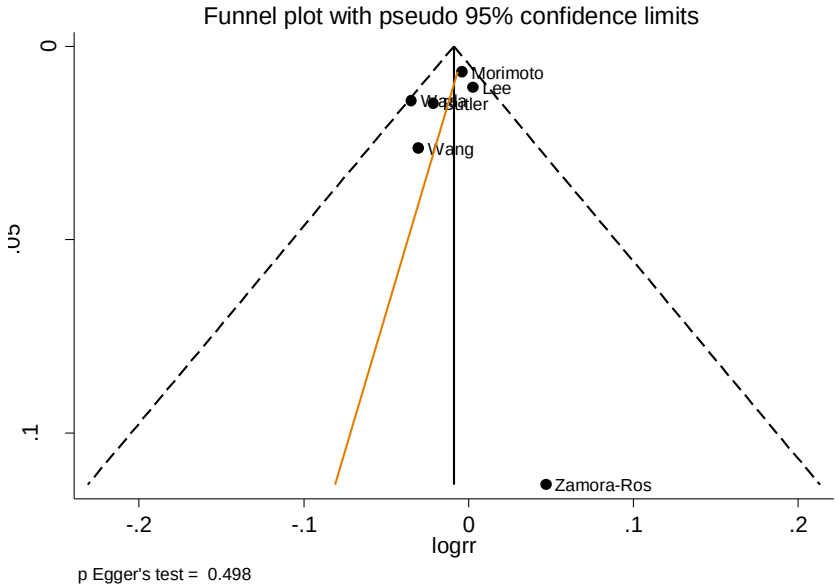
Note: Isoflavones from soy products only are reported for Wada (2013), Butler (2010) and Lee (2009). Hedelin (2008) based the effect of menopausal status on the mean age at menopause in Sweden, which is 50 years old. Morimoto (2014) reported invasive and in situ cancer cases. Wang (2014), Zamora-Ross (2013) and Hedelin (2008) reported invasive breast cancer cases only. Wada (2013) reported cancer cases with invasive breast cancer and one case with in situ breast cancer.

Figure 485 Relative risk of postmenopausal breast cancer for 3mg/day increment of dietary isoflavone intake



Note: Isoflavones from soy products only are reported for Wada (2013), Butler (2010) and Lee (2009). Morimoto (2014) reported invasive and in situ cancer cases. Wang (2014) and Zamora-Ross (2013) reported invasive breast cancer cases only. Wada (2013) reported cancer cases with invasive breast cancer and one case with in situ breast cancer.

Figure 486 Funnel plot of studies included in the linear dose response meta-analysis of dietary isoflavone intake and postmenopausal breast cancer



Lignans

Four studies from three cohorts were identified. Studies are not tabulated.

For the two cohorts (EPIC and SMC) inverse associations were reported between postmenopausal breast cancer and the highest lignans intake compare to the lowest (Zamora-Ros, 2013; Suzuki, 2008b), one being significant (Suzuki, 2008b). The WLHS cohort showed a positive non-significant association (Hedelin, 2008).

The E3N-EPIC (Touillaud, 2007) reported an inverse significant association between plant lignans intake and postmenopausal breast cancer, while an inverse non-significant association was found with enterolignans. Stratified analysis by combined estrogen and progesterone receptor showed that both plant lignans and enterolignans had an inverse significant association with ER+/PR+ postmenopausal breast cancer, whereas no significant association was found for ER+/PR-, ER-/PR+ and ER-/PR- postmenopausal breast cancer.

6 Physical activity

Because of differences between studies in the way physical activity was reported, it was not possible to conduct dose-response meta-analysis on most physical activity domains. Study results were therefore summarised for the highest compared with the lowest physical activity category. For recreational physical activity and vigorous physical activity, number of studies reported in comparable measurement unit (MET-hour/week and minutes/day, respectively) were sufficient and dose-response meta-analyses were conducted. Details of the physical activity assessment in each cohort included in the review are tabulated below.

Table 426 Main characteristics of physical activity assessment in studies include in the review

Study	Domains	Description of assessment	Validation
Adventist Health Study (AHS)	Total physical activity (recreational and occupational) (Fraser, 1997)	Questionnaire. Cross-classification of two questions relating to occupational and leisure activities: "Outside of your usual work or daily activities, do you usually get at least 15 minutes of vigorous exercise three or more times per week?" (with checklist of vigorous activities) "Does your usual daily work or responsibilities involve vigorous activities similar to those listed in the previous question?"	Not indicated
Aerobic Center Longitudinal Study (ACLS)	Recreational physical activity (Drake, 2001)	Questionnaire. On type, intensity, duration, and frequency of walking, jogging, biking, stationary biking, swimming, dancing, racket sports, stretching; participation in other exercise, calisthenics, weight-lifting, and treadmill exercises, at baseline fitness evaluation and subsequent mail-out surveys.	Not indicated
American Cancer Society Cancer Prevention Study II (CPS II); CPS II-Nutrition Cohort	Recreational physical activity Walking Sitting (Hildebrand, 2013; Patel, 2003; CPS II-Nutrition Cohort) Occupational (Calle, 1998, CPS II)	Questionnaire. 'During the past year, what was the average time per week you spent at the following kinds of activities: walking, jogging/running, lap swimming, tennis or racquetball, bicycling or stationary biking, aerobics/calisthenics, and dancing?' 'During the past year, what was the average time per week you spent at the following kinds of activities: gardening/mowing/planting, heavy housework/vacuuming, heavy home repair/painting, and shopping?' Questionnaire. Current occupation, job held for the longest period of time, if retired, last occupation	Not indicated
Atherosclerosis Risk in Communities Study (ARIC)	Recreational physical activity Occupational physical activity (Mertens, 2006)	Modified version of the Baecke physical activity questionnaire. Leisure index was derived from four questions regarding the frequency of walking, bicycling, television watching and walking or bicycling to/from work or shopping. Sports index was derived by (1) asking about the four most frequent sports or exercise, their average yearly frequency, and their weekly duration and assigning an intensity (low, medium or high) to each sport or exercise and (2) querying the frequency of sweating, the general frequency of sports play, and a self-rating of activity compared to others. Work index was derived from eight questions about the subject's main occupation, her rating of the physical demands of the work, and the frequency of sitting, standing, walking, lifting, sweating and fatigue.	Validated, no further information in article

Black Women's Health Study (BWHS)	Vigorous recreational physical activity Walking Sitting (Rosenberg, 2014)	Questionnaire. Number of hours per week spent in vigorous physical activity (e.g., basketball, swimming, running, aerobics). Hours per week and pace of walking for exercise. Hours per day spent sitting watching television and sitting at work. Physical activity updated on follow-up questionnaires.	Validated against actigraphs (activity monitors) during participants' waking hours for a week. Significantly correlated with BWHS questionnaire data on recent vigorous exercise.
Breast Cancer Detection Demonstration Project (BCDDP)	Total physical activity Recreational and household (non-occupational) activities (Leitzmann, 2008; Chang, 2006)	Questionnaire. Number of hours per typical weekday and weekend day participants spent engaging in moderate and vigorous physical activities that covered household, occupational, and recreational or sporting activities. Moderate activity (referred to as non-vigorous activity) included light housework, vacuuming, washing clothes, painting, home repairs, lawn mowing, general gardening, raking, light sports or exercise, walking, hiking, light jogging, recreational tennis, bowling, golf and bicycling on a level ground. Vigorous activities heavy housework such as scrubbing floors or washing windows, heavy yard-work, digging in the garden, chopping wood, strenuous sports or exercise, running, fast jogging, competitive tennis, aerobics, bicycling on hills and fast dancing. Also questioned sedentary behaviours (examples included sitting, office work, driving a car, occupations that involved standing or walking, watching television, and reading	Not undergone a direct comparison with physical activity logs or other validation tools. Physical activity assessment is similar to that employed in the Framingham Heart Study and the College Alumnus Physical Activity Questionnaire.
Canadian Study of Diet, Lifestyle, and Health (CSDLH)	Recreational physical activity Sitting (Catsburg, 2014b)	Questionnaire. Relating to amount of time per week spent walking, hiking, jogging, running, bicycling, in calisthenics or aerobics, playing tennis or squash, lap swimming, and in other aerobic recreation; flights of stairs climbed daily; and about markers for sedentary lifestyle such as time spent sitting at home or at work and time spent sitting in front of a television screen.	Physical activity duration portion of the questionnaire was developed by the Nurses' Health Study (NHS) and was validated
College Alumni Health Study (CAHS)	Recreational physical activity (Sesso, 1998)	Questionnaire. Daily number of flights of stairs climbed and city blocks walked, and sports participation, from which estimated index of weekly energy expenditure.	Validated. Estimates of energy expenditure from questionnaire yielded age-adjusted

			correlation coefficients of 0.54 compared with activity records, and 0.53 compared with $V0_2$ peak measurements, a measure of physical fitness.
Copenhagen City Heart Study (CCHS)	Recreational physical activity (Rod, 2009; Hoyer, 1998)	Questionnaire. On physical activity in leisure time; categories were: (a) almost entirely sedentary (reading, TV, cinema) or light physical activity <2 hr/wk, (b) light activity 2-4 hr/wk, e.g. walking, cycling, light gardening, (c) light activity >4 hr/wk or more vigorous physical activity 2-4 hr/wk, e.g. brisk walking, fast cycling, heavy gardening, sports where you get sweaty or exhausted, (d) highly vigorous activity >4 hr/wk or regular heavy exercise or competitive sports several times per week	Not indicated
The Copenhagen Centre for Prospective Population Studies (CCPPS)	Recreational physical activity (Schnohr, 2005)	Modified questionnaire constructed by Saltin & Grimby. (a) almost entirely sedentary (reading, TV, cinema) or light physical activity less than 2 hours per week, (b) light physical activity 2–4 hours per week, e.g. walking, cycling, light gardening, (c) light physical activity more than 4 hours per week or more vigorous physical activity 2–4 hours per week, e.g. brisk walking, fast cycling, heavy gardening, sports where you get sweaty or exhausted, (d) highly vigorous physical activity more than 4 hours per week or regular heavy exercise or competitive sports several times per week	The questionnaire discriminates sedentary persons well from their more active counterparts with regard to maximal oxygen uptake
California Teachers Study (CTS)	Vigorous or moderate recreational physical activity (Dallal, 2007)	Questionnaire. Long-term moderate (brisk walking, golf, and volleyball) and strenuous (swimming laps, aerobics/calisthenics, running, and jogging) recreational physical activities.	Not indicated
Canadian National Breast Screening Study (CNBSS)	Total physical activity Vigorous physical activity (recreational and household activity) (Catsburg, 2014a; Silvera, 2006)	Questionnaire. Women were queried about vigorous physical activity using a question that asked 'On an average weekday and weekend day, how much time did you spend on the following activities during the past one month: vigorous exercise (jogging, running, brisk walking, vigorous sports, bicycling, and heavy housework)?'	Not indicated
European Prospective	Total physical activity	Self-administered questionnaire in most centres and interview in a few.	Relative validity and

Investigation into Nutrition and Cancer (EPIC)	Recreational, Occupational, Household activities (McKenzie, 2015; Steindorf, 2013; Steindorf, 2012; Lahmann, 2007)	Occupational activity (unemployed, sedentary, standing, manual, heavy manual and unknown), non-occupational physical activity (housework, home repair, gardening, stair climbing), recreational activities (walking, cycling and all other sports combined), vigorous non-occupational activity (recreational and household activities causing sweating or faster heartbeat).	reproducibility undertaken; the questionnaire was found to be satisfactory for the ranking of subjects, less suitable for estimation of energy expenditure. Construct validity by correlation with BMI
E3N EPIC-France	Recreational physical activity Walking (Fournier, 2014; Tehard, 2006) Total physical activity Moderate or vigorous recreational physical activity Household activity (Tehard, 2006)	Questions derived from a modified version of the Baecke questionnaire. recreational physical activity, walking (including walking to work, shopping, and leisure time), cycling (including cycling to work, shopping, and leisure time), and engaging in sports during 2 typical weeks over the past year, one in summer and one in winter. Separate questions on household activity that also asked about the frequency and duration of the activities that were done.	Validated, no further information in article
Finland (Rintala, 2002)	Occupational physical activity (Rintala, 2002)	Census. An index for occupational physical activity was created based on the physical load information provided in randomly selected Finnish women. Class 1 – jobs involving sitting and the performance of light tasks with the hands only. Class 2 – the handling of heavier items, such as in work along industrial conveyor belts. Class 3 – bodily motion such as in light work incorporating walking and standing Class 4 – walking upstairs or long distances, bending from the waist, and carrying, (all activities that use the major muscle groups of the body and notably increase energy consumption) Class 5 – differed from class 4 in that heavy tasks were performed for most of the workday.	Not indicated
Finnish adult health behaviour survey	Recreational physical activity	Questionnaire. “How often do you exercise at leisure for at least 30 min at a time so that it makes you at least mildly short of breath and to perspire?"	Not indicated

(FAHBS)	Transportation (Luoto, 2000)	"How many minutes do you walk or bicycle when commuting (back and forth) to working place?"	
Framingham Heart Study (FHS); FHS-Offspring Cohort	Total physical activity Moderate or vigorous recreational or occupational physical activity (Makarem, 2015, FHS-Offspring Cohort; Dorgan, 1994, FHS)	Physician-administered questionnaire. On how many hours a day a woman usually spent at sleep and rest and, during work and leisure time, at sedentary (e.g., standing), slight (e.g., walking), moderate (e.g., greater than walking but less than running), and heavy (e.g., running) activities. The hours at each level of activity, weighted by the relative oxygen consumption for that activity, were summed to create a physical activity index	Not indicated
College alumni studies – Harvard Alumni Cohort (HAHS)	Recreational physical activity (Paffenbarger, 1987)	College entrance physical examinations records. Sports during early college experience	Not indicated
HEreditary Breast and Ovarian cancer study, the Netherlands (HEBON study)	Recreational physical activity (Pijpe, 2010)	Self-reported lifelong sport or sport at specific age periods sport (type, number of hours spent per week).	Not indicated
Iowa 65+ Rural Health Study (Iowa 65+ RHS)	Total physical activity (recreational and household activities) (Cerhan, 1998)	Questionnaire. "How often do you: garden or do yardwork in season? do housework? take walks? jog, bike ride, swim, or do other vigorous exercise? play horseshoes/golf or play other moderate exercise games in season?"	Not indicated
Iowa Women's Health Study (IWHS)	Recreational physical activity (Bardia, 2007; Moore, 2000)	Questions on non-occupational physical activity level: frequency of moderate activity (such as bowling, golf, light sports or physical exercise, gardening, long walks), vigorous physical activity (such as jogging, racquet sports, swimming, aerobics, strenuous sports)	The derived physical activity level variable has predictive validity for coronary heart disease incidence
Japan Collaborative Cohort Study for Evaluation of Cancer (JACC)	Recreational physical activity Walking (Suzuki, 2008c; Suzuki, 2007)	Questionnaire. On amount of time spent walking, and exercising (Suzuki, 2008c)	Validated. Physical activity level with the single-item question may be appropriate for establishing baseline data that reflect long-

			term physical activity in a large-scale cohort study
Japan Public Health Center-based Prospective Study (JPHC)	Total physical activity (Suzuki, 2011a; Inoue, 2008b) Recreational physical activity (Suzuki, 2011a)	Self-reported heavy physical work or strenuous exercise (4 METs), being sedentary (1.5 METs), standing or walking (2 METs), sleep or other passive activity (0.5 METs); the frequency of participation in non-occupational leisure-time physical activity (LPA) such as sports and exercise and daily total physical activity (DTPA) – strenuous exercise, standing or walking time, and sitting time	Validity of MET-hour score assessed in 55 men and 55 women from the cohort using a 4-day 24-h physical activity record . Rank correlation coefficient between MET-hour score and physical activity records was 0.64 ($p < 0.0001$)
Longitudinal Study on Aging (LSOA)	Total physical activity (recreational and household activities) (Wyrwich, 2000)	Questionnaire. Two items involving having a regular exercise routine and walking a mile or more at least once a week. Determined disability only among the women who were classified as inactive by using three items that asked "Do you have difficulty _____ without help (yes/no)?" The blank was filled in with "doing heavy housework," "walking up 10 steps without rest," and "walking a quarter of a mile." Those inactive women who were unable to do at least one of these three activities were considered to be disabled.	Not indicated
Malmo Diet and Cancer (MDCS)	Recreational physical activity Household activities (Ericson, 2009; Ericson, 2007; Wirfalt, 2005)	Questionnaire adapted from the Minnesota Leisure Time Physical Activity Questionnaire. The number of minutes per week of 18 different activities was multiplied by an activity-specific intensity coefficient, and an overall leisure-time physical activity score was created. Household activities were estimated in hours per week	Not indicated
National Institutes of Health – American Association of Retired Persons Diet and Healthy Study (NIH-AARP)	Vigorous (total or recreational) physical activity (Arem, 2014; Brinton, 2014; Nyante, 2013; Peters, 2009a,b) Occupational (and household) physical	Questionnaires. Frequency of activities of any type that lasted 20 minutes or more and caused either increases in breathing or heart rate or working up a sweat. Routine at work (sitting, walking, lifting light loads or climbing stairs or hills, heavy work or carry heavy loads)	Reliability and validity evaluated in similar U.S. cohorts and found to provide useful information

	activity (George, 2010) Sitting (George, 2010)		
National Health and Nutrition Examination Survey (NHANES I, 1971–1975) National Health Epidemiologic Follow-up Study (NHEFS, 1982-1984)	Recreational physical activity (Albanes, 1989; Breslow, 2001) Occupational physical activity (non-recreational) (Byrne, 1996; Steenland, 1995; Albanes, 1989)	Two questions concerning physical activity were asked during the baseline evaluation. "In your usual day, aside from recreation, how active are you?"; "Do you get much exercise in things you do for recreation?"	Not indicated
Netherlands Cohort Study (NLCS) (Dirx, 2001)	Recreational physical activity Vigorous sports Occupational Walking Sitting	Self-administered questionnaire: “How many minutes do you spend on average per day walking or cycling to your work, to go shopping, or to take out your dog?” “How many hours of your leisure time do you spend on average per week on the following activities: gardening/doing odd jobs, cycling/walking (other than in first question), and sports/gymnastics. Also reported type of sport.	Not indicated
National Health Screening Service Studies (NNHSSS) - the Norwegian Counties Study (1974–1988), the 40 years Cohort (1985–1999) and the Cohort of Norway (CONOR, 1994–2003).	Recreational physical activity (Bjerkaas, 2013)	Questionnaire on physical activities that are sedentary (reading, watching television and other sedentary activity), moderate (walking, bicycling or similar activities ≥ 4h per week), or heavy (light sports or heavy gardening ≥4 h per week, heavy exercise or daily competitive sports)	Not indicated
NNHSS (Norwegian National Health Screening - three Norwegian Counties)	Recreational physical activity Occupational physical activity (Thune, 1997)	Questionnaire. Combined score of occupational activity and physical activity during recreational hours(reading, watching TV or other sedentary activities; walking, bicycling or other physical activities, exercise, sport)	Not indicated.

Norwegian Women and Cancer (NOWAC) study	Total physical activity (Borch, 2014)	Questionnaire. Physical activity was defined as: "By physical activity we mean activity both at work and outside work, at home, as well as training/exercise and other physical activity, such as walking, etc."	Validated. Physical activity scale for the assessment at enrollment was moderately correlated (range: 0.36-0.46) with concurrent outcomes from criterion measures of a combined sensor monitoring heart rate and movement.
The National Surgical Adjuvant Breast and Bowel Project (NSABP P-1)	Recreational physical activity (Land, 2014)	Questions on physical inactivity, and light, moderate or vigorous leisure time physical activity	Not indicated
Nurses' Health Study (NHS); NHS II	Recreational physical activity (NHS – Zhang X, 2015; Eliassen, 2010; Rockhill, 1999; NHS II – Boeke, 2014b; Colditz, 2003) Moderate and/or vigorous recreational physical activity (NHS - Eliassen, 2010; NHS II – Maruti, 2008b; Rockhill, 1999; Rockhill, 1998) Walking (Zhang X, 2015; Maruti, 2008b; Coldtiz, 2003)	Self-reported questionnaires on usual walking pace and number of flights of stairs climbed daily; average in 8 leisure-time activities: walking or hiking outdoors, jogging, running, bicycling, lap swimming, playing tennis, squash or racquetball, calisthenics, aerobics, aerobic dance or use of a rowing machine. Activity converted to METs	Instrument reliable and valid in a similar cohort of younger nurses. Questionnaire had good correlation with a weekly recall (r = 0.79) and the average of four, 7-day activity diaries administered over 1 year (r = 0.56)
Prostate, Lung,	Vigorous physical	Questionnaire. ''About how many hours do you spend in vigorous activities,	Not indicated

Colorectal, and Ovarian (PLCO) Cancer Screening Trial (PLCO)	activity (Chang, 2003) Recreational physical activity (Chang, 2006)	such as swimming, brisk walking, etc.?''	
Southern Community Cohort Study (SCCS)	Total physical activity Moderate and vigorous recreational physical activity Occupational physical activity Sitting (Cohen, 2013)	Questionnaire. On sedentary and active behaviours done at home, at work, and during leisure-time. Sedentary behaviours – sitting in a car or bus, at work, watching television or seeing movies, using a computer at home, and for other reasons (e.g., sitting at meals, talking on the phone, reading, playing games, or sewing). Times spent in light (e.g., standing at work, light office work, shopping, cooking, child care, etc.), moderate (e.g., manufacturing work, cleaning house, gardening, mowing lawn, home repair, etc.), and strenuous activity (e.g., loading trucks, construction work, farming, etc.) at home and work were assessed separately for weekdays and weekends and then combined using weighted averages. Time spent in moderate sports (e.g., bowling, dancing, golf, or softball) and vigorous sports (e.g., jogging, aerobics, bicycling, tennis, swimming, weight lifting, or basketball).	Test–retest reliability methodology via comparisons with a physical activity monitor (accelerometer) and a last-month physical activity survey administered up to 4 times in each participant (n=118), and there was general consistency in the magnitude of correlations between Blacks and Whites in the validation study
Shanghai Women's Health Study cohort (SWHS)	Total physical activity (Pronk, 2011; Wen, 2009) Recreational physical activity Occupational physical activity Household activity Walking Sitting (Pronk, 2011)	Interviewed basing on a questionnaire. Non-occupational – exercise during adolescence and adulthood, time spent in household activities, active transportation (walking and cycling to and from work, and for daily errands), and flight of stairs. Occupational – name of the work place, job title including main duties and products, and year started and year ended for each job held longer than 1 year.	Validated; reproducibility of non-exercise physical activities tended to be lower than for exercise participation
Swedish twin cohort, 1969	Recreational physical activity Occupational physical	Questionnaire. On leisure-time physical exercise and physical activity at work: "How much physical exercise have you had from age 25 to 50?"; "Has your work been mainly: (i) sedentary, (ii) active, (iii) physically strenuous	Not indicated

	activity (Moradi, 2002)		
U.S. Radiologic Technologists cohort (USRT)	Total physical activity Vigorous recreational physical activity Walking (Howard, 2009)	Questionnaire. On the number of hours spent per week during the previous year engaging in exercising strenuously (e.g., aerobics, jogging, swimming), walking or hiking for exercise and walking at home or at work.	Not validated
VITamins And Lifestyle (VITAL) Cohort	Total physical activity (Hastert, 2013; Sczanieck, 2012)	Physical activity was assessed by a one-page questionnaire that asked about walking (including usual pace) and other moderate and strenuous recreational activities done at least once per week in the previous 10 years.	Not indicated
Wisconsin Longitudinal Study (WLS)	Light or vigorous recreational physical activity (Pudrovska, 2013)	Interviewed for participation in light exercise (such as walking) and vigorous exercise (such as jogging).	Not indicated
Women's Health Initative (WHI-CT and OS; WHI-OS)	Recreational physical activity (Phipps, 2011; Kabat, 2010; Chlebowski, 2007; McTiernan, 2003) Vigorous recreational physical activity (Phipps, 2011; McTiernan, 2003) Walking (Kwan, 2014; Hartz, 2013)	Questionnaire. On how often participants currently exercised and how long they typically exercised per session. Questions were structured to inquire separately about strenuous-, moderate-, and low-intensity recreational exercise. Strenuous exercise was defined as exercise that led to sweating and increased heart rate (e.g., aerobics, swimming laps, jogging). Moderate-intensity activity included biking outdoors, using an exercise machine, and calisthenics. Low-intensity activity included bowling and golf.	Validated in a random sample (n=536). The test-retest reliabilityfor the physical activity variables ranged from 0.53 to 0.72, and the intraclass correlation for the total physical activity variable was 0.77
Women's Health Study (WHS)	Recreational physical activity Vigorous recreational physical activity (Lee, 2001)	For each age period (12–18, 19–34, 35–49 and ≥ 50 years), women were asked to list their leisure-time physical activities. Estimated average lifetime physical activity by calculating a weighted average of the energy expended during the 4 age periods, with the weighting factor being the number of years in the time period	Tested reliability. Questionnaires administered 2–3 months apart to postmenopausal women, yielded Spearman correlation coefficients of 0.69–

			0.85 for the various ages
Norwegian-Swedish Women's Lifestyle and Health Cohort Study (WLHCS) (Included NOWAC)	Recreational physical activity Vigorous recreational physical activity (Margolis, 2005)	The women rated their level of physical activity (very low to very high) at three time points: age 14, age 30, and at enrollment. Norwegian women ranked activity on a scale of 1 (very low) to 10 (very high). On the Swedish questionnaire, women ranked their level of physical activity on a 5-point scale: 1 (very low) was described as mainly sitting, 3 (normal) as several long walks per week, and 5 (very high) as sports or jogging several times per week. Women were also asked whether they had participated in competitive sports, and if so, the number of years they participated.	Not indicated

Also Finnish physical education and language teachers cohort (FFTC) assessed occupational records (Rintala, 2003; Pukkala, 1993; Vihko, 1992) for language and physical education teachers; Korean Women's Cohort Study (KWC) (Lee, 2003) assessed self-reported total physical activity habit; National Walkers' and Runner's Health Studies (Williams, 2013) recruited walkers and runners; Norwegian World Class Athletes recruited athletes who had represented Norway in international championships or placed top 3 in national championships (Robsahm, 2010); Sweden, 1971 (Moradi, 1999) assessed occupations reported in the census questionnaires; Zheng, 1993 that assessed occupational physical activity levels were measured by using an index of sitting time and an index of energy expenditure; USA, 1981 (Wyshak, 2000, Frisch 1987, and Frisch, 1985) assessed college athletes activities in questionnaires; Washington State, 1974 that assessed sedentary, medium, and vigorous occupational physical activity (Vena, 1987).

6.1 Total physical activity

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Overall summary

Twenty-three publications from 17 studies that examined total physical activity were identified. No pooled analysis was identified.

The highest compared with the lowest meta-analyses were conducted to examine the association of total physical activity with risk of breast cancer, and of premenopausal and postmenopausal breast cancer.

Table 427 Summary of results of the highest versus the lowest meta-analysis in the CUP SLR

	Breast cancer	Premenopausal breast cancer	Postmenopausal breast cancer
Comparison	Highest versus lowest	Highest versus lowest	Highest versus lowest
Studies (n)	7	4	8
Cases	10 633	1 834	11 798
RR (95%CI)	0.91 (0.82-1.02)	0.93 (0.79-1.08)	0.87 (0.79-0.96)
Heterogeneity (I^2, p-value)	38%, 0.14	0%, 0.95	16%, 0.30

Breast cancer (any)

Summary

Main results:

Seven out of 11 studies (14 publications) identified could be included in the highest versus lowest meta-analysis (10 633 cases). Total physical activity was non-significantly inversely associated with breast cancer risk (summary RR for highest vs lowest activity level=0.91 (95% CI=0.82-1.02). Moderate heterogeneity was observed between studies. Summary RR ranged from 0.94 (95% CI=0.80-1.10) when Steindorf, 2013 (31% weight) was omitted to 0.89 (95% CI=0.82-0.97) when Dorgan, 1994 (4% weight) was omitted in influence analysis.

Three studies (Makarem, 2015; Catsburg, 2014a; Williams, 2013) that reported on physical activity guideline adherence or exercise recommendation achievement, and one component study (Tehard, 2006) of a multi-centre study (Steindorf, 2013) that was included in the analysis were excluded. Non-significant inverse associations with breast cancer risk (Makarem, 2015; Catsburg, 2014a) and a borderline significant inverse association with breast cancer mortality (Williams, 2013) were observed.

EPIC reported results by BMI categories (Steindorf, 2013). A significant inverse association of total physical activity index with breast cancer risk was observed among women of BMI <25 kg/m^2 (RR for active vs inactive=0.83, 95% CI=0.73-0.95, Ptrend=0.001), but not of BMI ≥25-<30 kg/m^2 (RR=1.01, 95% CI=0.84-1.22, Ptrend=0.88) or BMI≥30 kg/m^2 (RR=0.86, 95% CI=0.63-1.16, Ptrend=0.31). There was no evidence for effect modification of associations for BMI (Steindorf, 2013).

Three studies (Steindorf, 2013; Cohen, 2013; Suzuki, 2011a) reported results on hormone receptor subtypes of breast cancer observed mostly non-significant inverse associations.

Study quality:

Studies were from Asia, Europe, and North America. One study included Seven Day Adventists (Dorgan, 1994, AHS). All studies reported assessment of total physical activity by questionnaire, which was validated in four studies published in recent years (Cohen, 2013; Steindorf, 2013; Pronk, 2011; Suzuki, 2011a). Stronger associations were observed in two older studies (Fraser, 1997; Dorgan, 1994). Case ascertainment was through cancer registries or confirmed through medical records. Three studies (Steindorf, 2013; Suzuki, 2011a; Howard, 2009) were adjusted for age, BMI, alcohol intake, and reproductive factors.

Table 428 Total physical activity and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	11 (14 publications)
Studies included in forest plot of highest compared with lowest exposure	7 (7 publications)
Studies included in linear dose-response meta-analysis	Not enough studies
Studies included in non-linear dose-response meta-analysis	Not enough studies

Note: Include cohort and nested case-control designs.

Table 429 Total physical activity and breast cancer risk. Summary of the highest versus the lowest meta-analysis in the 2005 SLR and CUP

	2005 SLR	CUP
Comparison	-	Highest versus lowest
Studies (n)	-	7
Cases	-	10 633
RR (95%CI)	-	0.91 (0.82-1.02)
Heterogeneity (I^2, p-value)	-	38%, 0.14

Table 430 Physical activity and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Gao, 2014	15 studies (3 cohort[1], 12 case-control)	10 290	China	Incidence, any breast cancer in pre-, and/or postmenopausal women	Physical activity - yes vs no	0.73 (0.63-0.85)	77%, <0.001
Wu, 2013	31 cohort studies[2]	63 786, 10 846 ER+PR+, 2 619 ER-PR-	Canada, China, Europe, Japan, USA	Incidence, any breast cancer in pre-, and/or postmenopausal women	Highest vs lowest, any physical activity	0.87 (0.83-0.92)	30%
				ER+PR+ (8 studies)	Any physical activity		
				ER-PR- (7 studies)	<age 25 years	0.93 (0.87-0.98)	0%
					Age 25-50 years	0.77 (0.65-0.90)	45%
				(5 studies)	>age 50 years		
				(10 studies)	<25 kg/m^2	0.90 (0.81-1.02)	24%
				(11 studies)	>25 kg/m^2	0.89 (0.83-0.95)	17%
				(9 studies)		0.83 (0.76-0.91)	42%
				(8 studies)		0.72 (0.65-0.81)	0%
						0.93 (0.83-1.05)	0%

[1]Three cohorts (Pronk, 2011; Wang, 2006; Shannon, 2005) were identified in the meta-analysis of Gao (2014). Results of Wang, 2006 were published in a MSc thesis and Shannon, 2005 was a case-control study based in a RCT. Only Pronk, 2011 was included in the present review. [2]All studies identified in the meta-analysis of Wu (2013) were included in the present review under different physical activity sections.

Table 431 Total physical activity and breast cancer risk. Main characteristics of studies included in the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Cohen, 2013 BRE80470 USA	SCCS, Nested Case Control, Age: 40-79 years	459/ 546 9 years	Cancer registry		Incidence, Invasive breast cancer	≥27.1 vs ≤8.9 met-hours/day	0.97 (0.71-1.33)	Age, age at menarche, BMI, educational level, ethnicity, family history of breast cancer, health Insurance, household Income, HRT use, menopausal status, parity, smoking habbits, source type
		455/				≥27.1 vs ≤8.9 met-hours/day	0.99 (0.72-1.36)	Sedentary behaviour
		448/				≥68.1 vs ≤30.3 met-hours/day	1.02 (0.73-1.45)	Physical activity
		260/			Incidence, breast cancer ER+/PR+	≥27.1 vs ≤8.9 met-hours/day	1.00 (0.65-1.56)	
		117/			Incidence, breast cancer ER-/PR-	≥27.1 vs ≤8.9 met-hours/day	0.96 (0.52-1.76)	
Steindorf, 2013 BRE80425 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spai	EPIC, Prospective Cohort, Age: 35-70 years, W	8 034/ 257 805 11.6 years	Cancer registry	Questionnaire/interview	Incidence, Invasive breast cancer	active vs inactive	0.94 (0.87-1.00)	Age, age at first child, age at menarche, age at menopause, alcohol, BMI, breastfeeding,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
n,Sweden,UK								centre location, educational level, household physical activity, HRT use, menopausal status, number of full-term pregnancies, occupational activity, oral contraceptive history, recreational activity, smoking, total physical activity
						≥123 vs ≤50.5 met-hours/week	0.87 (0.81-0.94)	
						active vs inactive	0.87 (0.79-0.97)	
		4 860/			Incidence, breast cancer ER+	≥124 vs ≤51.5 met-hours/week	0.91 (0.82-1.00)	
						active vs inactive	0.95 (0.83-1.08)	
						active vs inactive	0.93 (0.84-1.03)	
		4 746/			Incidence, Invasive breast cancer, BMI 18.5-25 kg/m2	≥123 vs ≤50.5 met-hours/week	0.87 (0.79-0.96)	
						active vs inactive	0.83 (0.73-0.95)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
						active vs inactive	0.87 (0.79-0.97)	
		3 124/			Incidence, breast cancer PR+	active vs inactive	0.92 (0.81-1.05)	
						≥124 vs ≤51.5 met-hours/week	0.84 (0.75-0.96)	
						active vs inactive	0.91 (0.77-1.07)	
		2 943/			Incidence, breast cancer ER+/PR+	≥123 vs ≤50.5 met-hours/week	0.84 (0.74-0.96)	
						active vs inactive	0.91 (0.76-1.08)	
						active vs inactive	0.91 (0.79-1.03)	
		2 348/			Incidence, Invasive breast cancer, BMI 25-30	active vs inactive	1.01 (0.84-1.22)	
						active vs inactive	1.05 (0.91-1.22)	
						≥123 vs ≤50.5 met-hours/week	0.93 (0.82-1.07)	
		1 784/			Incidence, breast cancer ER+/PR+, BMI 18.5-25 kg/m2	≥123 vs ≤50.5 met-hours/week	0.95 (0.80-1.13)	
						active vs inactive	0.93 (0.74-1.17)	
						active vs inactive	0.92 (0.78-1.09)	
		1 690/			Incidence, breast cancer PR-	active vs inactive	1.02 (0.85-1.22)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
						≥124 vs ≤51.5 met-hours/week	0.92 (0.78-1.08)	
						active vs inactive	0.84 (0.65-1.09)	
		1 147/			Incidence, breast cancer ER-	≥124 vs ≤51.5 met-hours/week	0.88 (0.72-1.08)	
						active vs inactive	0.77 (0.58-1.02)	
						active vs inactive	0.98 (0.80-1.21)	
		940/			Incidence, Invasive breast cancer, BMI >=30	active vs inactive	0.96 (0.77-1.20)	
						≥123 vs ≤50.5 met-hours/week	0.75 (0.61-0.93)	
						active vs inactive	0.86 (0.63-1.16)	
		875/			Incidence, breast cancer ER+/PR-	≥123 vs ≤50.5 met-hours/week	0.93 (0.74-1.18)	
						active vs inactive	0.83 (0.57-1.21)	
						active vs inactive	1.02 (0.79-1.31)	
		809/			Incidence, breast cancer ER+/PR+, BMI 25-30	≥123 vs ≤50.5 met-hours/week	0.79 (0.63-1.01)	
						active vs inactive	0.93 (0.67-1.28)	
						active vs inactive	0.86 (0.67-1.10)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		808/			Incidence, breast cancer ER-/PR-	≥123 vs ≤50.5 met-hours/week	0.89 (0.70-1.14)	
						active vs inactive	0.82 (0.58-1.18)	
						active vs inactive	1.00 (0.78-1.29)	
		570/			Incidence, breast cancer ER+/PR-, BMI 18.5-25 kg/m2	≥123 vs ≤50.5 met-hours/week	0.96 (0.71-1.31)	
						active vs inactive	0.68 (0.41-1.15)	
						active vs inactive	1.01 (0.73-1.39)	
		503/			Incidence, breast cancer ER-/PR-, BMI 18.5-25 kg/m2	≥123 vs ≤50.5 met-hours/week	0.77 (0.55-1.07)	
						active vs inactive	0.86 (0.54-1.35)	
						active vs inactive	1.03 (0.74-1.44)	
		350/			Incidence, breast cancer ER+/PR+, BMI >=30	active vs inactive	0.79 (0.47-1.34)	
						active vs inactive	0.85 (0.58-1.25)	
					BMI >=30.0	≥123 vs ≤50.5 met-hours/week	0.65 (0.45-0.93)	
		235/			Incidence, breast cancer ER+/PR-, BMI 25-30	active vs inactive	1.22 (0.62-2.41)	
						active vs inactive	1.03 (0.64-1.65)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
						≥123 vs ≤50.5 met-hours/week	0.91 (0.59-1.41)	
		228/			Incidence, breast cancer ER-/PR-, BMI 25-30	active vs inactive	0.78 (0.37-1.63)	
						active vs inactive	0.92 (0.57-1.48)	
						≥123 vs ≤50.5 met-hours/week	1.23 (0.80-1.88)	
		77/			BMI >=30	active vs inactive	1.37 (0.62-3.05)	
					BMI >=30.0	≥123 vs ≤50.5 met-hours/week	0.59 (0.29-1.23)	
					BMI >=30	active vs inactive	1.09 (0.38-3.13)	
		70/			Incidence, breast cancer ER+/PR-, BMI >=30	active vs inactive	1.25 (0.54-2.90)	
					BMI >=30.0	≥123 vs ≤50.5 met-hours/week	0.65 (0.30-1.40)	
					BMI >=30	active vs inactive	1.05 (0.30-3.63)	
Pronk, 2011 BRE80388 China	SWHS, Prospective Cohort, Age: 40-70 years, W	717/ 73 049 9 years	Cancer registry	Interview	Incidence, breast cancer	≥131.5 vs 0-74.3 met-hour/week/year	0.98 (0.79-1.21)	Age, age at first child birth, educational level, family history of breast cancer, number of pregnancies
Suzuki, 2011a	JPHC,	228/	Cancer registry	Questionnaire/in	Incidence, breast	Q 3 vs Q 1	1.03 (0.75-1.41)	Age, age at first

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
BRE80307 Japan	Prospective Cohort, Age: 40-69 years, W, women	53 578 14.5 years		terview	cancer			child birth, age at menarche, age at menopause, alcohol Intake, area, BMI, BMI, energy-adjusted Intake of Isoflavones, height, HRT use, physical activity, smoking
		205/			Incidence, breast cancer unknown ER/PR status	Q 3 vs Q 1	0.95 (0.68-1.32)	Age, area
		97/			Incidence, breast cancer ER+/PR+	Q 3 vs Q 1	0.57 (0.27-1.17)	Age, area
		22/			Incidence, breast cancer ER+/PR-	Q 3 vs Q 1	0.79 (0.25-2.50)	Age, area
		21/			Incidence, breast cancer ER-/PR-	Q 3 vs Q 1	2.36 (0.72-7.70)	Age, area
Howard, 2009 BRE80286 USA	USRT, Prospective Cohort, Age: 47 years, W, radiologic technologists	864/ 45 631 8.9 years	Self-report verified by medical record	Questionnaire	Incidence, breast cancer	≥97 vs 0-9.5 met score	0.91 (0.74-1.13)	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, breast diseases , family history of cancer, menopausal

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								hormone use, oc use, parity, race, smoking habits
Fraser, 1997 BRE02940 USA	AHS, Prospective Cohort, Age: 24- years, W, Adventist	20 341 6 years	Partially histological - over 80%	Questionnaire	Incidence, Invasive breast cancer	low level vs not low level	1.46 (1.11-1.92)	Age at first child, BMI, family history, HRT use
Dorgan, 1994 BRE02385 USA	FHS, Prospective Cohort, Age: 35-68 years, W	2 298/ 2 307 28 years	All histology	Questionnaire	Incidence, breast cancer,	high vs low	1.60 (0.90-2.90)	Age , age at first child, alcohol, educational level, menopausal status, occupation, parity/pregnancies
						Replace sleep by per 1 hours/day sedentary to slight physical activity	1.00 (0.90-1.20)	
						Replace sleep by per 1 hours/day moderate to heavy physical activity	1.10 (0.90-1.30)	

Table 432 Total physical activity and breast cancer risk. Main characteristics of studies excluded from the highest versus the lowest meta-analysis

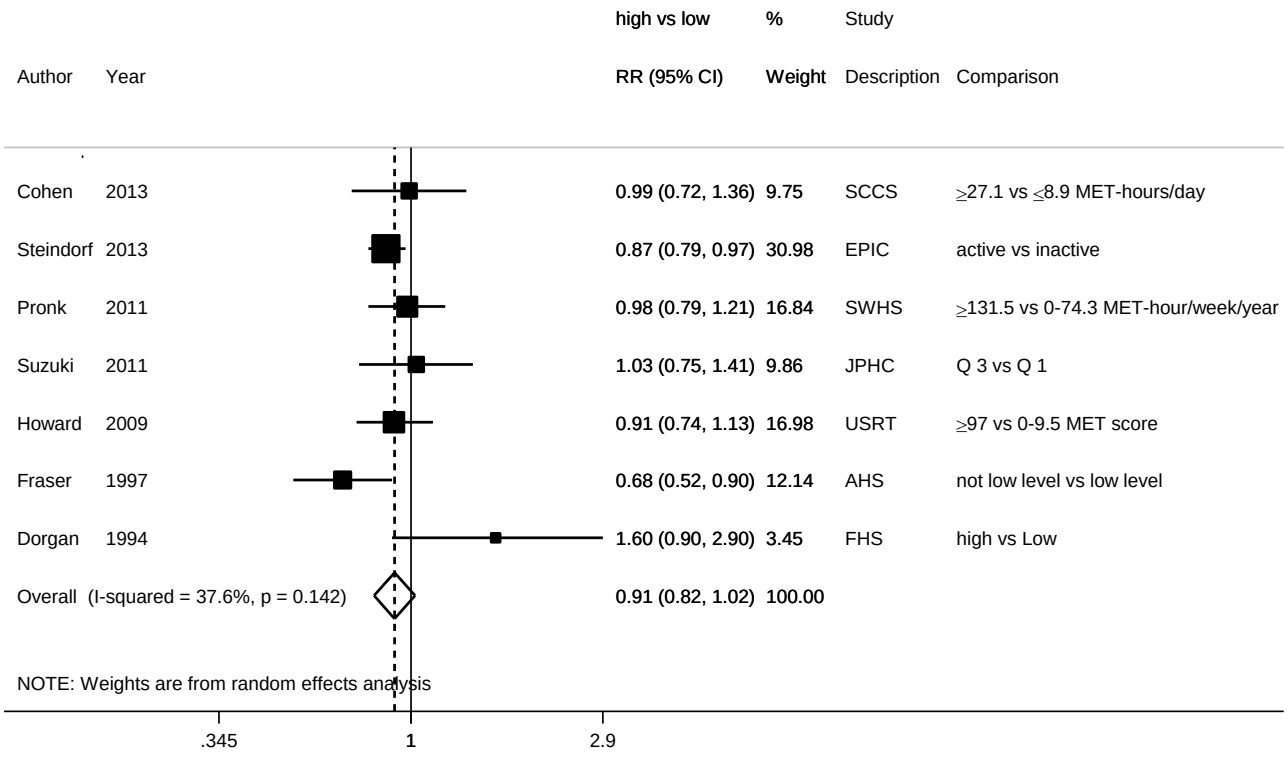
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Makarem, 2015 BRE80589 USA	FHS-Offspring Cohort, Prospective Cohort, W	124/ 1 602 11.5 years	Death certificate and medical records	Questionnaire, adherence to physical activity guidelines	Incidence, breast cancer	per 1 points	0.64 (0.39-1.07)	Age, smoking status	Excluded, exposure was on adherence to physical activity recommendation
Catsburg, 2014a BRE80536 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	48 840 16.6 years	Cancer registry	Questionnaire, adherence to physical activity guidelines	Incidence, Invasive breast cancer	adhered vs not adhered to WCRF guideline on physical activity	0.99 (0.91-1.09)	Age, age at first child birth, age at menarche, alcohol, BMI, energy, family history of breast cancer, history of breast disease, HRT use, menopausal status, oc use, parity, red and processed meat, sodium, study center, vegetable and fruit Intake, whole grains	Excluded, exposure was on adherence to physical activity recommendation
						adhered vs not adhered to ACS guideline on physical activity	0.98 (0.89-1.07)		
Williams, 2013 BRE80500 USA	National Walkers' and Runners' Health Studies, Prospective	111/ 79 124 11 years	National death Index	Questionnaire	Mortality, breast cancer	Achieved vs not achieved exercise recommendations	0.61 (0.39-1.00)	Age, BMI, bra cup size, hormone replacement therapy,	Excluded, special cohort of walkers and runners only; breast cancer

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Cohort, W							menopause status, oc use, race	mortality
Steindorf, 2012 BRE80432 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	1 059/ 283 827 11.7 years	Cancer registry	Questionnaire/interview	Incidence, In situ breast cancer	active vs inactive	1.02 (0.82-1.27)	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, breastfeeding, centre location, educational level, household physical activity, HRT use, menopausal status, number of full-term pregnancies, occupational physical activity, oral contraceptive history, recreational activity, smoking	Excluded, breast cancer in situ, not enough studies to analyse (Steindorf, 2013, publication on breast cancer risk was included)
						≥124 vs ≤51.5 met-hour/week	1.09 (0.88-1.34)	Total physical activity	
						active vs inactive	1.07 (0.81-1.40)		
		686/			BMI<25.0	≥124 vs ≤51.5	1.11 (0.86-1.45)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
						met-hour/week			
						active vs inactive	1.12 (0.80-1.57)		
						active vs inactive	0.95 (0.72-1.26)		
		281/			BMI=25-29	≥124 vs ≤51.5 met-hour/week	0.97 (0.65-1.46)		
						active vs inactive	1.19 (0.78-1.80)		
						active vs inactive	0.88 (0.51-1.51)		
		92/			BMI >=30.0	≥124 vs ≤51.5 met-hour/week	1.76 (0.82-3.77)		
					BMI >=30	active vs inactive	0.90 (0.41-2.00)		
						active vs inactive	1.49 (0.55-4.05)		
Wen, 2009 BRE80209 China	SWHS, Prospective Cohort, Age: 40-70 years, W	616/ 73 328 7.35 years	Cancer registry		Incidence, Invasive & In situ breast cancer	yes vs no	0.85 (0.71-1.00)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, anthropometry, benign breast disease, educational level, energy Intake, family history of cancer, HRT	Superseded by Pronk, 2011

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								use, smoking status	
Inoue, 2008b BRE80394 Japan	JPHC, Prospective Cohort, Age: 45-74 years, W	294/ 41 873 7.5 years	Hospital notifications and linkage with population-based cancer registries	Self completed questionnaire	Incidence	Q 4 vs Q 1	0.91 (0.64-1.29)	Age, alcohol consumption, area, BMI, history of diabetes, leisure time physical activity, smoking status, total energy Intake	Superseded by Suzuki, 2011a
Tehard, 2006 BRE80108 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W	2 284/ 98 995 11.4 years	Patient records/direct contact/health Insurance records	Questionnaire	Incidence, breast cancer,	≥57.8 vs ≤28.2 met-hour/week	0.90 (0.80-1.02)	Age at first child, age at menarche, age-underlying cox models, benign breast disease, BMI, family history, HRT use, marital status, menopausal status, oc use, occupation, parity/pregnancies	Superseded by Steindorf, 2013

Figure 487 RR (95% CI) of breast cancer for the highest compared with the lowest level of total physical activity



Premenopausal breast cancer

Summary

Main results:

Four studies (six publications) were identified. All studies could be included in the highest versus lowest meta-analysis (1 834 cases). Total physical activity was non-significantly inversely associated with premenopausal breast cancer risk (summary RR for highest vs lowest activity level=0.93 (95% CI=0.79-1.08). No heterogeneity was observed between studies. Summary RR did not change materially when study was omitted in turn in influence analysis.

EPIC reported results by BMI categories (Steindorf, 2013). Non-significant associations were observed for risk of breast cancer diagnosed ≤50 years, among normal (RR for active vs inactive=1.03, 95% CI=0.77-1.40, Ptrend=0.39), overweight (RR=0.68, 95% CI=0.39-1.21, Ptrend=0.09), or obese (RR=0.56, 95% CI=0.18-1.71, Ptrend=0.26) women. There was no evidence for effect modification of associations for BMI.

Non-significant inverse or positive associations were reported in JPHC, the Japanese study that examined joint hormone receptor subtypes of breast cancer in premenopausal women (Suzuki, 2011a).

Study quality:

Studies were from Asia, Europe, and North America. One study included radiologic technologists (Howard, 2009, USRT). One study included only parous premenopausal women (Lee, 2003). All studies reported assessment of total physical activity by questionnaire, which was validated in two studies (Steindorf, 2013; Suzuki, 2011a). Case ascertainment was through cancer registries or confirmed through medical records. Three studies (Steindorf, 2013; Suzuki, 2011a; Howard, 2009) were adjusted for age, BMI, alcohol intake, and reproductive factors. Lee, 2003 did not adjust for alcohol intake.

Table 433 Total physical activity and premenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	4 (6 publications)
Studies included in forest plot of highest compared with lowest exposure	4 (4 publications)
Studies included in linear dose-response meta-analysis	Not enough studies
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 434 Total physical activity and premenopausal breast cancer risk. Summary of the highest versus the lowest meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR	**CUP**
Comparison	-	Highest versus lowest
Studies (n)	-	4
Cases	-	1 834
RR (95%CI)	-	0.93 (0.79-1.08)
Heterogeneity (I^2, p-value)	-	0%, 0.95

Table 435 Physical activity and premenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Wu, 2013	31 cohort studies[1]	63 786, 10 846 ER+PR+, 2 619 ER-PR-	Canada, China, Europe, Japan, USA	Incidence, premenopausal breast cancer (6 studies)	Highest vs lowest, any physical activity	0.77 (0.69-0.86)	-	15%

[1]All studies identified in the meta-analysis of Wu (2013) were included in the present review under different physical activity sections.

Table 436 Total physical activity and premenopausal breast cancer risk. Main characteristics of studies included in the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Steindorf, 2013 BRE80425 Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, UK	EPIC, Prospective Cohort, Age: 35-70 years, W	936/ 257 805 11.6 years	Cancer registry	Questionnaire/interview	Incidence, Invasive breast cancer, age at diagnosis <=50yrs	active vs inactive	0.90 (0.72-1.14)	Age, age at first child, age at menarche, age at menopause, alcohol, BMI, breastfeeding, centre location, educational level, household physical activity, HRT use, menopausal status, number of full-term pregnancies, occupational activity, oral contraceptive history, recreational activity, smoking, total physical activity
						≥123 vs ≤50.5 met-hours/week	0.84 (0.68-1.04)	
						active vs inactive	0.92 (0.71-1.18)	
		686/			Normal BMI, age<=50y	active vs inactive	1.03 (0.77-1.40)	
		683/			Normal BMI, age<=50y	active vs inactive	0.83 (0.63-1.08)	
						≥123 vs ≤50.5 met-	0.96 (0.75-1.23)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
						hours/week		
		193/			Overweight, age<=50y	active vs inactive	1.14 (0.69-1.90)	
						≥123 vs ≤50.5 met-hours/week	0.73 (0.46-1.16)	
						active vs inactive	0.68 (0.39-1.21)	
		60/			Obese, age<=50y	active vs inactive	1.31 (0.53-3.21)	
						≥123 vs ≤50.5 met-hours/week	0.34 (0.15-0.80)	
						active vs inactive	0.56 (0.18-1.71)	
Suzuki, 2011a BRE80307 Japan	JPHC, Prospective Cohort, Age: 40-69 years, W, women	110/ 53 578 14.5 years	Cancer registry	Questionnaire/interview	Incidence, breast cancer, premenopausal	Q 3 vs Q 1	0.89 (0.55-1.43)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, area, BMI, BMI, energy-adjusted Intake of Isoflavones, height, HRT use, parity, physical activity, smoking
		95/			Incidence, breast cancer unknown ER/PR status,	Q 3 vs Q 1	0.83 (0.50-1.36)	Age, area

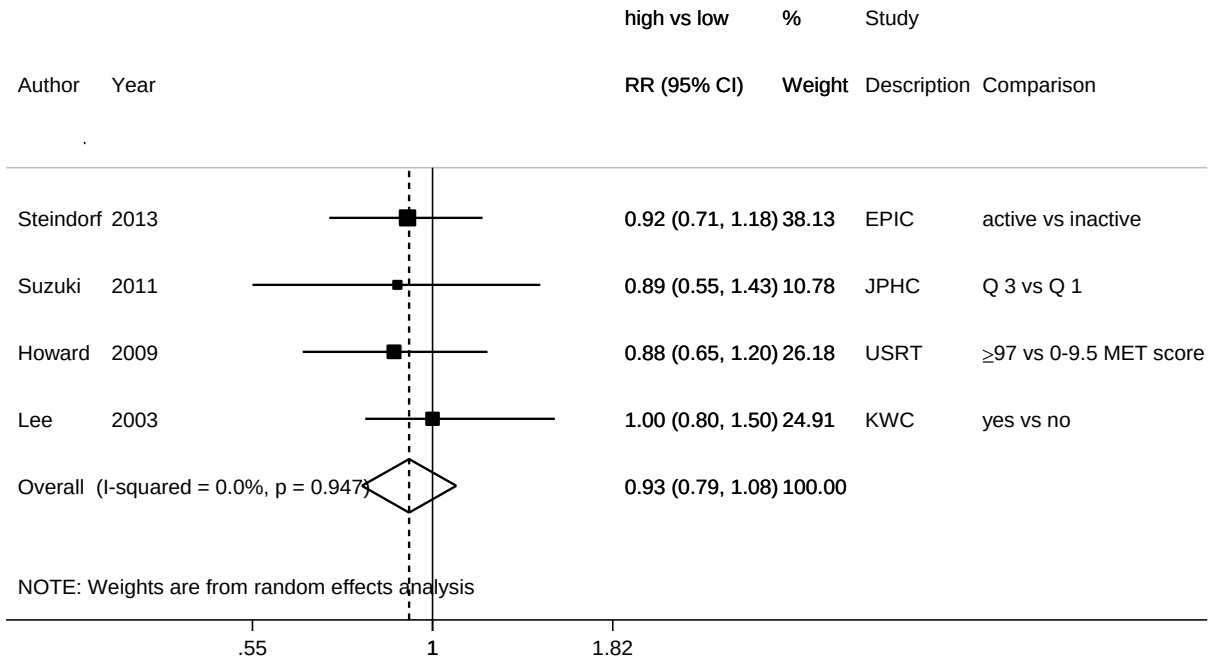
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					premenopausal			
		14/			Incidence, breast cancer ER+/PR+, premenopausal	Q 3 vs Q 1	1.19 (0.31-4.56)	Age, area
		11/			Incidence, breast cancer ER+/PR-, premenopausal	Q 3 vs Q 1	0.59 (0.13-2.64)	Age, area
		7/			Incidence, breast cancer ER-/PR-, premenopausal	Q 3 vs Q 1	0.90 (0.13-6.37)	Age, area
Howard, 2009 BRE80286 USA	USRT, Prospective Cohort, Age: 47 years, W, radiologic technologists	440/ 45 631 8.9 years	Self-report verified by medical record	Questionnaire	Incidence, breast cancer	≥97 vs 0-9.5 met score	0.88 (0.65-1.20)	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, breast diseases , family history of cancer, menopausal hormone use, OC use, parity, race, smoking habits
Lee, 2003 BRE17745 Korea	KWC, Prospective Cohort, Age: 20- years, W, Premenopausal parous women	348/ 110 604 6 years	Medical records + death certificate	Questionnaire	Incidence, breast cancer, premenopausal	yes vs no	1.00 (0.80-1.50)	Age , age at first child, age at menarche, BMI, OC use, parity/pregnancies, physical activity , smoking habits

Table 437 Total physical activity and premenopausal breast cancer risk. Main characteristics of studies excluded from the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Steindorf, 2012 BRE80432 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	138/ 283 827 11.7 years	Cancer registry	Questionnaire/interview	Incidence, In situ breast cancer, age at diagnosis <=50yrs	≥124 vs ≤51.5 met-hour/week	0.95 (0.55-1.65)	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, breastfeeding, centre location, educational level, HRT use, menopausal status, number of full-term pregnancies, occupational physical activity, oral contraceptive history, smoking	Excluded, breast cancer in situ, not enough studies to analyse (Results on breast cancer incidence from the same study (Steindorf, 2013) were included in the analysis)
						active vs inactive	1.32 (0.69-2.52)	Household physical activity, recreational activity	
					Age at diagnosis <50y	active vs inactive	1.11 (0.61-1.99)		
Lahmann, 2007 BRE20026 Denmark, France,	EPIC, Prospective Cohort, Age: 20-80	856/ 218 169 6.4 years	Population cancer registries and other procedures	Questionnaire	Incidence, Invasive breast cancer, premenopause	≥127 vs ≤54 met-hour/week	0.82 (0.66-1.03)	Age , age at first child, age at menarche, alcohol, BMI,	Superseded by Steindorf, 2013

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Germany, Greece, Italy, Netherlands, Spain, Sweden, UK	years, W							educational level, oc use, smoking habits, study center	
						≥127 vs ≤54 met-hour/week	0.80 (0.64-0.99)		
		820/			Premenopause	active vs inactive	1.02 (0.77-1.36)		
						active vs inactive	0.98 (0.72-1.25)		

Figure 488 RR (95% CI) of premenopausal breast cancer for the highest compared with the lowest level of total physical activity



Postmenopausal breast cancer

Summary

Main results:

Eight out of nine studies (13 publications) identified could be included in the highest versus lowest meta-analysis (11 798 cases). Total physical activity was significantly inversely associated with postmenopausal breast cancer risk (summary RR for highest vs lowest activity level=0.87 (95% CI=0.79-0.96). Low heterogeneity was observed between studies. EPIC (Steindorf, 2013) contributed 36% weight and BCDDP (Leitzmann, 2008), 24%, in the analysis; when omitted, summary RRs became non-significant or borderline significant (RR=0.88, 95% CI=0.76-1.01; RR=0.87, 95% CI=0.77-1.00), respectively. When two studies on elderly women (Wyrwich, 2000; Cerhan, 1998) were excluded, the significant inverse association remained (summary RR=0.88, 95% CI=0.81-0.95, I^2=0%).

One study (Cohen, 2013) which reported results from a sub-analysis on white women only was excluded. A non-significant inverse association was reported.

EPIC reported results by BMI categories (Steindorf, 2013). A significant inverse association of total physical activity index with risk of breast cancer diagnosed >50 years was observed among women of BMI <25 kg/m^2 (RR for active vs inactive=0.79, 95% CI=0.67-0.91, Ptrend=0.001), but not of BMI ≥25-<30 kg/m^2 (RR=1.07, 95% CI=0.88-1.31, Ptrend=0.46) or BMI≥30 kg/m^2

(RR=0.88, 95% CI=0.64-1.21, Ptrend=0.43). There was no evidence for effect modification of associations for BMI. BCDDP (Leitzmann, 2008) also reported no significant interaction of total physical activity with BMI and postmenopausal breast cancer risk (Pinteraction=0.19). Among BMI <25 kg/m^2, RR for highest vs lowest level=0.76, 95% CI=0.61-0.94, Ptrend=0.03 and among BMI ≥25 kg/m^2, RR=1.06, 95% CI=0.82-1.36, Ptrend=0.48).

Non-significant inverse or positive associations were reported in the two studies that examined joint hormone receptor subtypes (Borch, 2014; Suzuki, 2011a).

Study quality:

Studies were from Asia, Europe, and North America. BCDDP (Leitzmann, 2008) was a mammography demonstration program and included both in situ and invasive breast cancer. Another study (Cerhan, 1998) that included in situ breast cancer was of women over aged 65 years (46 cases, only 2 with the highest physical activity level). The Longitudinal Study on Aging (Wyrwich, 2000, LSOA) was also a study of elderly (70-98 years) (77 cases, only 7 with the highest physical activity level). The two studies (Wyrwich, 2000; Cerhan, 1998) contributed little weights in the meta-analysis. Other studies reported on invasive breast cancer only.

All studies reported assessment of total physical activity by questionnaire, which was validated in four studies published in recent years (Borch, 2014; Steindorf, 2013; Sczaniecka, 2012; Suzuki, 2011a). Case ascertainment was through cancer registries or confirmed through medical records. Five studies (Borch, 2014; Steindorf, 2013; Suzuki, 2011a; Howard, 2009; Leitzmann, 2008) were adjusted for age, BMI, alcohol intake, reproductive factors, and MHT use. Sczaniecka, 2012 only adjusted for age.

Table 438 Total physical activity and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	9 (13 publications)
Studies included in forest plot of highest compared with lowest exposure	8 (8 publications)
Studies included in linear dose-response meta-analysis	Not enough studies
Studies included in non-linear dose-response meta-analysis	Not enough studies

Note: Include cohort and nested case-control designs.

Table 439 Total physical activity and postmenopausal breast cancer risk. Summary of the highest versus the lowest meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR	CUP
Comparison	-	Highest versus lowest
Studies (n)	-	8
Cases	-	11 798
RR (95%CI)	-	0.87 (0.79-0.96)
Heterogeneity (I^2, p-value)	-	16%, 0.30

Table 440 Physical activity and postmenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Wu, 2013	31 cohort studies[1]	63 786, 10 846 ER+PR+, 2 619 ER-PR-	Canada, China, Europe, Japan, USA	Incidence, postmenopausal breast cancer (17 studies)	Highest vs lowest, any physical activity	0.87 (0.87-0.92)	-	18%

[1]All studies identified in the meta-analysis of Wu (2013) were included in the present review under different physical activity sections

Table 441 Total physical activity and postmenopausal breast cancer risk. Main characteristics of studies included in the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Borch, 2014 BRE80531 Norway	NOWAC, Prospective Cohort, Age: 34-70 years, W, Postmenopausal	1 767/ 80 202 8.2 years	Cancer registry	Questionnaire	Incidence, Invasive breast cancer, postmenopausal	very high vs moderate	0.91 (0.73-1.12)	Age at first child birth, age at menarche, age-underlying cox models, BMI, duration of smoking, family history of breast cancer, height, HRT use, oc use, parity, presence of other disease, smoking status	Used Hamling method to recalculate comparison for very high vs very low level, RR=0.86, 95% CI=0.65-1.13
		1 723/			Postmenopausal	very high vs moderate	0.91 (0.78-1.08)		
						inactive vs active	1.06 (0.89-1.27)	Age first smoked	
		1 712/			Postmenopausal	very high vs moderate	1.04 (0.90-1.19)		
						inactive vs active	0.82 (0.64-1.03)		
		1 697/			Postmenopausal	inactive vs active	0.78 (0.62-0.99)		
		872/			Incidence, breast cancer ER+/PR+, postmenopausal	very high vs moderate	1.03 (0.85-1.25)		
						very high vs moderate	0.87 (0.65-1.19)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
						very high vs moderate	0.90 (0.71-1.13)		
		856/			Postmenopausal	inactive vs active	1.15 (0.91-1.46)		
		846/			Postmenopausal	inactive vs active	0.75 (0.53-1.06)		
		839/			Postmenopausal	inactive vs active	0.79 (0.56-1.10)		
		294/			Incidence, breast cancer ER+/PR-, postmenopausal	very high vs moderate	1.03 (0.70-1.51)		
						very high vs moderate	1.28 (0.93-1.76)		
						very high vs moderate	1.32 (0.81-2.13)		
		288/			Postmenopausal	inactive vs active	1.05 (0.69-1.62)		
		286/			Postmenopausal	inactive vs active	0.63 (0.32-1.24)		
		285/			Postmenopausal	inactive vs active	0.53 (0.27-1.03)		
		206/			Incidence, breast cancer ER-/PR-, postmenopausal	very high vs moderate	0.81 (0.50-1.30)		
						very high vs moderate	1.15 (0.76-1.74)		
						very high vs moderate	0.57 (0.28-1.18)		
		201/			Postmenopausal	inactive vs active	0.72 (0.39-1.33)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		199/			Postmenopausal	inactive vs active	1.06 (0.56-2.03)		
		197/			Postmenopausal	inactive vs active	0.91 (0.48-1.73)		
Steindorf, 2013 BRE80425 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	7 098/ 257 805 11.6 years	Cancer registry	Questionnaire/interview	Incidence, Invasive breast cancer, age at diagnosis >50yrs	≥123 vs ≤50.5 met-hours/week	0.88 (0.81-0.95)	Age, age at first child, age at menarche, age at menopause, alcohol, BMI, breastfeeding, centre location, educational level, HRT use, menopausal status, number of full-term pregnancies, occupational activity, oral contraceptive history, smoking, total physical activity	
						active vs inactive	0.86 (0.77-0.97)	Household physical activity, recreational activity	
						active vs inactive	0.94 (0.86-1.02)		
		4 063/			Normal BMI, age>50y	active vs inactive	0.79 (0.67-0.91)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
						active vs inactive	0.88 (0.78-0.98)		
						≥123 vs ≤50.5 met-hours/week	0.85 (0.76-0.94)		
		2 155/			Overweight, age>50y	active vs inactive	1.05 (0.91-1.22)		
						≥123 vs ≤50.5 met-hours/week	0.96 (0.83-1.10)		
						active vs inactive	1.07 (0.88-1.31)		
		880/			Obese, age>50y	≥123 vs ≤50.5 met-hours/week	0.79 (0.63-0.98)		
						active vs inactive	0.88 (0.64-1.21)		
						active vs inactive	0.95 (0.75-1.20)		
Sczaniecka, 2012 BRE80434 USA	VITAL, Prospective Cohort, Age: 50-76 years, W, Postmenopausal	765/ 30 252 6 years	Seer registry		Incidence, breast cancer	≥14.2 vs ≤0 met-hours/week	0.90 (0.72-1.14)	Age	
Suzuki, 2011a BRE80307 Japan	JPHC, Prospective Cohort, Age: 40-69 years, W, women	118/ 53 578 14.5 years	Cancer registry	Questionnaire/interview	Incidence, breast cancer, postmenopausal	Q 3 vs Q 1	1.11 (0.72-1.70)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, area, BMI, BMI, energy-adjusted	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								Intake of Isoflavones, height, HRT use, parity, physical activity, smoking	
		110/			Incidence, breast cancer unknown ER/PR status, postmenopausal	Q 3 vs Q 1	1.03 (0.66-1.61)	Age, area	
		29/			Incidence, breast cancer ER+/PR+, postmenopausal	Q 3 vs Q 1	0.43 (0.17-1.08)	Age, area	
		14/			Incidence, breast cancer ER-/PR-, postmenopausal	Q 3 vs Q 1	4.17 (0.86-20.14)	Age, area	
		11/			Incidence, breast cancer ER+/PR-, postmenopausal	Q 3 vs Q 1	0.98 (0.16-5.91)	Age, area	
Howard, 2009 BRE80286 USA	USRT, Prospective Cohort, Age: 47 years, W, radiologic technologists	285/ 45 631 8.9 years	Self-report verified by medical record	Questionnaire	Incidence, breast cancer, ever used HRT	≥97 vs 0-9.5 met score	1.15 (0.78-1.70)	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, breast diseases , family history of cancer, menopausal	Combined results by MHT use using fixed effect model

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								hormone use, oc use, parity, race, smoking habits	
		139/			Never HRT users	≥97 vs 0-9.5 met score	0.71 (0.43-1.17)		
Leitzmann, 2008 BRE80204 USA	BCDDP, 1973, Prospective Cohort, W, Postmenopausal	1 506/ 32 269 11 years	Self-reported/death certificate/ medical records	Self-completed questionnaire	Incidence, Invasive & In situ breast cancer, postmenopausal	395-721 vs 105-244 met hr/week	0.86 (0.73-1.01)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, benign breast disease, dietary fat, educational level, family history of cancer, health screening, height, menopausal hormone use, oral contraceptive use, smoking habits	
						395-721 vs 105-244 met hr/week	0.87 (0.74-1.02)	BMI	
		876/			Postmenopausal, BMI<25	395-721 vs 105-244 met hr/week	0.76 (0.61-0.94)		
		630/			Postmenopausal, BMI>=25	395-721 vs 105-244 met hr/week	1.06 (0.82-1.36)		
Wyrwich, 2000 BRE13664	LSOA, 1984, Prospective	77/ 3 131	All histology	Interview	Incidence, breast cancer,	highly active vs inactive	0.43 (0.19-0.96)	Age , BMI, educational	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
USA	Cohort, Age: 70-96 years, W, Elderly	7 years						level, other specified factor	
		52/			Incidence, localized breast cancer,	highly active vs inactive	0.66 (0.29-1.53)		
Cerhan, 1998 BRE14588 USA	Iowa 65 and RHS, Prospective Cohort, Age: 65-102 years, W, Elderly	43/ 1 806 11 years	All histology	Interview	Incidence, breast cancer,	high active vs inactive	0.20 (0.05-1.00)	Age , age at first child, age at menarche, age at menopause, alcohol, BMI, educational level, HRT use, other specified factor, parity/pregnancies, smoking habits	
		34/			Incidence, In situ breast cancer,	high active vs inactive	0.30 (0.06-1.20)		

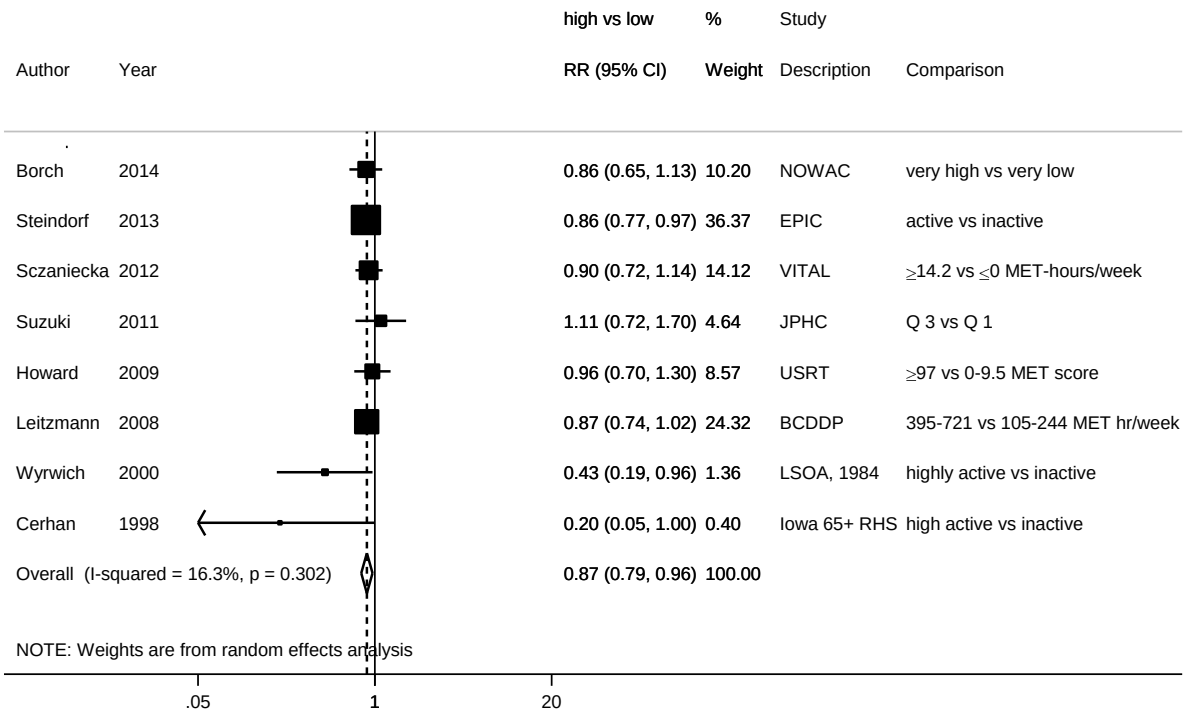
Table 442 Total physical activity and postmenopausal breast cancer risk. Main characteristics of studies excluded from the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
McKenzie, 2015 BRE80534 Europe	EPIC, Prospective Cohort, Age: 25-70 years, W, Postmenopausal	7 756/ 242 918 10.9 years	Record linkage with population-based In 6 countries, Insurance, cancer records & self-report verified by med.records In the rest	Questionnaire	Incidence, Invasive breast cancer, postmenopausal	≥134 vs ≤44.9 met /week	0.87 (0.80-0.95)	Age, age at first child, age at menarche, alcohol, breastfeeding, centre location, combined food score Index, educational level, height, HRT use, non-alcohol energy, oc use, other anthropometric Index, smoking	Excluded, exposure on healthy lifestyle index adherence (Other publication of the same study was included in analysis (Steindorf, 2013)
Cohen, 2013 BRE80470 USA	SCCS, Nested Case Control, Age: 40-79 years	371/ 9 years Unknown number of cases in white women	Cancer registry		Incidence, breast cancer, postmenopausal, White	≥27.1 vs ≤8.9 MET-hours/day	- 0.64 (0.32-1.27)	Age, age at menarche, BMI, educational level, ethnicity, family history of breast cancer, health Insurance, household Income, HRT use, menopausal status, parity, smoking habbits, source type	Excluded, white women only, no overall results on postmenopausal breast cancer
Hastert, 2013	VITAL,	899/	Seer registry	Questionnaire	Incidence, breast	met vs not met	0.95 (0.80-1.13)	Age at first child	Excluded,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
BRE80481 USA	Prospective Cohort, Age: 50-76 years, W, Postmenopausal	30 797 6.7 years			cancer	WCRF guideline on physical activity		birth, age at menarche, age at menopause, educational level, energy Intake, family history of breast cancer, mammography, other factors , race, years of HRT use	exposure on physical activity guideline adherence (Other publication of the same study was included in analysis (Sczaniecka, 2012)
						met vs not met	0.97 (0.81-1.16)	Other recommendations	
Steindorf, 2012 BRE80432 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	921/ 283 827 11.7 years	Cancer registry	Questionnaire/interview	Incidence, In situ breast cancer, age at diagnosis >50yrs	≥124 vs ≤51.5 met-hour/week	1.12 (0.90-1.40)	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, breastfeeding, centre location, educational level, HRT use, menopausal status, number of full-term pregnancies, occupational physical activity, oral contraceptive	Excluded, breast cancer in situ, not enough studies to analyse (Results on breast cancer incidence from the same study was included in analysis (Steindorf, 2013))

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								history, smoking	
						active vs inactive	1.00 (0.79-1.27)	Household physical activity, recreational activity	
						active vs inactive	1.03 (0.77-1.39)		
Lahmann, 2007 BRE20026 Denmark, France, Germany, Greece, Italy, Netherlands, Spain, Sweden, UK	EPIC, Prospective Cohort, Age: 20-80 years, W	2 547/ 218 169 6.4 years	Population cancer registries and other procedures	Questionnaire	Incidence, Invasive breast cancer, postmenopause	≥127 vs ≤54 met-hour/week	0.81 (0.71-0.92)	Age , study center	Superseded by Steindorf, 2013
						≥127 vs ≤54 met-hour/week	0.83 (0.73-0.95)	Age at first child, age at menarche, alcohol, BMI, educational level, HRT use, smoking habits	
		2 476/			Postmenopause	active vs inactive	0.87 (0.71-1.05)		
						active vs inactive	0.92 (0.76-1.12)		

Figure 489 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest level of total physical activity



6.1.1.1 Occupational physical activity

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Overall summary

Twenty-two publications from 17 studies that examined occupational physical activity were identified. No pooled analysis was identified.

The highest compared with the lowest meta-analyses were conducted to examine the association of occupational physical activity with risk of breast cancer, and of premenopausal and postmenopausal breast cancer.

Table 443 Summary of results of the highest versus the lowest meta-analysis in the CUP SLR

	Breast cancer (any)	Premenopausal breast cancer	Postmenopausal breast cancer
Comparison	Highest versus lowest	Highest versus lowest	Highest versus lowest
Studies (n)	7	6	8
Cases	17 688	4 494	22 352
RR (95%CI)	0.93 (0.87-0.99)	0.82 (0.59-1.15)	0.89 (0.83-0.96)
Heterogeneity (I^2, p-value)	0%, 0.55	76%, 0.001	0%, 0.57

Breast cancer (any)

Summary

Main results:

Seven out of 14 studies (17 publications) identified could be included in the highest versus lowest meta-analysis (17 688 cases). Occupational physical activity was significantly inversely associated with breast cancer risk (RR for highest vs lowest activity level=0.93 (95% CI=0.87-0.99). No heterogeneity was observed between studies. Two studies (Steindorf, 2013; Moradi, 1999) contributed large weights in the analysis (44% and 46%, respectively). Summary RR became non-significant when Moradi, 1999 was omitted (RR=0.95, 95% CI=0.87-1.03) but remained significant when Steindorf, 2013 was omitted (RR=0.91, 95% CI=0.83-0.98) in influence analysis.

Seven studies were excluded from the meta-analysis. Byrne, 1996 was a follow-up study of another study included in the analysis (Albanes, 1989). One excluded study (Pronk, 2011) reported a significant inverse association of long-term high energy expenditure job participation with breast cancer risk. Positive association between replacing 1 hour sleep with 1 hour moderate to heavy occupational activity was observed in one study (Dorgan, 1994). Being in different jobs compared to house wives was non-significantly associated (inverse or positive) with breast cancer mortality (Calle, 1998). Compared to the general populations, breast cancer incidence was lower in those with high energy expenditure jobs (Zheng, 1993) and higher in physical education teachers (Pukkala, 1993); mortality was lower in those with high physical activity jobs (Vena, 1987).

EPIC reported results by BMI categories (Steindorf, 2013). Non-significant associations were observed for risk of breast cancer overall among normal, overweight, or obese women. There was no evidence for effect modification of associations for BMI. Non-significant inverse or

positive associations for manual and heavy manual work versus sedentary occupation were observed for risk of breast cancer by hormone receptor status (RR ranged from 0.75 to 1.11).

Study quality:

Studies were from Europe and North America. Information on occupations was reported by the participants, or taken from records in one study (Moradi, 1999). Case ascertainment was through cancer registries or confirmed through medical records. Only one study (Steindorf, 2013) was adjusted for age, BMI, alcohol intake, and reproductive factors. Albanes, 1989 was only adjusted for age.

Table 444 Occupational physical activity and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	14 (17 publications)
Studies included in forest plot of highest compared with lowest exposure	7
Studies included in linear dose-response meta-analysis	Not enough studies
Studies included in non-linear dose-response meta-analysis	Not enough studies

Note: Include cohort and nested case-control designs.

Table 445 Occupational physical activity and breast cancer risk. Summary of the highest versus the lowest meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR	**CUP**
Comparison	-	Highest versus lowest
Studies (n)	-	7
Cases	-	17 688
RR (95%CI)	-	0.93 (0.87-0.99)
Heterogeneity (I^2, p-value)	-	0%, 0.55

Table 446 Occupational physical activity and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Wu, 2013	31 cohort studies[1]	63 786, 10 846 ER+PR+, 2 619 ER-PR-	Canada, China, Europe, Japan, USA	Incidence, any breast cancer in pre-, and/or postmenopausal women	Highest vs lowest occupational activity (7 studies)	0.84 (0.73-0.96)	-	46%

[1]All studies identified in the meta-analysis of Wu (2013) were included in the present review under different physical activity sections.

Table 447 Occupational physical activity and breast cancer risk. Main characteristics of studies included in the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Cohen, 2013 BRE80470 USA	SCCS, Nested Case Control, Age: 40-79 years	457/ 546 9 years	Cancer registry		Incidence, Invasive breast cancer	≥11.2 vs ≤3.2 MET-hours/day	1.00 (0.72-1.40)	Age, age at menarche, BMI, educational level, ethnicity, family history of breast cancer, health Insurance, household Income, HRT use, menopausal status, parity, physical activity, sedentary behaviour, smoking habits, source type
		456/				≥15.7 vs ≤3.9 met-hours/day	0.97 (0.69-1.38)	
		449/				≥18.5 vs ≤9.1 met-hours/day	1.05 (0.75-1.49)	Physical activity
						≥48 vs ≤11.9 met-hours/day	1.23 (0.85-1.78)	
		312/			Black	≥11.2 vs ≤3.2 met-hours/day	0.96 (0.64-1.43)	
		311/			Black	≥15.7 vs ≤3.9 met-hours/day	1.14 (0.74-1.76)	
		306/			Black	≥48 vs ≤11.9 met-hours/day	1.10 (0.71-1.71)	
		132/			White	≥15.7 vs ≤3.9 met-hours/day	0.60 (0.31-1.18)	
						≥11.2 vs ≤3.2 met-hours/day	1.08 (0.57-2.02)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		130/			White	≥18.5 vs ≤9.1 met-hours/day	1.27 (0.69-2.34)	
						≥48 vs ≤11.9 met-hours/day	1.74 (0.81-3.74)	
					Black	≥18.5 vs ≤9.1 met-hours/day	1.02 (0.66-1.59)	
Steindorf, 2013 BRE80425 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	8 034/ 257 805 11.6 years	Cancer registry	Questionnaire /interview	Incidence, Invasive breast cancer	manual/heavy vs sedentary	0.96 (0.88-1.06)	Age, age at first child, age at menarche, age at menopause, alcohol, BMI, breastfeeding, centre location, educational level, household physical activity, HRT use, menopausal status, number of full-term pregnancies, oral contraceptive history, recreational activity, smoking, total physical activity
		4 860/			Incidence, breast cancer ER+	manual/heavy vs sedentary	1.00 (0.89-1.13)	
		4 746/			Incidence, Invasive breast cancer, BMI 18.5-25 kg/m2	manual/heavy vs sedentary	0.92 (0.81-1.05)	
		3 124/			Incidence, breast cancer PR+	manual/heavy vs sedentary	0.95 (0.80-1.12)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		2 943/			Incidence, breast cancer ER+/PR+	manual/heavy vs sedentary	0.96 (0.81-1.13)	
		2 348/			Incidence, Invasive breast cancer, BMI 25-30	manual/heavy vs sedentary	1.02 (0.86-1.21)	
		1 784/			Incidence, breast cancer ER+/PR+, BMI 18.5-25 kg/m2	manual/heavy vs sedentary	0.98 (0.78-1.23)	
		1 690/			Incidence, breast cancer PR-	manual/heavy vs sedentary	0.92 (0.73-1.16)	
		1 147/			Incidence, breast cancer ER-	manual/heavy vs sedentary	0.79 (0.60-1.03)	
		940/			Incidence, Invasive breast cancer, BMI >=30	manual/heavy vs sedentary	1.02 (0.78-1.33)	
		875/			Incidence, breast cancer ER+/PR-	manual/heavy vs sedentary	1.04 (0.75-1.44)	
		809/			Incidence, breast cancer ER+/PR+, BMI 25-30	manual/heavy vs sedentary	0.91 (0.66-1.24)	
		808/			Incidence, breast cancer ER-/PR-	manual/heavy vs sedentary	0.78 (0.55-1.10)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		570/			Incidence, breast cancer ER+/PR-, BMI 18.5-25 kg/m2	manual/heavy vs sedentary	1.07 (0.70-1.63)	
		503/			Incidence, breast cancer ER-/PR-, BMI 18.5-25 kg/m2	manual/heavy vs sedentary	0.75 (0.47-1.20)	
		350/			Incidence, breast cancer ER+/PR+, BMI >=30.0	manual/heavy vs sedentary	0.92 (0.57-1.49)	
		235/			Incidence, breast cancer ER+/PR-, BMI 25-30	manual/heavy vs sedentary	1.04 (0.58-1.88)	
		228/			Incidence, breast cancer ER-/PR-, BMI 25-30	manual/heavy vs sedentary	0.80 (0.41-1.55)	
		77/			BMI >=30.0	manual/heavy vs sedentary	1.11 (0.42-2.95)	
		70/			Incidence, breast cancer ER+/PR-, BMI >=30.0	manual/heavy vs sedentary	1.11 (0.32-3.83)	
Mertens, 2006 BRE23405 USA	ARIC, Prospective Cohort, Age: 45-64 years,	7 994 13.1 years	Partially histological - over 80%	Questionnaire	Incidence, breast cancer,	Q 4 vs Q 1	0.87 (0.61-1.24)	Age , age at first child, age at menopause, ethnicity, family history, recruitment centre

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	W							
Moradi, 2002 BRE16129 Sweden	Swedish twin cohort, 1969, Prospective Cohort, Age: 42-70 years, W, Twins	248/ 9 539 30 years	Partially histological - over 80%	Questionnaire	Incidence, breast cancer,	strenuous vs sedentary	1.00 (0.70-1.50)	Age
Moradi, 1999 BRE16127 sweden	Sweden, 1971, Prospective Cohort, Age: 50-59 years, W	982 270 18 years	Partially histological - over 80%	Questionnaire	Incidence, Invasive breast cancer,	sedentary vs high	1.10 (1.00-1.20)	Age , place of residence, social class, year of Interview
Thune, 1997 BRE12313 Norway	Norway National Health Screening Service – three counties, 1974, Prospective Cohort, Age: 20-49 years, W	345/ 25 624 13.7 years	All histology	Questionnaire	Incidence, breast cancer	heavy manual labour vs sedentary	0.48 (0.25-0.92)	Age , BMI, height, parity/pregnancies, place of residence
Albanes, 1989 BRE00236 USA	NHANES I, Prospective Cohort, Age: 25-74 years, W	7 413 10 years	Medical records + death certificate	Interview	Incidence, breast cancer,	inactive vs very active	1.10 (0.60-2.00)	Age

Table 448 Occupational physical activity and breast cancer risk. Main characteristics of studies excluded from the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Steindorf, 2012 BRE80432 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	1 059/ 283 827 11.7 years	Cancer registry	Questionnaire/interview	Incidence, In situ breast cancer	manual and heavy vs sedentary	1.06 (0.81-1.38)	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, breastfeeding, centre location, educational level, household physical activity, HRT use, menopausal status, number of full-term pregnancies, oral contraceptive history, recreational activity, smoking, total physical activity	Excluded, breast cancer in situ, not enough studies to analysed (Results on breast cancer risk from the same study (Steindorf, 2013) was included in the analysis)
		686/			BMI<25.0	manual and heavy vs sedentary	0.90 (0.63-1.30)		
		281/			BMI=25-29	manual and heavy vs	1.12 (0.69-1.80)		

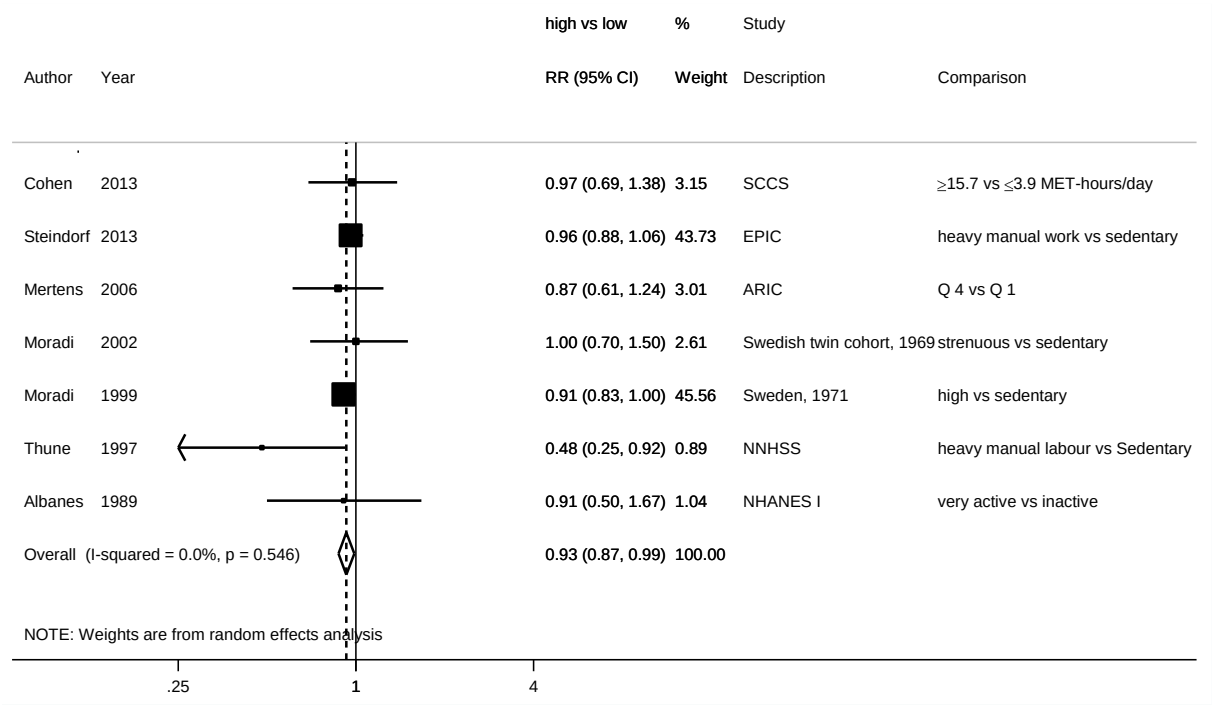
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
						sedentary			
		92/			BMI >=30.0	manual and heavy vs sedentary	1.85 (0.79-4.34)		
Pronk, 2011 BRE80388 China	SWHS, Prospective Cohort, Age: 40-70 years, W	717/ 73 049 9 years	Cancer registry	Duration in jobs with high energy expenditure > 12 kj/min (years)	Incidence, breast cancer	≥10 vs ≤0 years	0.66 (0.46-0.96)	Age, age at first child birth, educational level, family history of breast cancer, number of pregnancies	Excluded, exposure was on years of high energy expenditure at work
Calle, 1998 BRE80179 USA	CPS II, Prospective Cohort, Age: 56 years, W	563 395 9 years	Death certificate and national death Index	Self report	Mortality	beautician vs housewives	1.02 (0.62-1.69)	Age, age at first child birth, age at menarche, age at menopause, alcohol, BMI, educational level, oestrogen replacement therapy, exercise, family history of cancer, history of breast cyst, number of childbirths, oral contraceptive use, race, smoking status	Excluded, breast cancer mortality, not enough studies to analyse
						administrative assistant vs housewives	1.17 (0.77-1.78)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
						teacher/librarian vs housewives	0.89 (0.73-1.08)		
						manager vs housewives	0.89 (0.69-1.14)		
						factory worker vs housewives	0.99 (0.63-1.58)		
Byrne, 1996 BRE05719 USA	NHEFS, Prospective Cohort, Age: 25-74 years, W	53/ 6 156 3.9 years	Medical records + death certificate	Questionnaire	Incidence, breast cancer,	quite inactive vs very active	2.20 (0.90-5.50)	Age	Superseded by Albanes, 1989, BRE00236 (NHEFS was a follow-up study of NHANES I)
Steenland, 1995 BRE11742 USA	NHANES I, Prospective Cohort, Age: 25-74 years, W	7.7 years	Medical records + death certificate	Questionnaire	Incidence, breast cancer,	little vs a lot	0.86 (0.61-1.20)	Age , alcohol, BMI, menopausal status, smoking habits, socio-economic status	Superseded by Albanes, 1989, BRE00236
Dorgan, 1994 BRE02385 USA	FHS, Prospective Cohort, Age: 35-68 years, W	2 307 28 years	All histology	Questionnaire	Incidence, breast cancer,	Replace sleep by per 1 hours/day sedentary to slight occupational activity	1.00 (0.80-1.20)	Age , age at first child, alcohol, educational level, menopausal status, occupation, parity/pregnancies	Excluded from the highest vs lowest meta-analysis - dose response results only
						Replace sleep by per 1 hours/day moderate to heavy	1.10 (0.90-1.30)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
						occupational activity			
Pukkala, 1993 BRE24790 Finland	FFTC, Prospective Cohort, Age: 20-74 years, W, Registered teachers	63/ 10 118 7 years	Not specified		Incidence, breast cancer	physical education teachers vs general population	1.35 (0.95-1.87)	Age	Excluded, standardised incidence ratio comparing to the general population
Zheng, 1993 BRE13994 China	Chinese study, 1993 Historical Cohort, W	254/	Unknown		Incidence, breast cancer	high energy expenditure job vs general population	0.79 P ≤0.01	Age	Excluded, standardised incidence ratio comparing to the general population
Vihko, 1992 BRE12922 Finland	FFTC, Prospective Cohort, Age: 26- years, W, Registered teachers	924 20 years	Partially histological - over 80%	Questionnaire	Incidence, breast cancer,	PE teachers vs population	1.28 (P=0.99)		Excluded, standardised incidence ratio comparing to the general population (Same study as Pukkala, 1993)
Vena, 1987 BRE12852 USA	Washington State, 1974, Historical Cohort, W	876/ 25 000	Death certificate	Job category	Mortality, breast cancer,	medium physical activity job vs general population	0.83 (P=0.05)		Excluded, standardised mortality ratio comparing to the general population
		453/				high physical	0.85 (P=0.05)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
						activity job vs general population			
		349/				low physical activity job vs general population	1.15 (P=0.001)		

Figure 490 RR (95% CI) of breast cancer for the highest compared with the lowest level of occupational physical activity



Premenopausal breast cancer

Summary

Main results:

Six studies (10 publications) were identified and all could be included in the highest versus lowest meta-analysis (4 494 cases). Occupational physical activity was non-significantly inversely associated with premenopausal breast cancer risk (RR for highest vs lowest activity level=0.82 (95% CI=0.59-1.15). High heterogeneity was observed between studies. Summary RR ranged from 0.76 (95% CI=0.53-1.09) when Steindorf, 2013 was omitted to 0.94 (95% CI=0.71-1.24) when Rintala, 2002 was omitted in influence analysis.

EPIC reported results by BMI categories (Steindorf, 2013). Non-significant associations were observed for risk of breast cancer diagnosed ≤ 50 years among normal, overweight, or obese women. There was no evidence for effect modification of associations for BMI.

Study quality:

Studies were from Europe and North America. Information on occupations was reported by the participants, or taken from records in two studies (Rintala, 2003; Moradi, 1999). Case ascertainment was through cancer registries or confirmed through medical records. Only one study (Steindorf, 2013) was adjusted for age, BMI, alcohol intake, and reproductive factors.

Albanes, 1989 was only adjusted for age and Rintala, 2002, for social class and reproductive factors. The summary RR was attenuated when Rintala, 2002 was omitted.

Table 449 Occupational physical activity and premenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	6 (10 publications)
Studies included in forest plot of highest compared with lowest exposure	6
Studies included in linear dose-response meta-analysis	Not enough studies
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 450 Occupational physical activity and premenopausal breast cancer risk. Summary of the highest versus the lowest meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR	**CUP**
Comparison	-	Highest versus lowest
Studies (n)	-	6
Cases	-	4 494
RR (95%CI)	-	0.82 (0.59-1.15)
Heterogeneity (I^2, p-value)	-	76%, 0.001

Table 451 Occupational physical activity and premenopausal breast cancer risk. Main characteristics of studies included in the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Steindorf, 2013 BRE80425 Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, UK	EPIC, Prospective Cohort, Age: 35-70 years, W	936/ 257 805 11.6 years	Cancer registry	Questionnaire/interview	Incidence, Invasive breast cancer, age at diagnosis <=50yrs	manual/heavy vs sedentary	1.11 (0.84-1.48)	Age, age at first child, age at menarche, age at menopause, alcohol, BMI, breastfeeding, centre location, educational level, household physical activity, HRT use, menopausal status, number of full-term pregnancies, oral contraceptive history, recreational activity, smoking, total physical activity	
		683/			Normal BMI, age<=50y	manual/heavy vs sedentary	1.06 (0.75-1.50)		
		193/			Overweight, age<=50y	manual/heavy vs sedentary	1.09 (0.60-2.01)		
		60/			Obese, age<=50y	manual/heavy vs sedentary	1.52 (0.55-4.16)		
Rintala, 2003 BRE80177	Finnish physical education and	10 049	Cancer registry	Questionnaire	Incidence, premenopausal	physical education	0.79 (0.46-1.36)	Age, age at first child birth,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Finland	language teachers cohort, Prospective Cohort, Age: 25-80 years	34 years			breast cancer, age<50 years	teacher vs language teacher		calendar year of follow-up, number of children	
Rintala, 2002 BRE80178 Finland	Finland, Prospective Cohort, Age: 25-55 years, W		Cancer registry	Postal questionnaire	Incidence, premenopausal breast cancer, age 25-39 years	5 (excluding agricultural workers) vs class 1 +2	0.58 (0.45-0.69)	Social class and reproductive factors	
Moradi, 1999 BRE16127 sweden	Sweden, 1971, Prospective Cohort, Age: 50-59 years, W	1 597/ 982 270 18 years	Partially histological - over 80%	Questionnaire	Incidence, Invasive breast cancer, premenopausal	sedentary vs high	1.00 (0.80-1.40)	Adjustments unknown	
Thune, 1997 BRE12313 Norway	Norway National Health Screening Service – three counties, 1974, Prospective Cohort, Age: 20-49 years, W	98/ 25 624 13.7 years	All histology	Questionnaire	Incidence, breast cancer, premenopausal	lifting or heavy manual labour vs sedentary	0.48 (0.24-0.95)	Age , BMI, height, parity/pregnancies, place of residence	
Albanes, 1989 BRE00236 USA	NHANES I, Prospective Cohort, Age: 25-74 years,	46/ 7 413 10 years	Medical records + death certificate	Interview	Incidence, breast cancer, premenopausal	inactive vs moderately active	0.40 (0.10-1.80)	Age	

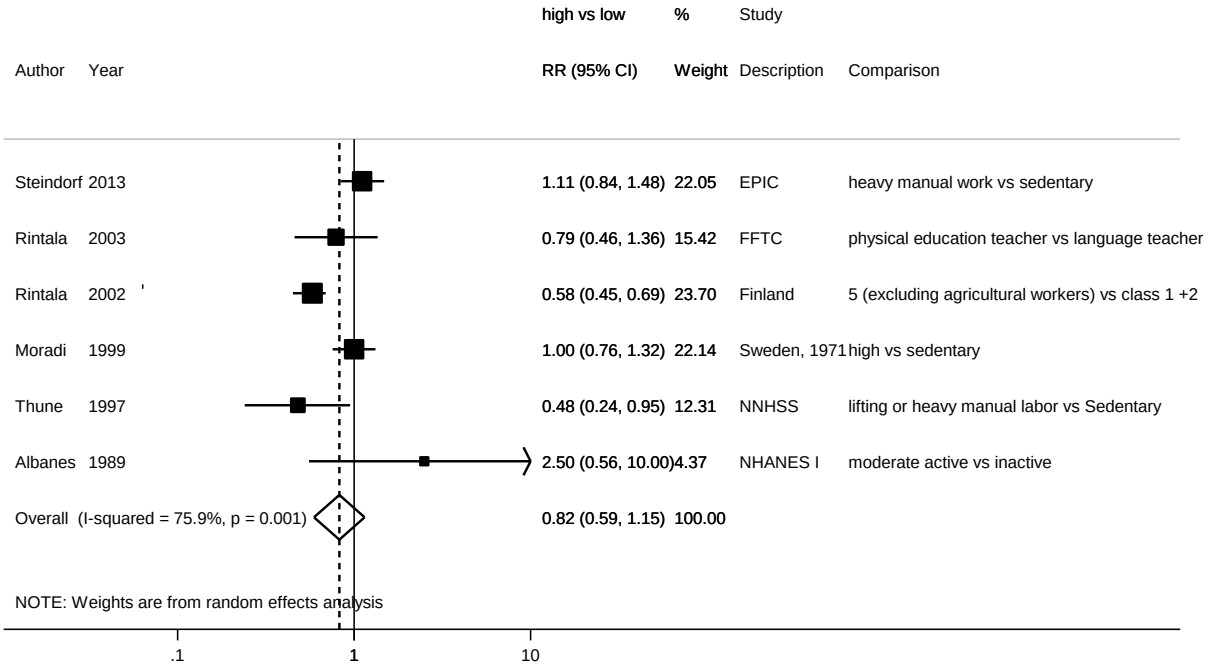
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	W								

Table 452 Occupational physical activity and premenopausal breast cancer risk. Main characteristics of studies excluded from the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Steindorf, 2012 BRE80432 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	138/ 283 827 11.7 years	Cancer registry	Questionnaire/interview	Incidence, In situ breast cancer, age at diagnosis <=50yrs	manual and heavy vs sedentary	1.35 (0.65-2.80)	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, breastfeeding, centre location, educational level, household physical activity, HRT use, menopausal status, number of full-term pregnancies, oral contraceptive history, recreational activity, smoking, total physical activity	Excluded, breast cancer in situ, not enough studies to analyse (Results on breast cancer incidence of the same study (Steindorf, 2013) was included in analysis)
Lahmann, 2007 BRE20026 Denmark, France, Germany, Greece, Italy, Netherlands, Spain, Sweden,	EPIC, Prospective Cohort, Age: 20-80 years, W	659/ 218 169 6.4 years	Population cancer registries and other procedures	Questionnaire	Incidence, Invasive breast cancer, premenopausal	manual and heavy manual vs sedentary	1.04 (0.78-1.38)	Age , age at first child, age at menarche, alcohol, BMI, educational level, OC use, smoking habits, study center	Superseded by Steindorf, 2013

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
UK									
Pukkala, 1993 BRE24790 Finland	FFTC, Prospective Cohort, Age: 20-74 years, W, Registered teachers	18/ 10 118 7 years	Not specified		Incidence, breast cancer, age 20-49 years	physical education teachers vs general population	1.01 (0.46-1.91)	Age	Superseded by Rintala, 2003
Vihko, 1992 BRE12922 Finland	FFTC, Prospective Cohort, Age: 26- years, W, Registered teachers	5/ 924 20 years	Partially histological - over 80%	Questionnaire	Incidence, breast cancer, premenopausal	Physical education teachers vs population	0.93 (P=0.99)		Superseded by Rintala, 2003

Figure 491 RR (95% CI) of premenopausal breast cancer for the highest compared with the lowest level of occupational physical activity



Postmenopausal breast cancer

Summary

Main results:

Eight out of nine studies (13 publications) identified could be included in the highest versus lowest meta-analysis (22 352 cases). Occupational physical activity was significantly inversely associated with breast cancer risk (summary RR for highest vs lowest activity level=0.89 (95% CI=0.83-0.96). No heterogeneity was observed between studies. When the two studies (Steindorf, 2013; Rintala, 2002) that contributed large weights (49% and 34%, respectively) in the analysis were omitted in influence analysis, the inverse association remained significant (RR=0.84, 95% CI=0.76-0.93 and 0.90 95% CI=0.83-0.99, respectively).

One study (Moradi, 1999) did not report overall results and was excluded from the meta-analysis. Sedentary compared with very high or high physical activity occupations was significantly positively associated with breast cancer risk in women aged 50-59 years at follow-up, not associated in aged 60-69 years, and non-significantly inversely associated in aged ≥70 years.

EPIC reported results by BMI categories (Steindorf, 2013). Non-significant associations were observed for risk of breast cancer diagnosed >50 years among normal, overweight, or obese women. There was no evidence for effect modification of associations for BMI.

Study quality:

Studies were from Europe and North America. Information on occupations was reported by the participants, or taken from records in one study (Rintala, 2003). Case ascertainment was through cancer registries or confirmed through medical records. Two studies (Steindorf, 2013; George, 2010) were adjusted for age, BMI, alcohol intake, reproductive factors, and MHT use. Albanes, 1989 was only adjusted for age and Rintala, 2002, for social class and reproductive factors. No study has strong influence on the summary RR which remained significant in influence analysis.

Table 453 Occupational physical activity and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	9 (13 publications)
Studies included in forest plot of highest compared with lowest exposure	8
Studies included in linear dose-response meta-analysis	Not enough studies
Studies included in non-linear dose-response meta-analysis	Not enough studies

Note: Include cohort and case-cohort designs.

Table 454 Occupational physical activity and postmenopausal breast cancer risk. Summary of the highest versus the lowest meta-analysis in the 2005/2008 SLR and CUP SLR

	2005/2008 SLR	**CUP**
Comparison	-	Highest versus lowest
Studies (n)	-	8
Cases	-	22 352
RR (95%CI)	-	0.89 (0.83-0.96)
Heterogeneity (I^2, p-value)	-	0%, 0.57

Table 455 Occupational physical activity and postmenopausal breast cancer risk. Main characteristics of studies included in the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Steindorf, 2013 BRE80425 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	7 098/ 257 805 11.6 years	Cancer registry	Questionnaire/interview	Incidence, Invasive breast cancer, age at diagnosis >50yrs	manual/heavy vs sedentary	0.95 (0.86-1.05)	Age, age at first child, age at menarche, age at menopause, alcohol, BMI, breastfeeding, centre location, educational level, household physical activity, HRT use, menopausal status, number of full-term pregnancies, oral contraceptive history, recreational activity, smoking, total physical activity	
		4 063/			Normal BMI, age>50y	manual/heavy vs sedentary	0.91 (0.79-1.04)		
		2 153/			Overweight, age>50y	manual/heavy vs sedentary	1.02 (0.86-1.22)		
		880/			Obese, age>50y	manual/heavy vs sedentary	1.00 (0.76-1.31)		
George, 2010 BRE80309	NIH-AARP, Prospective	2 866/ 97 039	Cancer registry	Self-administered	Incidence, Invasive breast	heavy lifting or carrying vs	0.64 (0.43-0.94)	Age, alcohol Intake, BMI,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
USA	Cohort, Age: 50-71 years, M/W, Postmenopausal	7 years		questionnaire	cancer, postmenopausal	sitting all day		breast biopsies, educational level, energy Intake, HRT use, parity, race, recreational activity	
						heavy lifting or carrying vs sitting all day	0.62 (0.42-0.91)		
		570/			Incidence, In situ breast cancer, postmenopausal	heavy lifting or carrying vs sitting all day	1.25 (0.58-2.68)		
						heavy lifting or carrying vs sitting all day	1.21 (0.56-2.61)		
Mertens, 2006 BRE23405 USA	ARIC, Prospective Cohort, Age: 45-64 years, W	7 994 13.1 years	Partially histological - over 80%	Questionnaire	Incidence, breast cancer, postmenopausal	Q 4 vs Q 1	0.85 (0.57-1.28)	Age , age at first child, age at menopause, ethnicity, family history, recruitment center	
Rintala, 2003 BRE80177 Finland	Finnish physical education and language teachers cohort, Prospective Cohort, Age: 25-80 years	10 049 34 years	Cancer registry	Questionnaire	Incidence, postmenopausal breast cancer, age >= 50 years	physical education teacher vs language teacher	0.86 (0.62-1.18)	Age, age at first child birth, calendar year of follow-up, number of children	
Rintala, 2002	Finland,		Cancer registry	Postal	Incidence, age	5 (excluding	0.77 (0.67-0.87)	Social class and	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
BRE80178 Finland	Prospective Cohort, Age: 25-55 years, W			questionnaire	40-54 years	agricultural workers) vs class 1 +2		reproductive factors	
					Incidence, postmenopausal breast cancer, age >=55 year	5 (excluding agricultural workers) vs class 1 +2	0.87 (0.77-0.98)		Included in analysis
Dirx, 2001 BRE02326 Netherlands	NLCS, Case Cohort, Age: 55-69 years, W, Postmenopausal	755/ 62 573 7.3 years	Not specified	Questionnaire	Incidence, breast cancer, postmenopausal	≥12.1 vs ≤7.9 kj/minute	0.83 (0.51-1.34)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, body weight, educational level, energy Intake , family history, parity/pregnancies	
Thune, 1997 BRE12313 Norway	Norway National Health Screening Service – three counties, 1974, Prospective Cohort, Age: 20-49 years, W	247/ 25 624 13.7 years	All histology	Questionnaire	Incidence, breast cancer, postmenopausal	lifting or heavy manual labour vs sedentary	0.78 (0.52-1.18)	Age , BMI, height, parity/pregnancies, place of residence	
Albanes, 1989 BRE00236 USA	NHANES I, Prospective Cohort,	7 413 10 years	Medical records + death certificate	Interview	Incidence, breast cancer, postmenopausal	inactive vs moderately active	1.50 (0.70-2.80)	Age	

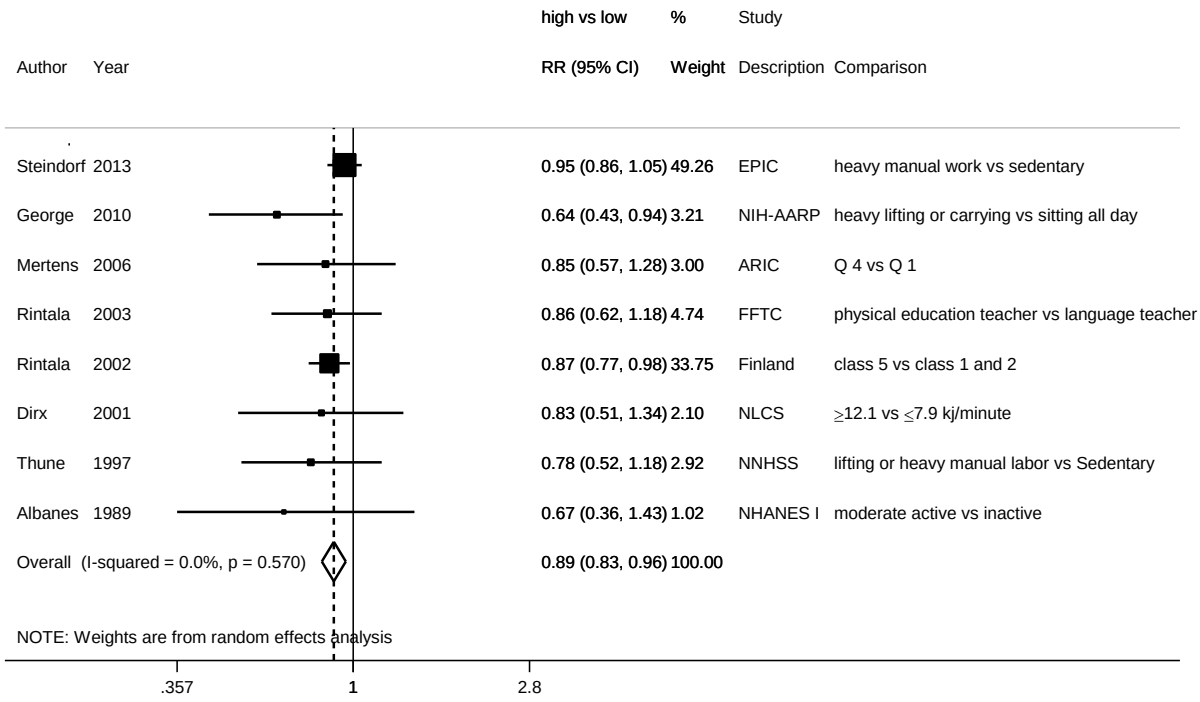
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Age: 25-74 years, W								

Table 456 Occupational physical activity and postmenopausal breast cancer risk. Main characteristics of studies excluded from the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Steindorf, 2012 BRE80432 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	921/ 283 827 11.7 years	Cancer registry	Questionnaire/interview	Incidence, In situ breast cancer, age at diagnosis >50yrs	manual and heavy vs sedentary	1.04 (0.77-1.39)	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, breastfeeding, centre location, educational level, household physical activity, HRT use, menopausal status, number of full-term pregnancies, oral contraceptive history, recreational activity,	Excluded, breast cancer in situ, not enough studies to analyse (Results on breast cancer incidence from the same study (Steindorf, 2013) was included in analysis)

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								smoking, total physical activity	
Lahmann, 2007 BRE20026 Denmark, France, Germany, Greece, Italy, Netherlands, Spain, Sweden, UK	EPIC, Prospective Cohort, Age: 20-80 years, W	1 225/ 218 169 6.4 years	Population cancer registries and other procedures	Questionnaire	Incidence, Invasive breast cancer, postmenopausal	manual and heavy manual vs sedentary	1.08 (0.91-1.29)	Age , age at first child, age at menarche, alcohol, BMI, educational level, HRT use, smoking habits, study center	Superseded by Steindorf, 2013, BRE80425
Moradi, 1999 BRE16127 Sweden	Sweden, 1971, Prospective Cohort, Age: 50-59 years, W	6 684/ 982 270 18 years	Partially histological - over 80%	Questionnaire	Incidence, Invasive breast cancer, attained age at follow-up Age 50-59 years Age 60-69 years Age ≥70 years	sedentary vs high	1.30 (1.10-1.70) 1.00 (0.80-1.30) 0.82 (0.60-1.10)	Age, place of residence, calendar year of follow-up, socioeconomic status	Excluded, no overall results, subgroups by attained age at follow-up
Pukkala, 1993 BRE24790 Finland	FFTC, Prospective Cohort, Age: 20-74 years, W, Registered teachers	45/ 10 118 7 years	Not specified		Incidence, breast cancer, age >= 50 years	physical education teachers vs general population	1.52 (1.00-2.21)	Age	Superseded by Rintala, 2003
Vihko, 1992 BRE12922 Finland	FFTC, Prospective Cohort, Age: 26- years, W, Registered teachers	17/ 924 20 years	Partially histological - over 80%	Questionnaire	Incidence, breast cancer, postmenopausal	PE teachers vs population	1.44 (P=0.99)		Superseded by Rintala, 2003

Figure 492 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest level of occupational physical activity



6.1.1.2 Recreational physical activity

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Overall summary

Forty-nine publications from 36 studies that examined recreational physical activity were identified. No pooled analysis was identified.

Dose-response and the highest compared with the lowest meta-analyses were conducted to examine the association of recreational physical activity with risk of breast cancer, and of premenopausal and postmenopausal breast cancer. Recreational physical activity was assessed either at study baseline, or for lifetime/long-term or recent activities.

Table 457 Summary of results of the dose-response and the highest versus the lowest meta-analysis of recreational physical activity in the CUP SLR

	Breast cancer (any)	Premenopausal breast cancer	Postmenopausal breast cancer
Increment unit used	Per 10 MET-hour/week	Per 10 MET-hour/week	Per 10 MET-hour/week
Studies (n)	5	3	5
Cases	15 453	2 331	18 486
RR (95%CI)	0.95 (0.92-0.99)	0.96 (0.90-1.03)	0.98 (0.97-0.99)
Heterogeneity (I^2, p-value)	60%, 0.04	69%, 0.04	0%, 0.68
P value Egger test	0.03	-	0.12
Comparison	Highest versus lowest	Highest versus lowest	Highest versus lowest
Studies (n)	19	10	17
Cases	28 659	>3 901*	>24 253*
RR (95%CI)	0.92 (0.89-0.96)	0.93 (0.74-1.16)	0.87 (0.81-0.94)
Heterogeneity (I^2, p-value)	10%, 0.33	59%, 0.01	37%, 0.06

*Number of pre- and postmenoapausal cancer cases unclear in some publications

Breast cancer (any)

Summary

Main results:

Out of 26 studies (28 publications) identified, five studies (15 453 cases) and 19 studies (28 659 cases) could be included in the dose-response and the highest versus lowest meta-analysis, respectively. Recreational physical activity was significantly inversely associated with breast cancer risk. Summary RR per 10 MET-hour/week was 0.95 (95% CI=0.92-0.99), and for highest vs lowest activity level, 0.92 (95% CI=0.89-0.96). High heterogeneity was observed between studies included in the dose-response analysis (60%, P=0.04), but not in the highest versus the lowest analysis (10%, P=0.33).

There was evidence of significant publication or small study bias (P for Egger's test = 0.03 and 0.04 for studies in the dose-response and the highest versus lowest analysis, respectively). Funnel

plots showed asymmetry with more small studies reported inverse associations (funnel plot of studies included in the highest versus lowest analysis not shown).

Seven studies were excluded from the meta-analyses. Study populations in Tehard, 2006, Breslow, 2001, and Thune, 1997 overlapped with Steindorf, 2013, Albanes, 1989, and Bjerkaas, 2013, respectively that were already included in the analysis. Wyshak, 2000 reported a significant inverse association of being an athlete versus not in college and Robsahm, 2010 observed a non-significant increased breast cancer incidence in world-class athletes compared to the general population. Drake, 2001 reported no significant difference in various exercises between breast cancer cases and non-cases. Paffenbarger Jr observed a non-significant inverse association with breast cancer mortality.

Subgroup analysis showed non-significant inverse associations for the highest versus the lowest level comparison were observed among normal weight (eight studies, low heterogeneity), overweight (eight studies, moderate heterogeneity), and obese (one study) women.

Non-significant or borderline significant associations of either direction were observed in the three studies (Steindorf, 2013; Suzuki, 2011a; Lee, 2001) that reported results by hormone receptor subtypes. RRs for the highest versus the lowest activity level in the JPHC study (Suzuki, 2011a) were 0.43 (95% CI=0.19-1.00) for ER+PR+, 1.06 (95% CI=0.49-2.26) for ER-PR-, and 1.93 (95% CI=0.87-4.26) for ER+PR- breast cancers.

Sensitivity analyses:

Summary RR became borderline significant when Zhang X, 2015 (25% weight) (RR per 10 MET-hr/wk=0.95, 95% CI=0.90-1.00) or Catsburg, 2014b (22% weight) (0.96, 95% CI=0.92-1.00) were omitted in influence analysis. Studies included in the dose-response analysis were not further stratified due to low number of studies in the strata. The Norwegian NNHSSS study (Bjerkaas, 2013) contributed 34% in the highest versus the lowest analysis. Removing this study or others in turn did not change the summary RR materially.

Non-linear dose-response meta-analysis:

Non-linear dose-response meta-analysis was not conducted due to insufficient data.

Study quality:

Studies were from Asia, Europe, and North America. Land, 2014 was based in a tamoxifen trial (NSABP) and Lee, 2001 was based in an aspirin and vitamin E clinical trial (WHS). Pijpe, 2010 included BRCA1/2 carriers only. All studies reported assessment of recreational physical activity by questionnaire, which was validated in six studies (Catsburg, 2014b; Bjerkaas, 2013; Steindorf, 2013; Pronk, 2011; Suzuki, 2011a; Suzuki, 2008c). Long-term (lifetime) recreational physical activity was assessed in Boeke, 2014b and Pijpe, 2010. Summary RR did not change materially when these studies were omitted in turn in influence analysis.

Case ascertainment was through cancer registries or confirmed through medical records. Nine studies (Zhang X, 2015; Boeke, 2014b; Catsburg, 2014b; Land, 2014; Steindorf, 2013; Suzuki,

2011a; Pijpe, 2010; Suzuki, 2008c; Lee, 2001) were adjusted for age, BMI, alcohol intake, and reproductive factors. Bjerkaas, 2013 did not adjust for alcohol intake. Two studies (Moradi, 2002; Albanes, 1989) only adjusted for age and Sesso, 1998 only adjusted for age and BMI.

Table 458 Recreational physical activity and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	26 (28 publications)
Studies included in forest plot of highest compared with lowest exposure	19*
Studies included in linear dose-response meta-analysis	5
Studies included in non-linear dose-response meta-analysis	Not enough studies

Note: Include cohort and nested case-control designs. * Three cohorts in NNHSSS (Bjerkaas, 2013)

Table 459 Recreational physical activity and breast cancer risk. Summary of the dose-response and the highest versus the lowest meta-analysis in the CUP SLR1

	CUP	**CUP**
Increment unit used/comparison	10 MET-hour/week	Highest versus lowest
Studies (n)	5	19
Cases	15 453	28 659
RR (95%CI)	0.95 (0.92-0.99)	0.92 (0.89-0.96)
Heterogeneity (I^2, p-value)	60%, 0.04	10%, 0.33
P value Egger test	0.03	0.04
Subgroup analysis in the CUP		
Comparison	Highest versus lowest	Highest versus lowest
BMI category[2]	**Normal weight**	**Overweight**
Studies (n)	8	8
Cases	>6718	>3500
RR (95%CI)	0.90 (0.78-1.03)	0.83 (0.67-1.02)
Heterogeneity (I^2, p-value)	29%, 0.20	36%, 0.14

[1]Meta-analysis was not conducted in the 2005 SLR; [2]One study (Steindorf, 2013) also reported results among obese women (RR for highest vs lowest=0.98, 95% CI=0.80-1.20, n=940)

Table 460 Recreational physical activity and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Wu, 2013	31 cohort studies[1]	63 786, 10 846 ER+PR+, 2 619 ER-PR-	Canada, China, Europe, Japan, USA	Incidence, any breast cancer in pre-, and/or postmenopausal women	Highest vs lowest, recreational physical activity (25 studies)	0.87 (0.83-0.91)	-	26%
					Non-occupational (27 studies)	0.87 (0.82-0.91)	-	28%

[1]All studies identified in the meta-analysis of Wu (2013) were included in the present review under different physical activity sections.

Table 461 Recreational physical activity and breast cancer risk. Main characteristics of studies included in the dose-response and the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Zhang X, 2015 BRE80578 USA	NHS, Prospective Cohort, Age: 30-55 years, W	5 410/ 103 577 26 years	Self-report verified by medical record	Questionnaire	Incidence, Invasive breast cancer	per 20 met-h/week	0.89 (0.81-0.98)	Age at menarche, age at menopause, alcohol Intake, BMI at age 18 years, family history of breast cancer, height, history of benign breast disease, parity and age at first birth, postmenopausal hormone use	
						≥27 vs ≤2.9 met-h/week	0.86 (0.78-0.95)		
		1 661/			Incidence, breast cancer AR+	≥27 vs ≤2.9 met-h/week	0.85 (0.71-1.01)		
						per 20 met-h/week	0.87 (0.73-1.04)		
		467/			Incidence, breast cancer AR-	≥27 vs ≤2.9 met-h/week	0.73 (0.49-1.07)		
						per 20 met-h/week	0.67 (0.45-0.99)		
Boeke, 2014b BRE80535 USA	NHS II, Prospective Cohort, W	2 697/ 75 669 975 258 person-years	Self-report verified by medical record	Questionnaire. Lifetime physical activity (mean of 14–17	Incidence, pre- and postmenopausal breast cancer	≥55 vs ≤17.9 met-h/week	0.89 (0.78-1.00)	Age, age at first child birth, age at menarche, alcohol, benign	Highest vs lowest meta-analysis only

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
				and 18–22 years and adult physical activity)				breast disease, body size, breastfeeding, calendar year, family history of breast cancer, height, menopausal status, parity, physical activity, weight change	
						high vs low adolescent and adult physical activity	0.87 (0.79-0.97)		
Catsburg, 2014b BRE80529 Canada	CSDLH, Case Cohort, W, alumnae	1 074/ 4 417 15 years	Cancer registry	Questionnaire	Incidence, Invasive breast cancer	≥31 vs ≤2.9 met-hours	0.79 (0.62-1.00)	Age at first child birth, age at menarche, alcohol Intake, BMI, family history of breast cancer, HRT use, menopausal status, number of childbirths, OC use	
						≥7.6 vs ≤0.9 hours	0.77 (0.61-0.97)		
		1 047/				≥7 vs ≤0.9 times	0.77 (0.46-1.30)		
		680/			BMI <25	≥7.6 vs ≤0.9	0.72 (0.54-0.97)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
						hours			
					BMI < 25	≥31 vs ≤2.9 met-hours	0.75 (0.55-1.02)		
		394/			BMI >=25	≥7.6 vs ≤0.9 hours	0.81 (0.55-1.22)		
					BMI >= 25	≥31 vs ≤2.9 met-hours	0.83 (0.56-1.24)		
Land, 2014 BRE80566 USA	NSABP, Prospective Cohort, Age: 54 years, W, High Risk population	13 388 7 years	Follow-up visits	Questionnaire	Incidence, Invasive breast cancer, tamoxifen	low/no activity vs more active	0.80 (0.58-1.11)	Age, alcohol consumption, diabetes, oestrogen use, gail model risk, menstrual status, race, smoking duration, smoking Intensity, smoking status, treatment allocation	Highest vs lowest meta-analysis only; Recalculate RRs for comparison of more active vs low/no activity; combined trial arms using fixed effect model
					Placebo-group	low/no activity vs more active	1.35 (1.05-1.75)		
Bjerkaas, 2013 BRE80485 Norway	NNHSSS, Prospective Cohort, Age: 44 years, W (NNHSSS - Norwegian Counties Study, 40-y Cohort,	7 490/ 302 865 14 years	Cancer registry		Incidence, breast cancer	heavy vs sedentary	0.97 (0.90-0.99)	Age, age at first child birth, age at study entry, BMI, educational level, number of children	Highest vs lowest meta-analysis only

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Cohort of Norway)								
Steindorf, 2013 BRE80425 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	8 034/ 257 805 11.6 years	Cancer registry	Questionnaire/interview	Incidence, Invasive breast cancer	≥42 vs ≤13.5 met-hours/week	0.96 (0.90-1.03)	Age, age at first child, age at menarche, age at menopause, alcohol, BMI, breastfeeding, centre location, educational level, household physical activity, HRT use, menopausal status, number of full-term pregnancies, occupational activity, oral contraceptive history, smoking, total physical activity	
		4 860/			Incidence, breast cancer ER+	≥42 vs ≤12 met-hour/week	0.95 (0.87-1.03)		
		4 746/			Incidence, Invasive breast cancer, BMI 18.5-25 kg/m2	≥42 vs ≤13.5 met-hour/week	0.95 (0.87-1.03)		
		3 124/			Incidence, breast cancer PR+	≥42 vs ≤12 met-hour/week	0.96 (0.86-1.07)		
		2 943/			Incidence, breast	≥42 vs ≤13.5	0.96 (0.86-1.07)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					cancer ER+/PR+	met-hour/week			
		2 348/			Incidence, Invasive breast cancer, BMI 25-30	≥42 vs ≤13.5 met-hour/week	0.98 (0.86-1.11)		
		1 784/			Incidence, breast cancer ER+/PR+, BMI 18.5-25 kg/m2	≥42 vs ≤13.5 met-hour/week	0.96 (0.83-1.10)		
		1 690/			Incidence, breast cancer PR-	≥42 vs ≤12 met-hour/week	1.06 (0.92-1.23)		
		1 147/			Incidence, breast cancer ER-	≥42 vs ≤12 met-hour/week	1.05 (0.88-1.26)		
		940/			Incidence, Invasive breast cancer, BMI >=30	≥42 vs ≤13.5 met-hour/week	0.98 (0.80-1.20)		
		875/			Incidence, breast cancer ER+/PR-	≥42 vs ≤13.5 met-hour/week	0.99 (0.81-1.22)		
		809/			Incidence, breast cancer ER+/PR+, BMI 25-30	≥42 vs ≤13.5 met-hour/week	0.98 (0.79-1.22)		
		808/			Incidence, breast cancer ER-/PR-	≥42 vs ≤13.5 met-hour/week	1.11 (0.90-1.37)		
		570/			Incidence, breast cancer ER+/PR-, BMI 18.5-25 kg/m2	≥42 vs ≤13.5 met-hour/week	1.02 (0.79-1.31)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		503/			Incidence, breast cancer ER-/PR-, BMI 18.5-25 kg/m2	≥42 vs ≤13.5 met-hour/week	1.01 (0.78-1.32)		
		350/			Incidence, breast cancer ER+/PR+, BMI >=30.0	≥42 vs ≤13.5 met-hour/week	0.91 (0.65-1.28)		
		235/			Incidence, breast cancer ER+/PR-, BMI 25-30	≥42 vs ≤13.5 met-hour/week	0.89 (0.60-1.32)		
		228/			Incidence, breast cancer ER-/PR-, BMI 25-30	≥42 vs ≤13.5 met-hour/week	1.20 (0.80-1.79)		
		77/			BMI >=30.0	≥42 vs ≤13.5 met-hour/week	1.96 (0.95-4.05)		
		70/			Incidence, breast cancer ER+/PR-, BMI >=30.0	≥42 vs ≤13.5 met-hour/week	1.19 (0.57-2.49)		
Pronk, 2011 BRE80388 China	SWHS, Prospective Cohort, Age: 40-70 years, W	717/ 73 049 9 years	Cancer registry	Interview	Incidence, breast cancer	≥17.6 vs ≤0 met-hour/week/year	0.92 (0.69-1.21)	Age, age at first child birth, educational level, family history of breast cancer, number of pregnancies	
Suzuki, 2011a BRE80307 Japan	JPHC, Prospective Cohort, Age: 40-69 years,	479/ 53 578 14.5 years	Cancer registry	Questionnaire/interview	Incidence, breast cancer	≥3d/week vs ≤3d/month	0.73 (0.54-1.00)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake,	Highest vs lowest meta-analysis only

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	W, women							area, BMI, energy-adjusted Intake of Isoflavones, height, HRT use, parity, physical activity, smoking	
		453/			BMI<25.0	≥1 day/week vs ≤3d/month	1.02 (0.81-1.28)		
		260/			Incidence, breast cancer unknown ER/PR status	≥3d/week vs ≤3d/month	0.64 (0.41-1.00)		
		199/			Incidence, breast cancer, BMI=>25	≥1 day/week vs ≤3d/month	0.65 (0.43-0.97)		
		101/			Incidence, breast cancer ER+/PR+	≥3d/week vs ≤3d/month	0.43 (0.19-1.00)		
		90/			BMI<25.0	≥1 day/week vs ≤3d/month	0.84 (0.48-1.48)		
		65/			Incidence, breast cancer ER-/PR-, BMI<25.0	≥1 day/week vs ≤3d/month	1.11 (0.61-2.01)		
		61/				≥3d/week vs ≤3d/month	1.06 (0.49-2.26)		
		46/			Incidence, breast cancer ER+/PR-	≥3d/week vs ≤3d/month	1.93 (0.87-4.26)		
		45/			Incidence, breast cancer	≥1 day/week vs ≤3d/month	0.50 (0.50-1.27)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					ER+/PR+, BMI=>25				
		44/			Incidence, breast cancer ER+/PR-, BMI<25.0	≥1 day/week vs ≤3d/month	1.61 (0.82-3.16)		
		20/			BMI=>25	≥1 day/week vs ≤3d/month	0.51 (0.12-2.23)		
		18/			Incidence, breast cancer ER-/PR-, BMI=>25	≥1 day/week vs ≤3d/month	0.93 (0.27-3.27)		
Pijpe, 2010 BRE80269 Netherlands	HEBON, Historical Cohort, Age: 45 years, W, BRCA1/2 mutation carriers	218/ 725	Self report, pathology report, national death Index, death cert, state cancer registries	Self-administered questionnaire	Incidence, breast cancer	≥22.7 vs ≤0 met-hours/week	0.83 (0.50-1.37)	Age, alcohol Intake, birth cohort, BMI, BRCA carrier, family history, HRT use, menopausal status, occupational physical activity, ocp use, parity	
						≥19 vs ≤0 years	0.83 (0.52-1.30)		
						≥3.3 vs ≤0 hours/week	0.78 (0.48-1.29)		
						≥14 vs ≤0 years	0.76 (0.48-1.20)		
						≥3.3 vs ≤0 hours/week	0.81 (0.48-1.36)		
						≥21.7 vs ≤0 met-hours/week	0.77 (0.46-1.28)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
						≥11 vs ≤0 years	0.64 (0.39-1.03)		
						≥3 vs ≤0 hours/week	0.66 (0.42-1.04)		
						≥21 vs ≤0 met-hours/week	0.68 (0.43-1.09)		
						yes vs no	0.79 (0.57-1.09)		
						yes vs no	0.77 (0.55-1.08)		
						yes vs no	0.78 (0.55-1.09)		
						yes vs no	0.76 (0.55-1.07)		
						≥21 vs ≤0 met-hours/week	0.92 (0.57-1.50)		
						≥21 vs ≤0 met-hours/week	0.95 (0.59-1.54)		
						≥21 vs ≤0 met-hours/week	0.93 (0.58-1.49)		
						≥21 vs ≤0 met-hours/week	0.88 (0.55-1.41)		
						≥50.1 vs ≤0 %	0.80 (0.57-1.13)		
						≥50.1 vs ≤0 %	0.83 (0.59-1.17)		
						≥50.1 vs ≤50 %	0.78 (0.55-1.09)		
						≥3 vs ≤0 hours/week	0.99 (0.63-1.55)		
						≥3 vs ≤0 hours/week	0.83 (0.53-1.30)		
						≥3 vs ≤0 hours/week	0.90 (0.58-1.40)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
						≥3 vs ≤0 hours/week	0.94 (0.61-1.44)		
						≥50.1 vs ≤0 %	0.84 (0.58-1.22)		
					Overweight	ever vs never	0.75 (0.49-1.15)		
					Lean	ever vs never	0.58 (0.38-0.88)		
Suzuki, 2008c BRE80201 Japan	JACC, Prospective Cohort, Age: 40-69 years, W	207/ 30 157 12.4 years	Cancer registry	Self-administered questionnaire	Incidence, breast cancer	≥3 vs ≤0 hours/week	0.85 (0.51-1.40)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, BMI, educational level, family history of cancer, hormone use, menopausal status, parity	Highest vs lowest meta-analysis only
					BMI >/= 24	most active vs others	0.44 (0.18-1.09)		
					BMI <24	most active vs others	0.42 (0.19-0.90)		
Mertens, 2006 BRE23405 USA	ARIC, Prospective Cohort, Age: 45-64 years, W	7 994 13.1 years	Partially histological - over 80%	Questionnaire	Incidence, breast cancer,	Q 4 vs Q 1	1.31 (0.87-1.96)	Age , age at first child, age at menopause, ethnicity, family history, recruitment center	Highest vs lowest meta-analysis only
						Q 4 vs Q 1	1.00 (0.64-1.54)		
Moradi, 2002	Swedish twin	442/	Partially	Questionnaire	Incidence, breast	regular activ vs	0.80 (0.60-1.20)	Age	Highest vs

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
BRE16129 Sweden	cohort, 1969, Prospective Cohort, Age: 42-70 years, W, Twins	9 539 30 years	histological - over 80%		cancer,	sedentary			lowest meta-analysis only
Lee, 2001 BRE15848 USA, Puerto Rico	WHS, Prospective Cohort, Age: 45- years, W, Registered nurses	411/ 39 322 48 months	Medical records + self-reported +death certificate	Questionnaire	Incidence, Invasive & In situ breast cancer,	≥6300 vs ≤839 kj/week	0.80 (0.58-1.12)	Age at first child, age at menarche, alcohol, BMI, family history, HRT use, menopausal status, OC use, parity/pregnancies	Highest vs lowest meta-analysis only
		222/			Incidence, breast cancer ER+/PR+,	≥6300 vs ≤839 kj/week	0.92 (0.58-1.45)		
Luoto, 2000 BRE80174 Finland	FAHBS, 1978, Prospective Cohort, Age: 15-64 years, W	314/ 30 548 0	Cancer registry	Questionnaire	Incidence, breast cancer	daily vs <once a week	1.01 (0.72-1.42)	Age at survey, BMI, education, length of follow-up, parity, age at first birth	Highest vs lowest meta-analysis only
					BMI >26	daily vs <once/week	0.94 (0.53-1.68)		
					BMI<21kg/m2	daily vs <once/week	0.88 (0.37-2.05)		
					BMI 21-26kg/m2	daily vs <once a week	1.11 (0.71-1.75)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Hoyer, 1998 BRE15433 Denmark	CopenhagenCHS, Nested Case Control, Age: 20- years, W	198/ 393 controls 17 years	Partially histological - over 80%	Questionnaire	Incidence, breast cancer,	heavy vs passive	0.72 (0.44-1.19)	Alcohol, body weight, educational level, height, Income, marital status, menopausal status, parity/pregnancies, physical activity , smoking habits	Highest vs lowest meta-analysis only
Sesso, 1998 BRE16626 USA	CAHS, Prospective Cohort, Age: 37-69 years, College alumnae	109/ 2 387 31 years	Medical records + self-reported +death certificate	Questionnaire	Incidence, breast cancer,	≥1000 vs ≤499 kcal/week	0.73 (0.46-1.14)	Age , BMI	Highest vs lowest meta-analysis only
		58/			Lean	≥1000 vs ≤499 kcal/week	0.77 (0.41-1.45)		
		51/			Overweight	≥1000 vs ≤499 kcal/week	0.72 (0.38-1.37)		
Albanes, 1989 BRE00236 USA	NHANES I, Prospective Cohort, Age: 25-74 years, W	7 413 10 years	Medical records + death certificate	Interview	Incidence, breast cancer,	litte/no exercise vs much exercise	1.00 (0.60-1.60)	Age	Highest vs lowest meta-analysis only

Table 462 Recreational physical activity and breast cancer risk. Main characteristics of studies excluded from the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Steindorf, 2012 BRE80432 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	1 059/ 283 827 11.7 years	Cancer registry	Questionnaire/interview	Incidence, In situ breast cancer	≥42 vs ≤12 met-hour/week	0.99 (0.82-1.19)	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, breastfeeding, centre location, educational level, household physical activity, HRT use, menopausal status, number of full-term pregnancies, occupational physical activity, oral contraceptive history, smoking, total physical activity	Excluded, breast cancer in situ, not enough studies to analyse (Results on breast cancer incidence from the same study (Steindorf, 2013) were included in analysis)
		686/			BMI<25.0	≥42 vs ≤12 met-hour/week	0.91 (0.72-1.15)		
		281/			BMI=25-29	≥42 vs ≤12 met-hour/week	1.13 (0.79-1.62)		
		92/			BMI >=30.0	≥42 vs ≤12 met-hour/week	1.10 (0.57-2.12)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Robsahm, 2010 BRE80391 Norway	Norwegian World Class Athletes, Prospective Cohort, Age: 17- years, W	20/ 1 424	Linkage to cancer registry	Questionnaire	Incidence, breast cancer	Athletes in endurance disciplines vs general population	1.11 (0.58-1.95)	Age, sex, birth cohort	Excluded, standardised incidence ratio comparing athletes to the general population
Suzuki, 2007 BRE80447 Japan	JACC, Prospective Cohort, Age: 40-79 years, W	77/ 109 778	Death certificate	Questionnaire	Mortality, breast cancer	<1 vs >3 hours/week	2.00 (0.72-5.51)	Age, study area	Excluded, breast cancer mortality, not enough studies to analyse (Results on breast cancer incidence from the same study (Suzuki, 2008c) were included in analysis)
		72/				yes vs little	1.01 (0.55-1.88)		
Tehard, 2006 BRE80108 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W	2 637/ 98 995 11.4 years	Patient records/direct contact/health Insurance records	Questionnaire	Incidence, breast cancer,	≥33.8 vs ≤0 met-hour/week	0.81 (0.72-0.92)	Age at first child, age at menarche, age-underlying cox models, benign breast disease, BMI, family history, HRT use, marital status, menopausal status, oc use,	Superseded by Steindorf, 2013, BRE80425

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								occupation, parity/pregnancies	
Breslow, 2001 BRE01123 USA	NHEFS, Prospective Cohort, Age: 24-75 years, W	138/ 6 160 9.2 years	Medical records + self-reported	Questionnaire	Incidence, breast cancer,	consistently high vs consistently low	0.58 (0.31-1.07)	Age , BMI, body weight, ethnicity, height, Income, socio-economic status	Superseded by Albanes, 1989 (NHEFS part of NHANES I)
					Lean	consistently high vs consistently low	0.40 (0.13-1.28)	Age , ethnicity, Income, socio-economic status	
					Overweight	consistently high vs consistently low	0.26 (0.06-1.13)		
Drake, 2001 BRE02418 USA	ACLS, 1970, Prospective Cohort, Age: 21-86 years, W, Fitness centre members	4 520 25 years	Not specified	Questionnaire	Incidence, breast cancer,	(mean exposure)			Excluded, comparison of mean of exposure only, cohort of fitness centre members
Wyshak, 2000 BRE13666 USA	USA, 1981, Prospective Cohort, Age: 21-80 years, W, College alumnae	175/ 3 940 15 years	Not specified	Questionnaire	Incidence, breast cancer,	athletes vs non-athletes	0.60 (0.40-0.80)	Age , family history, HRT use, oc use, other anthropometric Index, other specified factor, parous/nulliparous, smoking	Excluded, cohort of athletes only (Overlapped with Frisch, 1985 and 1987)

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								habits	
Thune, 1997 BRE12313 Norway	Norway National Health Screening Service – three counties, 1974, Prospective Cohort, Age: 20-49 years, W	346/ 25 624 13.7 years	All histology	Questionnaire	Incidence, breast cancer	Regular exercise vs sedentary	0.63 (0.42-0.95)	Age , BMI, height, parity/pregnancies, place of residence	Superseded by Bjerkaas, 2013, BRE80485, (Overlapped with NNHSSS)
		131/			BMI 22- kg /m2	consistently active vs consistently sedentary	0.23 (0.09-0.60)		
		101/			BMI 22-25 kg /m2	consistently active vs consistently sedentary	0.83 (0.33-2.09)		
		114/			BMI >=25.8 kg /m2	consistently active vs consistently sedentary	1.38 (0.60-3.17)		
Frisch, 1987 BRE02995 USA	USA, 1981, Historical Cohort, W	69/ 5 398 56 years	Self-reported	Temp	Prevalence, breast cancer,	not atlete vs atlete	1.86 (1.00-3.47)	Age , age at menarche, BMI, family history, HRT use, oc use, parity/pregnancies, physical activity , smoking habits	Excluded, cohort of athletes only (Overlapped with Wyshak, 2000 and Frisch, 1985)

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Paffenbarger RS Jr, 1987 BRE80538 USA	HAHS, Prospective Cohort, W	46/ 4 706	Death certificate, self-reported and records	Questionnaire	Mortality, breast cancer	sports play 5 ≥ hr/wk vs sports play 5 ≤ hr/wk	0.96 (P=0.92)	Age, sex, birthyear	Excluded, breast cancer mortality, not enough studies to analyse
Frisch, 1985 BRE02992 USA	USA, 1981, Historical Cohort, W, College alumnae	36/ 7 559	Self-reported	School records	Incidence, breast cancer, other	former athletes vs non-athletes	2.02 (1.03-3.94)	Age , age at menarche, BMI, family history, HRT use, leisure time physical activity, oc use, parity/pregnancies, smoking habits	Excluded, cohort of athletes only (Overlapped with Wyshak, 2000 and Frisch, 1987)
		26/				former athletes vs non-athletes	1.86 (1.00-3.47)		

Figure 493 RR estimates of breast cancer by levels of recreational physical activity

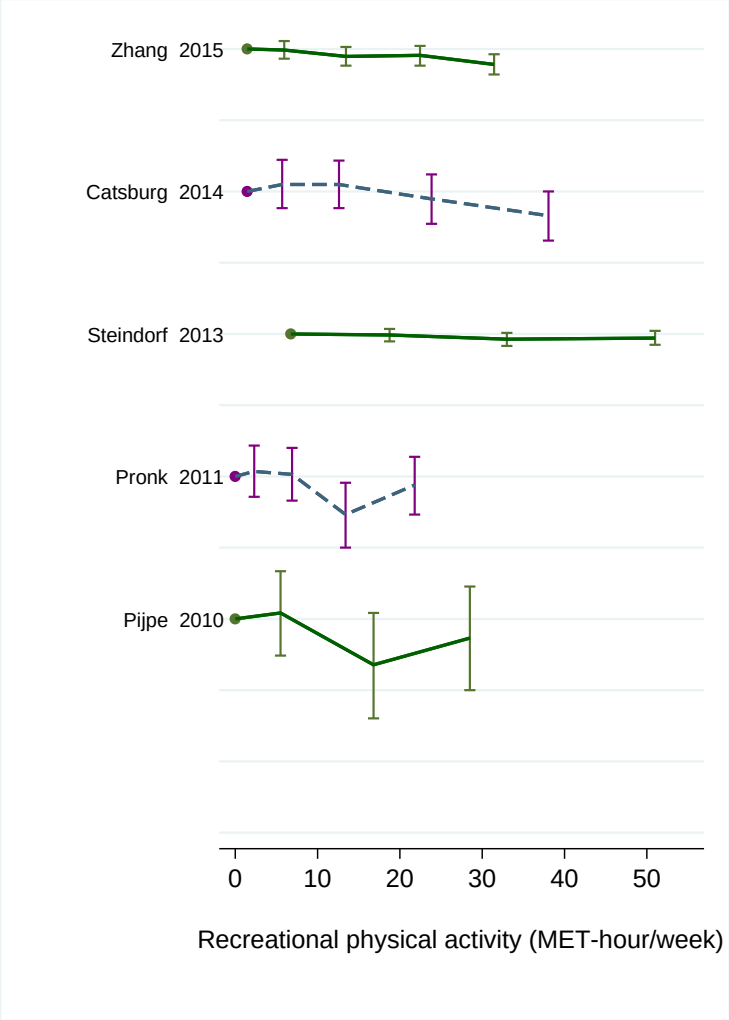


Figure 494 RR (95% CI) of breast cancer for the highest compared with the lowest level of recreational physical activity

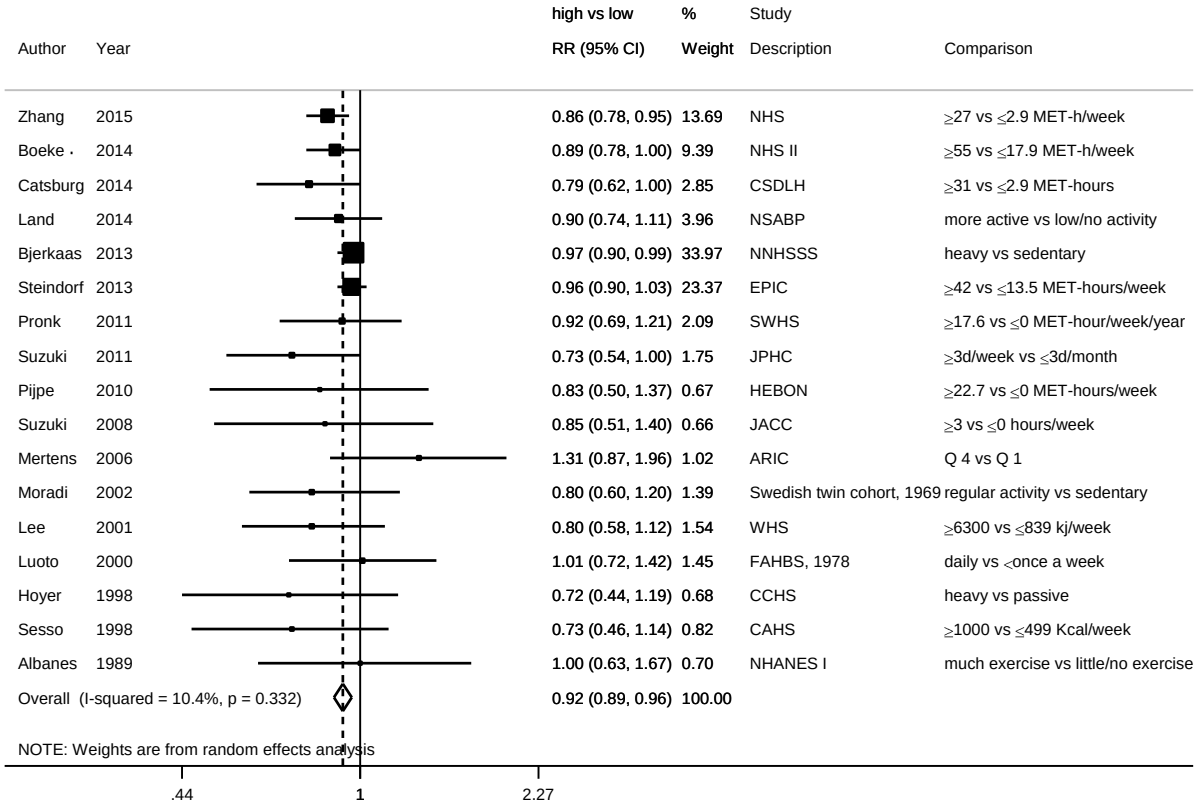


Figure 495 Relative risk of breast cancer for 10 MET-hour/week increase of recreational physical activity

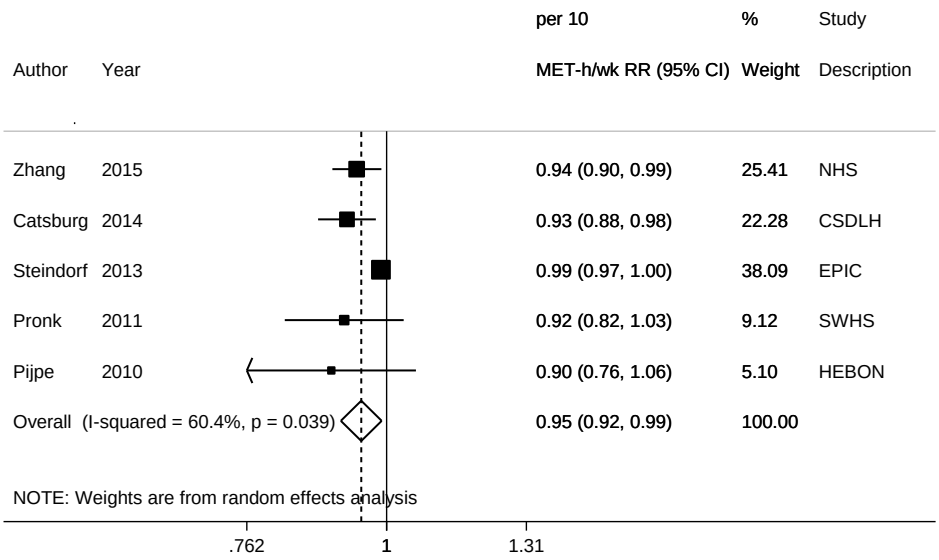


Figure 496 Funnel plot of studies included in the dose response meta-analysis of recreational physical activity and breast cancer

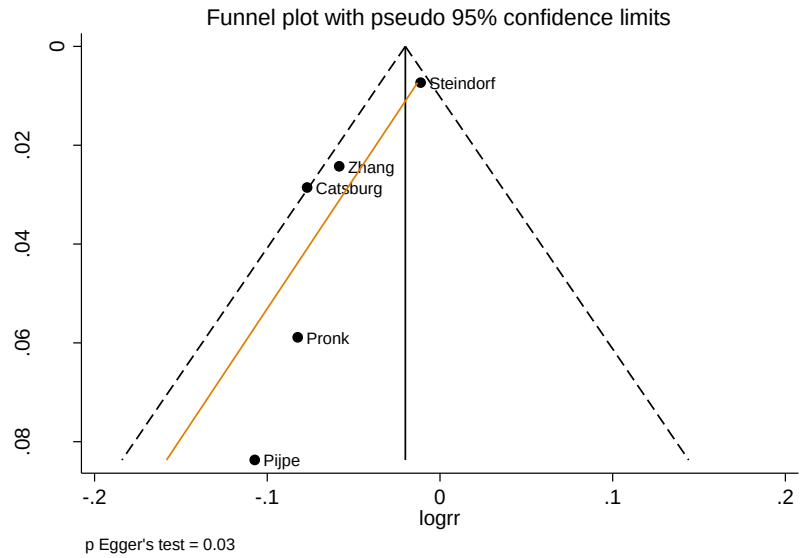
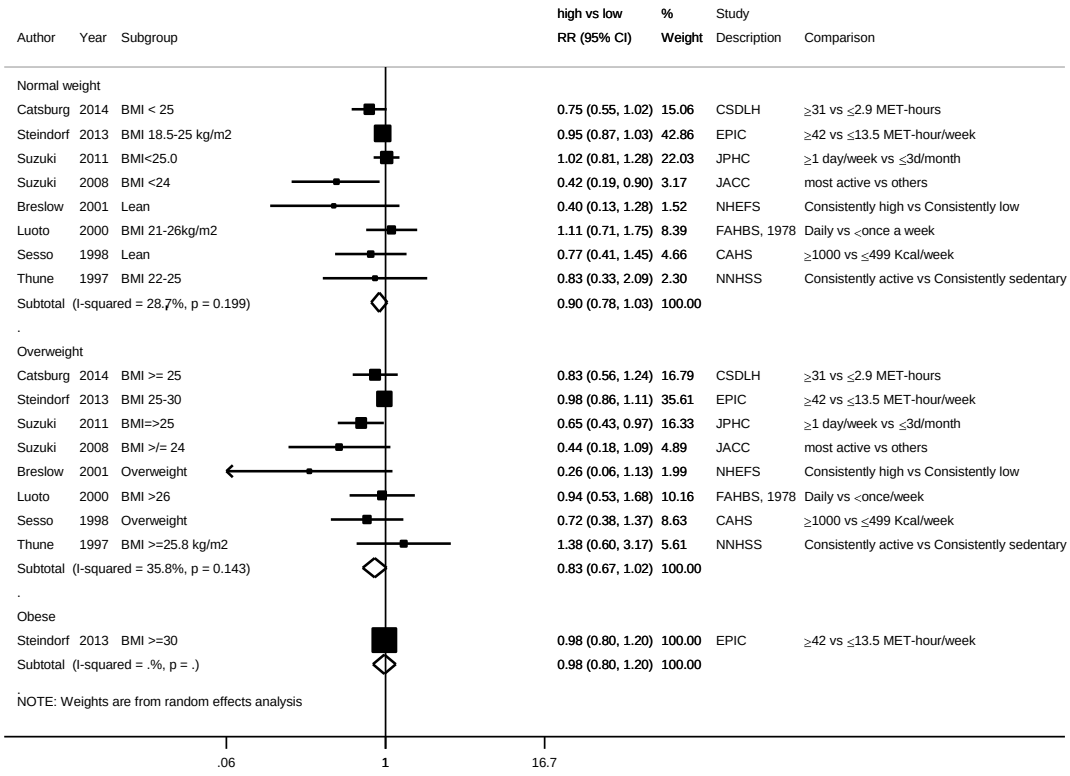


Figure 497 RR (95% CI) of breast cancer for the highest compared with the lowest level of recreational physical activity, by BMI category



Premenopausal breast cancer

Summary

Main results:

Out of 12 studies (15 publications) identified three studies (cases) and 10 studies (cases) could be included in the dose-response and the highest versus lowest meta-analysis, respectively. Recreational physical activity was non-significantly inversely associated with premenopausal breast cancer risk. Summary RR per 10 MET-hour/week was 0.96 (95% CI=0.90-1.03), and for highest vs lowest activity level, 0.93 (95% CI=0.74-1.16). High heterogeneity was observed between studies included in the dose-response analysis (69%, P=0.04), but not in the highest versus the lowest analysis (59%, P=0.01).

One cohort consisted of athletes only was excluded (Wyshak, 2000). Another excluded study (Breslow, 2001) was a follow-up study of a larger study (Albanes, 1989) included in the analysis.

Non-significant results for the highest versus the lowest activity level and premenopausal breast cancer were reported among normal weight, overweight, and obese women in one study identified after 2008 (Steindorf, 2013, EPIC).

The JPHC (Suzuki, 2011a) reported non-significant inverse associations with joint hormone receptor subtypes.

Sensitivity analyses:

Summary RR did not change materially in influence analysis.

Non-linear dose-response meta-analysis:

Non-linear dose-response meta-analysis was no conducted due to insufficient data.

Study quality:

Studies were from Asia, Europe, and North America. All studies reported assessment of recreational physical activity by questionnaire, which was validated in six recent studies (Catsburg, 2014b; Steindorf, 2013; Suzuki, 2011a; Suzuki, 2008c; Colditz, 2003; Thune, 1997). Case ascertainment was through cancer registries or confirmed through medical records. Six studies (Catsburg, 2014b; Steindorf, 2013; Suzuki, 2011a; Suzuki, 2008c; Margolis, 2005; Colditz, 2003) were adjusted for age, BMI, alcohol intake, and reproductive factors while four earlier studies (Luoto, 2000; Sesso, 1998; Thune, 1997; Albanes, 1989) did not.

Table 463 Recreational physical activity and premenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	12 (15 publications)
Studies included in forest plot of highest compared with lowest exposure	10
Studies included in linear dose-response meta-analysis	3
Studies included in non-linear dose-response meta-analysis	Not enough studies

Note: Include cohort and nested case-control designs.

Table 464 Recreational physical activity and premenopausal breast cancer risk. Summary of the dose-response and the highest versus the lowest meta-analysis in the CUP SLR[1]

	CUP	**CUP**
Increment unit used/comparison	Per 10 MET-hour/week	Highest versus lowest
Studies (n)	3	10
Cases	2 331	>3 901
RR (95%CI)	0.96 (0.90-1.03)	0.93 (0.74-1.16)
Heterogeneity (I^2, p-value)	69%, 0.04	59%, 0.01
P value Egger test	-	-

[1]Meta-analysis was not conducted in the 2005 SLR.

Table 465 Recreational physical activity and premenopausal breast cancer risk. Main characteristics of studies included in the dose-response and the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Catsburg, 2014b BRE80529 Canada	CSDLH, Case Cohort, W, alumnae	546/ 4 417 15 years	Cancer registry	Questionnaire	Incidence, Invasive breast cancer, premenopausal	≥31 vs ≤2.9 met-hours	0.62 (0.43-0.90)	Age at first child birth, age at menarche, alcohol Intake, BMI, family history of breast cancer, HRT use, menopausal status, number of childbirths, OC use
						≥7.6 vs ≤0.9 hours	0.62 (0.44-0.89)	
		540/			Premenopausal	≥7 vs ≤0.9 times	0.38 (0.14-1.01)	
Steindorf, 2013 BRE80425 Denmark,France, Germany,Greece, Italy,Netherlands, Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	936/ 257 805 11.6 years	Cancer registry	Questionnaire/interview	Incidence, Invasive breast cancer, age at diagnosis <=50yrs	≥42 vs ≤13.5 met-hours/week	0.88 (0.72-1.07)	Age, age at first child, age at menarche, age at menopause, alcohol, BMI, breastfeeding, centre location, educational level, household physical activity, HRT use, menopausal status, number of full-term pregnancies, occupational activity, oral contraceptive history, smoking, total physical activity
		683/			Normal BMI, age<=50y	≥42 vs ≤13.5 met-hour/week	0.85 (0.68-1.06)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		193/			Overweight, age<=50y	≥42 vs ≤13.5 met-hour/week	0.97 (0.61-1.54)	
		60/			Obese, age<=50y	≥42 vs ≤13.5 met-hour/week	1.11 (0.50-2.44)	
Suzuki, 2011a BRE80307 Japan	JPHC, Prospective Cohort, Age: 40-69 years, W, women	240/ 53 578 14.5 years	Cancer registry	Questionnaire/interview	Incidence, breast cancer, premenopausal	≥3d/week vs ≤3d/month	0.66 (0.40-1.09)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, area, energy-adjusted Intake of isoflavones, height, HRT use, parity, physical activity, smoking
		125/			Incidence, breast cancer unknown ER/PR status, premenopausal	≥3days/week vs ≤3d/month	0.51 (0.23-1.10)	BMI, BMI
		55/			Incidence, breast cancer ER+/PR+, premenopausal	≥3d/week vs ≤3d/month	0.64 (0.23-1.78)	
		25/			Incidence, breast cancer ER+/PR-, premenopausal	≥3d/week vs ≤3d/month	0.90 (0.20-3.94)	
						≥1day/week vs ≤3d/month	0.55 (0.16-1.86)	
Suzuki, 2008c BRE80201 Japan	JACC, Prospective Cohort, Age: 40-69 years, W	30 157 12.4 years	Cancer registry	Self-administered questionnaire	Incidence, breast cancer, premenopausal	most active vs others	0.13 (0.02-0.91)	Age, age at first child birth, age at menarche, alcohol Intake, BMI, educational level,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								family history of cancer, hormone use, parity
Margolis, 2005 BRE23306 Norway, Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W, Young women	1 158/ 99 504 9.1 years	Partially histological - over 80%	Questionnaire	Incidence, Invasive breast cancer,	vigorous vs none	1.24 (0.85-1.82)	Age , age at first child, age at menarche, alcohol, BMI, country of birth, duration of breastfeeding, educational level, family history, height, menopausal status, oc use, parity/pregnancies, smoking habits
		1 155/				vigorous vs none	1.05 (0.72-1.54)	
						vigorous vs none	1.20 (0.77-1.95)	
		1 150/				active-no change vs inactive-no change	1.10 (0.81-1.49)	
		1 148/				active-no change vs inactive-no change	0.98 (0.78-1.22)	
		1 147/				active-no change vs inactive-no change	1.20 (0.85-1.71)	
Colditz, 2003 BRE01782 USA	NHS II, Prospective Cohort,	849/ 110 468 10 years	Medical records + self-reported	Questionnaire, recreational physical activity	Incidence, Invasive breast cancer,	≥27 vs ≤2.9 met-hour/week	1.04 (0.82-1.33)	Age , age at first child, age at menarche, alcohol,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Age: 25-42 years, W, Registered nurses			at study baseline	premenopausal			benign breast disease, BMI, family history, height, OC use
		524/			Premenopausal and lean	≥27 vs ≤2.9 met-hour/week	1.04 (0.72-1.36)	Parity/ pregnancies
		134/			Premenopausal and overweight	≥27 vs ≤2.9 met-hour/week	1.53 (0.89-2.63)	
Luoto, 2000 BRE80174 Finland	FAHBS, 1978, Prospective Cohort, Age: 15-64 years, W	30 548 0	Cancer registry	Questionnaire	Incidence, breast cancer, age < 50 years	daily vs <one/week	1.25 (0.70-1.22)	
Sesso, 1998 BRE16626 USA	CAHS, Prospective Cohort, Age: 37-69 years, College alumnae	28/ 2 387 31 years	Medical records + self-reported +death certificate	Questionnaire	Incidence, breast cancer, premenopausal	≥1000 vs ≤499 kcal/week	1.83 (0.77-4.31)	Age , BMI
Thune, 1997 BRE12313 Norway	Norway National Health Screening Service – three counties, 1974, Prospective Cohort, Age: 20-49 years, W	98/ 25 624 13.7 years	All histology	Questionnaire	Incidence, breast cancer, premenopausal	regular exercise vs sedentary	0.53 (0.25-1.14)	Age , BMI, height, parity/pregnancies, place of residence
Albanes, 1989 BRE00236 USA	NHANES I, Prospective Cohort, Age: 25-74 years, W	7 413 10 years	Medical records + death certificate	Interview	Incidence, breast cancer, premenopausal	little/no exercise vs moderate exercise	0.60 (0.30-1.20)	Age

Table 466 Recreational physical activity and premenopausal breast cancer risk. Main characteristics of studies excluded from the dose-response and the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Steindorf, 2012 BRE80432 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	138/ 283 827 11.7 years	Cancer registry	Questionnaire/interview	Incidence, In situ breast cancer, age at diagnosis <=50yrs	≥42 vs ≤12 met-hour/week	0.81 (0.51-1.31)	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, breastfeeding, centre location, educational level, household physical activity, HRT use, menopausal status, number of full-term pregnancies, occupational physical activity, oral contraceptive history, smoking, total physical activity	Excluded, breast cancer in situ, not enough studies to analyse (Results on breast cancer incidence from the same study (Steindorf, 2013) was included in the analysis)
Maruti, 2008b BRE80219 USA	NHS II, Prospective Cohort, Age: 33-51 years, W, Premenopausal	550/ 64 777 6 years	Self-report verified by medical record	Self-completed questionnaire, long-term/lifetime recreational physical activity	Incidence, Invasive breast cancer, premenopausal	≥54 vs ≤19.9 met-h/week	0.77 (0.59-1.01)	Age, age at first child birth, alcohol Intake, benign breast disease, body shape, family history of cancer, height,	Excluded, lifetime physical activity (Baseline data was included in the analysis from the same

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								OC use, parity	study (Colditz, 2003,BRE01782))
						per 21 met-hours/week	0.91 (P=0.04)		
		319/			Premenopausal, BMI<25	≥54 vs ≤19.9 met-h/week	0.68 (0.48-0.98)		
		230/			Premenopausal, BMI>=25	≥54 vs ≤19.9 met-h/week	0.85 (0.56-1.30)		
		242/			Incidence, Invasive breast cancer, premenopausal	high youth/high adulthood vs low youth/low adulthood	0.70 (0.53-0.93)		
Lahmann, 2007 BRE20026 Denmark, France, Germany, Greece, Italy, Netherlands, Spain, Sweden, UK	EPIC, Prospective Cohort, Age: 20-80 years, W	856/ 218 169 6.4 years	Population cancer registries and other procedures	Questionnaire	Incidence, Invasive breast cancer, premenopause	≥43 vs ≤13 met-hour/week	0.94 (0.76-1.15)	Age , age at first child, age at menarche, alcohol, BMI, educational level, OC use, smoking habits, study centre	Superseded by Steindorf, 2013
						≥43 vs ≤13 met-hour/week	0.95 (0.77-1.16)		
Breslow, 2001 BRE01123 USA	NHEFS, Prospective Cohort, Age: 24-75 years, W	42/ 6 160 9.2 years	Medical records + self-reported	Questionnaire	Incidence, breast cancer, premenopausal	consistently high vs consistently low	1.19 (0.43-3.30)	Age , BMI, body weight, ethnicity, height, Income, socio-economic status	Superseded by Albanes, 1989 (NHEFS part of NHANES I)
Wyshak, 2000	USA, 1981,	12/	Not specified	Questionnaire	Incidence, breast	athletes vs non-	0.16 (0.04-0.64)	Age , family	Excluded,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
BRE13666 USA	Prospective Cohort, Age: 21-80 years, W, College alumnae	3 940 15 years			cancer, premenopausal	athletes		history, HRT use, OC use, other anthropometric Index, other specified factor, parous/nulliparous, smoking habits	cohort of athletes

Figure 498 RR estimates of premenopausal breast cancer by levels of recreational physical activity

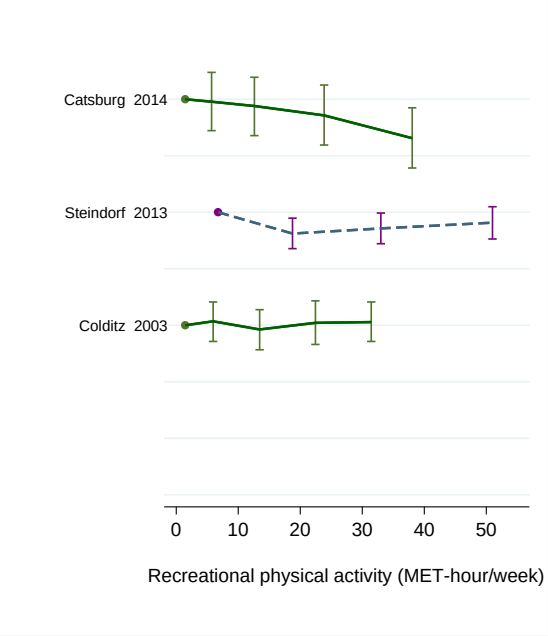


Figure 499 RR (95% CI) of premenopausal breast cancer for the highest compared with the lowest level of recreational physical activity

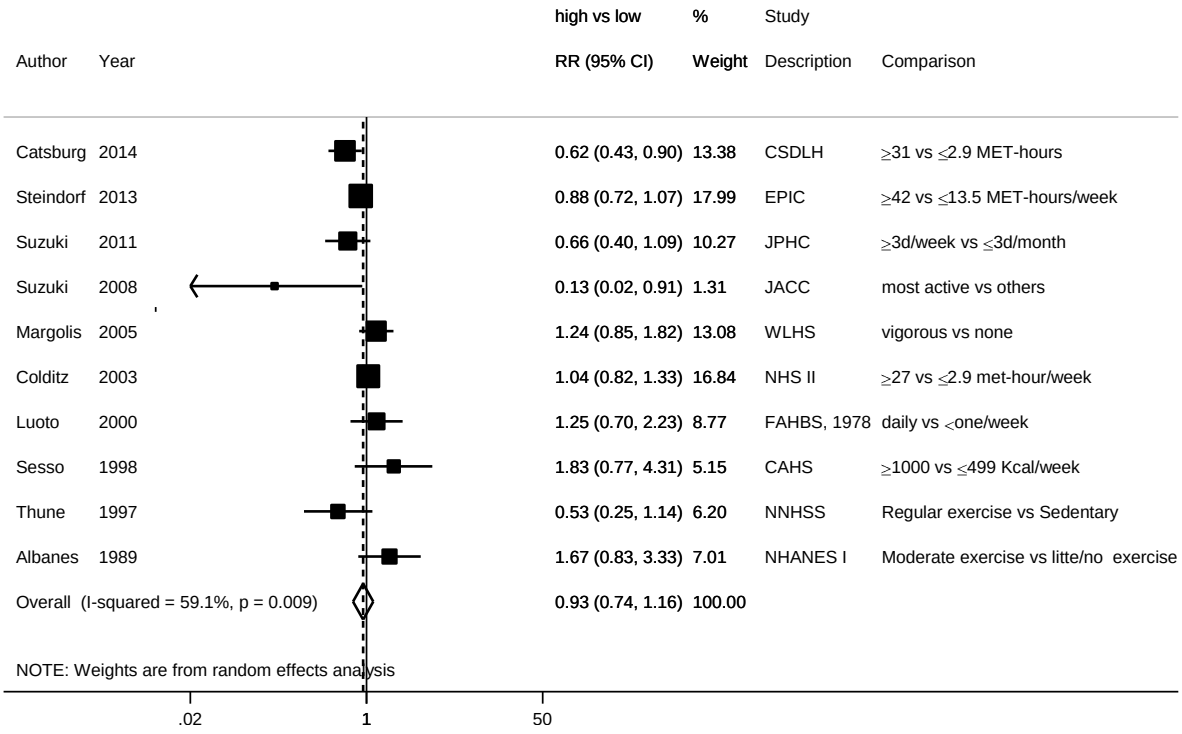
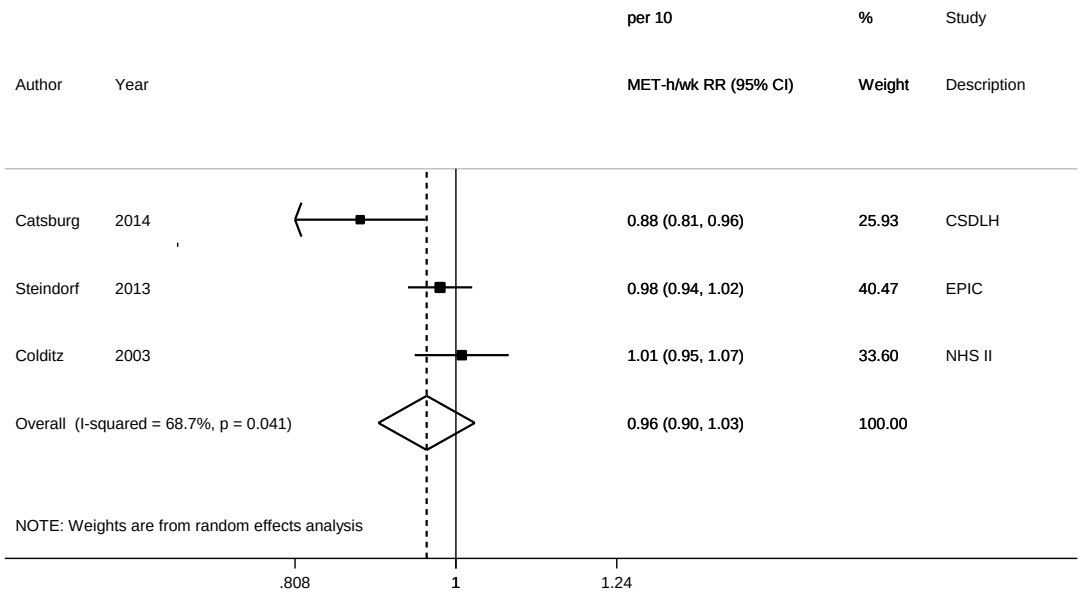


Figure 500 Relative risk of premenopausal breast cancer for 10 MET-hour/week increase of recreational physical activity



Postmenopausal breast cancer

Summary

Main results:

Out of 22 studies (30 publications) identified, five studies (18 486 cases) and 17 studies (>24 253 cases) could be included in the dose-response and the highest versus lowest meta-analysis, respectively. Recreational physical activity was significantly inversely associated with postmenopausal breast cancer risk. Summary RR per 10 MET-hour/week was 0.98 (95% CI=0.97-0.99, I^2=0%, P=0.68) and for highest vs lowest activity level, 0.87 (95% CI=0.81-0.94, I^2=37%, P=0.06).

There was evidence of publication or small study bias (P for Egger's test = 0.12 and 0.01 for studies in the dose-response and the highest versus the lowest analysis, respectively). Funnel plots showed asymmetry as more small studies reported inverse associations (funnel plot of studies included in the highest versus lowest analysis not shown).

Five studies (nine publications) overlapped with the studies included in the highest versus the lowest meta-analysis were excluded (E3N – Fournier, 2014; WHI – Phipps, 2011; Kabat, 2010; Chlebowski, 2007; MDCS – Ericson, 2009; Ericson, 2007; Wirfalt, 2005; CCHS – Rod, 2009; NHEFS – Breslow, 2001).

Non-significant results for the highest versus the lowest activity level and postmenopausal breast cancer were reported among normal weight, overweight, and obese women in one study identified after 2008 (Steindorf, 2013).

Five studies (six publications) reported results by hormone receptor subtypes. Meta-analysis was not conducted as number of study was small for each type. Results were display in a highest versus lowest forest plot. Studies reported non-significant inverse or positive associations. JPHC (Suzuki, 2011a) reported RR of 0.25 (95% CI=0.06-1.06) for ER+PR+, 1.07 (95% CI=0.41-2.82) for ER-PR-, and 3.12 (95% CI=1.15-8.50) for ER+PR- breast cancers.

Sensitivity analyses:

EPIC (Steindorf, 2013) contributed 52% weight in the analysis. Summary RR per 10 MET-hour/week remained borderline significance when studies were omitted in turn in influence analysis. Studies included in the dose-response analysis were not further stratified due to low number of studies in the strata.

Non-linear dose-response meta-analysis:

There was evidence of non-linear relationship (P non-linearity=0.05). The decreased risk was more pronounced after 25 MET-hour/ week.

Study quality:

Studies were from Asia, Europe, and North America. Lee, 2011 was based in a clinical trial of aspirin and vitamin E (WHS). All studies reported assessment of recreational physical activity by questionnaire, which was validated in seven studies (Catsburg, 2014b; Steindorf, 2013; Suzuki, 2011a; Eliassen, 2010; Suzuki, 2008c; McTiernan, 2003; Thune, 1997). Case ascertainment was through cancer registries or confirmed through medical records. Seven, mostly older studies, did not adjust for age, BMI, alcohol intake, and reproductive factors (Chang, 2006; Mertens, 2006; Dirx, 2001; Luoto, 2000; Sesso, 1998; Thune, 1997; Albanes, 1989).

Table 467 Recreational physical activity and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	22 (30 publications)
Studies included in forest plot of highest compared with lowest exposure	17
Studies included in linear dose-response meta-analysis	5
Studies included in non-linear dose-response meta-analysis	5

Note: Include cohort and nested case-control designs.

Table 468 Recreational physical activity and postmenopausal breast cancer risk. Summary of the dose-response and the highest versus the lowest meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR[1]	CUP
Increment unit used	Per 7 MET-hour/week	Per 10 MET-hour/week
Studies (n)	3	5
Cases	4 212	18 486
RR (95%CI)	0.97 (0.95-0.99)	0.98 (0.97-0.99)
Heterogeneity (I^2, p-value)	0%	0%, 0.68
P value Egger test	-	0.12
Comparison	-	Highest versus lowest
Studies (n)	-	17
Cases	-	>24 253
RR (95%CI)	-	0.87 (0.81-0.94)
Heterogeneity (I^2, p-value)	-	37%, 0.06
P value Egger test	-	0.01

[1]Dose-response meta-analyses of two studies (McTiernan, 2003; Dirx, 2001) that reported on lean and overweight women were conducted in 2005, summary RR per 7 MET-hr/wk=0.96 (95% CI=0.93-0.99) and 0.97 (95% CI=0.93-1.00), respectively. One study (Steindorf, 2013) were identified after 2008 and reported RRs for highest vs lowest level=0.97 (95% CI=0.88-1.06) in normal weight, 0.98 (95% CI=0.86-1.12) in overweight, and 0.97 (95% CI=0.79-1.20) in obese women.

Table 469 Recreational physical activity and postmenopausal breast cancer risk. Main characteristics of studies included in the dose-response and the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Catsburg, 2014b BRE80529 Canada	CSDLH, Case Cohort, W, alumnae	724/ 4 417 15 years	Cancer registry	Questionnaire	Incidence, Invasive breast cancer, HRT never	≥31 vs ≤2.9 met-hours	0.71 (0.53-0.95)	Age at first child birth, age at menarche, alcohol Intake, BMI, family history of breast cancer, menopausal status, number of childbirths, oc use
						≥7.6 vs ≤0.9 hours	0.73 (0.55-0.97)	
		528/			Postmenopausal	≥7.6 vs ≤0.9 hours	0.91 (0.66-1.25)	HRT use
						≥31 vs ≤2.9 met-hours	0.96 (0.69-1.32)	
		507/			Postmenopausal	≥7 vs ≤0.9 times	1.27 (0.69-2.34)	
		329/			HRT ever	≥7.6 vs ≤0.9 hours	0.83 (0.55-1.26)	
						≥31 vs ≤2.9 met-hours	0.93 (0.61-1.42)	
Hildebrand, 2013 BRE80490 USA	CPS II, Prospective Cohort, Age: 50-74 years, W, Postmenopausal	4 760/ 73 615 14.2 years	Self-report verified by medical record	Questionnaire	Incidence, breast cancer	≥42.1 vs 0.1-7 met-hours/week	0.75 (0.63-0.89)	Age, age at first child birth, age at menopause, alcohol, BMI, breast diseases , educational level, family history of breast cancer, HRT use, mammography, number of childbirths, oophorectomy/hysterectomy, race, smoking status, weight change

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Steindorf, 2013 BRE80425 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	7 098/ 257 805 11.6 years	Cancer registry	Questionnaire/interview	Incidence, Invasive breast cancer, age at diagnosis >50yrs	≥42 vs ≤13.5 met-hours/week	0.97 (0.91-1.05)	Age, age at first child, age at menarche, age at menopause, alcohol, BMI, breastfeeding, centre location, educational level, household physical activity, HRT use, menopausal status, number of full-term pregnancies, occupational activity, oral contraceptive history, smoking, total physical activity
		4 063/			Normal BMI, age>50y	≥42 vs ≤13.5 met-hour/week	0.97 (0.88-1.06)	
		2 155/			Overweight, age>50y	≥42 vs ≤13.5 met-hour/week	0.98 (0.86-1.12)	
		880/			Obese, age>50y	≥42 vs ≤13.5 met-hour/week	0.97 (0.79-1.20)	
Suzuki, 2011a BRE80307 Japan	JPHC, Prospective Cohort, Age: 40-69 years, W, women	239/ 53 578 14.5 years	Cancer registry	Questionnaire/interview	Incidence, breast cancer, postmenopausal	≥3d/week vs ≤3d/month	0.78 (0.52-1.17)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, area, BMI, energy-adjusted Intake of Isoflavones, height, HRT use, parity, physical activity, smoking
		135/			Incidence, breast cancer unknown ER/PR status, postmenopausal	≥3days/week vs ≤3d/month	0.72 (0.41-1.24)	
		46/			Incidence, breast cancer ER+/PR+,	≥3d/week vs ≤3d/month	0.25 (0.06-1.06)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					postmenopausal			
		36/			Incidence, breast cancer ER-/PR-, postmenopausal	≥3days/week vs ≤3d/month	1.07 (0.41-2.82)	
		21/			Incidence, breast cancer ER+/PR-, postmenopausal	≥3d/week vs ≤3d/month	3.12 (1.15-8.50)	
Eliassen, 2010 BRE80311 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Postmenopausal	4 782/ 95 396 20 years	Questionnaire	Self-report	Incidence, postmenopausal breast cancer	≥27 vs <3 met-hour/week	0.88 (0.79-0.98)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, BMI, family history of breast cancer, height, history of breast disease, HRT use, parity
						≥27 vs <3 met-hour/week	0.85 (0.78-0.93)	
						per 20 met-hours/week	0.96 (0.91-1.02)	
						per 20 met-hours/week	0.90 (0.85-0.95)	
						per 20 met-hours/week	0.92 (0.87-0.97)	
		4 332/				≥27 vs <3 met-hour/week	0.91 (0.83-1.01)	
Suzuki, 2008c BRE80201 Japan	JACC, Prospective Cohort, Age: 40-69 years, W	30 157 12.4 years	Cancer registry	Self-administered questionnaire	Incidence, breast cancer, postmenopausal	most active vs others	0.53 (0.29-0.96)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, BMI, educational level, family history of cancer, hormone use, menopausal

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								status, parity
Bardia, 2007 BRE20028 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	2 548/ 41 836 18 years	State health registry	Questionnaire	Incidence, breast cancer,	high vs low	0.91 (0.82-1.01)	Age , age at first child, age at menarche, age at menopause, alcohol, BMI, BMI, educational level, family history, HRT use, OC use, parity/pregnancies, smoking habits
		1 643/			Incidence, breast cancer ER+,	high vs low	0.87 (0.77-1.00)	
		1 366/			Incidence, breast cancer PR+,	high vs low	0.95 (0.82-1.09)	
		1 323/			Incidence, breast cancer ER+/PR+,	high vs low	0.94 (0.81-1.08)	
		687/			Incidence, breast cancer unknown ER/PR status, unknown ER/PR status	high vs low	0.96 (0.79-1.18)	
		497/			Incidence, breast cancer PR-,	high vs low	0.73 (0.65-0.94)	
		298/			Incidence, breast cancer ER-,	high vs low	0.92 (0.67-1.25)	
		252/			Incidence, breast cancer ER+/PR-,	high vs low	0.66 (0.46-0.94)	
		244/			Incidence, breast cancer ER-/PR-,	high vs low	0.80 (0.56-1.15)	
		42/			Incidence, breast	high vs low	1.42 (0.67-3.01)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					cancer ER-/PR+,			
Chang, 2006 BRE80110 USA	PLCO, Prospective Cohort, Age: 55-74 years, W, participants of a RCT	764/ 38 660 4.9 years	Cancer screening programme		Incidence, breast cancer, postmenopausal	≥4 vs ≤0 hours/week	0.81 (0.63-1.05)	Age at first child, age at menarche, age at menopause, benign breast disease, BMI, educational level, energy Intake , ethnicity, family history, height, HRT use, parity/pregnancies, recruitment center
						≥4 vs ≤0 hours/week	0.78 (0.61-0.99)	
Mertens, 2006 BRE23405 USA	ARIC, Prospective Cohort, Age: 45-64 years, W	7 994 13.1 years	Partially histological - over 80%	Questionnaire	Incidence, breast cancer, postmenopausal	Q 4 vs Q 1	1.06 (0.64-1.74)	Age , age at first child, age at menopause, ethnicity, family history, recruitment center
						Q 4 vs Q 1	1.22 (0.77-1.93)	
Schnohr, 2005 BRE24028 Denmark	CCPPS, Prospective Cohort, Age: 20-91 years, W, Previous study	13 216 14 years	Partially histological - over 80%	Questionnaire	Incidence, breast cancer, postmenopausal	vigorous vs low	1.12 (0.83-1.53)	Age , alcohol, birth cohort, BMI, educational level, other design Issue, parity/pregnancies, smoking habits, work - physical activity
McTiernan, 2003 BRE17819 USA	Women's Health Initiative - Observational study, Prospective Cohort, Age: 50-79	1 768/ 74 171 4.7 years	Medical record + pathology report + family report	Questionnaire	Incidence, Invasive & In situ breast cancer, postmenopausal	≥40.1 vs ≤0 met-hour/week	0.78 (0.62-1.00)	Age , age at first child, age at menarche, age at menopause, alcohol, BMI, breastfeeding, educational level, ethnicity, family history, HRT use, Income, mammography,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	years, W, Postmenopausal							oophorectomy/hysterectomy, parity/pregnancies, place of residence, smoking habits
		615/			Postmenopausal and lean	≥40.1 vs ≤0 met-hour/week	0.63 (0.43-0.93)	
		573/			Postmenopausal and overweight	≥40.1 vs ≤0 met-hour/week	0.94 (0.57-1.60)	
Dirx, 2001 BRE02326 Netherlands	NLCS, Case Cohort, Age: 55-69 years, W, Postmenopausal	943/ 62 573 7.3 years	Not specified	Questionnaire	Incidence, breast cancer, postmenopausal	≥2.1 vs ≤0 hours/week	0.98 (0.68-1.42)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, body weight, educational level, energy Intake , family history, parity/pregnancies
		941/			Postmenopausal	≥91 vs ≤29 min/day	0.76 (0.58-0.99)	
		488/			Incidence, postmenopausal breast cancer, normal weight	≥91 vs ≤29 min/day	0.74 (0.52-1.08)	
		445/			Incidence, breast cancer, postmenopausal	≥5 vs ≤0.9 hours/week	0.87 (0.57-1.32)	
		426/			Postmenopausal	>40 vs 1-10 years/life	0.99 (0.58-1.67)	
		367/			Incidence, postmenopausal breast cancer, overweight	≥91 vs ≤29 min/day	0.67 (0.42-1.08)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		84/			Obese	≥91 vs ≤29 min/day	0.94 (0.27-3.32)	
Lee, 2001 BRE15848 USA, Puerto Rico	WHS, Prospective Cohort, Age: 45- years, W, Registered nurses	261/ 39 322 48 months	Medical records + self-reported +death certificate	Questionnaire	Incidence, Invasive & In situ breast cancer, postmenopausal	≥6300 vs ≤839 kj/week	0.67 (0.44-1.02)	Age at first child, age at menarche, alcohol, BMI, family history, HRT use, menopausal status, OC use, parity/pregnancies
		157/			Incidence, breast cancer ER+/PR+, postmenopausal	≥6300 vs ≤839 kj/week	0.76 (0.43-1.34)	
Luoto, 2000 BRE80174 Finland	FAHBS, 1978, Prospective Cohort, Age: 15-64 years, W	30 548 0	Cancer registry	Questionnaire	Incidence, breast cancer, age >= 50 years	daily vs <one/week	0.97 (0.65-1.44)	
Sesso, 1998 BRE16626 USA	CAHS, Prospective Cohort, Age: 37-69 years, College alumnae	81/ 2 387 31 years	Medical records + self-reported +death certificate	Questionnaire	Incidence, breast cancer, postmenopausal	≥1000 vs ≤499 kcal/week	0.49 (0.28-0.86)	Age , BMI
Thune, 1997 BRE12313 Norway	Norway National Health Screening Service – three counties, 1974, Prospective Cohort, Age: 20-49 years,	248/ 25 624 13.7 years	All histology	Questionnaire	Incidence, breast cancer, postmenopausal	regular exercise vs sedentary	0.67 (0.41-1.10)	Age , BMI, height, parity/pregnancies, place of residence

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	W							
Albanes, 1989 BRE00236 USA	NHANES I, Prospective Cohort, Age: 25-74 years, W	7 413 10 years	Medical records + death certificate	Interview	Incidence, breast cancer, postmenopausal	litte/no exercise vs moderate exercise	1.70 (0.80-2.90)	Age

Table 470 Recreational physical activity and postmenopausal breast cancer risk. Main characteristics of studies excluded from the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Fournier, 2014 BRE80532 France	E3N EPIC-France, Prospective Cohort, W, Postmenopausal	2 097/ 59 308 8.5 years	Self-report, next of kin, death registry		Incidence, Invasive breast cancer, postmenopausal	≥12 vs <12 met-h/week	1.04 (0.92-1.18)	Age at first child birth, age at menarche, age at menopause, age-underlying cox models, alcohol Intake, BMI, family history of breast cancer In first degree relatives, history of benign breast disease, menopausal oestrogen use, parity,	Superseded by Steindorf, 2013, BRE80425

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								recreational activity, total energy Intake, year of birth	
						≥36 vs ≤11.9 met-h/week	0.93 (0.83-1.05)		
		1 584/			BMI < 25	≥12 vs <12 met-h/week	0.88 (0.78-0.98)		
		1 337/			Incidence, breast cancer ER+, postmenopausal	≥12 vs <12 met-h/week	0.89 (0.79-1.01)		
		1 008/			Incidence, breast cancer PR+, postmenopausal	≥12 vs <12 met-h/week	0.88 (0.77-1.02)		
		959/			Incidence, breast cancer ER+/PR+, postmenopausal	≥12 vs <12 met-h/week	0.90 (0.78-1.05)		
		644/			Incidence, breast cancer PR-, postmenopausal	≥12 vs <12 met-h/week	0.92 (0.77-1.10)		
		513/			Incidence, Invasive breast cancer, BMI >=25	≥12 vs <12 met-h/week	0.96 (0.80-1.16)		
		378/			Incidence, breast cancer ER+/PR-, postmenopausal	≥12 vs <12 met-h/week	0.87 (0.69-1.10)		
		315/			Incidence, breast cancer ER-,	≥12 vs <12 met-h/week	0.92 (0.71-1.19)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					postmenopausal				
		266/			Incidence, breast cancer ER-/PR-, postmenopausal	≥12 vs <12 met-h/week	1.00 (0.75-1.33)		
		49/			Incidence, breast cancer ER-/PR+, postmenopausal	≥12 vs <12 met-h/week	0.62 (0.34-1.13)		
					Incidence, Invasive breast cancer, postmenopausal	active to less active vs inactive at both times	1.06 (0.87-1.29)		
Steindorf, 2012 BRE80432 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	921/ 283 827 11.7 years	Cancer registry	Questionnaire/interview	Incidence, In situ breast cancer, age at diagnosis >50yrs	≥42 vs ≤12 met-hour/week	1.01 (0.82-1.23)	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, breastfeeding, centre location, educational level, household physical activity, HRT use, menopausal status, number of full-term pregnancies, occupational physical activity, oral contraceptive history,	Excluded, breast cancer in situ, not enough studies to analysis (Results on breast cancer incidence from the same study (Steindorf, 2013) were included in the analysis)

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								smoking, total physical activity	
Phipps, 2011 BRE80343 USA	Women's Health Initiative, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	2 761/ 155 723 7.9 years	Mail or telephone questionnaires verified by trained physician adjudicators	Questionnaire	Incidence, breast cancer ER+	≥16.5 vs ≤0	0.85 (0.74-0.98)	Age, educational level, family history of breast cancer, Income, mammography, mammography, race	Excluded, breast cancer subtype, not enough studies to analyse (Overlapped with WHI-OS (Mc Tiernan, 2003 that was included in the analysis)
		296/			Incidence, triple negative breast cancer	≥16.5 vs ≤0	0.77 (0.51-1.13)		
Kabat, 2010 BRE80312 USA	Women's Health Initiative, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	450/ 58 8 years	Pathology and medical record	Questionnaire	Incidence, ductal In situ breast cancer	≥20 vs none met-hours/week/met-hour/week	0.97 (0.70-1.34)	Age, age at first child birth, age at menarche, age at menopause, BMI, breast biopsies, educational level, ethnicity, family history of breast cancer, HRT use, mammogram In the past 2 years, oral contraceptive history,	Excluded, breast cancer subtype, not enough studies to analyse (Overlapped with WHI-OS (Mc Tiernan, 2003 that was included in the analysis)

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								randomisation, smoking, waist circumference	
		343/			Incidence, low grade ductal carcinoma In situ (DCIS)	≥20 vs none met-hours/week/met-hour/week	0.88 (0.61-1.27)		
		112/			Incidence, high grade ductal carcinoma In situ (DCIS)	≥20 vs none met-hours/week/met-hour/week	1.21 (0.62-2.36)		
Ericson, 2009 BRE80304 Sweden	MDCS, Nested Case Control, Age: 45-73 years, W, Postmenopausal	540/ 1079 controls 13 years	Cancer registry		Incidence, Invasive breast cancer	high vs low	0.96 (0.74-1.24)	Age, laboratory batch	Superseded by Steindorf, 2013
Rod, 2009 BRE80270 Denmark	CCHS, Prospective Cohort, Age: 62 years, W, Postmenopausal	263/ 5 054 20 years	Cancer registry	Self-completed questionnaire	Incidence, breast cancer	high vs none	1.49 (0.53-4.18)	Age, alcohol consumption, BMI, educational level, height, marital status, parity, physical activity, postmenopausal hormone use, psychological distress	Superseded by Schnohr, 2005, BRE24028 that included CCHS
Chlebowski, 2007	Women's Health Initiative,	2 318/ 147 916	Self-reported validated by	Questionnaire	Incidence, breast cancer ER+,	≥12 vs ≤0 met	0.90 (0.78-1.04)	Age at first child birth, age at	Superseded by Phipps, 2011,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
BRE80607 USA	Prospective Cohort, Age: 50-79 years, W, Postmenopausal	5 years	pathology report		postmenopause			menarche, age at menopause, age at screening, alcohol consumption, BMI, breast biopsies, breastfeeding, estrogen use, ethnicity, family history of breast cancer, parity, progestin + estrogen use, smoking	BRE80343 (Overlapped with WHI-OS (Mc Tiernan, 2003 that was included in the analysis)
		440/			Incidence, breast cancer ER-, postmenopause	≥12 vs ≤0 met	0.78 (0.57-1.07)		
Ericson, 2007 BRE80128 Sweden	MDCS, Prospective Cohort, Age: 50- years, Postmenopausal	389/ 11 699 9.5 years	Cancer registry	Questionnaire	Incidence, Invasive breast cancer, postmenopausal	Q 3 vs Q 1	0.93 (0.73-1.18)	Age	Superseded by Steindorf, 2013
Lahmann, 2007 BRE20026 Denmark,France,Germany,Greece,Italy,Netherlands,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 20-80 years, W	2 547/ 218 169 6.4 years	Population cancer registries and other procedures	Questionnaire	Incidence, Invasive breast cancer, postmenopause	≥43 vs ≤13 met-hour/week	0.95 (0.85-1.07)	Age , study center	Superseded by Steindorf, 2013
					Mortality, Invasive breast cancer, postmenopause	≥43 vs ≤13 met-hour/week	0.96 (0.85-1.08)	Age , age at first child, age at menarche, alcohol, BMI, educational level, HRT use,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								smoking habits, study center	
Wirfält, 2005 BRE11111 Sweden	MDCS, Nested Case Control, Age: 50- years, Postmenopausal	237/ 673 controls	Cancer registry	Questionnaire	Incidence, breast cancer,	(mean exposure)			Superseded by Steindorf, 2013
Patel, 2003 BRE16299 USA	CPS II, Prospective Cohort, Age: 63 years, W, Postmenopausal	1 503/ 72 608 5 years	Partially histological - over 80%	Interview	Incidence, breast cancer, postmenopausal	≥42 vs 0.1-7 met-hour	0.79 (0.61-1.03)	Age , age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, duration of oc use, educational level, energy Intake , ethnicity, family history, HRT use, mammography, parity/pregnancies, smoking habits	Superseded by Hildebrand, 2013, BRE80490
		880/			Incidence, localized breast cancer, postmenopausal	≥31.5 vs 0.1-7 met-hour	0.55 (0.38-0.80)		
		780/			Incidence, breast cancer, BMI < 25	≥31.6 vs 0.1-6.9 met-hour/week	0.75 (0.55-1.03)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		705/			HRT - no	≥31.6 vs 0.1-6.9 met-hour/week	0.64 (0.43-0.97)		
		587/			HRT - yes	≥31.6 vs 0.1-6.9 met-hour/week	0.98 (0.70-1.39)		
		453/			BMI 25- <30	≥31.6 vs 0.1-6.9 met-hour/week	0.90 (0.57-1.40)		
		290/			Incidence, regional and distant breast cancer, postmenopausal	≥31.5 vs 0.1-7 met-hour	0.85 (0.49-1.50)		
		266/			Incidence, breast cancer, BMI >=30	≥17.5 vs 0.1-6.9 met-hour/week	1.06 (0.75-1.50)		
		205/			Incidence, In situ breast cancer, postmenopausal	≥31.5 vs 0.1-7 met-hour	1.04 (0.57-1.90)		
		184/			Incidence, breast cancer, HRT - former	≥31.6 vs 0.1-6.9 met-hour/week	0.48 (0.21-1.09)		
Breslow, 2001 BRE01123 USA	NHEFS, Prospective Cohort, Age: 24-75 years, W	96/ 6 160 9.2 years	Medical records + self-reported	Questionnaire	Incidence, breast cancer, postmenopausal	consistently high vs consistently low	0.33 (0.14-0.82)	Age , BMI, body weight, ethnicity, height, Income, socio-economic status	Superseded by Albanes, 1989 (NHEFS part of NHANES I)
Moore, 2000 BRE16124	IWHS, Prospective	41 837	Cancer registry + death	Questionnaire	Incidence, breast cancer, lean	high vs low	1.01 (0.75-1.35)	Age , age at first child, age at	Superseded by Bardia, 2007

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
USA	Cohort, Age: 55-69 years, W, Postmenopausal	10 years	certificate					menopause, BMI, BMI, BMI, educational level, family history, HRT use, whr	
					HRT - no	high vs low	0.89 (0.74-1.06)		
					Overweight	high vs low	1.02 (0.78-1.33)		
					HRT - yes	high vs low	0.88 (0.61-1.28)		
					HRT - former	high vs low	0.97 (0.76-1.26)		

Figure 501 RR estimates of postmenopausal breast cancer by levels of recreational physical activity

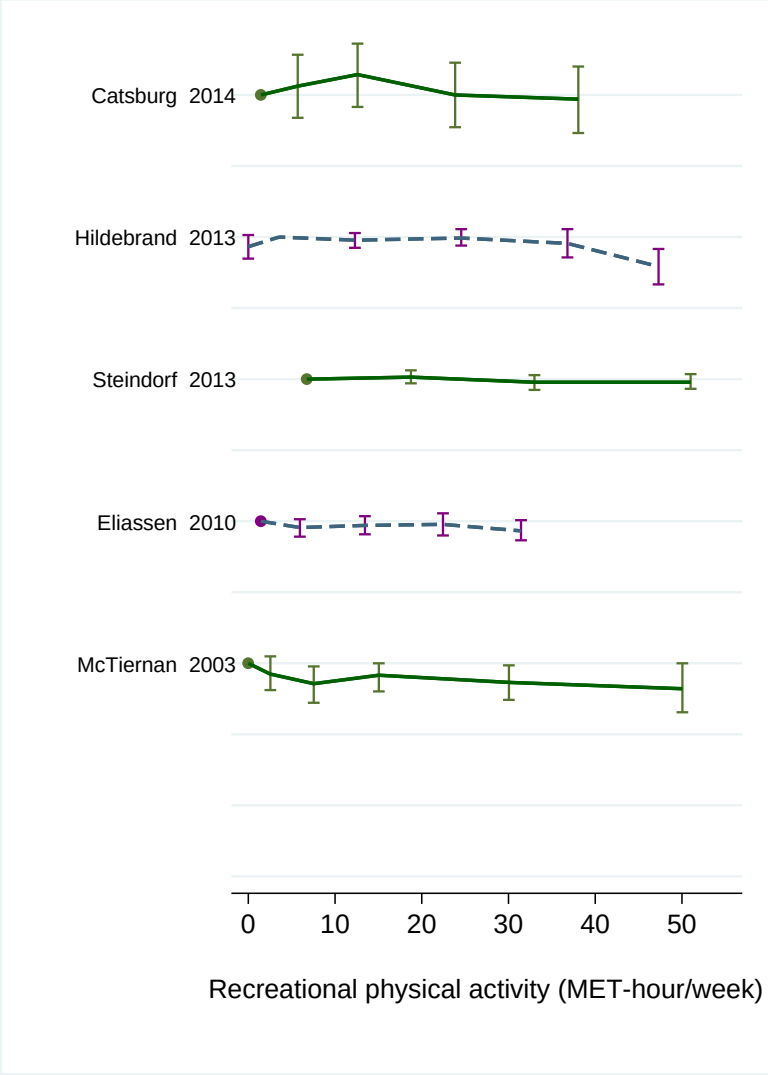


Figure 502 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest level of recreational physical activity

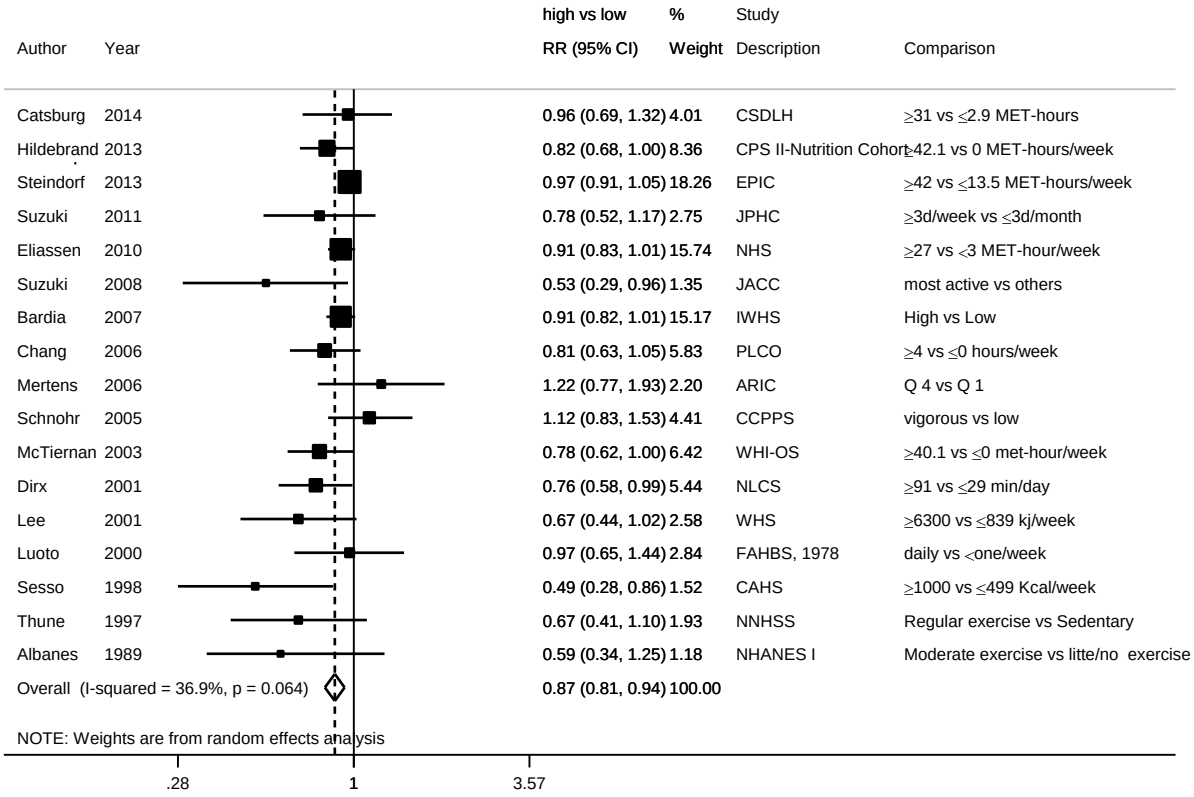


Figure 503 Relative risk of postmenopausal breast cancer for 10 MET-hour/week increase of recreational physical activity

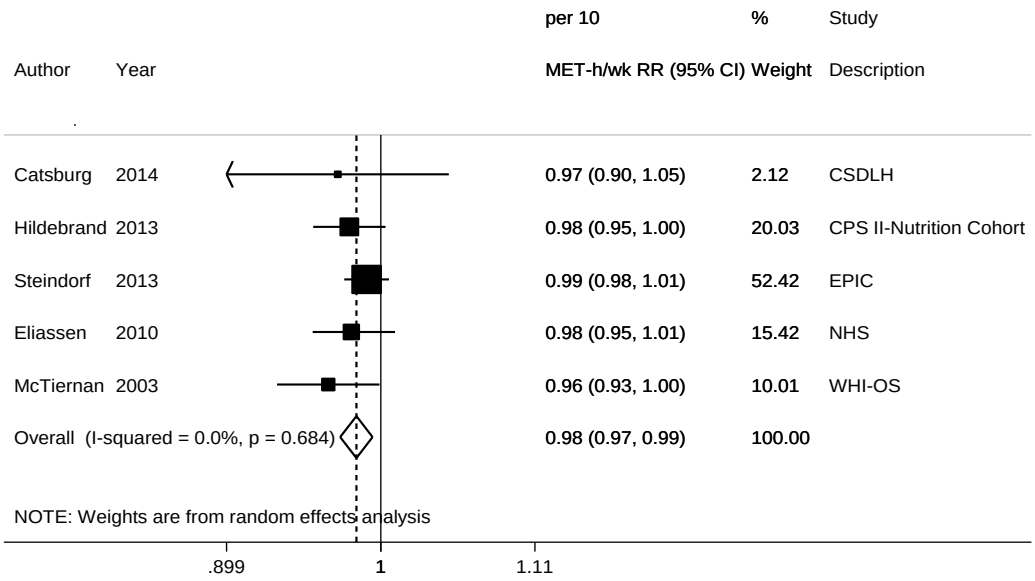


Figure 504 Funnel plot of studies included in the dose response meta-analysis of recreational physical activity and postmenopausal breast cancer

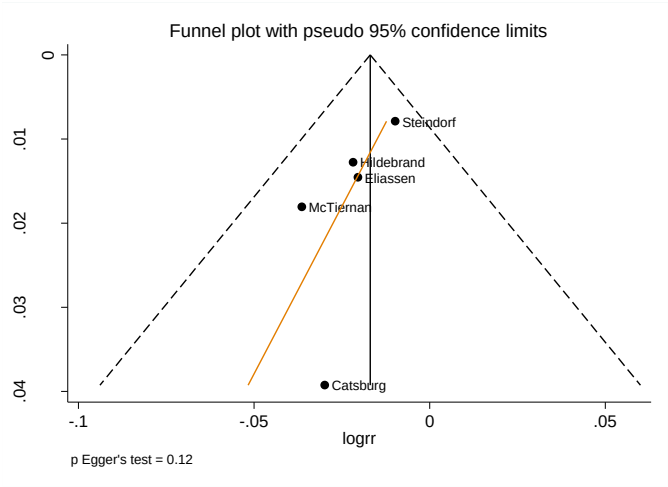


Figure 505 RR (95% CI) of postmenopausal breast cancer hormone receptor subtype for the highest compared with the lowest level of recreational physical activity, by cohorts

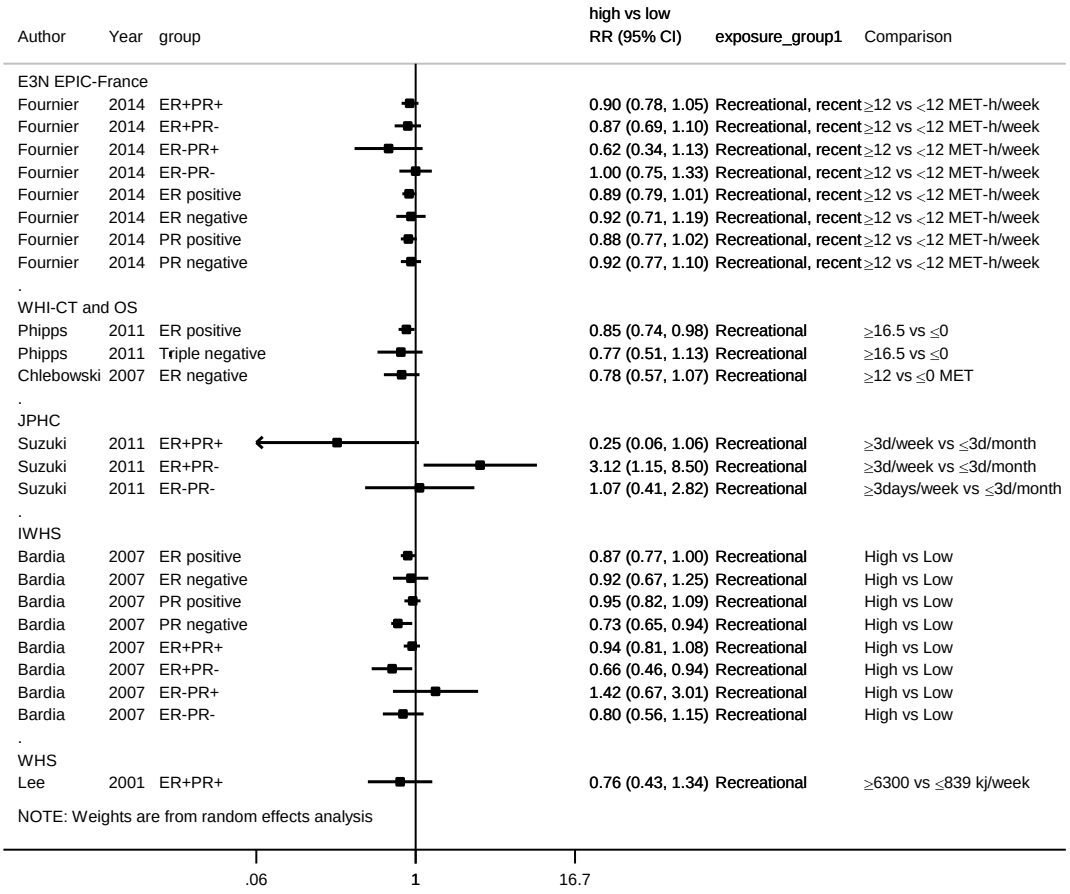
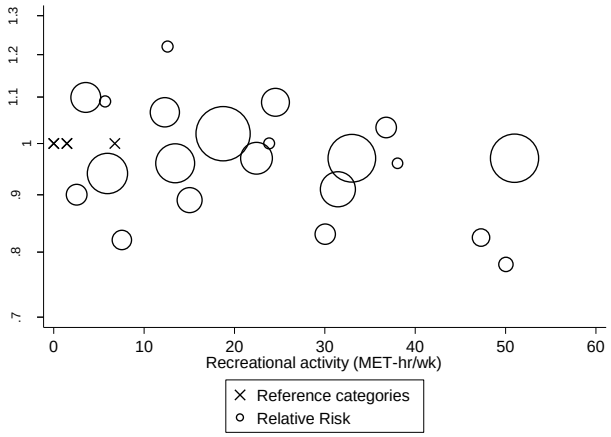
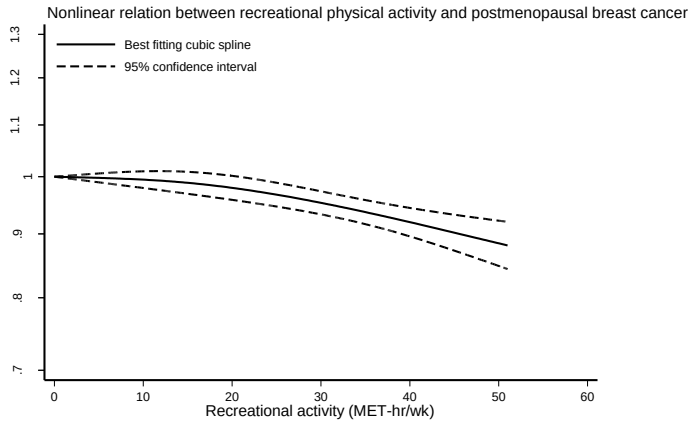


Figure 506 Non-linear analysis of recreational physical activity and postmenopausal breast cancer





P for non-liearity=0.05

Table 471 Relative risk of postmenopausal breast cancer and recreational physical activity estimated using non-linear models

MET-hour/week	RR (95%CI)
0	1.00
7.6	1.00 (0.98-1.01)
15.1	0.99 (0.97-1.01)
24.5	0.97 (0.95-0.99)
36.8	0.93 (0.91-0.95)
50.0	0.88 (0.85-0.92)

6.1.1.2 Recreational physical activity, at different age

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Overall summary

Meta-analysis was not conducted due to low number of studies. Study characteristics and results are tabulated.

Breast cancer (any)

Summary

Five studies (five publications) reported on recreational physical activity during adolescence and early adulthood and risk of breast cancer were identified. For the highest versus the lowest recreational activity, Boeke, 2014b reported inverse associations, significant for activities during

14-17 years but not 12-13 years. Rosenberg, 2014 and Suzuki, 2007 observed non-significant positive associations of activities during school.

For early adulthood periods, non-significant inverse associations were reported in three studies (Boeke, 2014b, 18-22 years; Cohen, 2013, 30s; Pijpe, 2010, <30 or ≥30 years), no significant association in one study (Rosenberg, 2014, 30 years), and non-significant positive associations in two studies (Boeke, 2014b, 23-29 years; Rosenberg, 2014, 21 years).

Premenopausal breast cancer

Summary

Two studies (four publications) reported on recreational physical activity during adolescence and early adulthood and risk of premenopausal breast cancer were identified. For the highest versus the lowest recreational activity, Boeke, 2014b reported inverse associations that were (borderline) significant for activities during 14-17 years with breast cancer overall and ER+ breast cancer but not 12-13 years. Margolis, 2005 observed a non-significant positive association.

For early adulthood periods, Boeke, 2014b mostly observed non-significant inverse associations for activities during age 18-22 years or 23-29 years. Margolis, 2005 reported a non-significant positive association for activities at 30 years.

Postmenopausal breast cancer

Summary

Four studies (four publications) reported on recreational physical activity during adolescence and early, middle, and late adulthood and risk of postmenopausal breast cancer were identified. For the highest versus the lowest recreational activity, studies mostly observed non-significant inverse associations (Boeke, 2014b, 12-13 years, 14-17 years, and 18-22 years; McTiernan, 2003, at 18 years, and 50 years; Patel, 2003, at 40 years; Fournier, 2014, recent activities in postmenopausal years). Three significant inverse associations were reported – McTiernan, 2003 for activities at 35 years, Fournier, 2014 for recent postmenopausal activities among BMI <25 kg/m^2, and Boeke, 2014b for activities during 18-22 years and ER-positive breast cancer.

Table 472 Recreational physical activity, at different age and breast cancer risk. Main study characteristics

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Boeke, 2014b BRE80535 USA	NHS II, Prospective Cohort, W	2 697/ 75 669 975 258 person-years	Self-report verified by medical record	Questionnaire	Incidence, breast cancer	Age 12-13 years ≥72 vs ≤20.9 met-h/week	0.97 (0.86-1.09) Ptrend:0.84	Age, age at first child birth, age at menarche, alcohol, alcohol, benign breast disease, body size, breastfeeding, calendar year, family history of breast cancer, height, menopausal status, parity, physical activity, weight change
						Age 14-17 years ≥72 vs ≤20.9 met-h/week	0.88 (0.78-0.98) Ptrend:0.16	
						Age 18-22 years ≥72 vs ≤20.9 met-h/week	0.91 (0.81-1.03) Ptrend:0.15	
						Age 23-29 years ≥57 vs ≤14.9 met-h/week	1.05 (0.93-1.20) Ptrend:0.60	
Rosenberg, 2014 BRE80563 USA	BWHS, Prospective Cohort, Age: 30- years, W	44 708 307 672 person-years	Self-report, linkage to cancer registries, medical and pathology records	Questionnaire	Incidence, Invasive breast cancer	Age 30 years ≥7 vs ≤0.9 hours/week	1.00 (0.82-1.24) Ptrend:0.05	Age, fruits and vegetables consumption, meat consumption, parity, time period, years of education
						Age 21 years ≥7 vs ≤0.9 hours/week	1.09 (0.92-1.31) Ptrend:	
						During high school	1.01 (0.84-1.20) Ptrend:	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
						≥7 vs ≤0.9 hours/week		
		79/			Incidence, breast cancer ER+	In every time period ≥5 vs ≤0.9 hours/week	0.84 (0.56-1.27)	
		49/			Incidence, breast cancer ER-	In every time period ≥5 vs ≤0.9 hours/week	0.66 (0.37-1.18)	
Cohen, 2013 BRE80470 USA	SCCS, Nested Case Control, Age: 40-79 years	448/ 546 9 years	Cancer registry		Incidence, Invasive breast cancer	During the 30s ≥2.1 vs ≤0 met-hours/day	0.79 (0.59-1.06) Ptrend:0.13	Age, age at menarche, BMI, educational level, ethnicity, family history of breast cancer, health Insurance, household Income, HRT use, menopausal status, parity, physical activity, sedentary behaviour, smoking habits, source type
Pijpe, 2010 BRE80269 Netherlands	HEBON, Historical Cohort, Age: 45 years, W, BRCA1/2 mutation carriers	218/ 725	Self report, pathology report, national death Index, death cert, state cancer registries	Self-administered questionnaire	Incidence, breast cancer	<Age 30 years ≥21.7 vs ≤0 met-hours/week	0.77 (0.46-1.28) Ptrend:0.113	Age, alcohol Intake, birth cohort, BMI, BRCA carrier, family history, HRT use, menopausal status, ocp use, parity
						≥Age 30 years ≥21 vs ≤0 met-hours/week	0.68 (0.43-1.09) Ptrend:0.157	
					Lean	≥Age 30 years	0.58 (0.38-0.88)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
						ever vs never		
					Overweight	≥Age 30 years ever vs never	0.75 (0.49-1.15)	
Suzuki, 2007 BRE80447 Japan	JACC, Prospective Cohort, Age: 40-79 years, W	72/ 109 778	Death certificate	Questionnaire	Mortality, breast cancer	At school yes vs little	1.01 (0.55-1.88)	Age, study area

Table 473 Recreational physical activity, at different age and premenopausal breast cancer risk. Main study characteristics

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Boeke, 2014b BRE80535 USA	NHS II, Prospective Cohort, W	1 351/ 75 669 975 258 person-years	Self-report verified by medical record	Questionnaire	Incidence, breast cancer, premenopausal	Age 12-13 years ≥72 vs ≤20.9 met-h/week	0.97 (0.82-1.14) Ptrend:0.80	Age, age at first child birth, age at menarche, alcohol, alcohol, benign breast disease, body size, breastfeeding, calendar year, family history of breast cancer, height, parity, physical activity, weight change
						Age 14-17 years ≥72 vs ≤20.9 met-h/week	0.85 (0.73-1.00) Ptrend:0.33	
						Age 18-22 years ≥72 vs ≤20.9	0.89 (0.74-1.06) Ptrend:0.17	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
						met-h/week		
						Age 23-29 years ≥57 vs ≤14.9 met-h/week	1.05 (0.87-1.27) Ptrend:0.39	
		697/			Incidence, breast cancer ER+, premenopausal	Age 12-13 years ≥72 vs ≤20.9 met-h/week	0.96 (0.77-1.20) Ptrend:0.98	
		170/			Incidence, breast cancer ER-, premenopausal	Age 12-13 years ≥72 vs ≤20.9 met-h/week	0.86 (0.55-1.35) Ptrend:0.44	
		697/			Incidence, breast cancer ER+, premenopausal	Age 14-17 years ≥72 vs ≤20.9 met-h/week	0.79 (0.63-0.99) Ptrend:0.20	
		170/			Incidence, breast cancer ER-, premenopausal	Age 14-17 years ≥72 vs ≤20.9 met-h/week	0.89 (0.57-1.38) Ptrend:0.71	
		697/			Incidence, breast cancer ER+, premenopausal	Age 18-22 years ≥72 vs ≤20.9 met-h/week	0.94 (0.74-1.20) Ptrend:0.65	
		170/			Incidence, breast cancer ER-, premenopausal	Age 18-22 years ≥72 vs ≤20.9 met-h/week	0.84 (0.50-1.41) Ptrend:0.55	
		697/			Incidence, breast cancer ER+, premenopausal	Age 23-29 years ≥57 vs ≤14.9 met-h/week	0.97 (0.75-1.25) Ptrend:0.35	
		107/			Incidence, breast cancer ER-, premenopausal	Age 23-29 years ≥57 vs ≤14.9 met-h/week	0.89 (0.52-1.54) Ptrend:0.19	
Maruti, 2008b	NHS II,	550/	Self-report	Self-completed	Incidence,	Age 12-22 years	0.75 (0.57-0.99)	Age, age at first child

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
BRE80219 USA	Prospective Cohort, Age: 33-51 years, W, Premenopausal	64 777 6 years	verified by medical record	questionnaire	Invasive breast cancer, premenopausal	≥72 vs ≤20.9 met-h/week	Ptrend:0.05	birth, alcohol Intake, benign breast disease, body shape, family history of cancer, height, OC use, parity
		550/				Age 23-34 years ≥57 vs ≤14.9 met-h/week	0.88 (0.65-1.19) Ptrend:0.06	
		549/				Age ≥35 years ≥33 vs ≤8.9 met-h/week	1.00 (0.77-1.30) Ptrend:0.27	
		550/				Age 12-22 years per 21 met-hours/week	0.94	
		550/				Age 23-34 years per 21 met-hours/week	0.94	
		549/				Age ≥35 years per 21 met-hours/week	0.96	
Margolis, 2005 BRE23306 Norway, Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W, Young women	1 155/ 99 504 9.1 years	Partially histological - over 80%	Questionnaire	Incidence, Invasive breast cancer,	Age 30 years vigorous vs none	1.20 (0.77-1.95) Ptrend:0.6	Age , age at first child, age at menarche, alcohol, BMI, country of birth, duration of breastfeeding, educational level, family history, height, menopausal status, oc use, parity/pregnancies, smoking habits
						Age 14 years	1.05 (0.72-1.54)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
						vigorous vs none	Ptrend:0.14	
Rockhill, 1998 BRE80176 USA	NHS II, Prospective Cohort, Age: 22-42 years, W, Premenopausal	116 671 6 years	Questionnaire/hospital records & pathology reports	Questionnaire	Incidence, Invasive & In situ breast cancer	Late adolescent 10-12 vs never months/year	1.10 (0.80-1.60)	Age at entry, age at first child birth, age at menarche, alcohol consumption, family history of cancer, family history of cancer, height, height, history of breast cyst, history of breast cyst, parity, recent alcohol consumption

Table 474 Recreational physical activity, at different age and postmenopausal breast cancer risk. Main study characteristics

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Boeke, 2014b BRE80535 USA	NHS II, Prospective Cohort, W	965/ 75 669 975 258 person-years	Self-report verified by medical record	Questionnaire	Incidence, breast cancer, postmenopausal	Age 12-13 years ≥72 vs ≤20.9 met-h/week	0.95 (0.79-1.16) Ptrend:0.84	Age, age at first child birth, age at menarche, age at menopause, alcohol, alcohol, benign breast disease, body size, breastfeeding, calendar year, family history of breast cancer, height, HRT use, parity, physical activity, weight change
						Age 14-17 years ≥72 vs ≤20.9 met-h/week	0.90 (0.74-1.09) Ptrend:0.37	
						Age 18-22 years ≥72 vs ≤20.9 met-h/week	0.89 (0.72-1.10) Ptrend:0.28	
						Age 23-29 years ≥57 vs ≤14.9 met-h/week	1.04 (0.84-1.28) Ptrend:0.87	
		536/			Incidence, breast cancer ER+, postmenopausal	Age 18-22 years ≥72 vs ≤20.9 met-h/week	0.72 (0.54-0.97) Ptrend:0.01	
		117/			Incidence, breast cancer ER-, postmenopausal	Age 18-22 years ≥72 vs ≤20.9 met-h/week	0.88 (0.47-1.64) Ptrend:0.86	
Fournier, 2014 BRE80532	E3N EPIC-France,	2 097/ 59 308	Self-report, next of kin, death		Incidence, Invasive breast	Within the previous four	0.93 (0.83-1.05)	Age at first child birth, age at menarche, age

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
France	Prospective Cohort, W, Postmenopausal	8.5 years	registry		cancer, postmenopausal	years ≥36 vs ≤11.9 met-h/week		at menopause, age-underlying cox models, alcohol Intake, BMI, family history of breast cancer In first degree relatives, history of benign breast disease, menopausal oestrogen use, parity, total energy Intake, year of birth
		959/			Incidence, breast cancer ER+/PR+, postmenopausal	Within the previous four years ≥12 vs <12 met-h/week	0.90 (0.78-1.05)	
		378/			Incidence, breast cancer ER+/PR-, postmenopausal	Within the previous four years ≥12 vs <12 met-h/week	0.87 (0.69-1.10)	
		49/			Incidence, breast cancer ER-/PR+, postmenopausal	Within the previous four years ≥12 vs <12 met-h/week	0.62 (0.34-1.13)	
		266/			Incidence, breast cancer ER-/PR-, postmenopausal	Within the previous four years ≥12 vs <12 met-h/week	1.00 (0.75-1.33)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		1 337/			Incidence, breast cancer ER+, postmenopausal	Within the previous four years ≥12 vs <12 met-h/week	0.89 (0.79-1.01)	
		315/			Incidence, breast cancer ER-, postmenopausal	Within the previous four years ≥12 vs <12 met-h/week	0.92 (0.71-1.19)	
		1 008/			Incidence, breast cancer PR+, postmenopausal	Within the previous four years ≥12 vs <12 met-h/week	0.88 (0.77-1.02)	
		644/			Incidence, breast cancer PR-, postmenopausal	Within the previous four years ≥12 vs <12 met-h/week	0.92 (0.77-1.10)	
		1 584/			Incidence, Invasive breast cancer, BMI < 25	Within the previous four years ≥12 vs <12 met-h/week	0.88 (0.78-0.98)	
		513/			BMI >=25	Within the previous four years ≥12 vs <12 met-h/week	0.96 (0.80-1.16)	
		2 097/			Postmenopausal	Within the previous four	0.88 (0.78-0.98)	Recreational activity 5-9 years earlier

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
						years ≥12 vs <12 met-h/week		
		2 097/			Postmenopausal	5-9 years earlier ≥12 vs <12 met-h/week	1.04 (0.92-1.18)	Recreational activity within the previous 4 years
McTiernan, 2003 BRE17819 USA	Women's Health Initiative - Observational study, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	1 709/ 74 171 4.7 years	Medical record + pathology report + family report	Questionnaire	Incidence, Invasive & In situ breast cancer, postmenopausal	Age 18 years yes vs no	0.94 (0.85-1.04)	Age , age at first child, age at menarche, age at menopause, alcohol, BMI, breastfeeding, educational level, ethnicity, family history, HRT use, Income, mammography, oophorectomy/hysterectomy, parity/pregnancies, place of residence, smoking habits
		1 719/			Postmenopausal	Age 35 years yes vs no	0.86 (0.78-0.95)	
		1 747/			Postmenopausal	Age 50 years yes vs no	0.92 (0.83-1.01)	
Patel, 2003 BRE16299 USA	CPS II, Prospective Cohort, Age: 63 years, W, Postmenopausal	1 503/ 72 608 5 years	Partially histological - over 80%	Interview	Incidence, breast cancer, postmenopausal	Age 40 years ≥42 vs 0.1-7 met-hour	0.79 (0.61-1.03) Ptrend:0.31	Age , age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, duration of oc use, educational level,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								energy Intake , ethnicity, family history, HRT use, mammography, parity/pregnancies, smoking habits

6.1.1.2 Walking

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Overall summary

Fifteen publications from 11 studies that examined walking were identified. No pooled analysis was identified.

The highest compared with the lowest meta-analyses were conducted to examine the association of walking with risk of breast cancer and postmenopausal breast cancer.

Table 475 Summary of results of the highest versus the lowest meta-analysis in the CUP SLR

	Breast cancer (any)	Premenopausal breast cancer	Postmenopausal breast cancer
Comparison	Highest versus lowest	-	Highest versus lowest
Studies (n)	5	-	4
Cases	6 472	-	7 300
RR (95%CI)	0.88 (0.81-0.96)	-	0.94 (0.86-1.04)
Heterogeneity (I^2, p-value)	0%, 0.47	-	0%, 0.99

Breast cancer (any)

Summary

Main results:

Five out of seven studies (eight publications) identified could be included in the highest versus the lowest meta-analysis (6 472). Walking was significantly inversely associated with breast cancer risk (RR for highest vs lowest activity level=0.88 (95% CI=0.81-0.96, I^2=0%, P=0.47). One study (Tehard, 2006, E3N) contributed 61% weight in the analysis. Summary RR did not change materially when studies were omitted in turn in influence analysis.

Two studies (Zhang X, 2015; Drake, 2001) were excluded. Drake, 2001 reported no significant difference in walking activity between breast cancer cases and non-cases. Zhang X, 2015 observed a significant inverse association of brisk walking with ER+PR+AR+ breast cancer and

non-significant inverse associations with other androgen receptor subtypes; except for ER+PR-AR+ breast cancer, where a non-significant positive association was observed.

Rosenberg, 2014 reported non-significant inverse associations of similar magnitude between brisk walking and ER-positive and ER-negative breast cancers.

Study quality:

Studies were from Asia, Europe, and North America. One study included radiologic technologists (Howard, 2009, USRT) and one study (Rosenberg, 2014, BWHS) was of black women only. All studies used self-reported information on walking. Case ascertainment was through cancer registries or confirmed through medical records. Two studies (Howard, 2009; Suzuki, 2008c) were adjusted for age, BMI, alcohol intake, and reproductive factors. Rosenberg, 2014 did not adjust for alcohol intake and MHT use as including these factors in the model did not change the relative risk estimates.

Table 476 Walking and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	7 (8 publications)
Studies included in forest plot of highest compared with lowest exposure	5
Studies included in linear dose-response meta-analysis	Not enough studies
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 477 Walking and breast cancer risk. Summary of the highest versus the lowest meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR	**CUP**
Comparison	-	Highest versus lowest
Studies (n)	-	5
Cases	-	6 472
RR (95%CI)	-	0.88 (0.81-0.96)
Heterogeneity (I^2, p-value)	-	0%, 0.47

Table 478 Walking and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Wu, 2013	31 cohort[1] studies overall	63 786, 10 846 ER+PR+, 2 619 ER-PR-	Canada, China, Europe, Japan, USA	Incidence, any breast cancer in pre-, and/or postmenopausal women	Highest vs lowest, walking (5 studies)	0.87 (0.79-0.96)	-	8%

[1]All studies identified in the meta-analysis of Wu (2013) were included in the present review under different physical activity sections.

Table 479 Walking and breast cancer risk. Main characteristics of studies included in the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Rosenberg, 2014 BRE80563 USA	BWHS, Prospective Cohort, Age: 30- years, W	1 359/ 44 708 307 672 person-years	Self-report, linkage to cancer registries, medical and pathology records	Questionnaire	Incidence, Invasive breast cancer	≥7 vs ≤0.9 hours/week	0.77 (0.53-1.13)	Age, BMI, fruits and vegetables consumption, meat consumption, parity, time period, vigorous activity, years of education
		686/			Incidence, breast cancer ER+	≥7 vs ≤0.9 hours/week	0.83 (0.50-1.38)	
		403/			Incidence, breast cancer ER-	≥7 vs ≤0.9 hours/week	0.88 (0.46-1.68)	
Pronk, 2011 BRE80388 China	SWHS, Prospective Cohort, Age: 40-70 years, W	717/ 73 049 9 years	Cancer registry	Interview	Incidence, breast cancer	≥69.3 vs 0-28.1 met-hour/week/year	0.95 (0.77-1.16)	Age, age at first child birth, educational level, family history of breast cancer, number of pregnancies
Howard, 2009 BRE80286 USA	USRT, Prospective Cohort, Age: 47 years, W, radiologic technologists	864/ 45 631 8.9 years	Self-report verified by medical record	Questionnaire	Incidence, breast cancer	Walking at home or work ≥40 vs 0.1-0.9 hours/week	0.90 (0.68-1.20)	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, breast diseases , family history of cancer, menopausal hormone use, oc use, parity, physical activity, race, smoking habits
						≥40 vs 0 hours/week	0.74 (0.53-1.05)	
						Walking/hiking for exercise ≥10 vs ≤0 hours/week	0.63 (0.37-1.07)	
Suzuki, 2008c	JACC,	207/	Cancer registry	Self-	Incidence, breast	60 vs ≥29.9	0.73 (0.53-1.01)	Age, age at first child birth,

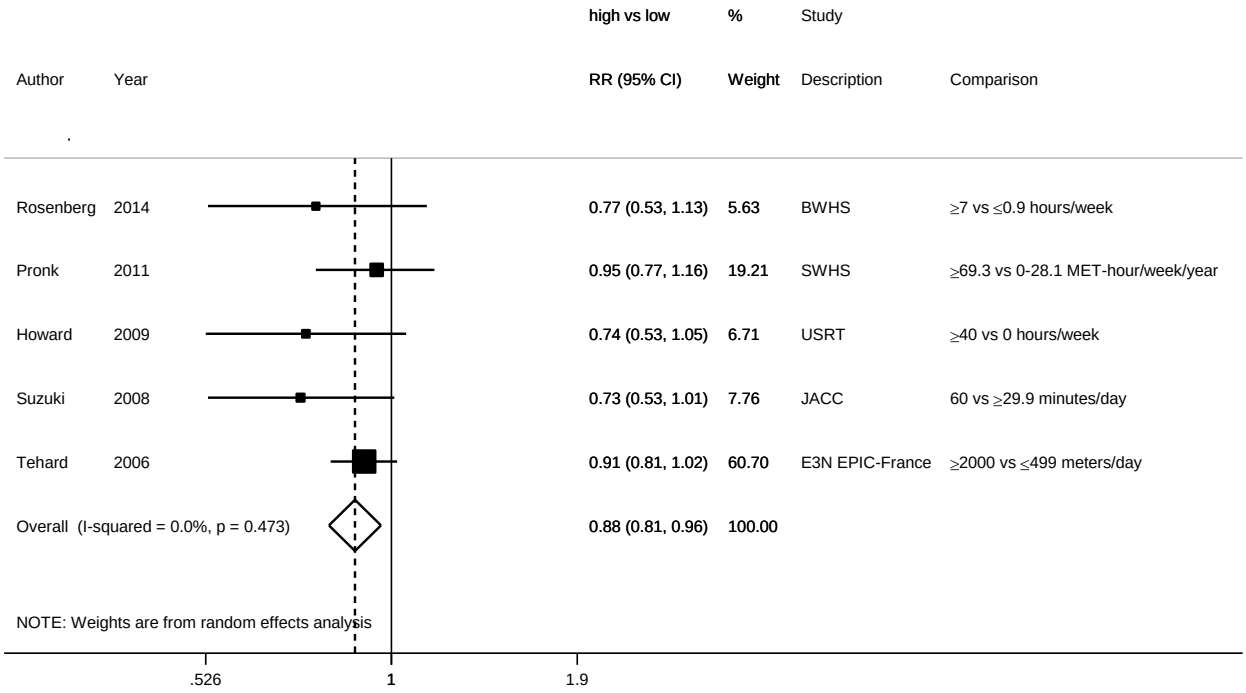
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
BRE80201 Japan	Prospective Cohort, Age: 40-69 years, W	30 157 12.4 years		administered questionnaire	cancer	minutes/day		age at menarche, age at menopause, alcohol Intake, BMI, educational level, family history of cancer, hormone use, menopausal status, parity
Tehard, 2006 BRE80108 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W	3 325/ 98 995 11.4 years	Patient records/direct contact/health Insurance records	Questionnaire	Incidence, breast cancer,	≥2000 vs ≤499 meters/day	0.91 (0.81-1.02)	Age at first child, age at menarche, age-underlying cox models, benign breast disease, BMI, family history, HRT use, marital status, menopausal status, oc use, occupation, parity/pregnancies

Table 480 Walking and breast cancer risk. Main characteristics of studies excluded from the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Zhang X, 2015 BRE80578 USA	NHS, Prospective Cohort, Age: 30-55 years, W	1 162/ 103 577 26 years	Self-report verified by medical record	Questionnaire	Incidence, breast cancer ER+PR+AR+	per 5 hours/week	0.81 (0.66-0.99)	Age at menarche, age at menopause, alcohol Intake, BMI at age 18 years, family history of breast cancer, height, history of benign breast disease, parity and age at first birth, postmenopausal hormone use	Excluded, breast cancer subtype, not enough studies to analyse
		233/			Incidence, breast cancer ER+PR-AR+	per 5 hours/week	1.01 (0.67-1.51)		
		186/			Incidence, breast cancer ER-PR-AR-	per 5 hours/week	0.72 (0.42-1.23)		
		180/			Incidence, breast cancer ER-PR-AR+	per 5 hours/week	0.78 (0.47-1.31)		
		177/			Incidence, breast cancer ER+PR+AR-	per 5 hours/week	0.73 (0.42-1.26)		
		68/			Incidence, breast cancer ER+PR-	per 5 hours/week	0.43 (0.15-1.27)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					AR-				
Suzuki, 2007 BRE80447 Japan	JACC, Prospective Cohort, Age: 40-79 years, W	71/ 109 778	Death certificate	Questionnaire	Mortality, breast cancer	<0.5 vs >1 hours/day	2.47 (1.43-4.25)	Age, study area	Excluded, breast cancer mortality, not enough studies to analyse
Drake, 2001 BRE02418 USA	ACLS, 1970, Prospective Cohort, Age: 21-86 years, W, Fitness centre members	4 520 25 years	Not specified	Questionnaire	Incidence, breast cancer,	(mean exposure)			Excluded, mean exposure comparison only
						(mean exposure)			

Figure 507 RR (95% CI) of breast cancer for the highest compared with the lowest level of walking



Premenopausal breast cancer

Summary

Two studies (three publications) reported on walking and premenopausal breast cancer (Howard, 2009; Maruti, 2008b; Colditz, 2003) were identified. Meta-analysis was not conducted as data was limited. Study characteristics and results are tabulated. USRT reported a significant inverse association for the highest level compared with no walking/hiking for exercise and a non-significant inverse association for the highest versus the lowest walking at home or work (Howard, 2009). NHS II reported a non-significant positive association for walking that was measured at study baseline (1989) (Colditz, 2003) and a non-significant inverse association for lifetime walking (Maruti, 2008b).

Table 481 Walking and premenopausal breast cancer risk. Main characteristics of studies

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Howard, 2009 BRE80286 USA	USRT, Prospective Cohort, Age: 47 years, W, radiologic technologists	440/ 45 631 8.9 years	Self-report verified by medical record	Questionnaire	Incidence, breast cancer, premenopausal	≥40 vs 0.1-0.9 hours/week of walking at home or work	0.82 (0.56-1.22)	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, breast diseases , family history of cancer, menopausal hormone use, OC use, parity, physical activity, race, smoking habits
						≥10 vs ≤0 hours/week of walking or hiking for exercise	0.41 (0.18-0.98)	
Maruti, 2008b BRE80219 USA	NHS II, Prospective Cohort, Age: 33-51 years, W, Premenopausal	550/ 64 777 6 years	Self-report verified by medical record	Self-completed questionnaire, lifetime walking	Incidence, Invasive breast cancer, premenopausal	≥2.5 vs ≤0.4 hours/week	0.79 (0.59-1.05)	Age, age at first child birth, alcohol Intake, benign breast disease, body shape, family history of cancer, height, OC use, parity
Colditz, 2003 BRE01782 USA	NHS II, Prospective Cohort, Age: 25-42 years, W, Registered nurses	849/ 110 468 10 years	Medical records + self-reported	Questionnaire	Incidence, Invasive breast cancer, premenopausal	≥4 vs ≤0.32 hours/week	1.07 (0.81-1.40)	Age , age at first child, age at menarche, alcohol, benign breast disease, family history, height, OC use, other physical activity Index

Postmenopausal breast cancer

Summary

Main results:

Four out of five studies (6 publications) identified could be included in the highest versus lowest meta-analysis (7 300 cases). Walking was non-significantly inversely associated with postmenopausal breast cancer risk (RR for highest vs lowest activity level=0.94 (95% CI=0.86-1.04). No heterogeneity was observed between studies (I^2=0%, P=0.99). Fournier, 2014 contributed 52% weight in the analysis. Summary RR did not change materially when studies were omitted in turn in influence analysis.

One study (Dirx, 2001) on cycling and walking was excluded from the analysis. A non-significant inverse association was reported.

Study quality:

Studies were from France and America. Howard, 2009 was a cohort of radiologic technologists (USRT). Information on walking was self-reported in the studies, except for WHI (Kwan, 2014) where walking speed for 10 meters was timed. Case ascertainment was through cancer registries or confirmed through medical records. All studies were adjusted for age, BMI, alcohol intake, reproductive factors, and MHT use.

Table 482 Walking and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	5 (6 publications)
Studies included in forest plot of highest compared with lowest exposure	4
Studies included in linear dose-response meta-analysis	Not enough studies
Studies included in non-linear dose-response meta-analysis	Not enough studies

Note: Include cohort and case-cohort designs.

Table 483 Walking and postmenopausal breast cancer risk. Summary of the highest versus the lowest meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR	CUP
Comparison	-	Highest versus lowest
Studies (n)	-	4
Cases	-	7 300
RR (95%CI)	-	0.94 (0.86-1.04)
Heterogeneity (I^2, p-value)	-	0%, 0.99

Table 484 Walking and postmenopausal breast cancer risk. Main characteristics of studies included in the highest versus the lowest meta-analysis

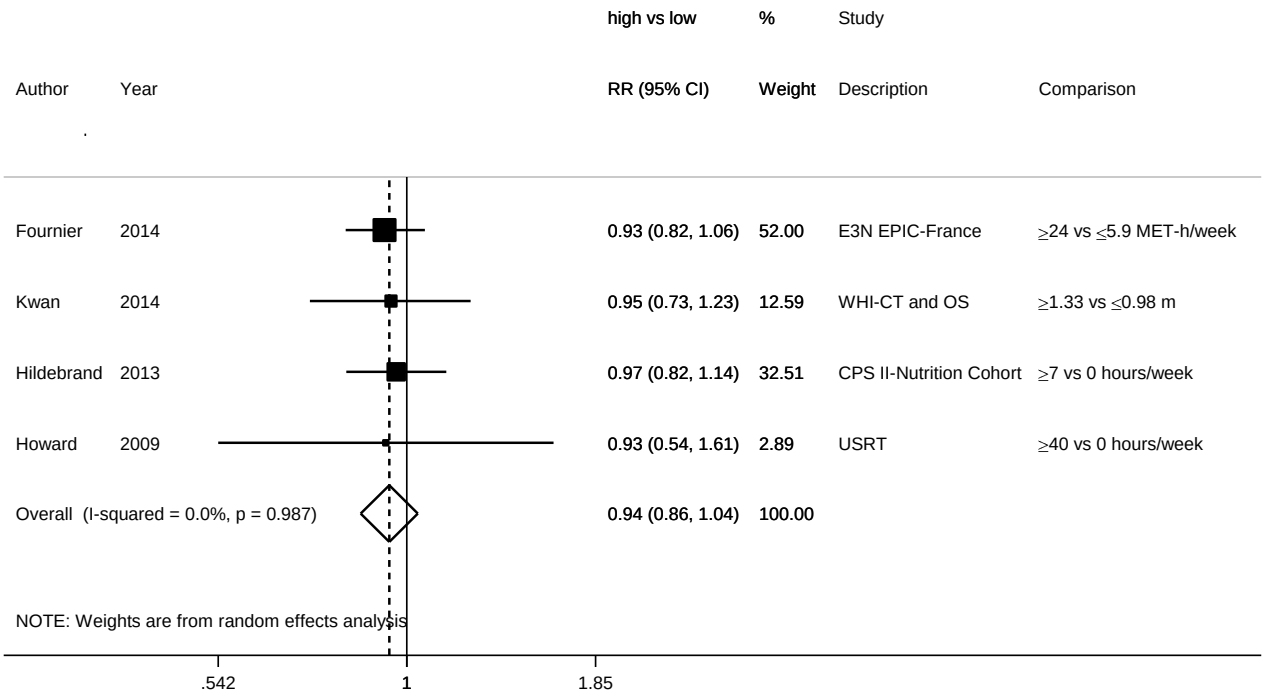
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Fournier, 2014 BRE80532 France	E3N EPIC-France, Prospective Cohort, W, Postmenopausal	2 097/ 59 308 8.5 years	Self-report, next of kin, death registry		Incidence, Invasive breast cancer, postmenopausal	≥24 vs ≤5.9 met-h/week	0.93 (0.82-1.06)	Age at first child birth, age at menarche, age at menopause, age-underlying cox models, alcohol Intake, BMI, family history of breast cancer In first degree relatives, history of benign breast disease, menopausal oestrogen use, parity, sport, total energy Intake, year of birth
Kwan, 2014 BRE80474 USA	Women's Health Initiative, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	762/ 14 719 12.4 years	Medical record		Incidence, Invasive breast cancer	≥1.33 vs ≤0.98 m	0.95 (0.73-1.23)	Age, age, alcohol consumption, BMI, oestrogen plus progesterone use, ethnicity, gail model risk, health status, Income, mammogram In the past 2 years, smoking status, trial Intervention group
Hildebrand, 2013 BRE80490 USA	CPS II, Prospective Cohort, Age: 50-74 years, W, Postmenopausal	4 017/ 73 615 14.2 years	Self-report verified by medical record	Questionnaire	Incidence, breast cancer	≥7 plus other activities vs ≤3 hours/week	0.83 (0.73-0.96)	Age, age at first child birth, age at menopause, alcohol, BMI, breast diseases , educational level, family history of breast cancer, HRT use, mammography, number of childbirths, oophorectomy/hysterectomy , race, smoking status, weight change
Howard, 2009 BRE80286	USRT, Prospective	285/ 45 631	Self-report verified by	Questionnaire	Incidence, breast cancer, ever	≥10 vs ≤0 hours/week	1.05 (0.48-2.31)	Age, age at first child birth, age at menarche, age at

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
USA	Cohort, Age: 47 years, W, radiologic technologists	8.9 years	medical record		used HRT			menopause, alcohol consumption, BMI, breast diseases , family history of cancer, menopausal hormone use, oc use, parity, physical activity, race, smoking habits
						≥40 vs 0.1-0.9 hours/week	1.10 (0.65-1.87)	
		139/			Never HRT users	≥40 vs 0.1-0.9 hours/week	0.84 (0.44-1.61)	
						≥10 vs ≤0 hours/week	0.55 (0.13-2.33)	

Table 485 Walking and postmenopausal breast cancer risk. Main characteristics of studies excluded from the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Hartz, 2013 BRE80483 USA	Women's Health Initiative, Prospective Cohort, Age: 55-70 years, W, Postmenopausal	147 202 8 years	Self-reported/ death certificate/ medical records		Incidence, breast cancer	≥15.1 vs 0-10 met-h/week	0.90 (0.81-1.00)	Age, alcohol, family history of prostate cancer, history of cancer, history of polyp diagnosis, medication, number of cigarettes smoked, osteoporosis, psychological character, race, study, weight	Superseded by Kwan, 2014, BRE80474
						per 1 sd	0.97 (0.94-0.99)		
Dirx, 2001 BRE02326 Netherlands	NLCS, Case Cohort, Age: 55-69 years, W, Postmenopausal	941/ 62 573 7.3 years	Not specified	Questionnaire	Incidence, breast cancer, postmenopausal	≥61 vs ≤9 min/day of cycling and walking	0.81 (0.06-1.09)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, body weight, educational level, energy Intake , family history, parity/ pregnancies	Excluded, exposure included cycling with walking

Figure 508 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest level of walking



6.1.1.3 Household activity

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Overall summary

Five studies (eight publications) were identified. Meta-analysis was not conducted due to low number of studies. Study characteristics and results are tabulated.

Breast cancer (any)

Summary

Four studies (five publications) reported on household activity and risk of breast cancer were identified. The French E3N cohort study (Tehard, 2006) was a component study of the multi-centre cohort, EPIC (Steindorf, 2013; Steindorf, 2012). For the highest versus the lowest level comparison, EPIC observed significant inverse associations between household activity and invasive breast cancer, and ER negative, PR negative, and joint ER-PR- breast cancers (Steindorf, 2013); the Chinese cohort, SWHS, reported a non-significant inverse association with

breast cancer (Pronk, 2011); and the Aerobic Center Longitudinal Study (ACLS) reported no significant difference in housework level between fitness centre members with and without breast cancer (Drake, 2001).

One published meta-analysis was identified. Wu, 2013 reported a significant inverse association with breast cancer for the highest versus the lowest household activity (summary RR=0.89, 95% CI=0.83-0.95; I^2=0%). Three prospective studies were included in the analysis (Steindorf, 2013; Pronk, 2011; Tehard, 2006).

Premenopausal breast cancer

Summary

One study (three publications) reported on household activity and risk of premenopausal breast cancer was identified. For the highest versus the lowest household activity level, EPIC reported significant inverse associations with breast cancer that was diagnosed before aged 50 years, in women overall and obese women (Steindorf, 2013).

Postmenopausal breast cancer

Summary

Two studies (five publications) reported on household activity and risk of postmenopausal breast cancer were identified. The Swedish MDCS study (Ericson, 2009; Ericson, 2007) is a component study of the multi-centre cohort, EPIC (Steindorf, 2013; Steindorf, 2012; Lahmann, 2007). For the highest versus the lowest household activity level, EPIC reported significant inverse associations with breast cancer that was diagnosed after aged 50 years, in women overall and women of normal weight (Steindorf, 2013). Non-significant inverse associations were observed among overweight and obese women in this study.

Table 486 Household activity and breast cancer risk. Main study characteristics

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Steindorf, 2013 BRE80425 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, W	8 034/ 257 805 11.6 years	Cancer registry	Questionnaire/interview	Incidence, Invasive breast cancer	≥84 vs ≤24.6 met-hours/week	0.88 (0.81-0.95) Ptrend:0.004	Age, age at first child, age at menarche, age at menopause, alcohol, BMI, breastfeeding, centre location, educational level, HRT use, menopausal status, number of full-term pregnancies, occupational activity, oral contraceptive history, recreational activity, smoking, total physical activity
		2 943/			Incidence, breast cancer ER+/PR+	≥84 vs ≤24.6 met-hour/week	0.91 (0.79-1.04) Ptrend:0.100	
		875/			Incidence, breast cancer ER+/PR-	≥84 vs ≤24.6 met-hour/week	0.93 (0.72-1.19) Ptrend:0.433	
		808/			Incidence, breast cancer ER-/PR-	≥84 vs ≤24.6 met-hour/week	0.62 (0.47-0.81) Ptrend:0.006	
		4 860/			Incidence, breast cancer ER+	≥86.6 vs ≤26 met-hour/week	0.95 (0.86-1.05) Ptrend:0.207	
		1 147/			Incidence, breast cancer ER-	≥86.6 vs ≤26 met-hour/week	0.66 (0.53-0.82) Ptrend:<0.001	
		3 124/			Incidence, breast cancer PR+	≥86.6 vs ≤26 met-hour/week	0.88 (0.77-1.01) Ptrend:0.043	
		1 690/			Incidence, breast cancer PR-	≥86.6 vs ≤26 met-hour/week	0.76 (0.63-0.91) Ptrend:0.003	
		936/			Incidence,	≥84 vs ≤24.6	0.77 (0.61-0.97)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					Invasive breast cancer, age at diagnosis <=50yrs	met-hours/week	Ptrend:0.118	
		7 098/			Age at diagnosis >50yrs	≥84 vs ≤24.6 met-hours/week	0.89 (0.82-0.97) Ptrend:0.002	
		4 746/			BMI 18.5-25 kg/m2	≥84 vs ≤24.6 met-hour/week	0.84 (0.76-0.94) Ptrend:0.001	
		2 348/			BMI 25-30	≥84 vs ≤24.6 met-hour/week	0.93 (0.80-1.07) Ptrend:0.276	
		940/			BMI >=30	≥84 vs ≤24.6 met-hour/week	0.92 (0.73-1.16) Ptrend:0.289	
		683/			Normal BMI, age<=50y	≥84 vs ≤24.6 met-hour/week	0.85 (0.65-1.11) Ptrend:0.556	
		193/			Overweight, age<=50y	≥84 vs ≤24.6 met-hour/week	0.71 (0.42-1.19) Ptrend:0.362	
		60/			Obese, age<=50y	≥84 vs ≤24.6 met-hour/week	0.28 (0.11-0.73) Ptrend:0.020	
		4 063/			Normal BMI, age>50y	≥84 vs ≤24.6 met-hour/week	0.83 (0.73-0.93) Ptrend:0.001	
		2 155/			Overweight, age>50y	≥84 vs ≤24.6 met-hour/week	0.95 (0.82-1.10) Ptrend:0.411	
		880/			Obese, age>50y	≥84 vs ≤24.6 met-hour/week	0.98 (0.78-1.25) Ptrend:0.623	
Steindorf, 2012 BRE80432 Denmark,France,Germany,Greece,Italy,Netherlan	EPIC, Prospective Cohort, Age: 35-70 years,	1 059/ 283 827 11.7 years	Cancer registry	Questionnaire/interview	Incidence, In situ breast cancer	≥86.6 vs ≤26 met-hour/week	1.15 (0.92-1.44) Ptrend:0.316	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, breastfeeding,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
ds,Norway,Spain,Sweden,UK	W							centre location, educational level, HRT use, menopausal status, number of full-term pregnancies, occupational physical activity, oral contraceptive history, recreational activity, smoking, total physical activity
		138/			Age at diagnosis <=50yrs	≥86.6 vs ≤26 met-hour/week	0.84 (0.46-1.54) Ptrend:0.745	
		921/			Age at diagnosis >50yrs	≥86.6 vs ≤26 met-hour/week	1.23 (0.97-1.56) Ptrend:0.180	
		686/			BMI<25.0	≥86.6 vs ≤26 met-hour/week	1.26 (0.96-1.67) Ptrend:0.102	
		281/			BMI=25-29	≥86.6 vs ≤26 met-hour/week	0.91 (0.59-1.40) Ptrend:0.460	
		92/			BMI >=30.0	≥86.6 vs ≤26 met-hour/week	1.94 (0.80-4.69) Ptrend:0.406	
Pronk, 2011 BRE80388 China	SWHS, Prospective Cohort, Age: 40-70 years, W	717/ 73 049 9 years	Cancer registry	Interview	Incidence, breast cancer	≥42 vs 0-28 met-hour/week/year	0.89 (0.73-1.09) Ptrend:0.34	Age, age at first child birth, educational level, family history of breast cancer, number of pregnancies
Ericson, 2009 BRE80304 Sweden	MDCS, Nested Case Control, Age: 45-73	534/ 1066 controls 13 years	Cancer registry		Incidence, Invasive breast cancer	≥30 vs 0-9 hrs/week	0.56 (0.38-0.82) Ptrend:0.006	Age, laboratory batch

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	years, W, Postmenopausal							
Ericson, 2007 BRE80128 Sweden	MDCS, Prospective Cohort, Age: 50- years, Postmenopausal	382/ 11 699 9.5 years	Cancer registry	Questionnaire	Incidence, Invasive breast cancer, postmenopausal	≥30 vs 0-9 hours/week	0.60 (0.41-0.87) Ptrend:0.01	Age
Lahmann, 2007 BRE20026 Denmark,France,Germany,Greece,Italy,Netherlands,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 20-80 years, W	2 547/ 218 169 6.4 years	Population cancer registries and other procedures	Questionnaire	Incidence, Invasive breast cancer, postmenopause	≥91 vs ≤27 met-hour/week	0.81 (0.70-0.93) Ptrend:0.001	Age , age at first child, age at menarche, alcohol, BMI, educational level, HRT use, smoking habits, study center
					Postmenopause	per 20 met-hour/week	0.97 (0.94-0.99)	
		856/			Premenopause	≥91 vs ≤27 met-hour/week	0.71 (0.55-0.90) Ptrend:0.003	Oc use
					Premenopause	per 20 met-hour/week	0.96 (0.92-1.00)	
Tehard, 2006 BRE80108 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W	3 181/ 98 995 11.4 years	Patient records/direct contact/health Insurance records	Questionnaire	Incidence, breast cancer,	≥14 vs ≤0 hours/week	0.82 (0.61-1.11) Ptrend:<0.05	Age at first child, age at menarche, age-underlying cox models, benign breast disease, BMI, family history, HRT use, marital status, menopausal status, oc use, occupation, parity/pregnancies
		2 875/				≥5 vs ≤0 hours/week	0.97 (0.81-1.15) Ptrend:0.47	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Drake, 2001 BRE02418 USA	ACLS, 1970, Prospective Cohort, Age: 21-86 years, W, Fitness centre members	4 520 25 years	Not specified	Questionnaire	Incidence, breast cancer,	(mean exposure)		

6.1.3 Vigorous physical activity

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Overall summary

Twenty-five publications from 19 studies that examined vigorous or moderate to vigorous physical activity (of any type) were identified. No pooled analysis was identified.

Dose-response and the highest compared with the lowest meta-analyses were conducted to examine the association of vigorous physical activity with risk of breast cancer, and of premenopausal and postmenopausal breast cancer.

Table 487 Summary of results of the dose-response and the highest versus the lowest meta-analysis in the CUP SLR

	Breast cancer (any)	**Premenopausal breast cancer**	**Postmenopausal breast cancer**
Increment unit used	Per 30 minutes/day	Per 30 minutes/day	Per 30 minutes/day
Studies (n)	6	3	3
Cases	6 944	1 473	3 293
RR (95%CI)	0.95 (0.91-1.00)	0.91 (0.83-1.01)	0.94 (0.86-1.02)
Heterogeneity (I^2, p-value)	37%, 0.16	0%, 0.63	0%, 0.95
P value Egger test	0.32	-	-
Comparison	Highest versus lowest	Highest versus lowest	Highest versus lowest
Studies (n)	7	6	11
Cases	7 694	4 452	20 171
RR (95%CI)	0.86 (0.79-0.93)	0.83 (0.73-0.95)	0.90 (0.85-0.95)
Heterogeneity (I^2, p-value)	0%, 0.72	17%, 0.31	0%, 0.96

Breast cancer (any)

Summary

Main results:

Out of 12 studies (12 publications) identified, six studies (6 944 cases) and seven studies (7 694 cases) could be included in the dose-response and the highest versus lowest meta-analysis, respectively. Vigorous physical activity was inversely associated with breast cancer risk. Summary RR per 30 minutes/day was 0.95 (95% CI=0.91-1.00), and for highest versus lowest activity level, 0.86 (95% CI=0.79-0.93). Moderate and no heterogeneity was observed between studies included in the dose-response and the highest versus the lowest meta-analysis (37%, P=0.16; 0%, P=0.72, respectively).

Five studies were excluded from the highest versus the lowest meta-analysis. Tehard, 2006 was a component study of a multi-centre study (Steindorf, 2013) that was included in the analysis. Pudrovska, 2013 and Dorgan, 1994 reported dose-response results in units other than MET-hour and were also excluded from the dose-response meta-analysis. Each increase in times of vigorous activity was non-significantly inversely associated with breast cancer risk (Pudrovska, 2013) and each hour of vigorous activity replacing sleep was positively related to breast cancer risk (Dorgan, 1994). Another excluded study (Chang, 2003) observed a borderline significant inverse association. For breast cancer mortality, Arem, 2014 observed a non-significant positive association.

There was no evidence of significant publication or small study bias (P for Egger's test = 0.32 and 0.60 for studies in the dose-response and the highest versus the lowest meta-analysis, respectively).

Two studies (Rosenberg, 2014; Dallal, 2007) reported results by BMI category. Inverse associations were observed. One study (Dallal, 2007) reported a significant association among women of <25 kg/m^2.

Three studies (Rosenberg, 2014; Dallal, 2007; Lee, 2001) on hormone receptor subtypes reported non-significant inverse associations, except in the CTS study (Dallal, 2007), significant inverse associations were observed for long-term strenuous recreational physical activity and ER negative or ER-PR- breast cancers. RRs for the highest versus the lowest activity level were 0.45 (95% CI=0.27-0.76) and 0.35 (95% CI=0.19-0.65), respectively.

Sensitivity analyses:

Summary RR per 30 minutes/day vigorous physical activity ranged from 0.93 (95% CI=0.89-0.97) when Dorgan, 1994 was omitted to 0.96 (95% CI=0.91-1.01) when Rosenberg, 2014 was omitted in influence analysis. Studies included in the dose-response analysis were not further stratified due to low number of studies in the strata. CTS (Dallal, 2007) included in the highest versus the lowest analysis contributed 31% weight. Omitted one study at a time did not change summary RR for the categorical comparison materially.

Non-linear dose-response meta-analysis:

Non-linear dose-response meta-analysis was not conducted due to insufficient data.

Study quality:

All studies were North American studies. Silvera, 2006 was based in a RCT of screening for breast cancer and Lee, 2001 was based in a RCT of asprin and vitamin E. Rosenberg, 2014 was of black women only. All studies reported assessment of vigorous physical activity by questionnaire, which was validated in three studies published in recent years (Rosenberg, 2014; Cohen, 2013; Rockhill, 1999). Case ascertainment was through cancer registries or confirmed through medical records. All but three studies (Rosenberg, 2014; Cohen, 2013; Rockhill, 1999) were adjusted for age, BMI, alcohol intake, and reproductive factors. Rosenberg, 2014 did not adjust for alcohol intake and MHT use as including these factors in the model did not change the relative risk estimates.

Table 488 Vigorous physical activity and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	12 (12 publications)
Studies included in forest plot of highest compared with lowest exposure	7
Studies included in linear dose-response meta-analysis	6
Studies included in non-linear dose-response meta-analysis	Not enough studies

Note: Include cohort and nested case-control designs.

Table 489 Vigorous physical activity and breast cancer risk. Summary of the dose-response and the highest versus the lowest meta-analysis in the CUP SLR[1]

	CUP	**CUP**
Increment unit used/comparison	Per 30 minutes/day	Highest versus lowest
Studies (n)	6	7
Cases	6 944	7 694
RR (95%CI)	0.95 (0.91-1.00)	0.86 (0.79-0.93)
Heterogeneity (I^2, p-value)	37%, 0.16	0%, 0.72
P value Egger test	0.32	0.60

[1]Meta-analysis was not conducted in the 2005 SLR.

Table 490 Vigorous physical activity and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Wu, 2013	31 cohort studies[1]	63 786, 10 846 ER+PR+, 2 619 ER-PR-	Canada, China, Europe, Japan, USA	Incidence, any breast cancer in pre-, and/or postmenopausal women	Highest vs lowest, moderate physical activity (16 studies)	0.95 (0.90-0.99)	-	27%
					Vigorous physical activity (21 studies)	0.85 (0.80-0.90	-	33%

[1]All studies identified in the meta-analysis of Wu (2013) were included in the present review under different physical activity sections.

Table 491 Vigorous physical activity and breast cancer risk. Main characteristics of studies included in the dose-response and the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Rosenberg, 2014 BRE80563 USA	BWHS, Prospective Cohort, Age: 30- years, W	1 330/ 44 708 307 672 person-years	Self-report, linkage to cancer registries, medical and pathology records	Questionnaire, Vigorous physical activity at study baseline	Incidence, Invasive breast cancer	≥7 vs ≤0.9 hours/week	0.74 (0.57-0.96)	Age, fruits and vegetables consumption, meat consumption, parity, time period, years of education
		791/			BMI < 30 kg/m2	≥7 vs ≤0.9 hours/week	0.73 (0.53-1.01)	
		532/			BMI >= 30 kg/m2	≥7 vs ≤0.9 hours/week	0.81 (0.52-1.25)	
		669/			Incidence, breast cancer ER+	≥7 vs ≤0.9 hours/week	0.75 (0.52-1.09)	
		398/			Incidence, breast cancer ER-	≥7 vs ≤0.9 hours/week	0.85 (0.55-1.33)	
Cohen, 2013 BRE80470 USA	SCCS, Nested Case Control, Age: 40-79 years	456/ 546 9 years	Cancer registry		Incidence, Invasive breast cancer	≥2.1 vs ≤0 met-hours/day	0.93 (0.67-1.29)	Age, age at menarche, BMI, educational level, ethnicity, family history of breast cancer, health Insurance, household Income, HRT use, menopausal status, parity, physical activity, sedentary behaviour, smoking habits, source type
		448/				≥2.1 vs ≤0 met-hours/day	0.79 (0.59-1.06)	Physical activity
		312/			Black	≥2.1 vs ≤0 met-hours/day	0.98 (0.66-1.47)	
		306/			Black	≥2.1 vs ≤0 met-hours/day	0.73 (0.51-1.05)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		131/			White	≥2.1 vs ≤0 met-hours/day	0.96 (0.52-1.17)	
		130/			White	≥2.1 vs ≤0 met-hours/day	1.09 (0.62-1.90)	
Howard, 2009 BRE80286 USA	USRT, Prospective Cohort, Age: 47 years, W, radiologic technologists	864/ 45 631 8.9 years	Self-report verified by medical record	Questionnaire	Incidence, breast cancer	≥10 vs ≤0 hours/week	0.90 (0.47-1.71)	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, breast diseases , family history of cancer, menopausal hormone use, oc use, parity, physical activity, race, smoking habits
Dallal, 2007 BRE80016 USA	CTS, Prospective Cohort, Age: 27-86 years, W	2 649/ 110 599 6.6 years	Cancer registry	Questionnaire	Incidence, Invasive breast cancer,	≥5.01 vs 0-0.5 hours/week	0.94 (0.81-1.08)	Age, age at first child, alcohol, BMI, breast biopsies, ethnicity, family history, hormonal variables , mammography, menopausal status, parity/pregnancies, smoking habits
						≥5.01 vs 0-0.5 hours/week	0.80 (0.69-0.94)	
						≥5.01 vs 0-0.5 hours/week	1.03 (0.88-1.19)	
						≥5.01 vs 0-0.5 hours/week	0.99 (0.81-1.21)	
		1 879/			Incidence, breast cancer ER+,	≥5.01 vs 0-0.5 hours/week	0.89 (0.74-1.06)	
						≥5.01 vs 0-0.5 hours/week	0.98 (0.82-1.16)	
		1 455/			Incidence,	≥5.01 vs 0-0.5	0.74 (0.60-0.91)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					Invasive breast cancer, BMI <25	hours/week		
		1 452/			Incidence, breast cancer ER+/PR+,	≥5.01 vs 0-0.5 hours/week	0.94 (0.77-1.16)	
						≥5.01 vs 0-0.5 hours/week	1.02 (0.84-1.24)	
		1 094/			Incidence, Invasive breast cancer, BMI=>25	≥5.01 vs 0-0.5 hours/week	0.85 (0.67-1.09)	
		593/			Incidence, In situ breast cancer,	≥5.01 vs 0-0.5 hours/week	0.80 (0.57-1.14)	
						≥5.01 vs 0-0.5 hours/week	0.57 (0.33-0.99)	
						≥5.01 vs 0-0.5 hours/week	0.78 (0.57-1.06)	
						≥5.01 vs 0-0.5 hours/week	0.69 (0.48-0.98)	
		345/			Incidence, breast cancer ER-,	≥5.01 vs 0-0.5 hours/week	0.45 (0.27-0.76)	
						≥5.01 vs 0-0.5 hours/week	0.53 (0.33-0.85)	
		309/			Incidence, breast cancer ER-/PR-,	≥5.01 vs 0-0.5 hours/week	0.35 (0.19-0.65)	
						≥5.01 vs 0-0.5 hours/week	0.50 (0.30-0.83)	
		305/			Incidence, breast cancer ER+/PR-,	≥5.01 vs 0-0.5 hours/week	0.75 (0.47-1.18)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
						≥5.01 vs 0-0.5 hours/week	0.95 (0.62-1.47)	
Silvera, 2006 BRE24118 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	1 158/ 38 645 16.4 years	Partially histological - over 80%		Incidence, breast cancer,	≥61 vs 0-30 min/day	0.93 (0.78-1.10)	Age , age at first child, age at menarche, alcohol, BMI, breast diseases , energy Intake , family history, HRT use, menopausal status, oc use, other design Issue, parity/pregnancies, recruitment center, smoking habits
Lee, 2001 BRE15848 USA, Puerto Rico	WHS, Prospective Cohort, Age: 45- years, W, Registered nurses	411/ 39 322 48 months	Medical records + self-reported +death certificate	Questionnaire	Incidence, Invasive & In situ breast cancer,	≥4200 vs ≤0 kj/week	0.98 (0.69-1.40)	Age at first child, age at menarche, alcohol, BMI, family history, HRT use, menopausal status, oc use, parity/pregnancies
		222/			Incidence, breast cancer ER+/PR+,	≥4200 vs ≤0 kj/week	0.89 (0.54-1.48)	
Rockhill, 1999 BRE80175 USA	NHS, Prospective Cohort, Age: 30-55 years, W	121 701 16 years	Questionnaire/hospital records & pathology reports	Questionnaire	Incidence	≥7 vs <1 hours/week	0.89 (0.80-0.98)	Age at entry, age at first child birth, age at menarche, BMI at age 18 years, family history of cancer, height, history of breast cyst, menopausal status, parity, postmenopausal hormone use
						≥7 vs <1 hours/week	0.82 (0.70-0.97)	
						≥7 (vigorous) vs <1 (any activity) hours/week	0.87 (0.71-1.06)	

Table 492 Vigorous physical activity and breast cancer risk. Main characteristics of studies excluded from the dose-response and the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Arem, 2014 BRE80498 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W, Retired	436/ 121 845 12.1 years	Linkage to the social security administration death master file and the national death Index	Questionnaire	Mortality, breast cancer	per 1 hours	1.01 (0.98-1.04)	Sex, age at menarche, alcohol, BMI, calories, diabetes, educational level, healthy eating Index 2010 score, HRT use, marital status, race, screening In the three years prior to questionnaire, smoking status and dose	Excluded, breast cancer mortality, not enough studies to analyse
						≥7.1 vs never/rare hours/week	1.08 (0.76-1.53)		
		247/			Never smokers	per 1 hours	1.02 (0.98-1.06)		
		189/			Never smokers	per 1 hours	0.99 (0.95-1.04)		
Pudrovska, 2013 BRE80477 USA	WLS, Prospective Cohort, W	261/ 3 682	Self-report and/or death certificate	Interview	Incidence, breast cancer, diagnosed after 1993	per 1 times	0.97 (0.91-1.05)	Adiposity, age at menarche, age at menopause, alcohol consumption, BMI,	Excluded, dose-response results per times of vigorous activity

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								educational level, family history of breast cancer, high-status job, household Income, HRT use, hysterectomy, marital status, number of childbirths, occupation, parity and age at first birth, parity/pregnancies, propensity score	
						per 1 times	1.07 (0.94-1.22)		
Tehard, 2006 BRE80108 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W	3 047/ 98 995 11.4 years	Patient records/direct contact/health Insurance records	Questionnaire	Incidence, breast cancer,	≥14 vs ≤0 hours/week	0.89 (0.65-1.24)	Age at first child, age at menarche, age-underlying cox models, benign breast disease, BMI, family history, HRT use, marital status, menopausal status, oc use, occupation, parity/pregnancies	Superseded by Steindorf, 2013

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		2 941/				≥5 vs ≤0 hours/week	0.62 (0.49-0.78)		
Chang, 2003 BRE18295 USA	PLCO, 1973, Prospective Cohort, Age: 55-74 years, W, Screening Program	27 534 7 years	Partially histological - over 80%	Questionnaire	Incidence, breast cancer,	≥4 vs ≤3.9 hours/week	0.83 (0.69-1.00)		Excluded, limited information from a poster abstract
Dorgan, 1994 BRE02385 USA	FHS, Prospective Cohort, Age: 35-68 years, W	2 307 28 years	All histology	Questionnaire, leisure time physical activity	Incidence, breast cancer,	Replace sleep by per 1 hours/day sedentary to slight physical activity	1.10 (0.90-1.30)	Age , age at first child, alcohol, educational level, menopausal status, occupation, parity/pregnancies	Excluded, dose-response results replace one hour of sleep by one hour of leisure time physical activity
						Replace sleep by per 1 hours/day moderate to heavy physical activity	1.20 (1.00-1.06)		

Figure 509 RR estimates of breast cancer by levels of vigorous physical activity

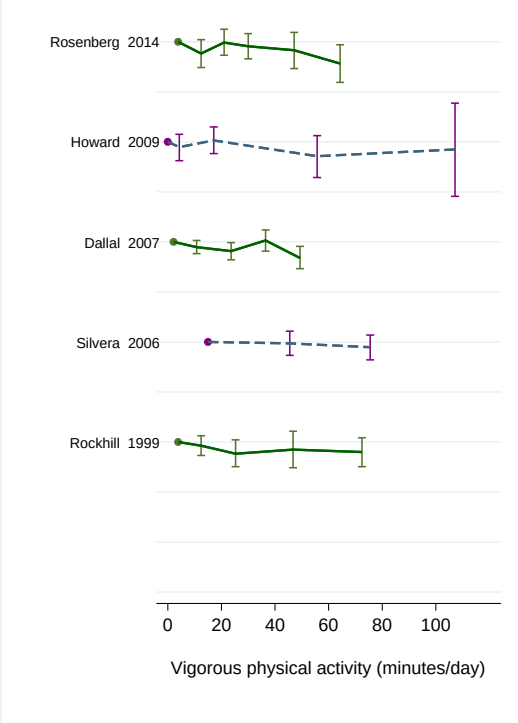


Figure 510 RR (95% CI) of breast cancer for the highest compared with the lowest level of vigorous physical activity

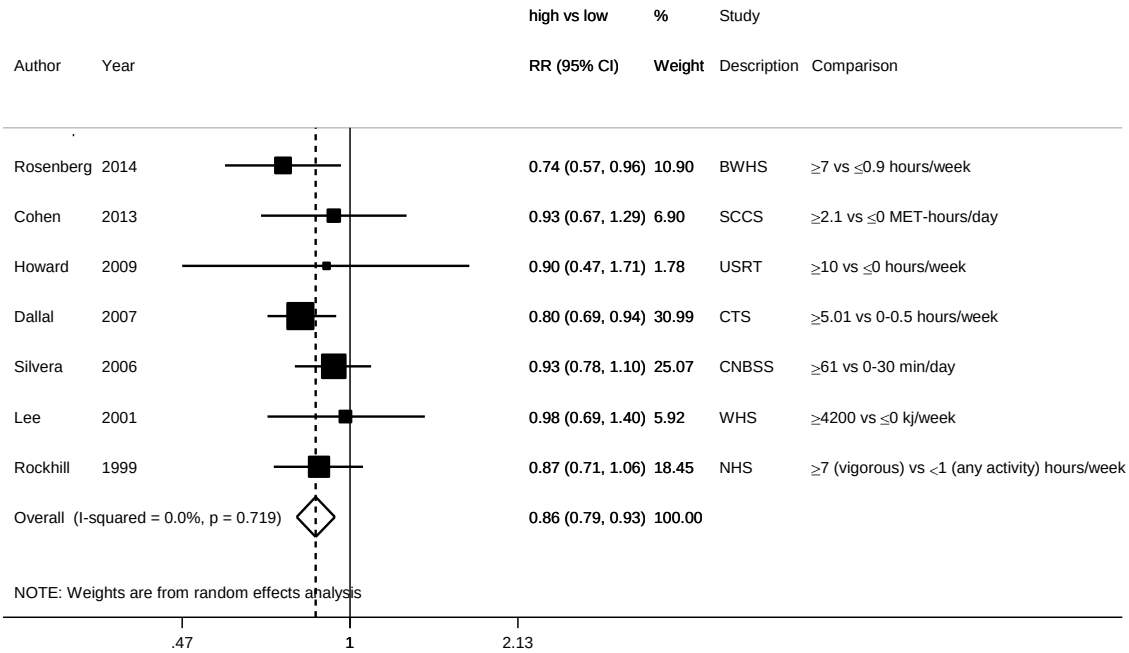


Figure 511 Relative risk of breast cancer for 30 minutes/day increase of vigorous physical activity

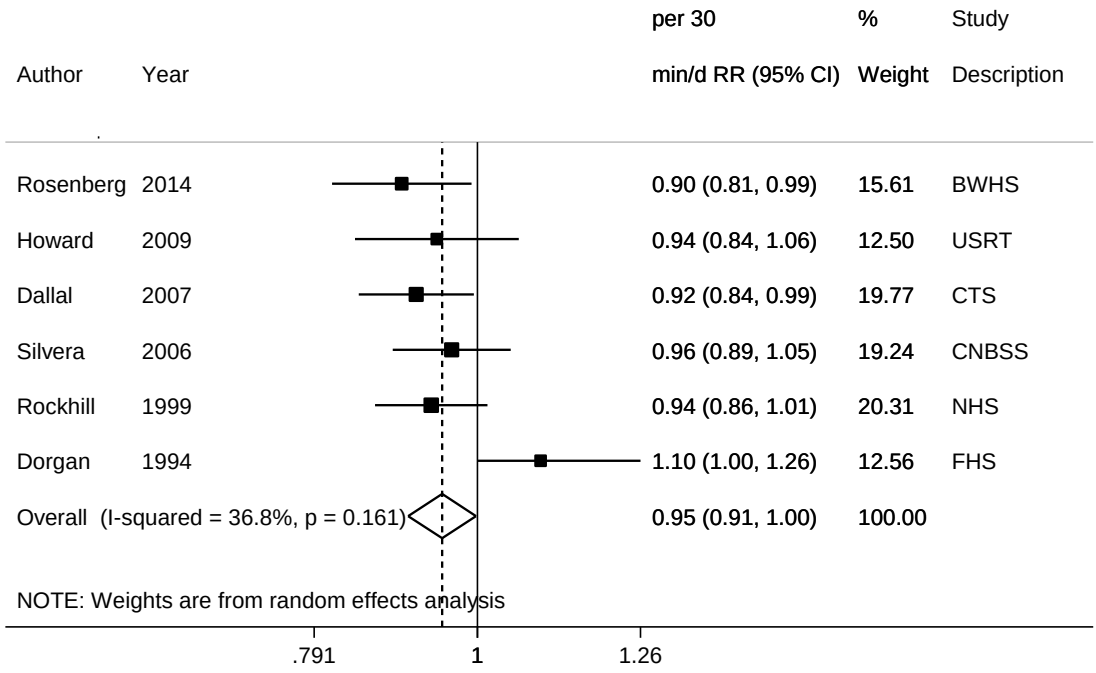
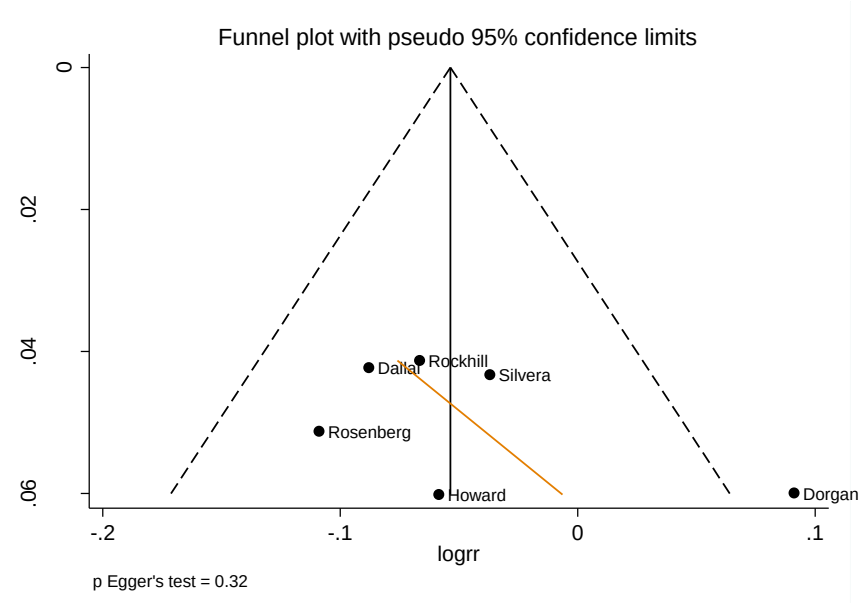


Figure 512 Funnel plot of studies included in the dose response meta-analysis of vigorous physical activity and breast cancer



Premenopausal breast cancer

Summary

Main results:

All six studies (seven publications) (4 452 cases) identified could be included in the highest versus lowest meta-analysis. Three studies (1 473 cases) were in the dose-response meta-analysis. Vigorous physical activity was inversely associated with premenopausal breast cancer risk. Summary RR per 30 minutes/day was 0.91 (95% CI=0.83-1.01, I^2=0%, P=0.63) and for the highest versus lowest activity level comparison, summary RR was 0.83 (95% CI=0.73-0.95, I^2=17%, P=0.31).

Sensitivity analyses:

Summary RR per 30 minutes/day vigorous physical activity ranged from 0.88 (95% CI=0.77-1.00) when Howard, 2009 was omitted to 0.94 (95% CI=0.83-1.06) when Rosenberg, 2014 was omitted in influence analysis.

Non-linear dose-response meta-analysis:

Non-linear dose-response meta-analysis was not conducted due to insufficient data.

Study quality:

Except for one multi-centre study that was based in Europe (Steindorf, 2013), all others were North American studies. Silvera, 2006 was based in a RCT of breast cancer screening. All studies reported assessment of vigorous physical activity by questionnaire, which was validated in one study published in recent years (Rosenberg, 2014). Case ascertainment was through cancer registries or confirmed through medical records. All but two studies (Rosenberg, 2014; Maruti, 2008b) was adjusted for age, BMI, alcohol intake, and reproductive factors. Rosenberg, 2014 did not adjust for alcohol intake as including this factor in the model did not change the relative risk estimates.

Table 493 Vigorous physical activity and premenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	6 (7 publications)
Studies included in forest plot of highest compared with lowest exposure	6
Studies included in linear dose-response meta-analysis	3
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 494 Vigorous physical activity and premenopausal breast cancer risk. Summary of the dose-response and the highest versus the lowest meta-analysis in the CUP SLR[1]

	CUP SLR	CUP
Increment unit used/comparison	Per 30 minutes/day	Highest versus lowest
Studies (n)	3	6
Cases	1 473	4 452
RR (95%CI)	0.91 (0.83-1.01)	0.83 (0.73-0.95)
Heterogeneity (I^2, p-value)	0%, 0.63	17%, 0.31
P value Egger test	-	

[1]Meta-analysis was not conducted in the 2005/2008 SLR.

Table 495 Vigorous physical activity and premenopausal breast cancer risk. Main characteristics of studies included in the dose-response and the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Rosenberg, 2014 BRE80563 USA	BWHS, Prospective Cohort, Age: 30- years, W	483/ 44 708 307 672 person-years	Self-report, linkage to cancer registries, medical and pathology records	Questionnaire	Incidence, Invasive breast cancer, premenopause	≥7 vs ≤0.9 hours/week	0.64 (0.42-0.98)	Age, fruits and vegetables consumption, meat consumption, parity, time period, years of education	
Howard, 2009 BRE80286 USA	USRT, Prospective Cohort, Age: 47 years, W, radiologic technologists	440/ 45 631 8.9 years	Self-report verified by medical record	Questionnaire	Incidence, breast cancer, premenopause	≥10 vs ≤0 hours/week	1.04 (0.45-2.40)	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, breast diseases , family history of cancer, menopausal hormone use, oc use, parity, physical activity, race, smoking habits	
Maruti, 2008b BRE80219 USA	NHS II, Prospective Cohort, Age: 33-51 years, W, Premenopausal	550/ 64 777 6 years	Self report verified by medical record	Self completed questionnaire, lifetime vigorous recreational physical activity	Incidence, Invasive breast cancer, premenopausal	≥4 vs ≤0.9 hours/week	0.90 (0.68-1.18)	Age, age at first child birth, alcohol Intake, benign breast disease, body shape, family history of	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								cancer, height, ocp use, parity	
						≥4 vs ≤0.9 hours/week	0.81 (0.59-1.10)		
Dallal, 2007 BRE80016 USA	CTS, Prospective Cohort, Age: 27-86 years, W	1 062/ 110 599 6.6 years	Cancer registry	Questionnaire	Incidence, Invasive breast cancer, age < 55 years	≥5.01 vs 0-0.5 hours/week	0.68 (0.53-0.87)	Age at first child, alcohol, BMI, breast biopsies, ethnicity, family history, hormonal variables , mammography, menopausal status, parity/pregnancies, smoking habits	Highest vs lowest analysis only, missing cases and person-years per category,
Silvera, 2006 BRE24118 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	818/ 38 645 16.4 years	Partially histological - over 80%		Incidence, breast cancer, premenopausal	≥61 vs 0-30 min/day	0.87 (0.68-1.09)	Age , age at first child, age at menarche, alcohol, BMI, breast diseases , energy Intake , family history, HRT use, menopausal status, oc use, other design Issue, parity/pregnancies, recruitment center, smoking	Highest vs lowest analysis only, missing cases and person-years per category,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								habits	
Margolis, 2005 BRE23306 Norway, Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W, Young women	1 099/ 99 504 9.1 years	Partially histological - over 80%	Questionnaire	Incidence, Invasive breast cancer,	≥5 vs ≤0 years/life	0.95 (0.75-1.19)	Age , age at first child, age at menarche, alcohol, BMI, country of birth, duration of breastfeeding, educational level, family history, height, menopausal status, oc use, parity/pregnancies, smoking habits	Highest vs lowest analysis only, exposure was per years of vigorous physical activity in life.

Table 496 Vigorous physical activity and premenopausal breast cancer risk. Main characteristics of studies excluded from the dose-response and the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Rockhill, 1998 BRE80176 USA	NHS II, Prospective Cohort, Age: 22-42 years,	116 671 6 years	Questionnaire/hospital records & pathology reports	Questionnaire	Incidence, Invasive & In situ breast cancer	≥7 vs ≤0.9 hours/week	1.10 (0.80-1.50)	Age at entry, age at first child birth, age at menarche, alcohol	Excluded, vigorous activity in recent years (Results on

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	W, Premenopausal							consumption, family history of cancer, family history of cancer, height, height, history of breast cyst, history of breast cyst, oral contraceptive history, oral contraceptive history, parity, recent alcohol consumption, recent alcohol consumption	long-term vigorous activity from the same study (Maruti, 2008b) was included in the analysis)

Figure 513 RR estimates of premenopausal breast cancer by levels of vigorous physical activity

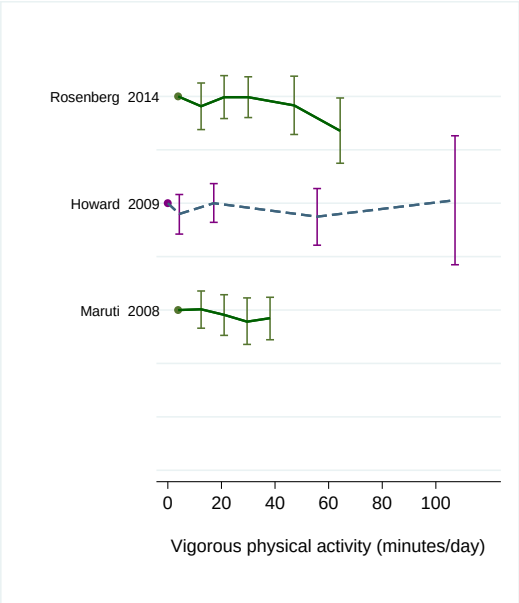


Figure 514 RR (95% CI) of premenopausal breast cancer for the highest compared with the lowest level of vigorous physical activity

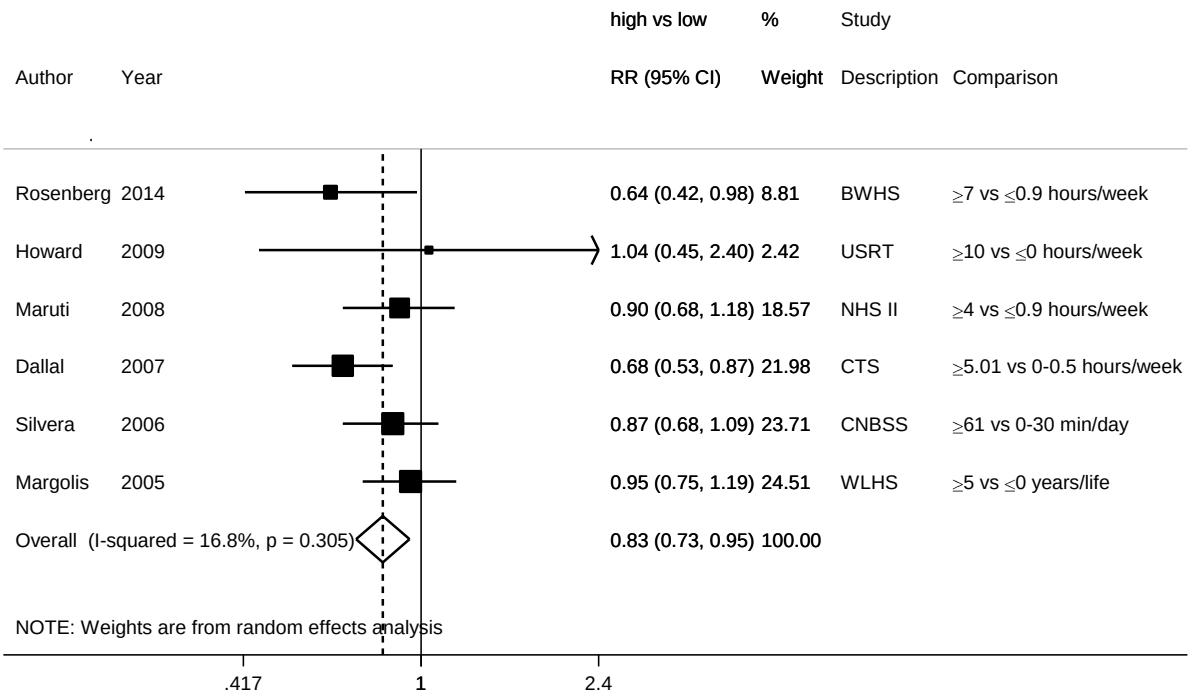
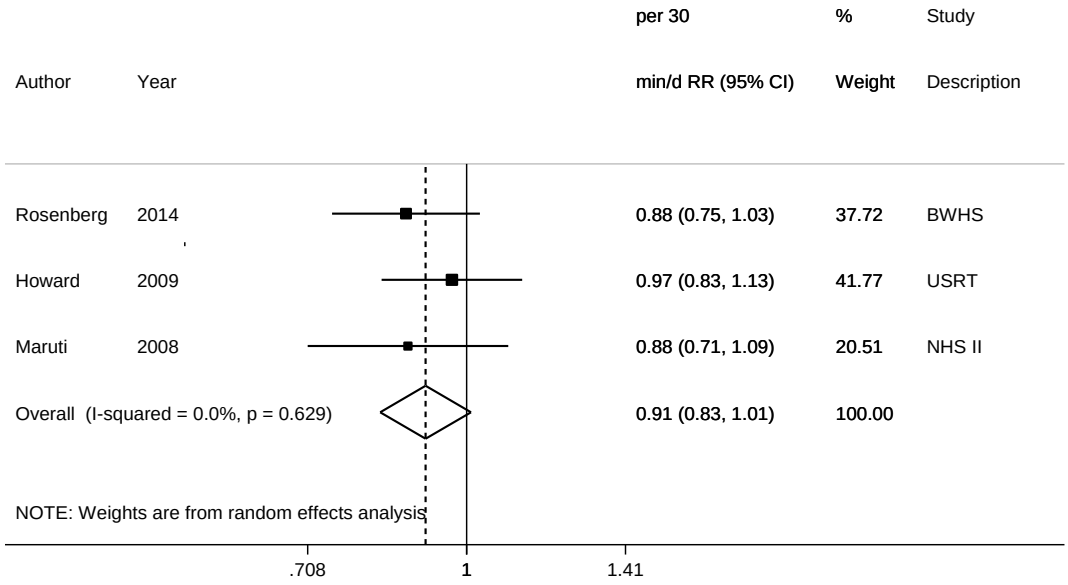


Figure 515 Relative risk of premenopausal breast cancer for 30 minutes/day increase of vigorous physical activity



Postmenopausal breast cancer

Summary

Main results:

Out of 12 studies (15 publications) identified, three studies (3 293 cases) and 11 studies (20 171 cases) could be included in the dose-response and the highest versus the lowest meta-analysis, respectively. Vigorous physical activity was non-significantly and significantly inversely associated with postmenopausal breast cancer risk, respectively. Summary RR per 30 minutes/day was 0.94 (95% CI=0.86-1.02, I^2=0%, P=0.95), and for the highest versus the lowest activity level, 0.90 (95% CI=0.85-0.95, I^2=0%, P=0.96).

WHI (CT and OS) (Phipps, 2011) was excluded as only results on breast cancer subtype were reported. Results on overall breast cancer in WHI-OS were included in the analysis (McTiernan, 2003).

One study (Leitzmann, 2008) reported a significant effect modification of BMI for vigorous activity in postmenopausal breast cancer risk (Pinteraction=0.008) (RRs for highest vs lowest=0.68, 95%CI=0.54-0.85 in BMI<25 kg/m^2 and 1.18, 95% CI=0.93-1.49 in BMI ≥25 kg/m^2). Another study (Peters, 2009a) observed inverse associations in the two BMI groups.

Four studies (Phipps, 2011; Peters, 2009b; Leitzmann, 2008; Lee, 2001) reported results by hormone receptor subtypes observed mostly non-significant inverse associations, except for NIH-AARP (Peters, 2009b) that reported a significant inverse association between high

moderate/vigorous activity compared with none in the past 10 years with ER positive breast cancer.

Sensitivity analyses:

Summary RR per 30 minutes/day did not change materially when studies were omitted in turn in influence analysis. Brinton, 2014 contributed 51% weight in the highest versus lowest analysis. Summary RR for highest vs lowest comparison did not change materially in influence analysis.

Non-linear dose-response meta-analysis:

Non-linear dose-response meta-analysis was not conducted due to insufficient data.

Study quality:

Except for one multi-centre study that was based in Europe (Steindorf, 2013), all others were North American studies. Silvera, 2006 was based in a RCT of breast cancer screening and Lee, 2001 was based in a RCT of asprin and vitamin E. All studies reported assessment of vigorous physical activity by questionnaire, which was validated in three studies published in recent years (Rosenberg, 2014; Eliassen, 2010; McTiernan, 2003). Case ascertainment was through cancer registries or confirmed through medical records. All but three studies (Rosenberg, 2014; Dirx, 2001; Moore, 2000) were adjusted for age, BMI, alcohol intake, and reproductive factors and Lee, 2001 was not further adjusted for MHT use. Rosenberg, 2014 did not adjust for alcohol intake as including this factor in the model did not change the relative risk estimates.

Table 497 Vigorous physical activity and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	12 (15 publications)
Studies included in forest plot of highest compared with lowest exposure	11
Studies included in linear dose-response meta-analysis	3
Studies included in non-linear dose-response meta-analysis	Not enough studies

Note: Include cohort and case-cohort designs.

Table 498 Vigorous physical activity and postmenopausal breast cancer risk. Summary of the dose-response and the highest versus the lowest meta-analysis in the CUP SLR[1]

	CUP	CUP
Increment unit used	Per 30 minutes/day	Highest versus lowest
Studies (n)	3	11
Cases	3 293	20 171
RR (95%CI)	0.94 (0.86-1.02)	0.90 (0.85-0.95)
Heterogeneity (I^2, p-value)	0%, 0.95	0%, 0.96
P value Egger test	-	

[1]Meta-analysis was not conducted in the 2005 SLR.

Table 499 Vigorous physical activity and postmenopausal breast cancer risk. Main characteristics of studies included in the dose-response and the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Brinton, 2014 BRE80579 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W, Postmenopausal	7 299/ 190 872 9.3 years	Cancer registry	Questionnaire	Incidence, Invasive breast cancer	≥5 vs 0-0.9 times/month	0.91 (0.85-0.99)	Age at menarche, alcohol Intake, BMI, breast biopsies, educational level, family history of breast cancer In first degree relatives, marital status, menopausal age, menopausal status, parity and age at first birth, postmenopausal hormone use, race	Highest vs lowest meta-analysis only
		3 830/			Age of follow-up 60-69 years	≥5 vs 0-0.9 times/month	0.86 (0.77-0.95)		
		2 668/			Age of follow-up >=70 years	≥5 vs 0-0.9 times/month	1.01 (0.90-1.15)		
		801/			Age of follow-up 50-59 years	≥5 vs 0-0.9 times/month	0.88 (0.68-1.13)		
Rosenberg, 2014 BRE80563 USA	BWHS, Prospective Cohort, Age: 30- years, W	661/ 44 708 307 672 person-years	Self-report, linkage to cancer registries, medical and pathology records	Questionnaire	Incidence, Invasive breast cancer, postmenopause	≥7 vs ≤0.9 hours/week	0.94 (0.66-1.36)	Age, fruits and vegetables consumption, meat consumption, parity, time	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								period, years of education	
Eliassen, 2010 BRE80311 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Postmenopausal	4 782/ 95 396 20 years	Questionnaire	Self-report	Incidence, postmenopausal breast cancer	per 20 met-hours/week	0.89 (0.82-0.97)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, BMI, family history of breast cancer, height, history of breast disease, HRT use, parity	Highest vs lowest meta-analysis only
						≥27 vs <3 met-hour/week	0.85 (0.69-1.05)		
						≥27 vs <3 met-hour/week	0.83 (0.70-0.98)		
						per 20 met-hours/week	0.88 (0.80-0.97)		
		4 332/				≥27 vs <3 met-hour/week	0.92 (0.78-1.09)		
						per 20 met-hours/week	0.95 (0.88-1.03)		
Howard, 2009 BRE80286 USA	USRT, Prospective Cohort, Age: 47 years, W, radiologic technologists	285/ 45 631 8.9 years	Self report verified by medical record	Questionnaire	Incidence, breast cancer, ever used HRT	≥10 vs ≤0 hours/week	1.19 (0.43-3.34)	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, breast diseases , family	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								history of cancer, menopausal hormone use, oc use, parity, physical activity, race, smoking habits	
		139/			Never HRT users	4-9 vs ≤0 hours/week	0.61 (0.24-1.53)		
Leitzmann, 2008 BRE80204 USA	BCDDP, 1973, Prospective Cohort, W, Postmenopausal	1 506/ 32 269 11 years	Self-reported/ death certificate/ medical records	Self-completed questionnaire	Incidence, Invasive & In situ breast cancer, postmenopausal	126.1-588 vs ≤0 met hr/week	0.86 (0.73-1.01)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, benign breast disease, dietary fat, educational level, family history of cancer, health screening, height, menopausal hormone use, oral contraceptive use, smoking habits	Highest vs lowest meta-analysis only
						299.1-504 vs 0-84 met hr/week	1.02 (0.87-1.19)	BMI, physical activity	
						126.1-588 vs ≤0 met hr/week	0.87 (0.74-1.02)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
						299.1-504 vs 0-84 met hr/week	1.01 (0.86-1.18)		
		876/			Postmenopausal, BMI<25	126.1-588 vs ≤0 met hr/week	0.68 (0.54-0.85)		
						299.1-504 vs 0-84 met hr/week	0.98 (0.79-1.21)		
		706/			Incidence, breast cancer ER+, postmenopausal	126.1-588 vs ≤0 met hr/week	0.91 (0.72-1.15)		
		630/			Incidence, Invasive & In situ breast cancer, postmenopausal, BMI>=25	126.1-588 vs ≤0 met hr/week	1.18 (0.93-1.49)		
						299.1-504 vs 0-84 met hr/week	1.09 (0.85-1.39)		
		588/			Incidence, breast cancer PR+, postmenopausal	126.1-588 vs ≤0 met hr/week	0.93 (0.72-1.22)		
		555/			Incidence, breast cancer ER+/PR+, postmenopausal	126.1-588 vs ≤0 met hr/week	0.93 (0.71-1.23)		
		417/			Incidence, breast cancer ER+, postmenopausal, BMI<25	126.1-588 vs ≤0 met hr/week	0.75 (0.54-1.03)		
		327/			Incidence, breast cancer ER+/PR+, postmenopausal, BMI<25	126.1-588 vs ≤0 met hr/week	0.81 (0.56-1.17)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		289/			Incidence, breast cancer ER+, postmenopausal, BMI>=25	126.1-588 vs ≤0 met hr/week	1.19 (0.83-1.69)		
		248/			Incidence, breast cancer PR-, postmenopausal	126.1-588 vs ≤0 met hr/week	0.77 (0.52-1.15)		
		228/			Incidence, breast cancer ER+/PR+, postmenopausal, BMI>=25	126.1-588 vs ≤0 met hr/week	1.14 (0.76-1.71)		
		161/			Incidence, breast cancer ER-, postmenopausal	126.1-588 vs ≤0 met hr/week	0.74 (0.44-1.27)		
		126/			Incidence, breast cancer ER-/PR-, postmenopausal	126.1-588 vs ≤0 met hr/week	0.76 (0.42-1.35)		
		115/			Incidence, breast cancer ER+/PR-, postmenopausal	126.1-588 vs ≤0 met hr/week	0.49 (0.10-2.32)		
		29/			Incidence, breast cancer ER-/PR+, postmenopausal	126.1-588 vs ≤0 met hr/week	0.81 (0.46-1.41)		
Dallal, 2007 BRE80016 USA	CTS, Prospective Cohort, Age: 27-86 years, W	1 587/ 110 599 6.6 years	Cancer registry	Questionnaire	Incidence, Invasive breast cancer, age >= 55 years	≥5.01 vs 0-0.5 hours/week	0.90 (0.74-1.10)	Age at first child, alcohol, BMI, breast biopsies, ethnicity, family history, hormonal	Highest vs lowest meta-analysis only; missing number of cases and non-cases per category

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								variables , mammography, menopausal status, parity/pregnancies, smoking habits	
Silvera, 2006 BRE24118 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	662/ 38 645 16.4 years	Partially histological - over 80%		Incidence, breast cancer, postmenopausal	≥61 vs 0-30 min/day	1.00 (0.78-1.29)	Age , age at first child, age at menarche, alcohol, BMI, breast diseases , energy Intake , family history, HRT use, menopausal status, oc use, other design Issue, parity/pregnancies, recruitment center, smoking habits	Highest vs lowest meta-analysis only; missing number of cases and non-cases per category
McTiernan, 2003 BRE17819 USA	Women's Health Initiative - Observational study, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	1 768/ 74 171 4.7 years	Medical record + pathology report + family report	Questionnaire	Incidence, Invasive & In situ breast cancer, postmenopausal	≥7 vs ≤0 hours/week	0.79 (0.63-0.99)	Age , age at first child, age at menarche, age at menopause, alcohol, BMI, breastfeeding, educational level, ethnicity, family history, HRT use, Income,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								mammography, oophorectomy/hysterectomy, parity/pregnancies, place of residence, smoking habits	
						≥4 vs ≤0 hours/week	0.91 (0.67-1.20)		
		1 747/			Postmenopausal	yes vs no	0.92 (0.83-1.01)		
		1 719/			Postmenopausal	yes vs no	0.86 (0.78-0.95)		
		1 709/			Postmenopausal	yes vs no	0.94 (0.85-1.04)		
Dirx, 2001 BRE02326 Netherlands	NLCS, Case Cohort, Age: 55-69 years, W, Postmenopausal	306/ 62 573 7.3 years	Not specified	Questionnaire	Incidence, breast cancer, postmenopausal	≥6.01 vs ≤4 met score	0.84 (0.55-1.29)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, body weight, educational level, energy Intake , family history, parity/pregnancies	Highest vs lowest meta-analysis only
Lee, 2001 BRE15848 USA, Puerto Rico	WHS, Prospective Cohort, Age: 45- years,	261/ 39 322 48 months	Medical records + self-reported +death certificate	Questionnaire	Incidence, Invasive & In situ breast cancer,	≥4200 vs ≤0 kj/week	0.76 (0.47-1.24)	Age at first child, age at menarche, alcohol, BMI,	Highest vs lowest meta-analysis only

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	W, Registered nurses				postmenopausal			family history, HRT use, menopausal status, oc use, parity/pregnancies	
		157/			Incidence, breast cancer ER+/PR+, postmenopausal	≥4200 vs ≤0 kj/week	0.79 (0.42-1.49)		
Moore, 2000 BRE16124 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	1 371/ 41 837 10 years	Cancer registry + death certificate	Questionnaire	Incidence, breast cancer,	>4 times/week vs rarely or never	0.92 (0.77-1.10)	Age , age at first child, age at menopause, BMI, BMI, BMI, educational level, family history, HRT use, whr	Highest vs lowest meta-analysis only
		1 365/				>4 times/week vs rarely or never	0.05 (0.72-1.52)		

Table 500 Vigorous physical activity and postmenopausal breast cancer risk. Main characteristics of studies excluded from the dose-response and the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Nyante, 2013 BRE80496 USA	NIH-AARP, Prospective Cohort,	5 267/ 192 076 9.6 years	Cancer registry	Questionnaire	Incidence, ductal carcinomas	≥5 vs ≤0 times/week	0.90 (0.82-0.99)	Age, age at first child birth, age at menarche, age	Excluded, breast cancer subtype, not enough

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Age: 50-71 years, W, Postmenopausal							at menopause, alcohol Intake, BMI, breast biopsies, educational level, family history of breast cancer, height, HRT use, marital status, OC use, parity, race, type of menopause, weight	studies to analyse (Results on overall breast cancer from the same study (Brinton, 2014) were included in the analysis)
		824/			Incidence, lobular carcinoma	≥5 vs ≤0 times/week	0.90 (0.70-1.16)		
		634/			Incidence, ductal-lobular breast cancer	≥5 vs ≤0 times/week	0.89 (0.68-1.18)		
		215/			Incidence, mucinous breast cancer	≥5 vs ≤0 times/week	1.11 (0.64-1.91)		
		131/			Incidence, tubular breast cancer	≥5 vs ≤0 times/week	0.58 (0.30-1.11)		
Phipps, 2011 BRE80343 USA	Women's Health Initiative, Prospective Cohort, Age: 50-79 years,	2 491/ 155 723 7.9 years	Mail or telephone questionnaires verified by trained physician	Questionnaire	Incidence, breast cancer ER+	≥5.75 vs ≤0	0.88 (0.79-0.98)	Age, educational level, family history of breast cancer, Income, mammography, mammography,	Excluded, breast cancer subtype, not enough studies to analyse

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	W, Postmenopausal		adjudicators					moderate activity, race	(Results on overall breast cancer from the same study (McTiernan, 2003) were included in the analysis)
						≥10.5 vs ≤0	0.95 (0.84-1.07)		
		296/			Incidence, triple negative breast cancer	≥5.75 vs ≤0	0.75 (0.54-1.04)		
						≥10.5 vs ≤0	0.98 (0.68-1.44)		
Peters, 2009a BRE80265 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W, Postmenopausal	6 609/ 182 862 7 years	Cancer registry	Self-administered questionnaire	Incidence, breast cancer	≥5 vs ≤0 times/week	0.87 (0.81-0.95)	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, educational level, ethnicity, family history of cancer, menopausal hormone use, parity, smoking status	Superseded by Brinton, 2014, BRE80579
						≥5 vs ≤0 times/week	0.92 (0.85-1.00)	BMI	
		2 083/			Incidence, breast cancer ER+	≥5 vs ≤0 times/week	0.97 (0.84-1.12)		
		411/			Incidence, breast	≥5 vs ≤0	0.75 (0.54-1.04)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					cancer ER-	times/week			
		1 649/			Incidence, breast cancer ER+/PR+	≥5 vs ≤0 times/week	0.96 (0.82-1.13)		
		338/			Incidence, breast cancer ER+/PR-	≥5 vs ≤0 times/week	1.05 (0.73-1.51)		
		48/			Incidence, breast cancer ER-/PR+	≥5 vs ≤0 times/week	0.62 (0.21-1.86)		
		359/			Incidence, breast cancer ER-/PR-	≥5 vs ≤0 times/week	0.78 (0.55-1.10)		
		3 039/			Incidence, breast cancer unknown ER/PR status	≥5 vs ≤0 times/week	0.81 (0.72-0.91)		
		1 176/			Incidence, In situ breast cancer	≥5 vs ≤0 times/week	0.93 (0.77-1.13)		
		5 433/			Incidence, Invasive breast cancer	≥5 vs ≤0 times/week	0.86 (0.79-0.94)		
		3 158/			Incidence, localized breast cancer	≥5 vs ≤0 times/week	0.85 (0.76-0.96)		
		1 298/			Incidence, regional and distant breast cancer	≥5 vs ≤0 times/week	0.85 (0.71-1.01)		
		3 568/			Incidence, ductal carcinomas	≥5 vs ≤0 times/week	0.89 (0.80-0.99)		
		436/			Incidence,	≥5 vs ≤0	0.89 (0.66-1.20)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					lobular carcinoma	times/week			
		2 822/			Incidence, breast cancer, BMI <25	≥5 vs ≤0 times/week	0.95 (0.87-1.05)		
		3 787/			BMI >=25	≥5 vs ≤0 times/week	0.86 (0.77-0.96)		
		4 073/			PMH - ever users	≥5 vs ≤0 times/week	0.97 (0.88-1.08)		
		2 528/			PMH - never users	≥5 vs ≤0 times/week	0.76 (0.67-0.86)		
Peters, 2009b BRE80266 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W, Postmenopausal	4 258/ 118 899 6.6 years	Cancer registry	Self-administered questionnaire	Incidence, breast cancer	≥7.1 vs ≤0 hours/week	0.87 (0.78-0.96)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, BMI, educational level, ethnicity, family history of cancer, menopausal hormone use, parity, smoking status	Excluded, exposure was moderate to vigorous physical activity in past 10 years (Baseline data from the same study (Brinton, 2014) was included in the analysis)
		1 352/			Incidence, breast cancer ER+	≥7.1 vs ≤0 hours/week	0.77 (0.64-0.92)		
		263/			Incidence, breast cancer ER-	≥7.1 vs ≤0 hours/week	0.87 (0.58-1.29)		
		3 522/			Incidence, invasive breast cancer	≥7.1 vs ≤0 hours/week	0.84 (0.75-0.94)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		736/			Incidence, in situ breast cancer	≥7.1 vs ≤0 hours/week	0.85 (0.66-1.08)		

Figure 516 RR estimates of postmenopausal breast cancer by levels of vigorous physical activity

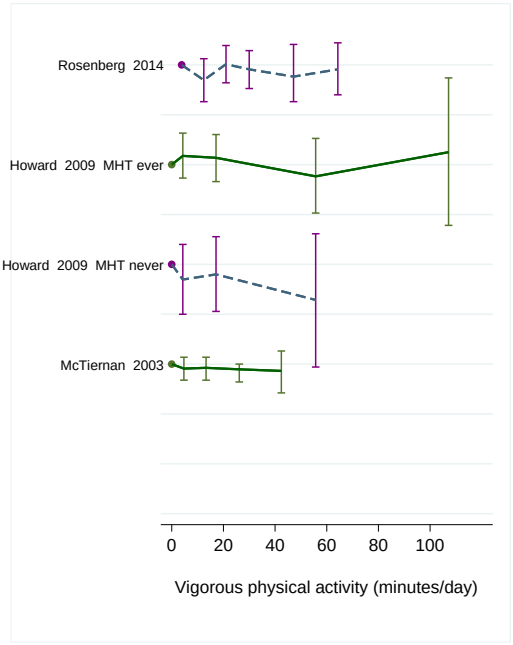


Figure 517 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest level of vigorous physical activity

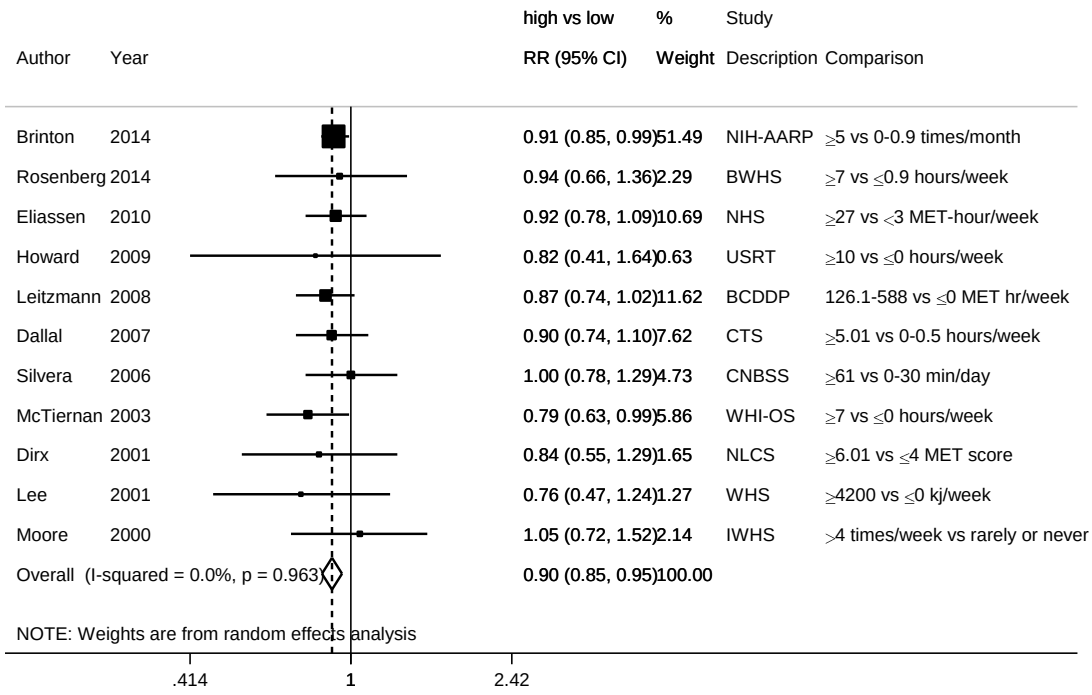
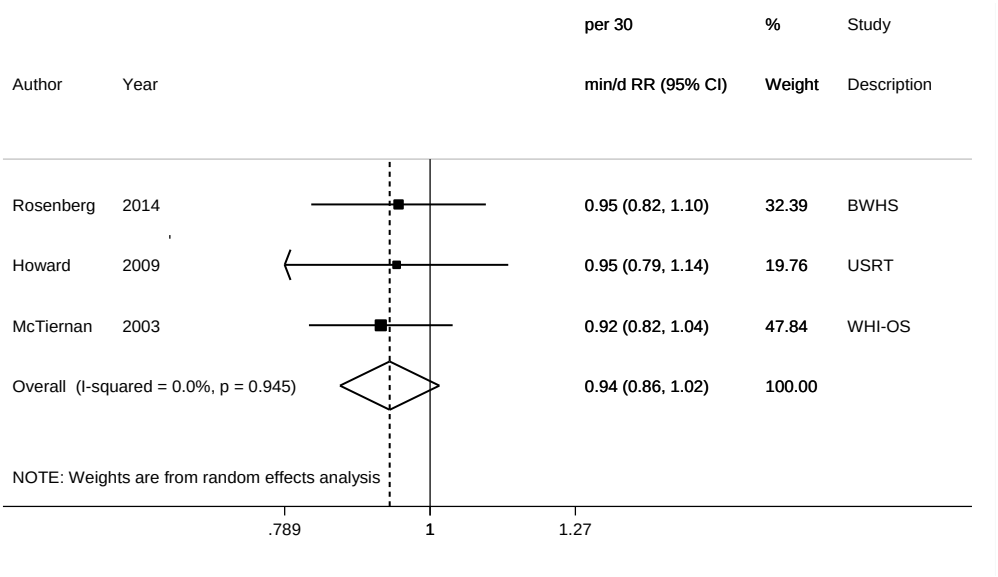


Figure 518 Relative risk of postmenopausal breast cancer for 30 minutes/day increase of vigorous physical activity



6.2 Physical inactivity

6.2 Sitting

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Overall summary

Eight studies (eight publications) that examined sitting, sitting while watching television, sitting at work, or other type of sitting were identified. No pooled analysis was identified.

The highest compared with the lowest meta-analyses were conducted to examine the association of sitting with risk of breast cancer and postmenopausal breast cancer.

Notes on methods: Study results that were adjusted for multiple confounding factors including physical activity were pooled in the meta-analysis. When a study presented results from the models with and without the adjustment of BMI, results not adjusted for BMI were used as obesity is considered as an intermediate factor between sedentary lifestyle and risk of breast cancer.

Table 501 Summary of results of the highest versus the lowest meta-analysis in the CUP SLR

	Breast cancer (any)	Premenopausal breast cancer	Postmenopausal breast cancer
Comparison	Highest versus lowest	-	Highest versus lowest
Sitting			
Studies (n)	3	-	3
Cases	2 828	-	8 073
RR (95%CI)	1.09 (0.92-1.29)	-	1.17 (0.95-1.45)
Heterogeneity (I^2, p-value)	38%, 0.20	-	43%, 0.17
Sitting while watching television			
Studies (n)	3	-	3
Cases	2 861	-	3 739
RR (95%CI)	1.10 (0.94-1.29)	-	1.07 (0.98-1.17)
Heterogeneity (I^2, p-value)	0%, 0.68	-	0%, 0.59
Sitting at work			
Studies (n)	3	-	-
Cases	2 492	-	-
RR (95%CI)	1.11 (0.99-1.25)	-	-
Heterogeneity (I^2, p-value)	0%, 0.49	-	-

Breast cancer (any)

Summary

Main results:

Five publications from five studies were identified. Overall four studies could be included in the highest versus the lowest meta-analysis of sitting, by type, and breast cancer risk. Non-significant positive associations were observed for sitting (summary RR = 1.09, 95% CI=0.92-

1.29) (3 studies, I^2=38%, P=0.20), sitting while watching television (1.10, 95% CI=0.94-1.29) (3 studies, I^2=0%, P=0.68), and sitting at work (1.11, 95% CI=0.99-1.25) (3 studies, I^2=0%, P=0.49).

The excluded study from China observed an increased breast cancer incidence in those who worked with long sitting hours compared with the general population (Zheng, 1993).

Study quality:

Except for one Chinese study (Pronk, 2011), all others were North American studies. All studies reported assessment of sitting by questionnaire. Case ascertainment was through cancer registries or confirmed through medical records. Age, BMI, alcohol intake, and reproductive factors were not all adjusted for in the studies. Rosenberg, 2014 did not adjust for alcohol intake and MHT use, and Cohen, 2013 did not adjust for alcohol consumption and BMI at study baseline as including these factors in the models did not change the relative risk estimates.

Table 502 Sitting and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	5 (5 publications)
Studies included in forest plot of highest compared with lowest exposure	3 (sitting) 3 (sitting for TV) 3 (sitting at work)
Studies included in linear dose-response meta-analysis	Not enough studies
Studies included in non-linear dose-response meta-analysis	Not enough studies

Note: Include cohort, nested case-control, and case-cohort designs.

Table 503 Sitting and breast cancer risk. Summary of the highest versus the lowest meta-analysis in the CUP SLR[1]

	CUP	CUP	CUP
Exposure[2]	**Sitting**	**Sitting while watching television**	**Sitting at work**
Comparison	Highest versus lowest	Highest versus lowest	Highest versus lowest
Studies (n)	3	3	3
Cases	2 828	2 861	2 492
RR (95%CI)	1.09 (0.92-1.29)	1.10 (0.94-1.29)	1.11 (0.99-1.25)
Heterogeneity (I^2, p-value)	38%, 0.20	0%, 0.68	0%, 0.49

[1]Meta-analysis was not conducted in the 2005 SLR; [2]One study (Cohen, 2013, SCCS) also reported results on other sitting, for example, at home, at meals, playing games (RR = 1.28, 95%CI=0.91-1.80) and sitting in car or bus (RR=1.05, 95%CI=0.72-1.53).

Table 504 Sitting/sedentary behaviour and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Shen, 2014	3 cohort*	4 699	America, China	Incidence, breast cancer	Highest vs lowest sitting	1.17 (1.03-1.33)	-	14%, 0.31
Schmid, 2014	12 studies (5 cohorts, 7 case-control)	18 162	America, Canada, China, India, The Netherlands, Poland, Turkey	Incidence, any breast cancer	Per 2 h/day sitting time	1.01 (0.98-1.04)	-	-
					Highest vs lowest Sedentary behaviour (13 estimates)	1.03 (0.95-1.12)	-	27%, 0.27
					Cohort (4 estimates)	1.06 (0.92-1.22)	-	-
					Case-control (9 estimates)	1.01 (0.90-1.13)	-	36%
					Total sitting time (2 estimates)	1.20 (0.98-1.48)	-	0%
					TV viewing time (4 estimates)	1.07 (0.92-1.23)	-	46%
					Occupational sitting time (9 estimates)	1.03 (0.90-1.18)		

Table 505 Sitting and breast cancer risk. Main characteristics of studies included in the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Catsburg, 2014b BRE80529 Canada	CSDLH, Case Cohort, W, alumnae	1 069/ 4 417 15 years	Cancer registry	Questionnaire Sitting, TV	Incidence, Invasive breast cancer	≥21 vs ≤1 hours/week	1.17 (0.86-1.59)	Age at first child birth, age at menarche, alcohol Intake, BMI, family history of breast cancer, HRT use, menopausal status, number of childbirths, OC use
		1 040/		Sitting		≥54.1 vs ≤12.4 hours/week	0.98 (0.76-1.25)	
Rosenberg, 2014 BRE80563 USA	BWHS, Prospective Cohort, Age: 30- years, W	1 333/ 44 708 307 672 person-years	Self-report, linkage to cancer registries, medical and pathology records	Questionnaire Sitting, TV	Incidence, Invasive breast cancer	≥5 vs ≤0.9 hours/day	1.13 (0.91-1.40)	Age, BMI, fruits and vegetables consumption, meat consumption, parity, sitting at work, time period, vigorous activity, years of education
		1 316/		Sitting at work		≥5 vs ≤0.9 hours/day	1.05 (0.90-1.22)	Sitting watching tv
				Sitting		≥10 vs ≤2.9 hours/week	1.05 (0.86-1.17)	
Cohen, 2013 BRE80470	SCCS, Nested Case	459/ 546	Cancer registry	Questionnaire Sitting, TV	Incidence, Invasive breast	≥5 vs ≤1.9 hours/day	0.97 (0.70-1.35)	Age, age at menarche, BMI, educational

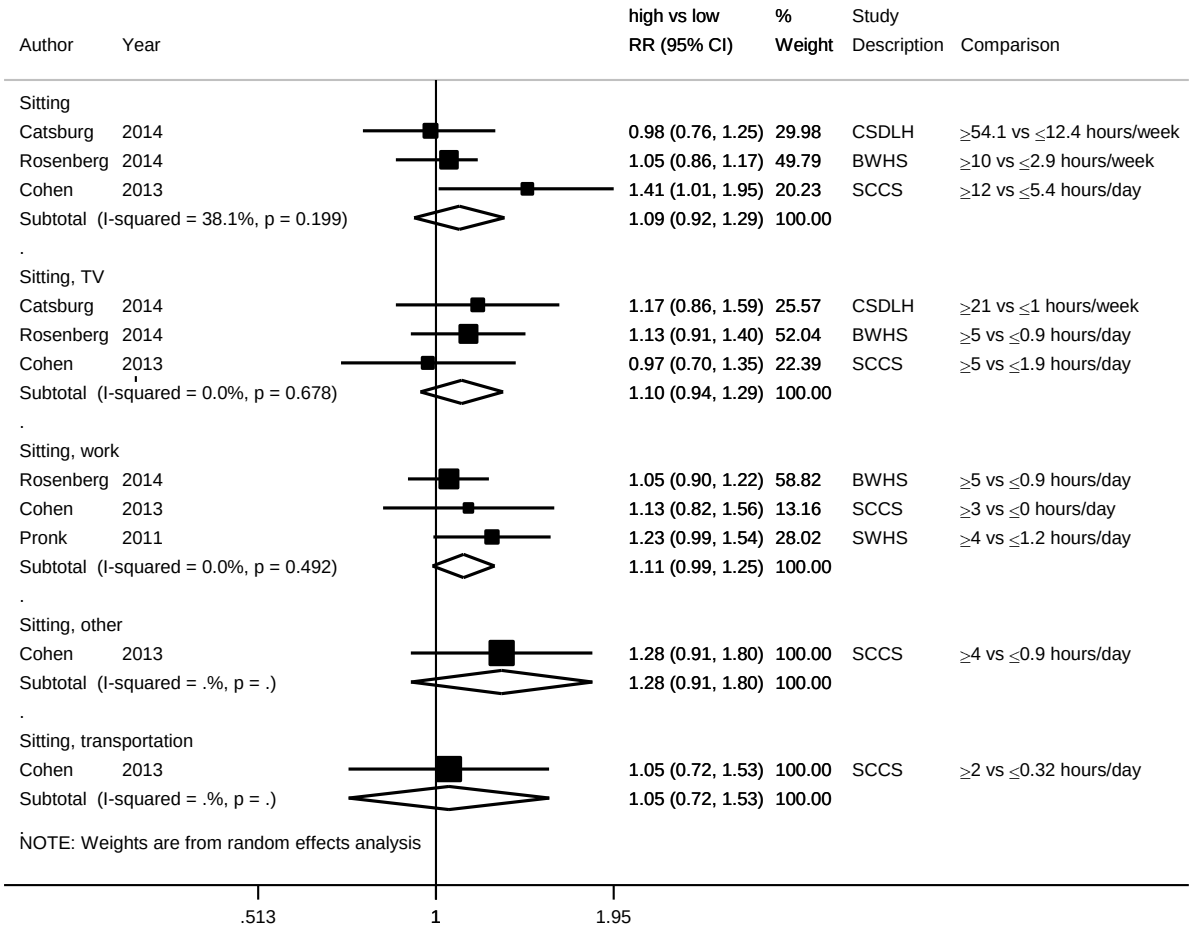
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
USA	Control, Age: 40-79 years	9 years			cancer			level, ethnicity, family history of breast cancer, health Insurance, household Income, HRT use, menopausal status, parity, physical activity, sedentary behaviour, smoking habits, source type
				Sitting at work		≥3 vs ≤0 hours/day	1.13 (0.82-1.56)	
		458/		Sitting		≥12 vs ≤5.4 hours/day	1.37 (0.99-1.90)	
		457/		Sitting in a car or bus		≥2 vs ≤0.32 hours/day	1.05 (0.72-1.53)	
				Other sitting includes using computer at home, sitting at meals, talking on the phone, reading, playing games, or sewing		≥4 vs ≤0.9 hours/day	1.28 (0.91-1.80)	
		455/		Sitting		≥12 vs ≤5.4 hours/day	1.41 (1.01-1.95)	Physical activity

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Pronk, 2011 BRE80388 China	SWHS, Prospective Cohort, Age: 40-70 years, W	717/ 73 049 9 years	Cancer registry	Interview Sitting at work	Incidence, breast cancer	≤1.2 vs ≥4 hours/day	0.81 (0.65-1.01)	Age, age at first child birth, educational level, family history of breast cancer, number of pregnancies

Table 506 Sitting and breast cancer risk. Main characteristics of studies excluded from the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Zheng, 1993 BRE13994 China	TEMP, Historical Cohort, W	516/	Partially histological - over 80%	Sitting at work	Incidence, breast cancer,	> 80% working vs general population	1.27 (P=0.01)	Age	Excluded, standardised incidence ratio comparing to the general population

Figure 519 RR (95% CI) of breast cancer for the highest compared with the lowest level of sitting



Premenopausal breast cancer

Summary

One Canadian study (Catsburg, 2014b, CSDLH) on sitting and risk of premenopausal breast cancer was identified. A non-significant inverse association of time spent sitting and a non-significant positive association of time spent in front of the television was observed.

Table 507 Sitting and premenopausal breast cancer risk. Main studies characteristics.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Catsburg, 2014b BRE80529 Canada	CSDLH, Case Cohort, W, alumnae	543/ 4 417 15 years	Cancer registry	Questionnaire Sitting, TV	Incidence, Invasive breast cancer, premenopausal	≥21 vs ≤1 hours/week	1.08 (0.65-1.79)	Age at first child birth, age at menarche, alcohol Intake, BMI, family history of breast cancer, HRT use, menopausal status, number of childbirths, oc use
		538/		Sitting	Premenopausal	≥54.1 vs ≤12.4 hours/week	0.99 (0.68-1.43)	

Postmenopausal breast cancer

Summary

Main results:

Five studies from five publications were identified. All studies could be included in the highest versus the lowest meta-analysis of sitting, by type. Non-significant positive associations of sitting (summary RR=1.17, 95% CI=0.95-1.45) (3 studies, I^2=43%, P=0.17) and sitting while watching television (1.07, 95% CI=0.98-1.17) (3 studies, I^2=0%, P=0.59) with postmenopausal breast cancer risk were observed.

Study quality:

Except for one Dutch study (Dirx, 2001), all others were North American studies. All studies reported assessment of sitting by questionnaire. Case ascertainment was through cancer registries or confirmed through medical records. Hildebrand, 2013; George, 2010; Dirx, 2001 were adjusted for age, BMI, alcohol intake, and reproductive factors. Cohen, 2013 did not adjust for alcohol consumption and BMI at study baseline as including these factors in the model did not change the relative risk estimates. All studies apart from Dirx, 2001 were adjusted for MHT use.

Table 508 Sitting and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	5 (5 publications)
Studies included in forest plot of highest compared with lowest exposure	3 (sitting) 3 (sitting for TV) 1 (sitting at work)
Studies included in linear dose-response meta-analysis	Not enough studies
Studies included in non-linear dose-response meta-analysis	Not enough studies

Note: Include cohort, nested case-control, and case-cohort designs.

Table 509 Sitting and postmenopausal breast cancer risk. Summary of the highest versus the lowest meta-analysis in the CUP SLR[1]

	CUP	**CUP**
Exposure[2]	**Sitting**	**Sitting while watching television**
Comparison	Highest versus lowest	Highest versus lowest
Studies (n)	3	3
Cases	8 073	3 739
RR (95%CI)	1.17 (0.95-1.45)	1.07 (0.98-1.17)
Heterogeneity (I^2, p-value)	43%, 0.17	0%, 0.59

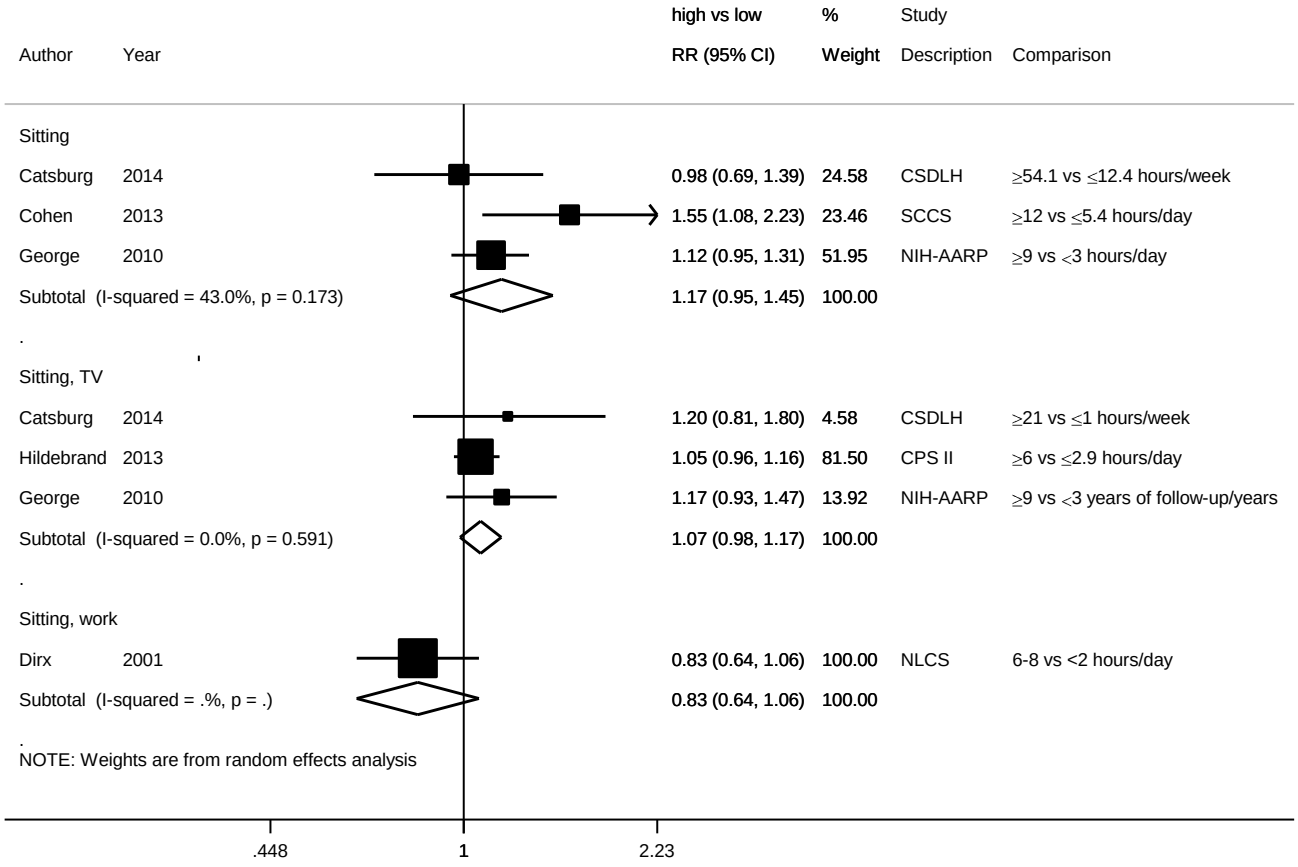
[1]Meta-analysis was not conducted in the 2005 SLR; [2]One study (Dirx, 2001, NLCS) reported results on sitting at work (RR for the highest vs lowest level of sitting=0.83, 95% CI=0.64-1.06).

Table 510 Sitting and postmenopausal breast cancer risk. Main characteristics of studies included in the highest versus the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Catsburg, 2014b BRE80529 Canada	CSDLH, Case Cohort, W, alumnae	526/ 4 417 15 years	Cancer registry	Questionnaire Sitting, TV	Incidence, Invasive breast cancer, postmenopausal	≥21 vs ≤1 hours/week	1.20 (0.81-1.80)	Age at first child birth, age at menarche, alcohol Intake, BMI, family history of breast cancer, HRT use, menopausal status, number of childbirths, OC use
		502/		Sitting	Postmenopausal	≥54.1 vs ≤12.4 hours/week	0.98 (0.69-1.39)	
Cohen, 2013 BRE80470 USA	SCCS, Nested Case Control, Age: 40-79 years	371/ 546 9 years	Cancer registry	Questionnaire Sitting	Incidence, postmenopausal breast cancer, postmenopause	≥12 vs ≤5.4 hours/day	1.55 (1.08-2.23)	Age, age at menarche, BMI, educational level, ethnicity, family history of breast cancer, health Insurance, household Income, HRT use, parity, smoking habits, source type
Hildebrand, 2013 BRE80490 USA	CPS II, Prospective Cohort, Age: 50-74 years, W, Postmenopausal	4 681/ 73 615 14.2 years	Self-report verified by medical record	Questionnaire Sitting, TV	Incidence, breast cancer	≥6 vs ≤2.9 hours/day	1.05 (0.96-1.16)	Age, age at first child birth, age at menopause, alcohol, BMI, breast diseases , educational level, family history of breast cancer, HRT use, mammography, number of childbirths,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								oophorectomy/hysterectomy, race, recreational activity, smoking status, weight change
George, 2010 BRE80309 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Postmenopausal	2 866/ 97 039 7 years	Cancer registry	Self-administered questionnaire Sitting, TV	Incidence, Invasive breast cancer, postmenopausal	≥9 vs <3 years of follow-up/years	1.12 (0.89-1.41)	Age, alcohol Intake, BMI, breast biopsies, educational level, energy Intake, HRT use, parity, race, recreational activity
				Sitting		≥9 vs <3 hours/day	1.08 (0.92-1.27)	
				Sitting, TV		≥9 vs <3 years of follow-up/years	1.17 (0.93-1.47)	As above, without BMI
				Sitting		≥9 vs <3 hours/day	1.12 (0.95-1.31)	
Dirx, 2001 BRE02326 Netherlands	NLCS, Case Cohort, Age: 55-69 years, W, Postmenopausal	755/ 62 573 7.3 years	Not specified	Questionnaire Sitting at work	Incidence, breast cancer, postmenopausal	<2 vs 6-8 hours/day	1.21 (0.94-1.56) Ptrend:0.54	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, body weight, educational level, energy Intake , family history, parity/ pregnancies

Figure 520 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest level of sitting



7 Energy balance

7.1 Energy intake

Cohort studies

Overall summary

Thirty-eight publications from 24 studies that examined energy intake were identified. One pooled study of seven cohorts was identified (Hunter, 1996, the Pooling Project).

Dose-response meta-analysis was conducted to examine the associations of total energy intake with risk of postmenopausal breast cancer.

Table 511 Summary of results of the dose-response meta-analysis in the 2016 CUP SLR

	Breast cancer	**Premenopausal breast cancer**	**Postmenopausal breast cancer**
Energy intake Increment unit used	-	-	500 kcal/day
Studies (n)	-	-	9
Cases	-	-	7 803
RR (95%CI)	-	-	1.02 (0.97-1.06)
Heterogeneity (I^2, p-value)	-	-	45%, 0.07
P value Egger test	-	-	0.36

Breast cancer (any)

Sixteen studies from 19 publications were identified. This included one study that pooled data from seven cohorts (Hunter, 1996, the Pooling Project). Meta-analysis was not conducted as there were not enough new studies with sufficient data.

Fourteen studies reported results on energy intake during adulthood and breast cancer risk. One study observed a significant positive association (Chang, 2003). Nine studies observed non-significant positive associations (Trichopoulou, 2010; Hunter, 1996, the Pooling Project, seven cohorts; Gaard, 1995). One study reported no significant association (Horn-Ross, 2002). Three studies (Byrne, 1996; Knekt, 1990; Jones, 1987), of which two consisted of overlapping study populations (Byrne, 1996, NHEFS; Jones, 1987, NHANES I) reported non-significant inverse associations.

One study (Makarem, 2015) and another publication from CNBSS (Catsburg, 2014a) reported results on adherence to the WCRF cancer prevention guideline on energy dense foods. A non-significant positive association and a significant inverse association were reported, respectively. One study (Iso, 2007) observed a non-significant inverse association with breast cancer mortality for modification of energy intake as advised by health professional versus no change. One publication from NHS (Farvid, 2015a) reported a non-

significant inverse association between energy intake during adolescence and breast cancer risk.

Table 512 Energy intake and breast cancer risk. Main characteristics of studies identified.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Farvid, 2015a BRE80545 USA	NHS, Prospective Cohort, Age: 24-43 years, W, Registered nurses	467/ 44 231 13 years	Biennial questionnaires or via death certificate and confirmed by medical record by a pathologist	FFQ, diet during adolescence	Incidence, breast cancer	Q5 vs Q1	0.94 (0.78-1.14) Ptrend:0.59	Age, adolescent alcohol Intake, age at menarche, age at menopause, alcohol Intake, BMI at age 18 years, family history of breast cancer, height, history of benign breast disease, hormone use, menopausal status, oral contraceptive use, parity and age at first birth, race, smoking, weight gain since 18	
Makarem, 2015 BRE80589 USA	FHS-Offspring Cohort, Prospective Cohort, W	124/ 1 602 11.5 years	Death certificate and medical records	Semi-quantitative FFQ	Incidence, breast cancer	per 1 point adherence to WCRF guideline on energy dense foods	1.26 (0.81-1.97)	Age, smoking status	
Catsburg, 2014a BRE80536 Canada	CNBSS, Prospective Cohort, Age: 40-59	48 840 16.6 years	Cancer registry	FFQ	Incidence, Invasive breast cancer	adhered vs not adhered to WCRF guideline on energy dense	0.88 (0.80-0.97)	Age, age at first child birth, age at menarche, alcohol, BMI,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	years, W					foods		family history of breast cancer, history of breast disease, HRT use, menopausal status, OC use, parity, physical activity, red and processed meat, sodium, study center, vegetable and fruit Intake, whole grains	
Trichopoulou, 2010 BRE80320 Greece	EPIC-Greece, Prospective Cohort, Age: 20-68 years	240/ 14 807 9.8 years	Medical records and pathology reports	FFQ	Incidence, breast cancer	per 568 kcal/day	1.03 (0.90-1.17)	Age, age at first child birth, age at menarche, age at menopause, BMI, educational level, energy Intake, height, HRT use, menopausal status, metabolic equivalents, parity	
Iso, 2007 BRE80427 Japan	JACC, Prospective Cohort, Age: 40-79 years, W	99/ 15 years	Municipal resident registration records, death certificates	FFQ	Mortality, breast cancer	modified vs no change	0.36 (0.11-1.14)	Age, centre location	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Silvera, 2006 BRE24118 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	1 671/ 38 645 16.4 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer	≥2406 vs ≤1629 kcal/day	1.19 (0.99-1.42) Ptrend:0.01	Age , age at first child, age at menarche, alcohol, BMI, breast diseases , family history, HRT use, leisure time physical activity, menopausal status, OC use, other design Issue, parity/pregnancies, recruitment center, smoking habits	
Chang, 2003 BRE18295 USA	BCDDP, Prospective Cohort, Age: 55-74 years, W, Screening Program	27 534 7 years	Partially histological - over 80%	Questionnaire	Incidence, breast cancer	Highest vs lowest	1.25 (1.02-1.54) Ptrend:0.07		
Horn-Ross, 2002 BRE15412 USA	CTS, Prospective Cohort, Age: 21-103 years, W, Registered	111 383 2 years	Partially histological - over 80%	FFQ	Incidence, Invasive breast cancer	Q5 vs Q1	1.00 (0.80-1.30) Ptrend:0.7	Age , age at first child, age at menarche, BMI, energy Intake , ethnicity, family history, menopausal	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	teachers							status, physical activity	
Holmes, 1999 BRE04008 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	121 700 14 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, Invasive breast cancer	per 100 kcal/day	0.99 (0.98-1.00)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, family history, height, HRT use, menopausal status, nutrients	
Fraser, 1997 BRE02940 USA	AHS, Prospective Cohort, Age: 24- years, W, Adventist	20 341 6 years	Partially histological - over 80%		Incidence, Invasive breast cancer	≥1777.3 vs ≤1777.2 kcal/day	1.15 (0.84-1.56)		
Byrne, 1996 BRE05719 USA	NHEFS, Prospective Cohort, Age: 25-74 years, W	52/ 6 156 3.9 years	Medical records + death certificate	FFQ	Incidence, breast cancer	6.62-17.9 vs ≤4.41 mj/day	0.42 (0.20-1.10)	Age	
Hunter, 1996 Canada, USA, the Netherlands, Sweden	The Pooling Project, Pooled study of 7 cohorts* Age: 28-90	4 980/ 337 819	Self-reported and verified by medical records and/or record linkage with	FFQ	Incidence, breast cancer	Q5 vs Q1	1.11 (0.99-1.25) Ptrend: 0.15	Age at menarche, menopausal status, parity, age at birth of	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	years, W (*AHS, CNBSS, IWHS, NLCS, NYSC, NHS(a), NHS(b), SMC)		cancer registries					first child, BMI, height, education, history of benign breast disease, maternal history of breast cancer, history of breast cancer in a sister, OC use, fibre intake, alcohol intake, energy intake	
						Per 100 kcal	1.01 (0.99-1.02)		
	AHS	153/ 15 172				Per 100 kcal			
	CNBSS	514/ 56 837				Per 100 kcal	1.00 (0.98-1.03)		
	IWHS	723/ 34 406				Per 100 kcal	1.00 (0.98-1.02)		
	NLCS	434/ 62 412				Per 100 kcal	1.01 (0.97-1.05)		
	NYSC	376/ 18 475				Per 100 kcal	0.98 (0.93-1.03)		
	NHS(a)	1 094/ 89 046				Per 100 kcal	1.00 (0.98-1.01)		
	NHS(b)	911/ 68 817				Per 100 kcal	1.00 (0.99-1.02)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	SMC	775/ 61 471				Per 100 kcal	1.05 (1.02-1.07)		
Gaard, 1995 BRE17516 Norway	Norway National Health Screening Service, 1974, Prospective Cohort, Age: 35-49 years, W, Screening Program	248/ 24 897 10 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer	≥6654 vs ≤4453.9 kj/day	1.37 (0.95-1.98) Ptrend:0.11	Age , age-underlying cox models, BMI, height, menopausal status, smoking habits	
Kushi, 1995 BRE05142 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	329/ 34 388 6 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer ER+/PR+	≥1972 vs ≤1499 kcal/day	1.06 (0.81-1.40) Ptrend:0.59	Age	
		75/			Incidence, breast cancer ER+/PR-	≥1972 vs ≤1499 kcal/day	1.18 (0.67-2.05) Ptrend:0.57		
		14/			Incidence, breast cancer ER-/PR+	≥1972 vs ≤1499 kcal/day	1.31 (0.29-5.87) Ptrend:0.82		
		61/			Incidence, breast cancer ER-/PR-	≥1972 vs ≤1499 kcal/day	0.87 (0.47-1.60) Ptrend:0.65		
Giovannucci, 1993a BRE03262 USA	NHS, Nested Case Control, Age: 30-55 years, W, Registered nurses	392/ 786 controls 2 years	Medical records + death certificate	FFQ-semi-quantitative	Incidence, breast cancer	Q5 vs Q1	1.01 (0.65-1.56) Ptrend:0.50	Age	
Willett, 1992	NHS,	1 439/	Medical records	FFQ-semi-	Incidence, breast	≥8230 vs	1.00 (0.85-1.18)	Age , age at first	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
BRE13438 USA	Prospective Cohort, Age: 30-55 years, W, Registered nurses	89 494 8 years	+ self-reported	quantitative	cancer	≤4745.9 kj/day	Ptrend:0.83	child, age at menarche, alcohol, benign breast disease, BMI, energy Intake , family history, menopausal status, nutrients, other design Issue, parity/pregnancies	
Howe, 1991 BRE17622 Canada	CNBSS, Nested Case Control, Age: 40-59 years, W, Screening Program	519/ 1182 controls 5 years	All histology	Dietary history questionnaire	Incidence, breast cancer	Q4 vs Q1	0.95 (0.71-1.26) Ptrend:.51	Age , recruitment center, time of recruitment	
Knekt, 1990 BRE04898 Finland	Mobile Clinic Health Examination Survey, 1973, Prospective Cohort, Age: 20-69 years, W, Screening Program	3 988 20 years	All histology	Dietary history questionnaire	Incidence, breast cancer	≥2335 vs ≤1791 kcal/day	0.58 (0.29-1.18) Ptrend:0.15	Age , energy Intake	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Jones, 1987 BRE04461 USA	NHANES I, Prospective Cohort, Age: 25-74 years, W	86/ 5 485 10 years	Medical records + self-reported +death certificate	24h recall	Incidence, breast cancer	≥1776 vs ≤1029.9 kcal/day	0.70 (0.36-1.40)	Age , age at menarche, age at menopause, BMI, educational level, family history, menopausal status	

Premenopausal breast cancer

Five studies from six publications were identified. Meta-analysis was not conducted as there were not enough new studies with sufficient data.

One study observed a significant positive association (Silvera, 2006). Two studies observed non-significant positive associations (Trichopoulou, 2010; Frazier, 2004). Two studies observed non-significant inverse associations (Couto, 2013; Holmes, 1999).

One publication from NHS (Farvid, 2015a) reported a non-significant inverse association between energy intake during adolescence and premenopausal breast cancer risk.

Table 513 Energy intake and premenopausal breast cancer risk. Main characteristics of studies identified.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Farvid, 2015a BRE80545 USA	NHS, Prospective Cohort, Age: 24-43 years, W, Registered nurses	229/ 44 231 13 years	Biennial questionnaires or via death certificate and confirmed by medical record by a pathologist	FFQ, diet during adolescence	Incidence, breast cancer, premenopausal	Q5 vs Q1	0.78 (0.59-1.02) Ptrend:0.14	Age, adolescent alcohol Intake, age at menarche, alcohol Intake, BMI at age 18 years, family history of breast cancer, height, history of benign breast disease, oral contraceptive use, parity and age at first birth, race, smoking, weight gain since 18	
Couto, 2013 BRE80454 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	736/ 49 258 16 years	Cancer registry	FFQ	Incidence, breast cancer, premenopausal	≥7725 vs <5590 kj	0.94 (0.78-1.13)	Age at first child birth, age at menarche, alcohol, benign breast disease, contraception, educational level, energy Intake, height, history of breast cancer, hormone use, number of childbirths, smoking	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Trichopoulou, 2010 BRE80320 Greece	EPIC-Greece, Prospective Cohort, Age: 20-68 years	14 807 9.8 years	Medical records and pathology reports	FFQ	Incidence, breast cancer, premenopausal	per 568 kcal/day	1.10 (0.93-1.30)	Age, age at first child birth, age at menarche, BMI, energy Intake, height, metabolic equivalents, parity	
Silvera, 2006 BRE24118 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	818/ 38 645 16.4 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer, premenopausal	≥2406 vs ≤1629 kcal/day	1.45 (1.13-1.85) Ptrend:0.001	Age , age at first child, age at menarche, alcohol, BMI, breast diseases , family history, HRT use, leisure time physical activity, menopausal status, OC use, other design Issue, parity/pregnancies, recruitment center, smoking habits	
Frazier, 2004 BRE02942 USA	NHS II, Historical Cohort, Age: 34-51 years, W, Registered	361/ 47 355 9 years	All histology	FFQ	Incidence, breast cancer, premenopausal	3833 vs 1782 kcal/day	1.39 (0.99-1.96) Ptrend:0.01	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, energy Intake , family	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	nurses							history, menopausal status, OC use, other anthropometric Index, other design Issue, parity/pregnancies	
Holmes, 1999 BRE04008 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	121 700 14 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, Invasive breast cancer, premenopausal	per 100 kcal/day	0.99 (0.98-1.01)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, family history, height, HRT use, menopausal status, nutrients	

Postmenopausal breast cancer

Summary

Main results:

Nine out of 14 studies (21 publications) identified could be included in the dose-response meta-analysis.

Energy intake was not significantly associated with postmenopausal breast cancer risk (summary RR per 500 kcal/day=1.02 (95% CI=0.97-1.06, I^2=45%, P=0.07).

There was no evidence of publication bias or small study bias (P for Egger's test=0.36).

Five studies did not have sufficient data and were excluded from the meta-analysis. One study reported a significant positive association between biomarker-calibrated total energy intake and postmenopausal breast cancer risk (Prentice, 2013a). One study observed a non-significant positive association (Sieri, 2002) and two studies reported non-significant inverse association (Silvera, 2006; Velie, 2000). Wirfalt, 2004 reported no significant difference in mean energy intake between the cases and the non-cases.

Sensitivity analyses:

Summary RR did not change materially when studies were omitted in turn in influence analysis. No significant associations were observed in the subgroup analyses by geographic location and confounder adjustments.

Nonlinear dose-response meta-analysis:

There was no evidence of significant nonlinear relationship (P for non-linearity=0.11) (graph not shown).

Study quality:

One study (Barrett-Connor, 1993) observed a strong positive association. There were only 15 postmenopausal breast cancer cases after 15 years of follow-up in 590 women. All other studies included in the analysis had more than 100 cases. The RCT of lung, colorectal, and ovarian cancer screening (Sue, 2009) observed a significant positive association that was attenuated after the adjustment of BMI and physical activity for the highest compared with the lowest energy intake. Studies used FFQ to assess energy intake, apart from Barrett-Connor, 1993, which used a 24-hour dietary recall. Case ascertainment was through cancer registries or confirmed through medical records. Sczaniecka, 2012 adjusted for age only. Graham, 1992 and Trichopoulou, 2010 did not adjust for alcohol intake. Summary RR was the same in studies adjusted or not for BMI. None of the studies had a strong influence in the summary RR which remained non-significant in influence analysis.

Table 514 Energy intake and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	14 (21 publications)
Studies included in forest plot of highest compared with lowest exposure	11 (11 publications)
Studies included in linear dose-response meta-analysis[2]	9 (9 publications)
Studies included in non-linear dose-response meta-analysis	5 (5 publications)

Note: Include cohort, case-cohort, and nested case-control designs

Table 515 Energy intake and postmenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and 2016 CUP

	2005 SLR	**CUP SLR**
Increment unit used	300 kcal/day	500 kcal/day
Studies (n)	5	9
Cases	2 968	7 803
RR (95%CI)	0.98 (0.96-1.01)	1.02 (0.97-1.06)
Heterogeneity (I^2, p-value)	69%	45%, 0.07
P value Egger test	-	0.36
Stratified analysis in the CUP SLR		
Geographic locations	**Europe**	**North America**
Studies (n)	3	6
Cases	1 358	6 445
RR (95%CI)	1.00 (0.92-1.08)	1.03 (0.97-1.09)
Heterogeneity (I^2, p-value)	0%, 0.74	64%, 0.02
Adjustment for age, alcohol intake, reproductive factors	**Adjusted**	**Not adjusted**
Studies (n)	6	3
Cases	6 561	1 242
RR (95%CI)	1.04 (0.97-1.11)	0.98 (0.92-1.05)
Heterogeneity (I^2, p-value)	61%, 0.03	0%, 0.76
Adjustment for BMI	**Adjusted**	**Not adjusted**

Studies (n)	5	4
Cases	4 921	2 882
RR (95%CI)	1.03 (0.93-1.14)	1.03 (0.98-1.07)
Heterogeneity (I^2, p-value)	66%, 0.02	0%, 0.45

Table 516 Energy intake and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Couto, 2013 BRE80454 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	448/ 49 258 16 years	Cancer registry	FFQ	Incidence, breast cancer, postmenopausal	≥7725 vs <5590 kJ	1.02 (0.80-1.29)	Age at first child birth, age at menarche, alcohol, benign breast disease, contraception, educational level, energy Intake, height, history of breast cancer, hormone use, number of childbirths, smoking	
Sczaniecka, 2012 BRE80434 USA	VITAL, Prospective Cohort, Age: 50-76 years, W, Postmenopausal	771/ 30 252 6 years	SEER registry	Semi-quantitative FFQ	Incidence, breast cancer	≥1910 vs ≤1015 kcal/day	0.93 (0.74-1.15) Ptrend:0.925	Age	
Trichopoulou, 2010 BRE80320 Greece	EPIC-Greece, Prospective Cohort, Age: 20-68 years	14 807 9.8 years	Medical records and pathology reports	FFQ	Incidence, breast cancer, postmenopausal	per 568 kcal/day	0.93 (0.76-1.14)	Age, age at first child birth, age at menarche, age at menopause, BMI, educational	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								level, energy Intake, height, HRT use, menopausal status, metabolic equivalents, parity	
Sue, 2009 BRE80282 USA	PLCO, Prospective Cohort, Age: 55-75 years, W, Postmenopausal, prostate, lung, colorectal, ovarian cancer screening RCT	1 319/ 29 170 8.7 years	Self report verified by medical record	Dietary Questionnaire (DQx) (137-food item FFQ) administered at study baseline	Incidence, breast cancer	≥2081 vs ≤1311 kcal/day	1.21 (1.03-1.42) Ptrend:0.03	Age, age at first child birth, age at menarche, age at menopause, benign breast disease, duration of HRT use, educational level, family history of cancer, height, mammography, parity, race, study center (addition of alcohol consumption and OC use did not change RR and were not included in final model)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
							1.18 (1.00-139) Ptrend:0.07	BMI and physical activity	
Kim, 2006 BRE80115 USA	NHS, Prospective Cohort, W, Postmenopausal	3 537/ 121 701 20 years	Medical records	FFQ	Incidence, Invasive breast cancer	per 500 kcal	1.01 (0.97-1.04)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, energy Intake , family history, height, HRT use, other design Issue, parity/pregnancies	
		1 653/			Incidence, breast cancer ER+/PR+	per 500 kcal	1.00 (0.94-1.06)		
		517/			Incidence, breast cancer ER-/PR-	per 500 kcal	1.07 (0.97-1.18)		
		477/			Incidence, breast cancer ER+/PR-	per 500 kcal	0.97 (0.87-1.08)		
		83/			Incidence, breast cancer ER-/PR-	per 500 kcal	1.16 (0.91-1.48)		
Voorrips, 2002 BRE13011 Netherlands	NLCS, Case Cohort, Age: 55-69	783/ 62 573 6.3 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer	9247 vs 5079 kJ/day	1.04 (0.77-1.40) Ptrend:0.61	Age , age at first child, age at menarche, age at	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	years, W, Postmenopausal							menopause, alcohol, benign breast disease, BMI, educational level, family history, OC use, parity/pregnancies, smoking habits	
Barrett-Connor, 1993 BRE00581 USA	Rancho Bernardo, 1972, Prospective Cohort, Age: 40-79 years, W	15/ 590 15 years	Medical records + death certificate	24h recall	Incidence, breast cancer, postmenopausal	per 500 kcal/day	2.72 (1.51-4.89)	Age , age at menopause, alcohol, BMI, parity/pregnancies	
Graham, 1992 BRE03424 USA	New York State Cohort, 1980, Prospective Cohort, Age: 50-107 years, W, Postmenopausal	344/ 18 586 8 years	Partially histological - over 80%	FFQ	Incidence, breast cancer, postmenopausal	62-318 vs 7-35 *1000 kcal/month	0.91 (0.64-1.27)	Age , educational level (adjustment for parity did not change RR and not included)	
Kushi L H, 1992 BRE05141 USA	IWHS, Prospective Cohort, Age: 55-69	459/ 34 388 4 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	2264 vs 1168 kcal/day	1.06 (0.80-1.39) Ptrend:0.82	Age , age at first child, age at menarche, age at menopause, age-	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	years, W, Postmenopausal							underlying cox models, alcohol, benign breast disease, BMI, BMI at 18 years, family history, WHR	

Table 517 Energy intake and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Hartz, 2013 BRE80483 USA	WHI, Prospective Cohort, Age: 55-70 years, W, Postmenopausal	147 202 8 years	Self reported/death certificate/ medical records	Questionnaire	Incidence, breast cancer	per 1 SD	1.00 (0.98-1.03)	Age, alcohol, family history of prostate cancer, history of cancer, history of polyp diagnosis, medication, number of cigarettes smoked, osteoporosis, psychological character, race,	Excluded, RR per 1 SD increase of intake (same study as Prentice, 2009; Prentice 2013)

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								study, weight	
Hastert, 2013 BRE80481 USA	VITAL, Prospective Cohort, Age: 50-76 years, W, Postmenopausal	899/ 30 797 6.7 years	SEER registry	FFQ	Incidence, breast cancer	Met vs not met WCRF guideline on energy dense foods	1.04 (0.88-1.22)	Age, age at first child birth, age at menarche, age at menopause, educational level, energy Intake, family history of breast cancer, mammography, other factors , race, years of HRT use	Superseded by Sczaniecka, 2012
Prentice, 2013a BRE80586 USA	WHI (DM-comparison group and OS), Prospective Cohort, Age: 50-79 years, W, Postmenopausal	5 061/ 103 426 16 years	Self report verified by medical record	4-day food record & FFQ	Incidence, Invasive breast cancer	per 20 % increase of energy intake, not calibrated	1.01 (1.00-1.03)	Age, cohort, date of enrollment, educational level, Gail model risk, participant type, postmenopausal hormone use, race/ethnicity, randomization group, recreational physical activity,	Excluded, RR per 20% increase of intake (same study as Hastert, 2013; Prentice 2009)

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								smoking	
						per 20 % increase of energy intake, calibrated	1.22 (1.15-1.30)		
						per 20 % increase of energy intake, not calibrated	1.01 (0.99-1.02)	BMI	
						per 20 % increase of energy intake, calibrated	0.94 (0.73-1.22)	BMI	
Prentice, 2009 BRE80301 USA	WHI, (DM-comparison group and OS), Prospective Cohort, Age: 50-79 years, W, Postmenopausal	1 703/ 80 816 12 years	Self report verified by medical record	FFQ, biomarker calibrated energy intake	Incidence, breast cancer	per 20 % increase of energy intake, calibrated	1.24 (1.11-1.38)	Age, alcohol, educational level, estrogen use, family history of cancer, Gail model risk, hormone use, physical activity, race, smoking status	Excluded, RR per 20% increase of intake (same study as Hastert, 2013; Prentice 2013)
							1.11 (0.81-1.53)	BMI	
						Q4 vs Q1 energy intake,	1.33 (1.12-1.58)	Age, alcohol, educational	Missing number of cases and

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
						calibrated		level, estrogen use, family history of cancer, Gail model risk, hormone use, physical activity, race, smoking status	non-cases and exposure level per category
Chang, 2006 BRE80110 USA	PLCO, Prospective Cohort, Age: 55-74 years, W, lung, colorectal, and ovarian cancer screening RCT	764/ 38 660 4.9 years	Cancer screening programme	FFQ	Incidence, breast cancer, postmenopausal	≥2084 vs ≤1315 kcal/day	1.25 (1.02-1.53) Ptrend:0.064	Age at first child, age at menarche, age at menopause, benign breast disease, educational level, ethnicity, family history, height, HRT use, parity/pregnancies, recruitment center	Superseded by Sue, 2009
Silvera, 2006 BRE24118 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	662/ 38 645 16.4 years	Partially histological - over 80%	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	≥2406 vs ≤1629 kcal/day	0.94 (0.72-1.23) Ptrend:0.86	Age , age at first child, age at menarche, alcohol, BMI, breast diseases , family history,	Excluded, missing number of cases and non-cases per category

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								HRT use, leisure time physical activity, menopausal status, OC use, other design Issue, parity/pregnancies, recruitment center, smoking habits	
Wirfalt, 2004 BRE17083 Sweden	MDCS, Nested Case Control, Age: 50- years, W, Postmenopausal	12 803 8 years	Partially histological - over 80%	7-day record + questionnaire	Incidence, breast cancer, postmenopausal	(mean exposure)			Excluded, mean exposure comparison only
Byrne, 2002 BRE01315 USA	NHS, Prospective Cohort, Age: 57 years, W, Postmenopausal	1 071/ 44 697 14 years	All histology	FFQ-semi-quantitative	Incidence, Invasive breast cancer, postmenopausal	Q5 vs Q1	0.81 (0.67-0.99) Ptrend:0.03	Age , age at first child, age at menopause, age at menopause, alcohol, BMI, family history, height, nutrients, parity/pregnancies	Superseded by Kim, 2006 (included in the highest versus lowest forest plot)
Sieri, 2002 BRE20941 Italy	ORDET, Nested Case Control,	56/ 214 controls 5.5 years	Cancer registry + death certificate	FFQ-semi-quantitative	Incidence, breast cancer, postmenopausal	1786.4-3474.4 vs ≤1410.6 kcal/day	1.02 (0.48-2.16) Ptrend:0.959	Birth cohort, educational level,	Excluded, missing number of cases and

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	Age: 41-70 years, W, Postmenopausal							parity/pregnancies	non-cases per category
Velie, 2000 BRE12851 USA	BCDDP, 1973, Prospective Cohort, W, Screening Program	996/ 40 022 5.3 years	Medical records + self-reported	FFQ	Incidence, breast cancer, postmenopausal	Q5 vs Q1	0.94 (0.77-1.16) Ptrend:.39	Age at first child, age at menarche, alcohol, benign breast disease, BMI, educational level, energy Intake , family history, height, parity/pregnancies	Excluded, missing exposure level per category
Holmes, 1999 BRE04008 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	121 700 14 years	Medical records + self-reported +death certificate	FFQ-semi-quantitative	Incidence, Invasive breast cancer, postmenopausal	per 100 kcal/day	0.99 (0.98-1.00)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, family history, height, HRT use, menopausal status, nutrients	Superseded by Kim, 2006
van den Brandt,	NLCS,	437/	All histology	FFQ-semi-	Incidence,	High vs low	0.99 (0.70-1.39)	Age	Superseded by

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
1993 BRE16919 Netherlands	Prospective Cohort, Age: 55-69 years, W, Postmenopausal	1 598 3.3 years		quantitative	Invasive breast cancer		Ptrend:0.81		Voorrips, 2002

Figure 521 RR estimates of postmenopausal breast cancer by energy intake

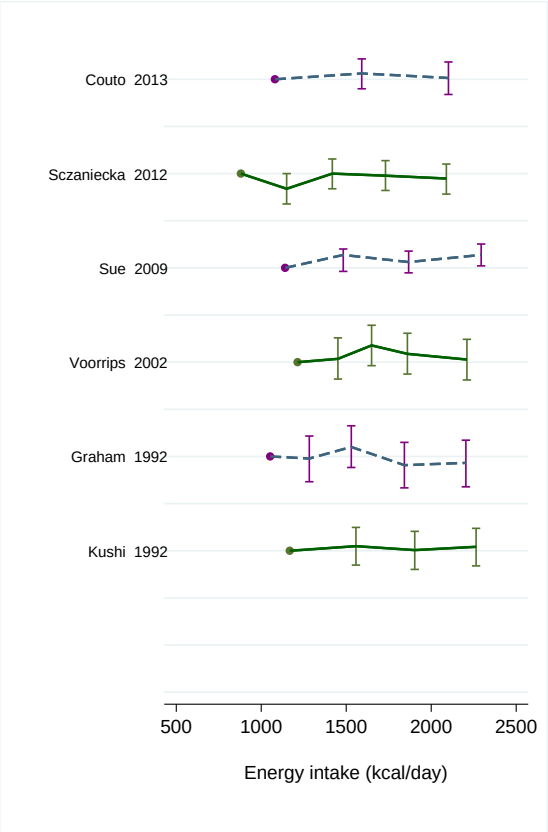


Figure 522 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest level of energy intake

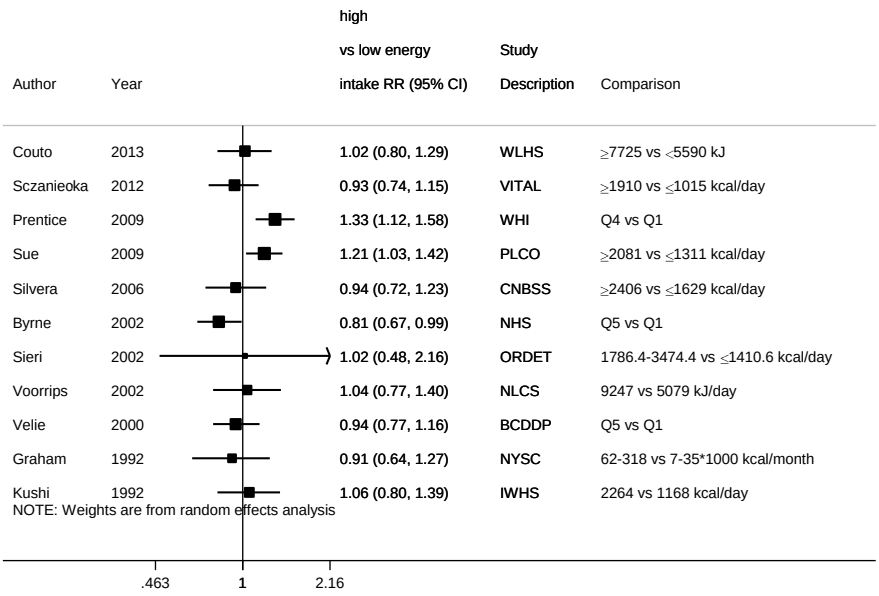


Figure 523 Relative risk of postmenopausal breast cancer for 500 kcal/day increase of energy intake

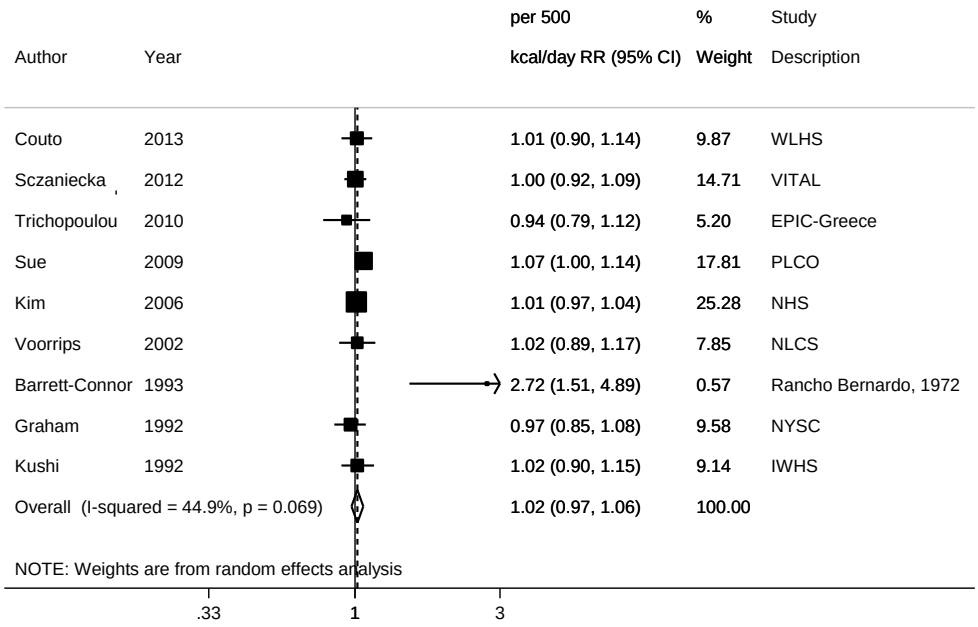
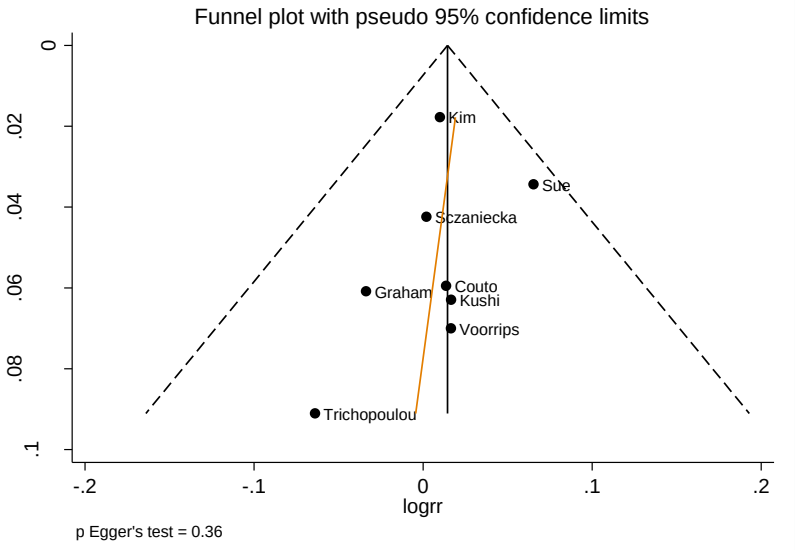
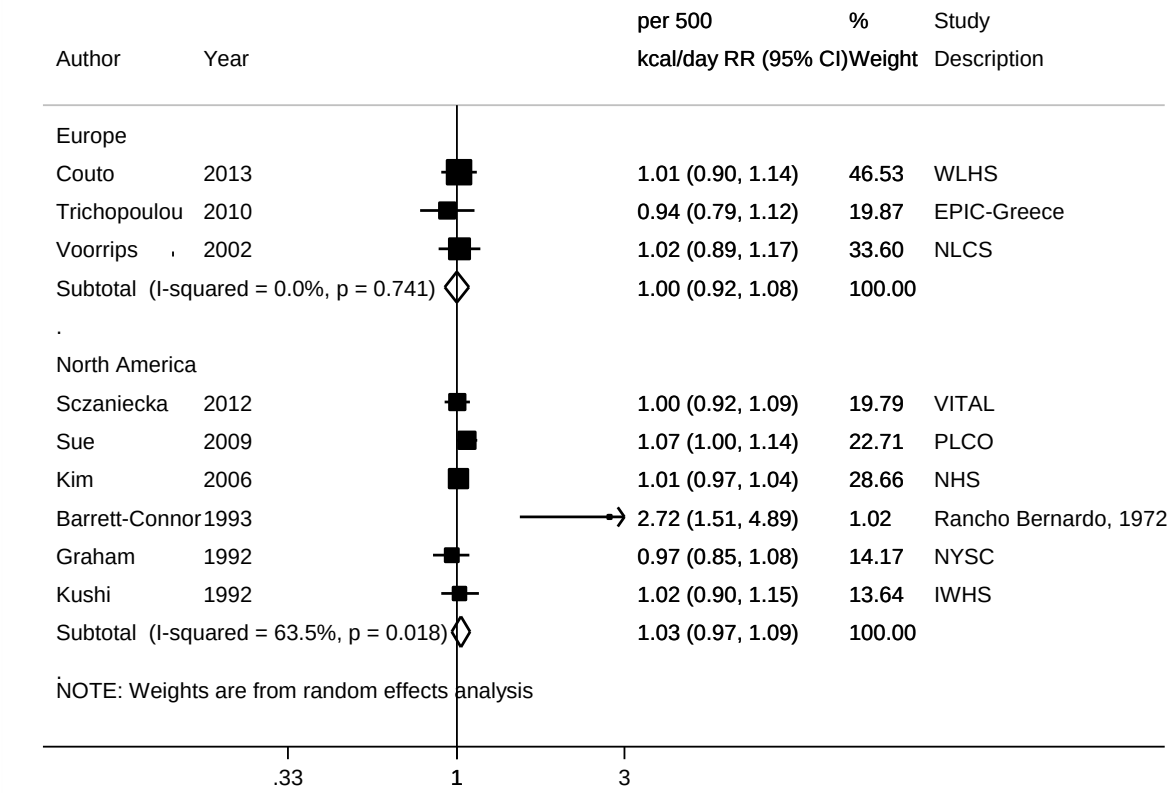


Figure 524 Funnel plot of studies included in the dose response meta-analysis of energy intake and postmenopausal breast cancer



Note: The small study that found a strong significant positive association (Barrett-Connor, 1993) was excluded from the forest plot to facilitate presentation.

Figure 525 Relative risk of postmenopausal breast cancer for 500 kcal/day increase of energy intake, by geographic location



8 Anthropometry

8.1.1 Body mass index

Overall summary

One hundred and eighty-three publications from 181 studies that examined body mass index (BMI) during adulthood were identified. This included seven publications of pooled studies on breast cancer incidence (Bandera, 2015, AMBER Consortium, two cohorts and two case-control studies; Harding, 2015, ANZDCC, ten cohorts; Wada, 2014, eight Japanese cohorts; Schonfeld, 2011, four US cohorts; Bjorge, 2010, Me-Can, six cohorts; Yang XR, 2011, BCAC, three cohorts and nine case-control studies in case-control analysis; van den Brandt, 2000, The Pooling Project, seven cohorts) and two on breast cancer mortality (Parr, 2010, APCSC, 37 cohorts; Whitlock, 2009, PSC, 35 cohorts).

Dose-response meta-analyses were conducted to examine the associations between BMI and breast cancer, overall and subtypes, by menopausal status. Further analyses were conducted by menopausal hormone therapy (MHT) use in postmenopausal women.

Table 518 Summary of results of the dose-response meta-analysis in the CUP SLR

	Breast cancer (any)	**Premenopausal breast cancer**	**Postmenopausal breast cancer**
Increment unit used	5 kg/m^2	5 kg/m^2	5 kg/m^2
Studies (n)	34	37	56
Cases	30 550	16 371	80 404
RR (95%CI)	1.07 (1.04-1.11)	0.93 (0.90-0.97)	1.12 (1.09-1.15)
Heterogeneity (I^2, p-value)	58%, <0.001	55%, <0.01	75%, <0.001
P value Egger test	0.28	0.13	0.03

Breast cancer (any)

Summary

Main results:

Thirty-eight out of 60 studies (69 publications) identified could be included in the dose-response meta-analyses, 34 studies (28 publications) on BMI and breast cancer risk and 10 studies (5 publications) on breast cancer mortality.

BMI was significantly positively associated with breast cancer risk (summary RR per 5 kg/m^2=1.07 (95% CI=1.04-1.11). When analysed by geographic location, positive associations that were significant in Asian studies (summary RR=1.20, 95% CI=1.10-1.31) and European studies (1.06, 95% CI=1.01-1.11), and borderline significant in North American studies (1.06, 95% CI=1.00-1.12) were observed. There was evidence of high

heterogeneity between studies overall (I^2=58%, p<0.01), and between European studies (60%, <0.01), and North American studies (63%, <0.01), but not Asian studies (0%, 0.84). For breast cancer mortality, a non-significant positive association was observed (summary RR=1.09, 95% CI=0.99-1.19, I^2=11%, p=0.34).

As in the 2008 SLR report, heterogeneity between studies was not explored because these studies included both pre- and postmenopausal women, and the relationship of BMI with breast cancer risk is thought to be in opposite direction in both cancer types.

There was no significant evidence of publication bias or small study bias (P for Egger's test=0.28). The asymmetry in the funnel plot could be driven by the smaller studies that reported stronger associations than the average.

Twenty-two studies and 37 publications were excluded from the dose-response meta-analyses. Study populations in seven studies (6 publications) (Lin, 2013; Harlid, 2012, MDC, MSP; Key, 2009; Kikkinen, 2004; Gaard, 1994; Tornberg, 1988) overlapped with other studies that were already included in the analyses. One excluded study (Makarem, 2015) was on guideline adherence, two (Burton, 2010; Bjorge, 2008) on BMI at young adulthood and one (Davey Smith, 2009) used offspring BMI as an indicator of own BMI.

Nine studies did not report sufficient data to be included in the meta-analyses. Three studies (Osaki, 2012; Li, 2009; Wen, 2009) observed significant positive associations with breast cancer risk, two (Pudrovska, 2013; Hoyer, 1992) non-significant positive associations, one (Gibson, 2010) no association, and one (Song, 2014) non-significant inverse association. Overvad, 1991 and Rissanen, 2003 reported on average similar BMI between the cases and non-cases.

Two studies (Setiawan, 2009; Colditz, 2004) on breast cancer subtype were not analysed as data was limited. Significant positive associations were observed with ER+PR+ breast cancer overall (Setiawan, 2009) and among MHT non-users (Coldtiz, 2004), and with ER-PR+ among MHT non-users (Coldtiz, 2004). No significant associations were observed for other breast cancer subtypes (ER+PR-, ER-PR-).

Sensitivity analyses:

Summary RR did not change materially when studies were omitted in turn in influence analysis. Significant positive association remained in studies that reported results specifically on invasive breast cancer.

Nonlinear dose-response meta-analysis:

Breast cancer risk increased monotonically through all ranges of BMI (P for non-linearity=0.53) (graph not shown).

Study quality:

One study included diabetic subjects (Onitilo, 2014) and one included patients with manifest vascular diseases (van Kruijsdijk, 2013). Non-significant inverse associations were observe in these two studies. One study that observed a positive association included kin members of women with breast cancer or history of breast disease (Chun, 2006). The cohort of atomic

bomb survivors (Key, 1999) observed a borderline significant positive association and the cohort of Seventh-Day Adventists (Mills, 1989) found a significant positive association.

Five studies (Fourkala, 2014; Wie, 2014; Silvera, 2006; Wu, 2006; Wolk, 1998) involved cancer screening. The Ovarian cancer screening trial (Fourkala, 2014, UKCTOCS) and the mammography screening cohort (Wolk, 1998, SMC) found significant positive associations. The study that originated from a breast cancer screening randomised controlled trial (Silvera, 2006, CNBSS) observed a borderline significant positive association. Two other Asian cancer screening studies observed non-significant inverse (Wie, 2014, CSECK, 29 cases only) and positive (Wu, 2006, Taiwan, 1990) associations. These studies observed similar results to other studies included in the analysis, apart from Wie, 2014 where there were only 29 cases.

The significant positive association observed remained when the studies were omitted in turn in influence analysis.

About half of the studies included in the analyses measured the participants for their height and weight and another half used measurements reported by the participants. Two studies (Miao Jonasson, 2014; Onitilo, 2014) used data from records. One study (Emaus, 2014) used self-reported or measured data. Case ascertainment was through cancer registries or confirmed through medical records.

Only five studies (Catsburg, 2014b; Emaus, 2014; Fourkala, 2014; Silvera, 2006; Schatzkin, 1989) were simultaneously adjusted for age, alcohol intake, and reproductive factors. On average studies adjusted or not adjusted for these factors observed similar results.

Table 519 BMI and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	60[1] (69 publications)
Studies included in forest plot of highest compared with lowest exposure	38 (32 publications) breast cancer risk 10 (5 publications) breast cancer mortality
Studies included in linear dose-response meta-analysis[2]	34 (28 publications) breast cancer risk 10 (5 publications) breast cancer mortality
Studies included in non-linear dose-response meta-analysis	22 (17 publications) breast cancer risk

Note: Included cohorts, case-cohort, and nested case-control designs. [1]Included one study that pooled data from six cohorts (Bjorge, 2010, Me-Can). [2]In total, 38 studies (32 publications) were included in the dose-response meta-analyses.

Table 520 BMI and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2008 SLR and CUP SLR

	2008 SLR	CUP	
Increment unit used	2 kg/m^2	5 kg/m^2	
Studies (n)	15	34	
Cases	7 200	30 550	
RR (95%CI)	1.02 (0.99-1.05)	1.07 (1.04-1.11)	
Heterogeneity (I^2, p-value)	68%, <0.001	58%, <0.001	
P value Egger test	-	0.28	
Subgroup analysis in the CUP			
Geographic area	**Asia**	**Europe**	**North America**
Studies (n)	6	16	12
Cases	5 035	15 526	9 989
RR (95%CI)	1.20 (1.10-1.31)	1.06 (1.01-1.11)	1.06 (1.00-1.12)
Heterogeneity (I^2, p-value)	0%, 0.84	60%, <0.01	63%, <0.01
Other analyses in the CUP			
	Invasive breast cancer	**Breast cancer mortality**	
Studies (n)	18	10	
Cases	14 782	1 169	
RR (95%CI)	1.07 (1.02-1.12)	1.09 (0.99-1.19)	
Heterogeneity (I^2, p-value)	61%, 0.002	11%, 0.34	

Table 521 BMI and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Pierobon, 2013[2]	11 observational studies in case-case and case-control analysis[1]	933 in case-control studies, 3 845 in case-case studies;	USA	Incidence, triple negative breast cancer	>30 vs <30 kg/m^2 Case-control analysis (5 studies) Case-case analysis (11 studies)	 1.24 (1.06-1.46) 1.20 (1.03-1.40)		 0%, 0.91 62$, <0.01

[1]The cohort study (Phipps, 2011) identified were included in the present review of postmenopausal breast cancer. [2] Pierobon, 2013 used raw data from published studies and no adjustments were applied to analyses.

Table 522 BMI and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Taghizadeh, 2015 BRE80575 Netherlands	VCS, Prospective Cohort, Age: 20-65 years, W	103/ 8 645 40 years	National death certificate	Measured	Mortality, breast cancer	≥30 vs ≤25 kg/m^2	1.52 (0.88-2.63)	Age, residence, smoking
		51/				≥30 vs ≤25 kg/m^2	1.55 (0.69-3.49)	
						≥30 vs ≤25 kg/m^2	2.52 (1.15-5.54)	
Catsburg, 2014b BRE80529 Canada	CSDLH, Case Cohort, W	1 097/ 4 417 15 years	Cancer registry	Self-reported	Incidence, Invasive breast cancer	≥30 vs 18.5-24.99 kg/m^2	1.09 (0.85-1.39) Ptrend:0.22	Age at first child birth, age at menarche, alcohol Intake, family history of breast cancer, HRT use, menopausal status, number of childbirths, OC use, physical activity
Emaus, 2014 BRE80540 Europe	EPIC-PANACEA, Prospective Cohort, Age: 25-70 years, W	4 663/ 205 723 1 396 538 person-years	Active follow up and cancer registry	Measured or self-reported	Incidence, Invasive breast cancer	28.1-59.7 vs 16-21.3 kg/m^2	1.16 (1.04-1.28) Ptrend:0.00	Age, age at first child birth, age at menarche, alcohol consumption, alcohol drinking, educational level, energy Intake, HRT use, physical activity, smoking, study center, use of oral contraception
Fourkala, 2014 BRE80562 UK	UKCTOCS, Prospective Cohort, Age: 50- years, W	1 021/ 92 834 3.19 years	NHS records	Self-reported	Incidence, breast cancer	per 5 kg/m^2	1.08 (1.01-1.14)	Age at menarche, age at menopause, alcohol consumption, cancer diagnosis, deprivation category, educational level, family history of

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								cancer, health status, HRT use, hysterectomy, Infertility, oral contraceptive use, parity, smoking, sterilisation, trouser/skirt size
Guo, 2014 BRE80541 China	Northern China 2006-2011, Prospective Cohort, Age: 18- years, W	91/ 26 643 4.28 years	Self report, next of kin, medical and pathological records	Measured	Incidence, breast cancer	≥28 vs 18.5-23.9	1.86 (1.05-3.31) Ptrend:0.022	Age, alcohol consumption, educational level, smoking
Lee, 2014 BRE80580 Singapore	SCHS, Nested Case Control, Age: 45-74 years, W	411 cases 1212 controls	Cancer registry	Self-reported	Incidence, breast cancer	≥28 vs ≤19.9 kg/m^2	1.99 (1.21-3.29)	Age at first child birth, age at menarche, breast biopsies, educational level, family history, genetic factors
						per 1 category	1.17 (1.02-1.35)	
Miao Jonasson J, 2014 BRE80530 Sweden	Swedish National Diabetes Register Cohort Study, Prospective Cohort, Age: 30-90 years, W, Type 2 diabetic patients	307/ 11 093 8.6 years	Swedish cancer registry & record linkage with Swedish cause-of-death registry	From registry records	Incidence, invasive breast cancer	≥30 vs 18.5-24.9 kg/m^2	1.30 (0.97-1.75)	Age, diabetes, diabetes medication use, hba1c, smoking
						per 5 kg/m^2	1.14 (1.03-1.26)	
Onitilo, 2014	WMCS,	1 973/	Cancer registry	From records	Incidence,	≥30 vs ≤24.9	1.04 (0.92-1.16)	Age, charlson comorbidity

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
BRE80469 USA	Historical Cohort, Age: 30- years, W	31 769 16 years	and medical records		invasive breast cancer, before diabetes onset	kg/m^2		Index, date of diagnosis, health Insurance, residence, smoking status
		852/			After diabetes onset	≥30 vs ≤24.9 kg/m^2	1.19 (0.96-1.46)	
Wie, 2014 BRE80609 Korea	Cancer Screening Examination Cohort, Korea (CSECK), Prospective Cohort, W	29/ 3 486 7 years	Cancer registry and medical records	Measured	Incidence, invasive breast cancer	per 1 kg/m^2	0.88 (0.60-1.31)	Age, alcohol Intake, educational level, energy, Income, marital status, physical activity, smoking
						≥25 vs <25 kg/m^2	0.22 (0.01-3.27)	
						≥25 vs <25 kg/m^2	1.32 (0.53-3.31)	
van Kruijsdijk RC, 2013 BRE80475 Netherlands	SMART study, Prospective Cohort, Age: 18-80 years, W, Patients with Vascular disease	25/ 1 589 5.5 years	Cancer registry	Measured	Incidence, invasive breast cancer	per 4.8 kg/m^2	0.88 (0.62-1.25)	Age, alcohol consumption, pack yrs of smoking, smoking status
Redaniel, 2012 BRE80428 UK	UKGPR, Prospective Cohort, Age: 35- years, W	1 528/ 52 657	Medical record	Measured	Incidence, breast cancer	≥30 vs 18.5-24.9 kg/m^2	1.45 (1.12-1.88)	Age, period, region
Bessonova, 2011 BRE80306 USA	CTS, Prospective Cohort, Age: 53 years,	302/ 1 322 634 person-years	Mortality records	Self-reported	Mortality, breast cancer	≥30 vs 18.5-24.9 kg/m^2	1.57 (1.07-2.31)	Age, alcohol consumption, calories derived from fat, HRT use, morbidity, phyisical activity,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	W, teachers							smoking, weight change
		134/			Ever smoker	≥30 vs 18.5-24.9 kg/m^2	1.53 (0.85-2.76)	
		165/			Never smoked	≥30 vs 18.5-24.9 kg/m^2	1.52 (0.91-2.55)	
Dehal, 2011 BRE80393 USA	NHEFS, Prospective Cohort, Age: 25-74 years, W	35/ 3 889 16.96 years	Death Index & social security administration death file	Measured	Mortality	≥30 vs 18.5-24.9 kg/m^2	1.36 (0.60-3.08) Ptrend:0.12	Alcohol, baseline residence type area, educational level, family Income level, fruits and vegetables consumption, marital satus, race/ethnicity, smoking
					Mortality, breast cancer	≥30 vs 18.5-24.9 kg/m^2	1.43 (0.66-3.11) Ptrend:0.02	
Andreotti, 2010 BRE80313 USA	AHS, Prospective Cohort, M/W, Spouse of pesticide applicator	622/ 28 319 10 years	Cancer registry	Self-reported	Incidence, breast cancer	≥35 vs 18.5-24.9 kg/m^2	0.79 (0.50-1.25)	Diabetes, family history of breast cancer, meat consumption
						per 1 kg/m^2	1.00 (0.99-1.02)	
Bjorge, 2010 Austria, Norway, Sweden	Me-Can, Pooled study, 6 cohorts W (NCS; CONOR; 40-y; VHM&PP; VIP, MPP)	4 862/ 287 320 11 years follow-up Mean age: 58 years at diagnosis	Record linkage to cancer registries, and death register and population registers	Measured	Incidence, invasive breast cancer	≥31.7 vs ≤ 20 kg/m^2	0.98 (0.88-1.09) Ptrend:0.7	Year of birth, age at measurement, smoking, stratified for cohort
		633/			Mortality, breast cancer	≥31.7 vs ≤ 20 kg/m^2	0.99 (0.74-1.32) Ptrend: 0.7	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Brinton, 2008 BRE80203 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W	3 559/ 126 638 6 years	Cancer registry	Self-reported	Incidence, Invasive & In situ breast cancer	≥30 vs ≤24.9 kg/m^2	1.13 (1.04-1.23)	Age, age at first child birth, breast biopsies, family history of cancer, mammography, menopausal status, race
Jee, 2008 BRE80195 Korea	KNHIC, Prospective Cohort, Age: 30-95 years, W	3 973/ 443 273 10.8 years	Cancer registry and hospital records	Measured In light clothing at physical examination	Incidence, breast cancer	≥30 vs 23-24.9 kg/m^2	1.13 (0.84-1.53) Ptrend:0.0003	Age, smoking status
Fujino, 2007 BRE80442 Japan	JACC, Prospective Cohort, W	96/		Obtained from survey, no further details were provided.	Mortality, breast cancer	≥30 vs 18.5-24 kg/m^2	0.97 (0.23-4.01)	Age, study area
Chun, 2006 BRE80134 USA	WRC, New York, Prospective Cohort, Age: 47 years, W, High Risk population	62/ 1 553 5 years	Cancer registry	Self-reported	Incidence, breast cancer	≥30 vs 19-24	2.22 (1.14-4.35)	Age, atypical ductal hyperplasia, lobular carcinoma In situ
Silvera, 2006 BRE24118 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W, Participants of a	1 671/ 38 645 16.4 years	Partially histological - over 80%	Measured	Incidence, breast cancer	≥30 vs ≤24 kg/m^2	1.14 (0.92-1.39) Ptrend:0.34	Age , age at first child, age at menarche, alcohol, breast diseases , energy Intake , family history, HRT use, leisure time physical activity, menopausal status, OC

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	RCT of screening for breast cancer							use, other design Issue, parity/pregnancies, recruitment center, smoking habits
Wu, 2006 BRE24628 China	Taiwan 1990, Prospective Cohort, Age: 47 years, W, Screening Program	104/ 11 899 10.3 years	Partially histological - over 80%	Measured	Incidence, invasive breast cancer	≥26.31 vs ≤21.59 kg/m^2	1.60 (0.50-5.10)	Age at first child, age at menarche, other anthropometric Index, waist circumference
Jonsson, 2003 BRE04482 Sweden	Swedish twin cohort, 1969, Prospective Cohort, Age: 44-83 years, W, Twins	580/ 11 598 29 years	Partially histological - over 80%	Self-reported	Incidence, breast cancer	≥30 vs 18.5-24.99 kg/m^2	1.20 (0.80-1.60)	Age
Luoto, 2000 BRE80174 Finland	FAHBS, 1978, Prospective Cohort, Age: 15-64 years, W	313/ 30 548	Cancer registry	Self-reported	Incidence, breast cancer	≥26.1 vs ≤20.9 kg/m^2	1.04 (0.73-1.48)	Age at first child birth, BMI, educational level, lenght of follow-up, parity
Key, 1999 BRE04758 Japan	LSS, 1969, Prospective Cohort, W	427/ 34 759 24 years	Partially histological - over 80%	Self-reported	Incidence, breast cancer	≥25 vs ≤19.9 kg/m^2	1.37 (1.02-1.84) Ptrend:0.05	Age , calendar year, other factors , other factors , place of residence
Wu, 1999 BRE13618	CLUE I, Nested Case	133 cases 133 controls	Partially histological -	Self-reported	Incidence, breast cancer	≥26 vs ≤22 kg/m^2	0.75 (0.32-1.77)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
USA	Control, Age: 18-90 years, W, blood donors	21 years	over 80%					
Wu, 1999 BRE63618 USA	CLUE II, Nested Case Control, Age: 18-90 years, W, blood donors	110 cases 110 controls 6 years	Partially histological - over 80%	Self-reported	Incidence, breast cancer	≥26 vs ≤22 kg/m^2	0.77 (0.35-1.70)	
Galanis, 1998 BRE03058 hawaii	Hawaii State Department of Health, 1975, Prospective Cohort, Age: 43 years, W	378/ 17 628 14.9 years	Partially histological - over 80%	Self-reported	Incidence, invasive breast cancer	≥26.1 vs ≤19.5 kg/m^2	1.80 (1.30-2.60) Ptrend:0.0001	Age , alcohol, educational level, ethnicity
Wolk, 1998 BRE13548 Sweden	SMC, Prospective Cohort, Age: 40-76 years, W, Screening Program	61 147 4.2 years	All histology	Self-reported	Incidence, Invasive breast cancer	per 1 kg/m^2	1.02 (1.00-1.04)	Age at first child, educational level, family history, parity/pregnancies
Byrne, 1996 BRE05719 USA	NHEFS, Prospective Cohort, Age: 25-74	52/ 6 156 3.9 years	Medical records + death certificate	Self-reported	Incidence, breast cancer	≥29.3 vs ≤22.34 kg/m^2	1.30 (0.60-3.00)	Age

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	years, W							
Knekt, 1996 BRE04900 Finland	Finland, 1966, Prospective Cohort, Age: 15-90 years, W, Screening Program	87/ 4 697 25 years	Cancer registry + death certificate	Measured	Incidence, breast cancer	28.68-99.99 vs 0-20.94 kg/m^2	0.47 (0.21-1.04)	Age
Tornberg, 1994 BRE12417 Sweden	Sweden, 1971, Prospective Cohort, Age: 25-75 years, W, Screening Program	1 466/ 47 003 25 years	Partially histological - over 80%	Measured	Incidence, breast cancer	≥28 vs 0-21.9 kg/m^2	0.92 Ptrend:0.73	Age
						per 2 kg/m^2	1.01 (0.97-1.05)	
Mills, 1989 BRE17837 USA	AHS, 1974 Prospective Cohort, Age: 25-99 years, W, Adventist	189/ 20 341 6 years	Medical records	Self-reported	Incidence, breast cancer	≥25.2 vs ≤21.7 kg/m^2	1.56 (1.07-2.27) Ptrend:0.03	Age
Schatzkin, 1989 BRE18013 USA	FHS, Prospective Cohort, Age: 31-64 years, W	143/ 2 636 26 years	All histology	Measured	Incidence, breast cancer	≥28.8 vs ≤21.7 kg/m^2	0.60 (0.40-1.10)	Age , alcohol, educational level, height, menopausal status, parity/pregnancies, smoking habits

Table 523 BMI and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Makarem, 2015 BRE80589 USA	FHS-Offspring Cohort, Prospective Cohort, W	124/ 1 602 11.5 years	Death certificate and medical records	Measured	Incidence, breast cancer	per 1 points	0.91 (0.59-1.42)	Age, smoking status	Excluded, exposure was on obesity guideline adherence
						per 1 points	0.93 (0.60-1.45)		
Catsburg, 2014a BRE80536 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W, Participants of a RCT of screening for breast cancer	48 840 16.6 years	Cancer registry	Measured	Incidence, Invasive breast cancer	adhered vs not adhered	1.07 (0.98-1.18)	Age, age at first child birth, age at menarche, alcohol, energy, family history of breast cancer, history of breast disease, HRT use, menopausal status, OC use, parity, physical activity, red and processed meat, sodium, study center, vegetable and fruit Intake, whole grains	Superseded publication
						adhered vs not adhered	1.03 (0.94-1.14)		
Engel, 2014 BRE80554 USA (one publication	AHS, Prospective Cohort, Age: 18-86 years,	428/ 31 021 8.6 years	Cancer registry	Self-reported	Incidence, breast cancer	≥30 vs ≤24.9 kg/m^2	1.20 (1.00-1.60)	Age, age at first child birth, age at menarche, age at menopause, educational	Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
two study designs)	W							level, family history of breast cancer In first degree relatives, menopausal status, parity, race, smoking status, state of residence, sun screen use	
Engel, 2014 BRE80501 USA (one publication two study designs)	AHS, Nested Case Control, Age: 18-86 years, W	234/ 458 controls 8.6 years	Cancer registry	Self-reported	Incidence, breast cancer	≥30 vs ≤24.9 kg/m^2	0.80 (0.50-1.30)	Age, age at first child birth, age at menarche, age at menopause, educational level, family history of breast cancer In first degree relatives, menopausal status, parity, race, smoking status, state of residence	Superseded publication
Song, 2014 BRE80519 Finland	FINRISK , Prospective Cohort, Age: 24-74 years, W	1 086/ 28 089 20.6 years	Cancer and mortality registries	Mesured	Incidence, breast cancer	≥35 vs 23.0-24.9 kg/m^2	0.79 (0.56-1.10)	Age, area, educational level, leisure time physical activity, smoking	Excluded, insufficient data
Bjerkaas, 2013 BRE80485	NNHSSS (NCS; CONOR; 40-y	7 490/ 302 865	Cancer registry	Measured at health	Incidence, breast cancer	≥30 vs ≤24.9 kg/m^2	0.88 (0.81-0.96)	Age, age at first child birth, age	Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Norway	Cohort), Prospective Cohort, Age: 44 years, W	14 years		examination				at study entry, educational level, number of children, physical activity	
Lin, 2013 BRE80465 USA	NHANES III, Prospective Cohort, Age: 50- years, W	26/ 2 730 12.4	Cancer registry	Measured	Mortality, breast cancer	≥30 vs ≥24.9 kg/m^2	3.44 (0.82-14.40) Ptrend:0.24	Age, alcohol Intake, calories Intake, race/ethnicity, smoking status, urinary cadmium, zinc	Superseded study
Pudrovska, 2013 BRE80477 USA	WLS, Prospective Cohort, W	261/ 3 682	Self report and/or death certificate	Measured	Incidence, breast cancer, diagnosed after 1993	≥30 vs ≤24.9 kg/m^2	1.19 (0.87-1.63)	Adiposity, age at menarche, age at menopause, alcohol consumption, educational level, family history of breast cancer, high-status job, household Income, HRT use, hysterectomy, marital status, number of childbirths, occupation, parity and age at first birth,	Excluded, insufficient data

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								parity/pregnancies, physical activity, propensity score	
Harlid, 2012 BRE80422 Sweden	NSHDC (VIP and MSP), Prospective Cohort, Age: 27-95 years, W	1 243/ 3 994	Cancer registry	Self-reported	Incidence, invasive breast cancer	≥30 vs 18.5-25	0.91 (0.74-1.14)	Age	Superseded study (MSP), superseded publication (VIP)
Harlid, 2012 BRE80421 Sweden	MDCS, Prospective Cohort, Age: 45-84 years, W	666/ 17 035 16 years	Cancer registry	Measured	Incidence, invasive breast cancer	≥30 vs 18.5-25 kg/m^2	1.25 (0.94-1.66)	Age	Superseded study
Osaki, 2012 BRE80387 Japan	Tottori Prefecture Japan Cohort, Historical Cohort, W	77/ 15 386 9.1 years	Cancer registry and death certificates	Measured	Incidence, breast cancer	≥25 vs <25 kg/m^2	2.39 (1.47-3.91) Ptrend:0.000	Age, drinking amount, metabolic syndrome factors, smoking	Excluded, two exposure categories
Wilson, 2011 BRE80380 USA	NHS, Nested Case Control, W, mothers and daughters	713/ 1556 controls	Medical record	Self reported	Incidence, breast cancer	≥30 vs ≤20 kg/m^2	0.76 (0.34-1.73) Ptrend:0.48	Age, age at menarche, BMI, family history of breast cancer, height, smoking	Excluded, exposure was on pre-pregnancy BMI and risk of BC in daughters; publication superseded by other NHS

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
									publication
		383/ 1556 controls			Incidence, breast cancer ER+	≥25 vs ≤20 kg/m^2	1.01 (0.66-1.56) Ptrend:0.60		
		137/ 1556 controls			Incidence, breast cancer ER-	≥25 vs ≤20 kg/m^2	0.95 (0.51-1.77) Ptrend:0.75		
Burton, 2010 BRE80315 Scotland	Glasgow Alumni Cohort study, Prospective Cohort, Age: 20 years, M/W, University students	95/ 2 657 49 years	Cancer registry/ death certificate	Measured	Incidence, breast cancer	per 1 kg/m^2	0.99 (0.91-1.08)	Age at menarche, height, smoking, social class	Excluded, exposure was on BMI at a younger age
						>25 vs 19-23 kg/m^2	0.85 (0.37-1.96)		
Gibson, 2010 BRE80237 Philippines	CBET Manila, Nested Case Control, Age: 48 years, W	110/ 864 controls	Cancer registry	Measured	Incidence, breast cancer	≥25 vs ≤24.9 kg/m^2	1.00 (0.50-1.70)	Age, age at first child birth, area of residence, date of enrollment, educational level, parity	Excluded, two exposure categories
Lee, 2010 BRE80556 China	SWHS, Nested Case Control, Age: 52 years, W	324/ 621 controls 7 years	Active follow up and cancer registry	Measured	Incidence, breast cancer	≥23.4 vs ≤23.3 kg/m^2	0.99 (0.76-1.30)	Age, antibiotics use, date of urine collection, history of cancer, menopausal status	Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Davey Smith, 2009 BRE80459 Sweden	SIMS, Prospective Cohort, W	6 103/ 1 018 012 50 years	Death record & Swedish cause of death register	Measured	Mortality, breast cancer	per 1 standard deviation	0.96 (0.94-0.99)	Educational level, parental age, social class	Excluded. proxy BMI
Key, 2009 BRE80560 UK	EPIC, Prospective Cohort, Age: 20-89 years, W, Vegetarians	714/ 40 476 12 years	National cancer registers	Self-reported	Incidence, breast cancer	≥27.5 vs 20-22.4 kg/m^2	1.02 (0.81-1.28)	Age-underlying cox models, method of recruitment, smoking	Superseded study
Li, 2009 BRE80285 USA	KPMCP, Prospective Cohort, Age: 41 years, W	2 107/ 70 033 16 years	SEER registry	Self-reported	Incidence, breast cancer	≥30 vs ≤24.9 kg/m^2	1.50 (1.40-1.70)	Age, alcohol consumption, BMI, breast diseases , educational level, ethnicity, family history, marital status, parity, smoking habits	Excluded, two exposure categories
Setiawan, 2009 BRE80272 USA	MEC, Prospective Cohort, Age: 45-75 years, W	1 672/ 84 427 10.4 years	SEER registry	Self-reported	Incidence, breast cancer ER+/PR+	30.0 vs ≥24.9	1.52 (1.32-1.75) Ptrend:<0.001	Age, age at first child birth, age at menarche, alcohol consumption, ethnicity, family history of cancer, HRT use, menopausal status, parity, study center,	Results on breast cancer subtypes only, not analysed

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								year of recruitment	
		303/			Incidence, breast cancer ER+/PR-	30.0 vs ≥24.9	0.90 (0.63-1.30) Ptrend:0.75		
		491/			Incidence, breast cancer ER-/PR-	30.0 vs ≥24.9	0.79 (0.60-1.03) Ptrend:0.07		
Wen, 2009 BRE80209 China	SWHS, Prospective Cohort, Age: 40-70 years, W	616/ 73 328 7.35 years	Cancer registry	Measured	Incidence, Invasive & In situ breast cancer	>25 vs ≤25 kg/m^2	1.31 (1.11-1.55)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, benign breast disease, educational level, energy Intake, family history of cancer, HRT use, physical activity, smoking status, waist-hip ratio	Excluded, two exposure categories
Bjørge, 2008 BRE80226 Norway	NSPT, Historical Cohort, Age: 14-19 years, W	437/ 111 701 34.9 years	Death register	Measured	Mortality, breast cancer	q 4 vs q 2	0.90 (0.60-1.20) Ptrend:0.6	Age, birthyear	Excluded, exposure was on BMI at a young age
Visvanathan, 2007 BRE80020	CLUE II, Nested Case Control,	100/ 100 controls		Self-reported	Incidence, breast cancer	≥30 vs ≤24.9	1.60 (1.04-2.45) Ptrend:0.02		Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
USA	Age: 57 years, W								
Lukanova, 2006 BRE80100 Sweden	NSHDC (VIP and MSP), Prospective Cohort, Age: 29-61 years, W	514/ 74 207 8.2 years	Medical records	Measured	Incidence, invasive breast cancer	≥27.1 vs 18.5-22.1	0.95 (0.74-1.23) Ptrend:0.36	Age , calendar year, smoking habits	Superseded publication
Kuriyama, 2005 BRE22995 Japan	Miyagi, 1993, Prospective Cohort, Age: 40- years, W	115/ 15 054 9 years	Partially histological - over 80%	Self-reported	Incidence, breast cancer	≥30 vs 18.5-24.9 kg/m^2	1.90 (0.87-4.15) Ptrend:0.04	Age , age at first child, age at menarche, alcohol, food, menopausal status, smoking habits	Superseded publication
Rapp, 2005 BRE23858 Austria	VHM-PP, Prospective Cohort, Age: 35-54 years, W, Screening Program	1 045/ 78 484 9.9 years	Partially histological - over 80%	Measured	Incidence, breast cancer	≥35 vs 18.5-24.9 kg/m^2	1.01 (0.72-1.42) Ptrend:0.8	Age , occupation, smoking habits	Superseded publication
Colditz, 2004 BRE01783 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered	1 281/ 66 145 19 years	All histology	Self-reported	Incidence, invasive breast cancer ER+/PR+, HRT - no	per 35 year*(kg/m^2	1.17 (1.11-1.23)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, duration of HRT	Results on breast cancer subtypes, not analysed

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	nurses							use, family history, height, menopausal status, other menstrual characteristics	
					HRT - yes	per 35 year*(kg/m^2	0.97 (0.95-0.99)		
						consistently obese vs average woman kg/m^2	1.17 (1.05-1.30)	HRT use	
		318/			Incidence, breast cancer ER+/PR-, HRT - yes	per 35 year*(kg/m^2	0.95 (0.91-0.99)		
					HRT - no	per 35 year*(kg/m^2	1.05 (0.94-1.17)		
						consistently obese vs average woman kg/m^2	0.82 (0.65-1.03)		
		80/			Incidence, breast cancer ER-/PR+, HRT - yes	per 35 year*(kg/m^2	0.95 (0.88-1.02)		
					HRT - no	per 35 year*(kg/m^2	1.39 (1.14-1.70)		
						consistently obese vs average woman kg/m^2	1.15 (0.80-1.67)		
		417/			Incidence, breast cancer ER-/PR-,	per 35 year*(kg/m^2	0.98 (0.94-1.01)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					HRT - yes				
					HRT - no	per 35 year*(kg/m^2	1.02 (0.91-1.13)		
						consistently obese vs average woman kg/m^2	0.90 (0.76-1.08)		
Kilkkinen, 2004 BRE17698 Finland	Helsinki and Oulu, 1982, Nested Case Control, Age: 25-74 years, W	15 497 15 years	Partially histological - over 80%	Measured	Incidence, breast cancer	(mean exposure)		Age , place of residence	Superseded study
Rissanen, 2003 BRE17954 Finland	Mobile Clinic Health Examination Survey, 1973, Nested Case Control, Age: 18-89 years, W	8 196 10 years	Partially histological - over 80%	Measured	Incidence, breast cancer	(mean exposure)			Excluded, mean exposure comparison
Zhang, 2003 BRE13958 USA	NHS, Nested Case Control, Age: 43-69 years, W, Registered nurses	32 826 40 months	Medical records + self-reported +death certificate	Self-reported	Incidence, breast cancer	(mean exposure)			Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Goodman, 1997 BRE03352 Japan	LSS, 1969, Prospective Cohort, W, Atomic bomb survivors	149/ 22 200 8.31 years	Partially histological - over 80%	Self-reported	Incidence, breast cancer	≥24.67 vs ≤19.9 kg/m^2	1.21 (0.77-1.19) Ptrend:0.23	Age , other age Indicator, other specified factor, place of residence	Superseded publication
Gaard, 1994 BRE03044 Norway	NNHSS, 1974, Prospective Cohort, Age: 20-54 years, W	31 209 13 years	Partially histological - over 80%	Measured	Incidence, breast cancer	2.66-5.27 vs ≤2.17 g/cm^2	0.75 (0.54-1.04) Ptrend:0.06	Age	Superseded study
Hoyer, 1992 BRE04086 Denmark	Glostrup Population Studies, 1982, Prospective Cohort, Age: 30-80 years, W	5 207 26 years	Partially histological - over 80%	Self-reported	Incidence, breast cancer	≥33 vs ≤25.9 kg/m^2	2.50 (0.80-7.20) Ptrend:0.03		Excluded, insufficient data
Vatten, 1992 BRE12828 Norway	NNHSS, 1974, Prospective Cohort, Age: 26-49 years, W	291/ 25 967 14 years	Partially histological - over 80%	Measured	Incidence, breast cancer	≥28 vs ≤21 kg/m^2	0.78 (0.65-0.94) Ptrend:0.002	Age , age at first child, occupation, parity/pregnancies, place of residence	Superseded publication
Overvad, 1991 BRE17893 Guernsey	Guernsey, 1967, Case Cohort, Age: 35- years, W	5 162 11 years	All histology	Self-reported	Incidence, breast cancer	(mean exposure)			Excluded, mean exposure comparison
Vatten, 1990c	NNHSS, 1974,	236/	Partially	Measured	Incidence, breast	≥2.68 vs ≤2.19	0.52 (0.34-0.77)	Age	Superseded

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
BRE12826 Norway	Prospective Cohort, Age: 35-51 years, W	23 826 11.9 years	histological - over 80%		cancer	g/cm^2	Ptrend:0.001		publication
Vatten, 1990b BRE12833 Norway	NNHSS, 1974, Prospective Cohort, W	14 593 12 years	Partially histological - over 80%	Measured	Incidence, breast cancer	≥24 vs ≤23.9 kg/m^2	0.70	Age	Superseded publication
Tornberg, 1988 BRE12418 sweden	Swedish cohort, 1963, Prospective Cohort, Age: 17-74 years, W	46 570 20 years	Partially histological - over 80%	Measured	Incidence, breast cancer	per 1 unit	1.01 (0.99-1.03)	Age, place of residence	Superseded study

Figure 526 RR estimates of breast cancer by levels of BMI

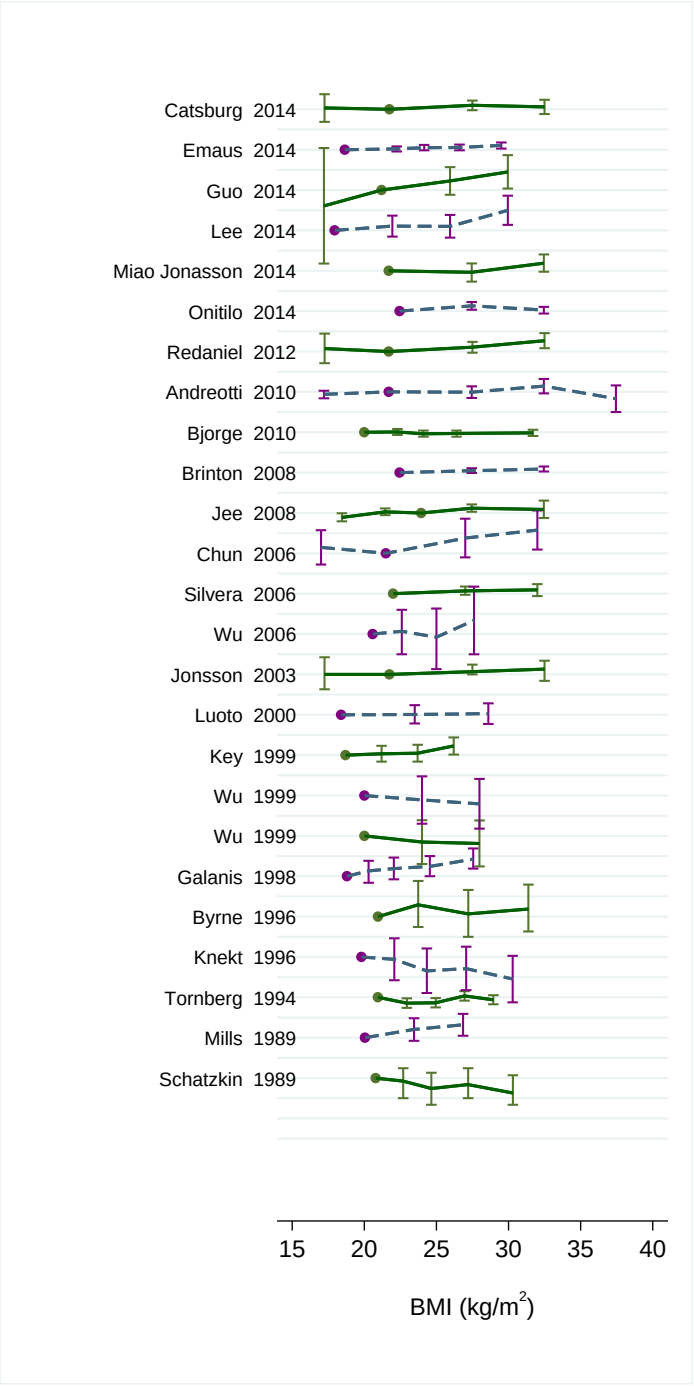


Figure 527 RR (95% CI) of breast cancer for the highest compared with the lowest level of BMI

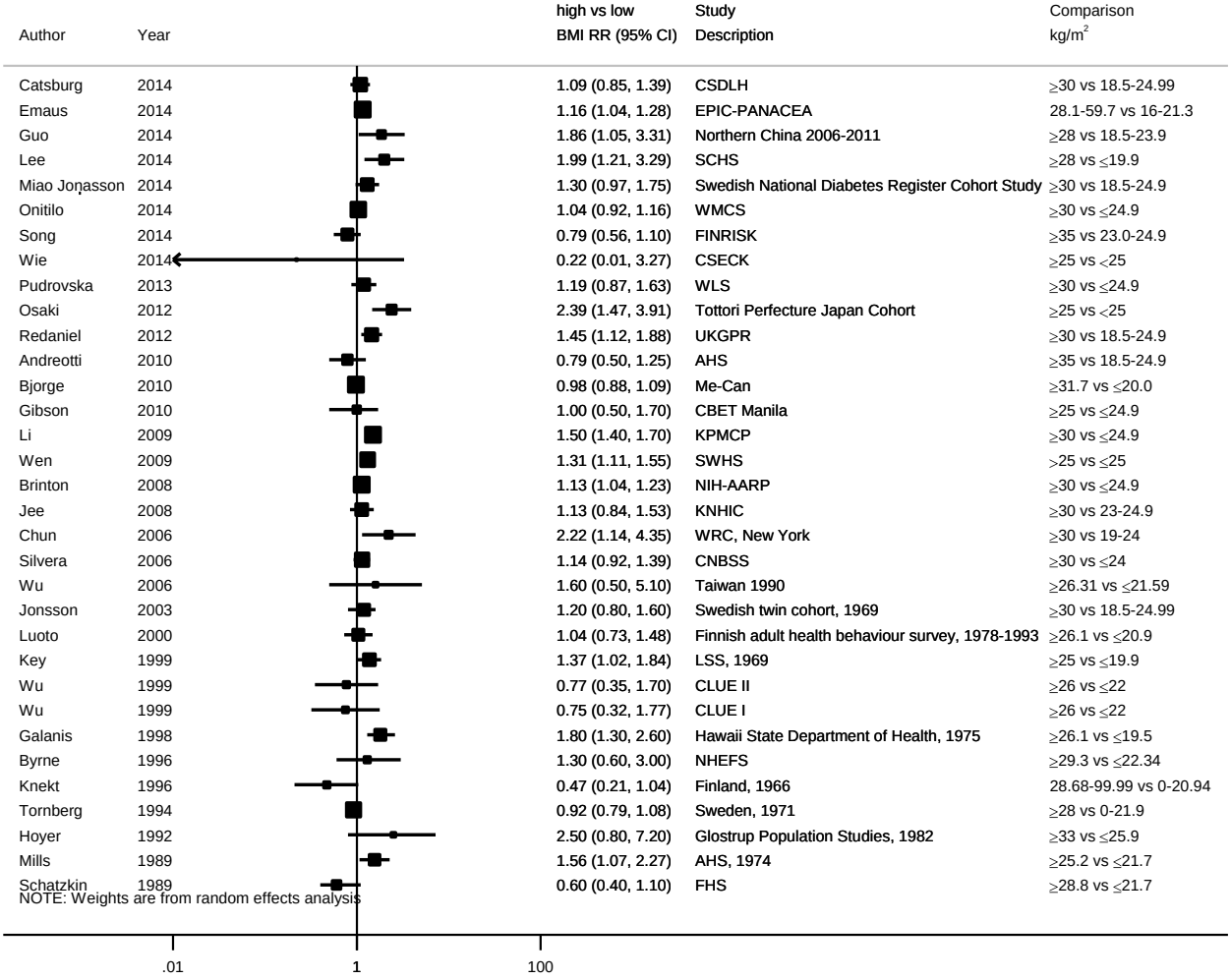


Figure 528 Relative risk of breast cancer for 5 kg/m^2 increase of BMI

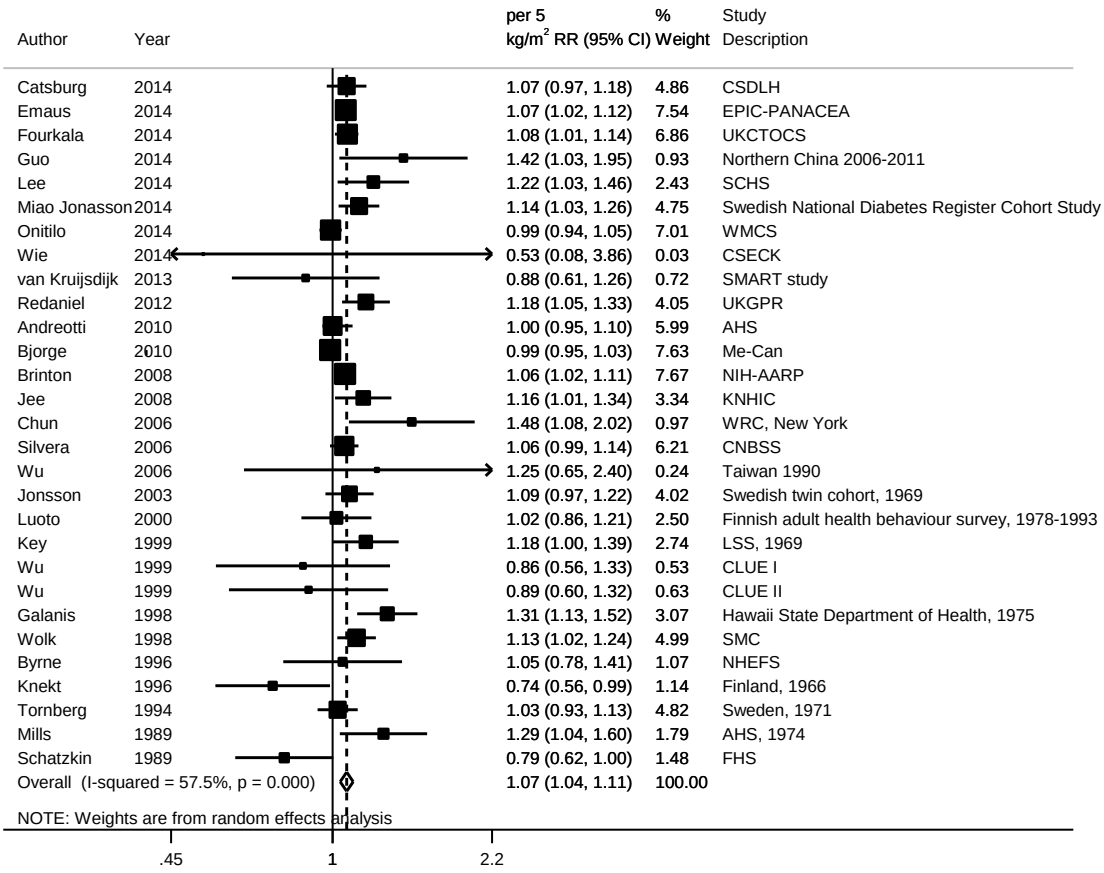
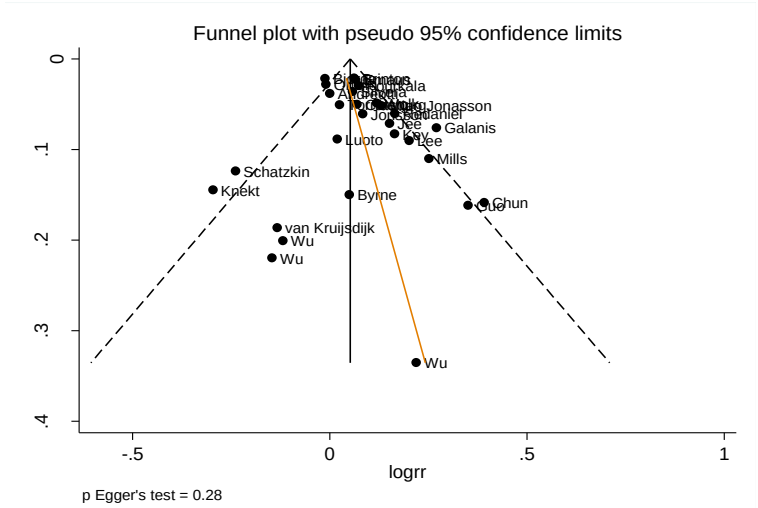


Figure 529 Funnel plot of studies included in the dose response meta-analysis of BMI and breast cancer



Note: The small study that found a non-significant inverse association (RR per 5kg/m^2=0.53, 95% CI=0.08-3.86) (Wie, 2014) was excluded from the forest plot to facilitate presentation.

Figure 530 Relative risk of breast cancer for 5 kg/m^2 increase of BMI, by geographic location

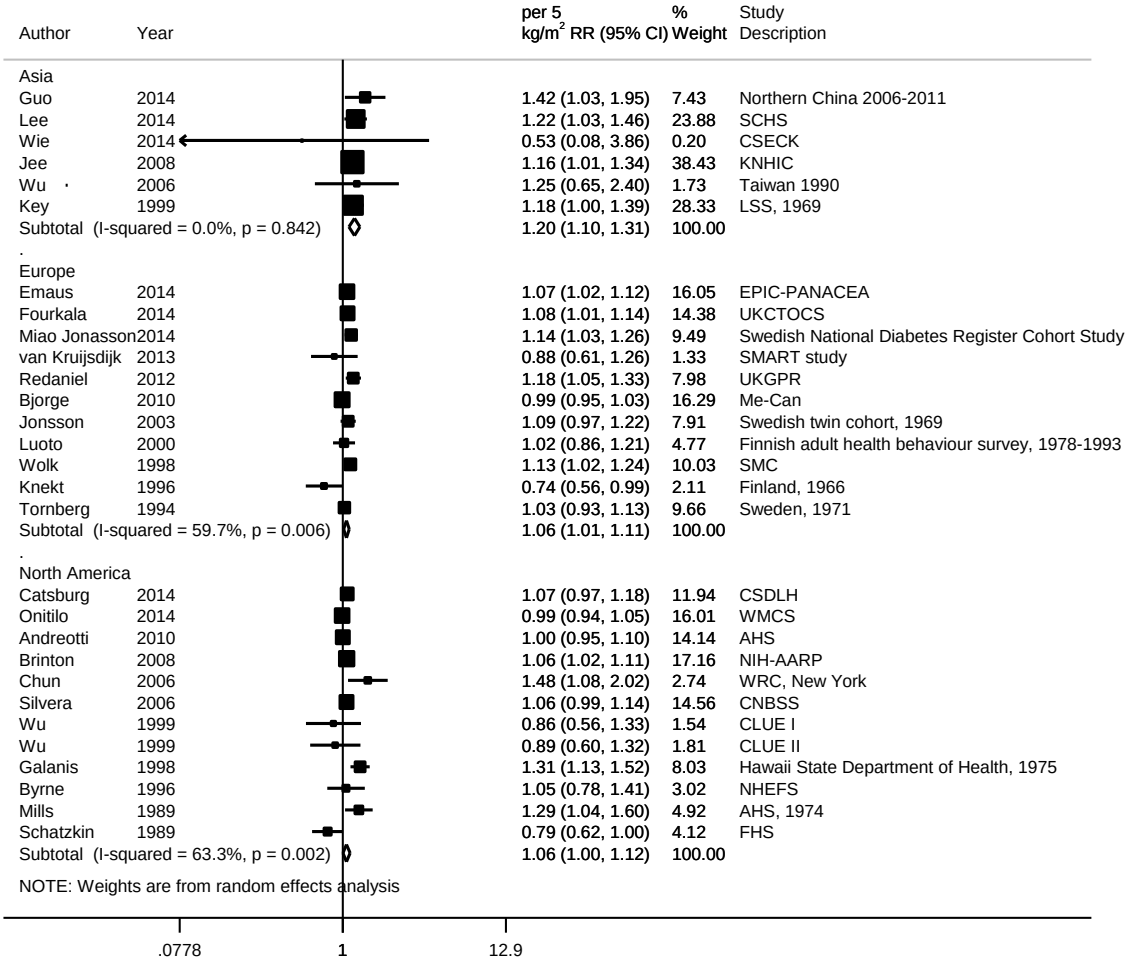


Figure 531 RR (95% CI) of breast cancer mortality for the highest compared with the lowest level of BMI

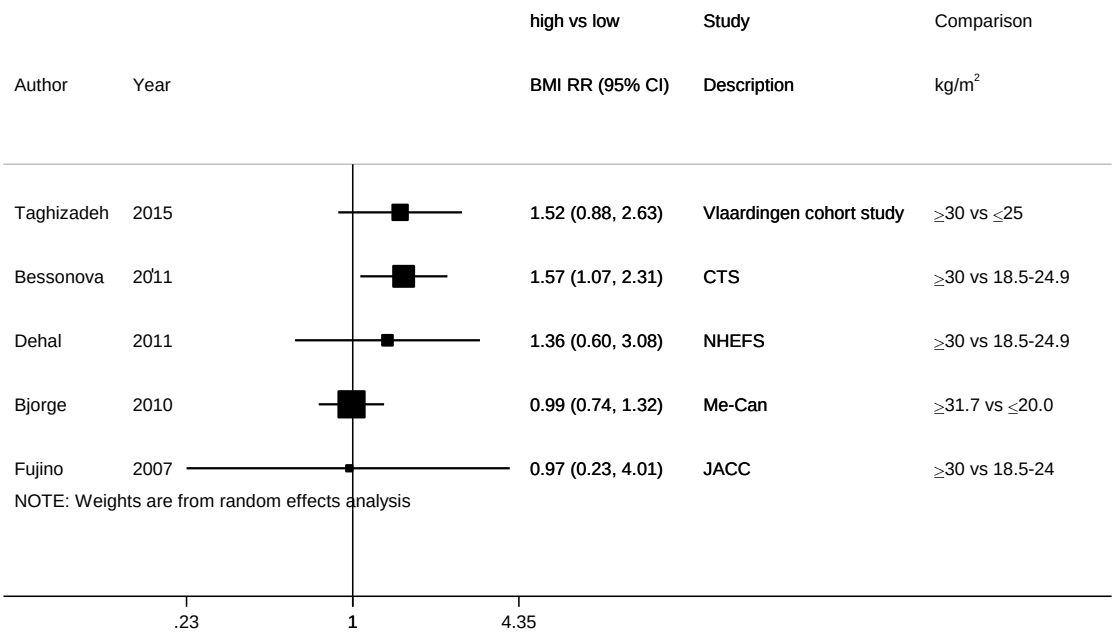
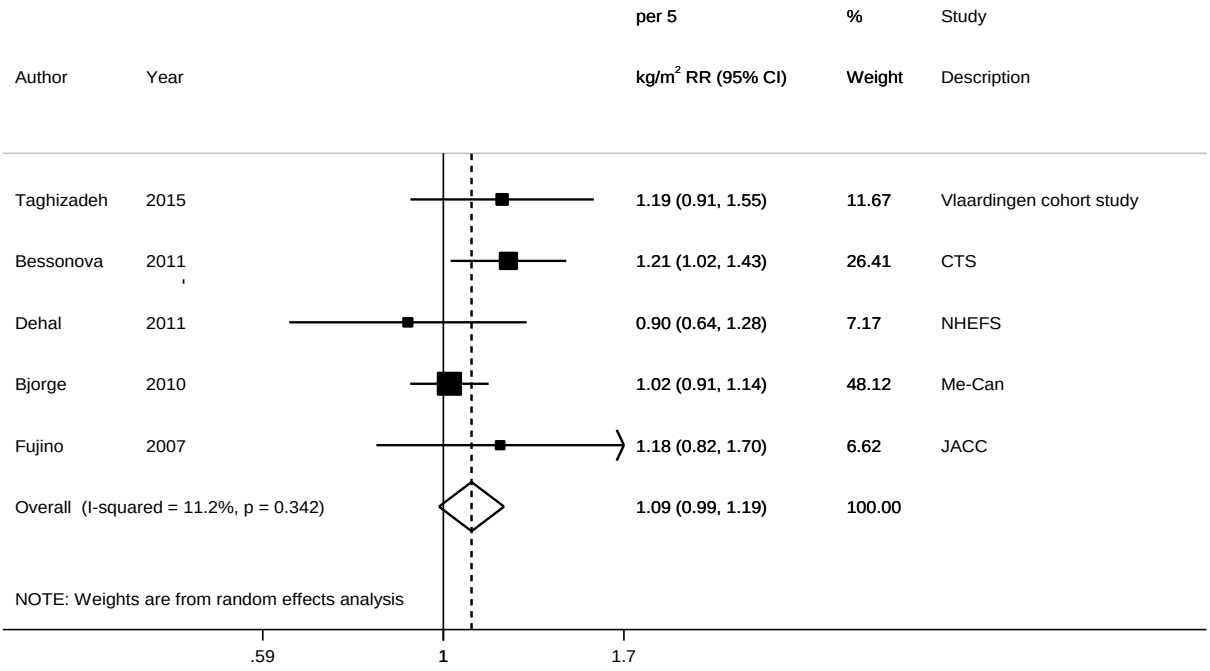


Figure 532 Relative risk of breast cancer mortality for 5 kg/m^2 increase of BMI



Premenopausal breast cancer

Summary

Main results:

Seventy-one out of 128 studies (57 publications) identified could be included in the dose-response meta-analyses. There were 37 studies (24 publications) on BMI and premenopausal breast cancer risk overall, and seven studies (four publications) by hormone-receptor subtypes. Thirty-six studies (two publications) were included in the meta-analysis of breast cancer mortality.

BMI was significantly inversely associated with premenopausal breast cancer risk (summary RR per 5 kg/m^2=0.93 (95% CI=0.90-0.97). There was evidence of high heterogeneity between studies (I^2=55%, P=0.001), which could partly explained by the geographical locations of the cohorts. Inverse associations were only observed in European studies (summary RR=0.89, 95% CI=0.86-0.92, I^2=11%, P=0.33) and North American studies (summary RR=0.97, 95% CI= 0.91-1.03, I^2=40%, P=0.09); but not in Asian countries, where a positive association was found (summary RR=1.16, 95% CI=0.99-1.37, I^2=0%, P=0.40).

For breast cancer mortality in premenopausal women/women <60 years of age, no significant association was observed (summary RR=1.00, 95% CI=0.73-1.38, I^2=75%, p=0.05). The only study (Reeves, 2007, MWS) that provided additional data to the Prospective Studies Consortium (Whitlock, 2009, PSC) observed opposite association. Two pooled studies that could not be included in the analysis due to missing data or overlapping of studies, reported a non-significant positive association (Bjorge, 2010, Me-Can) and a non-significant inverse association (Parr, 2010, APCSC) for the highest compared with the lowest BMI category.

There was no significant evidence of publication bias or small study bias (P for Egger's test=0.13). The asymmetry in the funnel plot could be driven by the smaller studies that reported stronger associations than the average.

Non-significant positive associations of similar magnitude were observed with ER-positive (summary RR per 5 kg/m^2=1.02, 95% CI=0.90-1.15), and ER-negative (RR=1.01, 95% CI= 0.94-1.08) breast cancer. High heterogeneity was observed between the studies on ER-positive breast cancer (I^2=68%, P=0.02, seven studies). No heterogeneity between ER-negative breast cancer (I^2=0%, P=0.49, seven studies).

Fifty-seven studies and 31 publications were excluded from the dose-response meta-analyses. Study populations in four studies (Emaus, 2014; Tehard, 2006; Lundqvist, 2007, case-control analysis; Tornberg, 1988) overlapped with other studies that were already included in the analyses. Some studies were common between the two pooled studies on breast cancer mortality (Parr, 2010, APCSC; Whitlock, 2009, PSC) and the one with less number of deaths (Parr, 2010, APCSC, 32 non-overlapping studies) were excluded. One excluded study (Burton, 2010) was on BMI at young adulthood and one (Davey Smith, 2009) used offspring BMI as an indicator of own BMI.

Eight studies (five publications) did not report sufficient data to be included in the meta-analysis of premenopausal breast cancer risk. For the highest versus the lowest BMI

comparison, one study from Hawaii (Le Marchand, 1988) and the pooled study of African Americans (Bjorge, 2010, four non-overlapping studies) observed inverse associations, with a significant dose-response trend. The other two Asian cohorts found either no association (Lee, 2003) or a non-significant positive association (Guo, 2014). Rissanen, 2003 reported on average similar BMI between the cases and non-cases.

One excluded study (Schairer, 2013) reported results on specific breast cancer types only. A significant positive association was observed for inflammatory breast cancer (RR for highest vs lowest= 3.62, 95% CI=1.30-10.04), but not for non-inflammatory breast cancer (RR=0.98, 95% CI=0.69-1.39) nor non-inflammatory locally advanced breast cancer (RR=1.03, 95% CI= 0.59-1.81).

Another pooled study (Yang XR, 2011, 10 non-overlapping studies) on breast cancer hormone receptor subtypes was excluded because of insufficient data to be included in the dose-response meta-analysis. For the highest versus the lowest BMI comparison, a significant inverse association was observed with ER+ (RR=0.81, 95% CI=0.69-0.95) but not ER- (1.10, 95% CI=0.92-1.30) breast cancer (Yang XR, 2011).

Sensitivity and stratified analyses:

Summary RR did not change materially when studies were omitted in turn in influence analysis. This included the omission of the AMBER Consortium (Bandera, 2015) that pooled data from one cohort and two case-control studies of African American women. When the NSABP P-1 breast cancer prevention trial (Cecchini, 2012) was excluded from the influence analysis restricted to North American studies, the summary RR per 5 kg/m^2 was 0.95 (95% CI=0.92-0.99) and heterogeneity dropped from 40% (P=0.09) to 2% (P=0.42).

The inverse association remained significant among studies that measured participants for height and weight data (summary RR= 0.94, 95% CI=0.86-0.98) (14 studies, high heterogeneity), but became non-significant when restricted only to invasive breast cancer (RR=0.96, 95% CI= 0.90-1.02) (20 studies, high heterogeneity); studies that involved breast/mammography screening (RR=0.99, 95% CI=0.87-1.14) (six studies, moderate heterogeneity); and studies that simultaneously adjusted for age, alcohol consumption, and reproductive factors (RR=0.95, 95% CI= 0.88-1.02) (15 studies, high heterogeneity). The borderline positive association observed in the Japanese pooled study (Wada, 2014) may explain the non-significant result and high heterogeneity in the latter analysis.

Nonlinear dose-response meta-analysis:

Premenopausal breast cancer risk decreased monotonically through all ranges of BMI (P for non-linearity=0.78) (graph not shown).

Study quality:

There were only nine Asian studies reported results on breast cancer risk and eight (all Japanese) were from a pooled study (Wada, 2014). HEBON (Manders, 2011) consisted of BRCA1/2 carriers only and observed a non- significant inverse association.

NSABP P-1 (Cecchini, 2012) was a chemoprevention (tamoxifen) trial in women at high risk for developing breast cancer and observed a positive association. Participants had bilateral

mammograms annually during follow-up. This study only had little influence (3% weight) in the overall analysis. Five other studies involved breast/mammography screening (van den Brandt, 2000, CNBSS and SMC; Reinier, 2007, VMC; Kaaks, 1998, DOM-project) or recruited participants from breast screening clinics (Sonnenschein, 1999, NYUWHS). On average, these studies found a non-significant inverse association with premenopausal breast cancer.

About half of the studies measured the participants for their height and weight and anther half used measurements as reported by the participants. Subgroup analysis showed similar inverse associations that were significant in the studies that took measurements. Case ascertainment was through cancer registries or confirmed through medical records. Only fifteen studies (Catsburg, 2014b; Wada, 2014, eight studes; Coudo, 2013; Reeve, 2007; Lahmann, 2004a; van den Brandt, 2000, three studies) were simultaneously adjusted for age, alcohol intake, and reproductive factors.

Table 524 BMI and premenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	128[1] (57 publications)
Studies included in forest plot of highest compared with lowest exposure	46 (27 publications) breast cancer risk 18 (5 publications) breast cancer subtypes 44 (3 publications) breast cancer mortality
Studies included in linear dose-response meta-analysis[2]	37 (24 publications) breast cancer risk 7 (4 publications) ER+ and ER- breast cancer 36 (2 publications) breast cancer mortality
Studies included in non-linear dose-response meta-analysis	28 (19 publications) breast cancer risk

Note: Included cohorts, case-cohort, and nested case-control designs. AMBER Consortium (Bandera, 2015) included one cohort and two case-control studies. [1]Included six pooled studies (Bandera, 2015, AMBER Consortium, three studies in the analysis of premenopausal women; Wada, 2014, Eight Japanese studies; Bjorge, 2010, Me-Can, six studies; Yang XR, 2011, BCAC, 12 studies in case-control analysis; Whitlock, 2009, PSC, 35 studies; van den Brandt, 2000, the Pooling Project, three studies in the analysis of premenopausal women). [2]In total, 71 studies (26 publications) were included in the dose-response meta-analyses.

Table 525 BMI and premenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2008 SLR and CUP SLR

	2008 SLR	CUP	
Increment unit used	2 kg/m^2	5 kg/m^2	
Studies (n)	16	37	
Cases	8 274	16 371	
RR (95%CI)	0.97 (0.95-0.99)	0.93 (0.90-0.97)	
Heterogeneity (I^2, p-value)	50%, 0.01	55%, <0.01	
P value Egger test	-	0.13	
Stratified analyses in the CUP			
Geographic area[1]	**Asia**	**Europe**	**North America**
Studies (n)	9	17	11
Cases	522	11 491	3 655
RR (95%CI)	1.16 (0.99-1.37)	0.89 (0.86-0.92)	0.97 (0.91-1.03)
Heterogeneity (I^2, p-value)	0%, 0.40	11%, 0.33	40%, 0.09
Anthropometric measurement methods	**Measured**	**Self-reported**	
Studies (n)	14	23	
Cases	9 014	7 357	
RR (95%CI)	0.92 (0.86-0.98)	0.95 (0.90-1.00)	
Heterogeneity (I^2, p-value)	53%, 0.02	43%, 0.06	
Screening studies[1]	**Yes**	**No**	
Studies (n)	6	31	
Cases	803	15 568	
RR (95%CI)	0.99 (0.87-1.14)	0.92 (0.89-0.96)	
Heterogeneity (I^2, p-value)	30%, 0.21	52%, <0.01	
Adjustment for age, alcohol intake and reproductive factors	**Adjusted**	**Not adjusted**	
Studies (n)	15	22	
Cases	3 949	12 422	
RR (95%CI)	0.95 (0.88-1.02)	0.93 (0.88-0.98)	

Heterogeneity (I^2, p-value)	52%, 0.06	56%, <0.01	
Other analyses in the CUP			
	Invasive breast cancer	**Breast cancer mortality**	
Studies (n)	20	36	
Cases	11 569	545	
RR (95%CI)	0.96 (0.90-1.02)	1.00 (0.73-1.38)	
Heterogeneity (I^2, p-value)	68%, <0.001	75%, 0.05	

[1]Individual study results within the Pooling Project (van den Brandt, 2000) were used.

Table 526 BMI and hormone receptor-defined premenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the CUP SLR

ER-status	**ER-positive**	**ER-negative**
Increment unit used	5 kg/m^2	5 kg/m^2
Studies (n)	7	7
Cases	1 499	823
RR (95%CI)	1.02 (0.90-1.15)	1.01 (0.94-1.08)
Heterogeneity (I^2, p-value)	68%, 0.02	0%, 0.49

Table 527 BMI and premenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies[1]	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Munsell, 2014	6 cohort studies, 16 case-control studies	17 407	USA, Europe	Incidence, premenopausal breast cancer (6 cohort studies, 4469 cases)	25-29.9 vs <25 kg/m^2	0.99 (0.92-1.07)		47%, 0.09
					≥30 vs <25 kg/m^2	0.72 (0.55-0.94)		77%, <0.01
				ER+PR+ (4 case control or cohort studies, 2 486 cases)	25-29.9 vs <25 kg/m^2	0.94 (0.76-1.17)		45%, 0.14
					≥30 vs <25 kg/m^2	0.78 (0.67-0.92)		0%, 0.67
				ER-PR- (4 studies, 1 360 cases)	25-29.9 vs <25 kg/m^2	1.26 (1.07-1.49)		0%, 0.41
					≥30 vs <25 kg/m^2	1.06 (0.70-1.60)		77%, 0.004
				ER+PR unknown (2 studies, 800 cases)	25-29.9 vs <25 kg/m^2	1.02 (0.85-1.21)		0%, 0.52
					≥30 vs <25 kg/m^2	(0.83-1.24)		0%, 0.56
				ER-PR unknown (2 studies, 347 cases)	25-29.9 vs <25 kg/m^2	0.98 (0.74-1.29)		57%, 0.13
					≥30 vs <25 kg/m^2	1.15 (0.86-1.55)		67%, 0.08
Xia, 2014	12 cohort studies	4 699	China, France, Japan, The Netherlands, Norway, Sweden, North America	Incidence, premenopausal breast cancer	Per 5 kg/m^2	0.99 (0.98-1.00) Non-significant non-linear relationship		0.06 P for non-linearity = 0.61
Amadou, 2013	29 studies overall (11 cohorts, 18 case-control	20 346	Canada, China, France, Germany, Japan, Nigeria, Norway/Sweden,	Incidence, premenopausal breast cancer	Per 5 kg/m^2 Overall	0.95 (0.94-0.97)		61%, <0.001
					Asian	1.05 (1.01-1.09)		50%, 0.04

	studies)		Thailand, UK, USA,		African Caucasian	0.95 (0.91-0.98) 0.93 (0.91-0.95)		0%, 0.53 34%, <0.09
Pierobon, 2013[2]	5 case-case and case-control studies	-	USA	Incidence, premenopausal triple negative breast cancer	>30 vs <30 kg/m^2	1.43 (1.23-1.65)		22%, 0.27
Cheraghi, 2012[3]	4 cohort studies	564	France, USA, Norway and Sweden	Incidence, premenopausal breast cancer	Overweight vs normal weight Obese vs normal weight	1.01 (0.77-1.31) 0.91 (0.71-1.18)		72%, 0.01 34%, 0.21
Suzuki, 2009		2 643 ER+PR+ cases, 1 471 ER-PR- cases, 199 ER+PR- cases, 191 ER-PR+ cases		Incidence, premenopausal breast cancer ER+PR+ ER-PR- ER+PR- ER-PR+ ER+ ER- PR+ PR- ER+PR+ (4 studies, 1 720 cases)	Highest vs lowest Per 5 kg/m^2	 0.80 (0.70-0.92) 1.03 (0.87-1.22) 1.06 (0.76-1.49) 1.01 (0.73-1.39) 0.86 (0.77-0.95) No summary RE 0.83 (0.74-0.92) 1.03 (0.90-1.18) 0.90 (0.82-0.99)		 0.51 0.39 0.90 0.97 0.41 Significant 0.66 0.79 -

[1]All cohort studies identified were included in the present review, apart from Barlow, 2006 that was identified in Cheraghi, 2012; as this study from the Breast Cancer Surveillance Consortium estimated the risk of developing breast cancer within a year of mammography screening.

[2]Pierobon, 2013 used raw data from published studies and no adjustments were applied to analyses.

Table 528 BMI and premenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Bandera, 2015 USA	AMBER Consortium, Pooled study, 2 cohorts and 2 case-control studies* W African American (*CBCS; WCHS; BWHS; MEC)	1 149 cases 4087 controls	Record linkage to cancer registries, identified through hospitals, self-reported and verified with medical records and cancer registry data	Self-reported and measured	Incidence, premenopausal breast cancer	≥ 35 vs < 25 kg/m^2	0.85 (0.69-1.06) Prend: 0.20	Age, education, study, time period, geographical region, family history of breast cancer, age at menarche, parity, breastfeeding, age at first birth, hormone therapy use, OC use	
		691 cases			ER+	≥ 35 vs < 25 kg/m^2	0.82 (0.63-1.06) Ptrend: 0.26		
		458 cases			ER-	≥ 35 vs < 25 kg/m^2	0.92 (0.67-1.27) Ptrend: 0.45		
		227 cases			Triple-negative	≥ 35 vs < 25 kg/m^2	1.25 (0.80-1.94) Ptrend: 0.39		
Bhaskaran, 2014 BRE80518 UK	CPRD, Prospective Cohort, Age: 16- years, W	6 298/ 2 864 658 25 years	Medical record	Measured	Incidence, premenopausal breast cancer	per 5 kg/m^2	0.89, 99% CI:(0.86-0.92)	Age, sex, alcohol, calendar year, diabetes, smoking, socio-economic status	
						>35 vs 18.5-24.9 kg/m^2	0.64, 99% CI (0.55-0.75)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					Never smokers	per 5 kg/m^2	0.89, 99% CI:(0.85-0.94)		
Catsburg, 2014b BRE80529 Canada	CSDLH, Case Cohort, W	556/ 4 417 15 years	Cancer registry	Self-reported	Incidence, Invasive breast cancer, premenopausal	≥30 vs 18.5-24.99 kg/m^2	0.97 (0.66-1.43) Ptrend:0.88	Age at first child birth, age at menarche, alcohol Intake, family history of breast cancer, HRT use, menopausal status, number of childbirths, OC use, physical activity	
Wada, 2014, Japan	Eight Japanese cohorts, Pooled study*, W (*JPHC-I and II, JACC, OHSAKI, MIYAGI-I and II, AICHI, TAKAYAMA)	301/ 333 822 person-years Mean age 55.3 years 11.93 years of follow-up	Through cancer registries and/or active patient notification from hospitals	Self-reported	Incidence, invasive premenopausal breast cancer	≥30 vs 23-24.9 kg/m^2 Per 1 kg/m^2	2.25 (1.10--4.60) Ptrend:0.47 1.04 (1.00-1.08)	Age, area, smoking status, alcohol consumption, age at menarche, age at first delivery, parity number	
Couto, 2013 BRE80454 Sweden	WLHS (Sweden), Prospective Cohort, Age: 30-49 years, W	736/ 49 258 16 years	Cancer registry	Self-reported	Incidence, breast cancer, premenopausal	≥25 vs ≤20 kg/m^2	0.88 (0.68-1.12)	Age at first child birth, age at menarche, alcohol, benign breast disease, contraception, educational	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								level, energy Intake, height, history of breast cancer, hormone use, number of childbirths, smoking	
Cecchini, 2012 BRE80405 USA (one publication, two studies)	P-1, Prospective Cohort, W, Women at high risk for developing breast cancer	126/ 31 731	Mammography screening program	Measured	Incidence, breast cancer, premenopausal	≥30 vs ≤25	1.66 (1.06-2.58) Ptrend:0.02	Age, diabetes, estrogen use, gail score, oral contraceptive history, smoking	
		43/			Tamoxifen	≥30 vs ≤25	2.33 (1.10-4.90) Ptrend:0.02	Gail score	
		83/			Placebo-group	≥30 vs ≤25	1.41 (0.82-2.43) Ptrend:0.17	Gail score	
		77/			Incidence, breast cancer ER+, premenopausal	≥30 vs ≤25	1.78 (1.03-3.07) Ptrend:0.04	Gail score	
		39/			Incidence, breast cancer ER-, premenopausal	≥30 vs ≤25	1.79 (0.76-4.22) Ptrend:0.12	Gail score	
Manders, 2011 BRE80314 Netherlands	HEBON, Historical Cohort, W, Subjects with BRCA1/2 mutation	155/ 609 10 years	Cancer registry	Self-reported	Incidence, breast cancer, premenopausal	≥25 vs 18.5-22.49 kg/m^2	0.75 (0.43-1.31)		
Whitlock, 2009	Prospective	Overall 353 124	Death	Self-reported or	Mortality, breast				

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Studies Collaboration (PSC), Pooled study of 35 cohorts*, W	women, mean age: 46 years, 8 years of follow-up 462/	certificates, medical records and autopsy findings	measured	cancer, Women <60 years, excluding first 5 years of follow-up	Per 5 kg/m^2, In the range of 15-50 kg/m^2	1.15 (1.02-1.31)	Age at risk, study, smoking status	
		291/				Per 5 kg/m^2 In the range of 15-25 kg/m^2	1.51 (1.01-2.25)		
		171/				Per 5 kg/m^2 In the range of 25-50 kg/m^2	1.10 (0.88-1.39)		
*ARIC; BIRNH; Busselton; CHS; CB Project; Charleston; CCHS; Finnish Mobile Clinic Survey; FINRISK; FLEMENGHO; Glostrup Population Studies; Ikawa; Noichi; Kyowa; IPC, Paris; LRC; Midspan Collaborative Study; MHHP; MHS; NHEFS; FHS; Norwegian Counties Study; NPHS; NHS; Ohasama; Perth; PROCAM; Gothenburg Women, Sweden; Rancho Bernado; Renfew and Paisley study; Saitama Cohort Study; SHHS; Shibata; Tecumseh; Tromso									
Iwasaki, 2007b BRE20027 Japan	JPHC I and II, Prospective Cohort, Age: 40-69 years, W	201/ 53 857 9.9 years	Cancer registry	Self-reported	Incidence, breast cancer, premenopausal	≥30 vs ≤18 kg/m^2	1.35 (0.53-3.47) Ptrend:0.19	Age , age at first child, area, height, parity/pregnancies	
		62/			Incidence, breast cancer ER+, premenopausal	per 1 kg/m^2	1.04 (0.98-1.11)		Included in analysis of breast cancer subtypes
		41/			Incidence, breast cancer ER-, premenopausal	per 1 kg/m^2	1.02 (0.93-1.13)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		53/			Incidence, breast cancer PR+, premenopausal	per 1 kg/m^2	1.06 (0.99-1.13)		
		42/			Incidence, breast cancer PR-, premenopausal	per 1 kg/m^2	0.99 (0.89-1.10)		
Lundqvist, 2007 BRE80002 Sweden, Finland (one publication, two studies)	Sweden,Finland Co-twin study-cohort analysis,1975, Prospective Cohort, Age: 44 years, W	881/ 36 490 25.2 years	Cancer registry	Measured	Incidence, breast cancer, younger subjects	per 1 kg/m^2	0.99 (0.96-1.01)	Sex, age , country of birth, diabetes, educational level, physical activity , smoking habits	
						≥30 vs 18.5-24.9 kg/m^2	0.80 (0.40-1.30)		
Reeves, 2007 BRE80146 UK	MWS, Prospective Cohort, Age: 50-64 years, W	1 179/ 1 222 630 5.4 years	National health records	Self-reported	Incidence, breast cancer, premenopausal	per 10 kg/m^2	0.86 (0.73-1.00)	Age, alcohol consumption, geographic area, physical activity, reproductive factors, smoking habits, socio-economic status	
						≥30 vs 22.5-24.9 kg/m^2	0.79 (0.68-0.92)		
		636/			Premenopausal never smokers	per 10 kg/m^2	0.84 (0.68-1.04)		
		83/			Mortality, breast	per 10 kg/m^2	0.68 (0.37-1.24)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					cancer, premenopausal	≥30 vs 22.5-24.9 kg/m^2	0.64 (0.34-1.21)		
Reinier, 2007 BRE80038 USA	VMC, Prospective Cohort, W	231/ 61 844 3.1 years	Screening examinations	Self-reported	Incidence, Invasive breast cancer, premenopausal	≥30 vs ≤21.9 kg/m^2	0.90 (0.60-1.30)	Age, age at first child birth, breast density, family history of cancer	
		104/			Incidence, In situ breast cancer, premenopausal	≥30 vs ≤21.9 kg/m^2	1.00 (0.50-1.90)		
Li, 2006 BRE80166 China	SWHS, Prospective Cohort, Age: 40-70 years, W	221/ 73 410 5.66 years	Medical records	Measured by trained Interviewers	Incidence, breast cancer, premenopausal	≥25.21 vs ≤22.34	1.04 (0.73-1.49) Ptrend:0.78	Age, age at first child birth, breastfeeding, educational level, energy Intake, family history, family history of cancer	
Lukanova, 2006 BRE80100 Sweden	NSHDC (VIP and MSP), Prospective Cohort, Age: 29-61 years, W	92/ 74 207 8.2 years	Medical records	Measured by nurse	Incidence, breast cancer, premenopausal	≥26 vs 18.5-21.5	0.58 (0.29-1.11) Ptrend:0.04	Age , calendar year, smoking habits	
Michels, 2006a BRE80033 USA	NHS II, Prospective Cohort, Age: 25-42 years,	1 398/ 116 609 14 years	Self report verified by medical record	Self-reported	Incidence, breast cancer	≥30 vs 20-22.4 kg/m^2	0.81 (0.68-0.96) Ptrend:0.002	Age , age at first child, age at menarche, alcohol, benign breast disease,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Premenopausal							family history of cancer, height, OC use, parity/pregnancies, physical activity	
						per 5 units	0.91 (0.86-0.97)	Family history	
					Menstrual cycle < 32 d	per 5 units	0.95 (0.89-1.01)		
					Menstrual cycle >= 32 d	per 5 units	0.84 (0.75-0.95)		
					Current OC users	per 5 units	0.99 (0.79-1.21)	Age, age at first child birth, alcohol consumption, parity, physical activity	
					Never OC users	per 5 units	0.84 (0.73-0.98)		
					Past OC users	per 5 units	0.93 (0.87-0.99)		
					Age < 40 yrs	per 5 units	0.94 (0.84-1.06)		
					Age >= 40 yrs	per 5 units	0.91 (0.85-0.97)		
		300/			Incidence, breast cancer PR-	≥30 vs 20-22.4 kg/m^2	1.01 (0.71-1.45) Ptrend:0.87		
						per 5 units	0.98 (0.86-1.10)	Oral contraceptive use	
		669/			Incidence, breast	≥30 vs 20-22.4	0.76 (0.59-0.97)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					cancer ER+	kg/m^2	Ptrend:0.02		
						per 5 units	0.91 (0.84-0.99)		
		285/			Incidence, breast cancer ER-	≥30 vs 20-22.4 kg/m^2	1.10 (0.76-1.58) Ptrend:0.52		
						per 5 units	1.03 (0.91-1.15)		
		636/			Incidence, breast cancer PR+	≥30 vs 20-22.4 kg/m^2	0.81 (0.63-1.05) Ptrend:0.12		
						per 5 units	0.94 (0.86-1.02)		
Lahmann, 2004a BRE15804 Europe	EPIC, Prospective Cohort, Age: 18-80 years, W	474/ 176 886 4.7 years	Partially histological - over 80%	Measurements performed by trained personnel	Incidence, breast cancer, premenopausal	per 1 unit	0.98 (0.96-1.00)	Age , age at first child, age at menarche, alcohol, educational level, OC use, parity/pregnancies, smoking habits	
						≥28.8 vs ≤21.5 kg/m^2	0.82 (0.59-1.14) Ptrend:0.100	Recruitment center	
Weiderpass, 2004 BRE18151 Sweden, Norway	WLHS, Sweden and Norway, Prospective Cohort, Age: 30-49 years, W, Premenopausal	716/ 99 717 8 years	Partially histological - over 80%	Self-reported	Incidence, breast cancer, premenopausal	per 1 kg/m^2	0.96 (0.94-0.98)	Age, age at first child, age at menarche, duration of breastfeeding, family history of breast cancer, OC use, parity, place of residence	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
						≥30 vs 20-24.9 kg/m^2	0.62 (0.40-0.97) Ptrend:0.0003		
		641/			Family history breast cancer - no and premenopausal	≥30 vs 20-24.9 kg/m^2	0.58 (0.36-0.95) Ptrend:0.0004		
		75/			Family history breast cancer - yes and premenopausal	≥30 vs 20-24.9 kg/m^2	0.96 (0.30-3.13) Ptrend:0.37		
Manjer, 2001b BRE17790 Sweden	MPP, Prospective Cohort, Age: 55 years, W	112/ 9 738 13.1 years	Partially histological - over 80%	Measured by trained personnel	Incidence, Invasive breast cancer, premenopausal	≥25.47 vs ≤20.61 kg/m^2	1.00 (0.57-1.75) Ptrend:0.77	Age	
van den Brandt, 2000 North America and Europe	The Pooling Project, Pooled study of 7 cohorts*, W (*AHS; CNBSS; IWHS; NLCS; NYSC; NHS(a); NHS(b); SMC)	723/	Follow-up questionnaires and inspection of medical records and/or tumour registry linkage	Self-reported	Incidence, premenopausal breast cancer	≥33 vs <21 kg/m^2	0.58 (0.34-1.00) Ptrend:0.007	Age at menarche, parity, age at birth of first child, postmenopausal hormone use, oral contraceptive use, history of benign breast disease, maternal history of breast cancer, history of breast cancer in a	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								sister, smoking status, education, fat intake, fibre intake, energy intake, alcohol intake	
						per 4 kg/m^2	0.89 (0.81-0.97)		
	CNBSS	122/				per 4 kg/m^2	0.86 (0.60-1.25)		
	NHS(a)	383/				per 4 kg/m^2	0.86 (0.77-0.96)		
	NHS(b)	130/				per 4 kg/m^2	0.95 (0.80-1.12)		
	SMC	68/				per 4 kg/m^2	0.90 (0.62-1.32)		
Sonnenschein, 1999 BRE11604 USA	NYUWHS, Prospective Cohort, Age: 35-65 years, W	109/ 8 416 6.6 years	All histology	Measured	Incidence, breast cancer, premenopausal	≥26.37 vs ≤21.4 kg/m^2	1.00 (0.58-1.73)	Age , age at first child, age at menarche, breast biopsies, family history	
Galanis, 1998 BRE03058 hawaii	Hawaii State Department of Health, 1975, Prospective Cohort, Age: 43 years, W	86/ 17 628 14.9 years	Partially histological - over 80%	Self-reported	Incidence, breast cancer, premenopausal	≥26.1 vs ≤19.5 kg/m^2	1.90 (0.90-3.90) Ptrend:0.2	Age , alcohol, educational level, ethnicity	
Kaaks, 1998 BRE04522 Netherlands	DOM-project Utrecht, Prospective Cohort,	147/ 11 480 7.1 years	Partially histological - over 80%	Self-reported	Incidence, breast cancer, premenopausal	≥27.15 vs ≤22.5 kg/m^2	1.04 (0.65-1.68) Ptrend:0.73	Age , age at first child, age at menarche, menopausal	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Age: 39-73 years, W, Mammography screening cohort							status, parity/pregnancies	
Tulinius, 1997 BRE12565 Iceland	Reykjavik Study, 1968, Prospective Cohort, Age: 45-59 years, W	91/ 11 580 27 years	Partially histological - over 80%	Measured	Incidence, breast cancer, premenopausal	per 1 kg/m^2	1.01 (0.96-1.05)	Age	
Tornberg, 1994 BRE12417 Sweden	Sweden, 1971, Prospective Cohort, Age: 25-75 years, W	373/ 47 003 25 years	Partially histological - over 80%	Measured	Incidence, breast cancer, premenopausal	≥28 vs ≤21.9 kg/m^2	0.41 Ptrend:0.0004	Age	
						per 2 kg/m^2	0.86 (0.80-0.94)		
De Stavola, 1993 BRE02122 UK (one publication, two studies)	Guernsey G2 and G3, Prospective Cohort, W	73/ 4 528 15 years	Partially histological - over 80%	Measurements performed by trained personnel	Incidence, breast cancer, premenopausal	≥26.5 vs ≤21.9 kg/m^2	1.10 (0.60-2.10) Ptrend:1	Age	
Vatten, 1992 BRE12828 Norway	Norway, 1974, Prospective Cohort, Age: 26-49 years, W	164/ 25 967 14 years	Partially histological - over 80%	Measured	Incidence, breast cancer, premenopausal	≥28 vs ≤21 kg/m^2	0.63 (0.48-0.82) Ptrend:0.001	Age , age at first child, occupation, parity/pregnancies, place of residence	

Table 529 BMI and premenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Emaus, 2014 BRE80540 Europe	EPIC-PANACEA, Prospective Cohort, Age: 25-70 years, W	298/ 205 723 1 396 538 person-years	Active follow up and cancer registry	Measured or self-reported	Incidence, Invasive breast cancer, age at diagnosis <=50yrs	28.1-59.7 vs 16-21.3 kg/m^2	0.87 (0.56-1.34) Ptrend:0.34	Age, age at first child birth, age at menarche, alcohol consumption, alcohol drinking, BMI at baseline, educational level, energy Intake, HRT use, physical activity, smoking, study center, time between measurements, use of oral contraception	Superseded study
Guo, 2014 BRE80541 China	Northern China 2006-2011, Prospective Cohort, Age: 18- years, W	34/ 26 643 4.28 years	Self-report, next of kin, medical and pathological records	Measured	Incidence, breast cancer, premenopausal	≥28 vs 18.5-23.9	1.09 (0.31-3.78)	Age, alcohol consumption, educational level, smoking	Excluded, insufficient data
Schairer, 2013 BRE80568 USA	BCSC, Nested Case Control, W	1 744/ 93 654	Seer registry/hospital records/pathology	Self-reported	Incidence, non-inflammatory breast cancer, premenopausal	≥30 vs ≤24.9 kg/m^2	0.98 (0.69-1.39)	Age at first child birth, breast biopsies, educational level, family	Results by specific breast cancer subtypes, not analysed

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								history of breast cancer In first degree relatives, height, mammographic density, parous/nulliparous, race/ethnicity	
						≥30 vs ≤24.9 kg/m^2	1.08 (0.78-1.48)		
		255/			Incidence, non-inflammatory locally advanced breast cancer, premenopausal	≥30 vs ≤24.9 kg/m^2	1.03 (0.59-1.81)		
						≥30 vs ≤24.9 kg/m^2	1.02 (0.59-1.77)		
		182/			Incidence, Inflammatory breast cancer, premenopausal	≥30 vs ≤24.9 kg/m^2	3.62 (1.30-10.04)		
						≥30 vs ≤24.9 kg/m^2	3.90 (1.50-10.14)		
					Incidence, Inflammatory breast cancer ER+, premenopausal	≥30 vs ≤24.9 kg/m^2	3.53 (1.20-10.39)		
					Incidence, LABC ER+, premenopausal	≥30 vs ≤24.9 kg/m^2	1.05 (0.56-1.97)		
					Incidence, non-inflammatory	≥30 vs ≤24.9 kg/m^2	0.94 (0.65-1.35)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					breast cancer ER+, premenopausal				
					Incidence, Inflammatory breast cancer ER-, premenopausal	≥30 vs ≤24.9 kg/m^2	4.67 (1.45-15.02)		
					Incidence, LABC ER-, premenopausal	≥30 vs ≤24.9 kg/m^2	0.96 (0.38-2.44)		
					Incidence, non-inflammatory breast cancer ER-, premenopausal	≥30 vs ≤24.9 kg/m^2	1.48 (1.00-2.19)		
Suzuki, 2013 BRE80452 Japan	JACC, Prospective Cohort, Age: 40-79 years, W	62/ 36 164 12.3 years	Cancer registry	Self-reported	Incidence, breast cancer, premenopausal	≥29 vs 20-23.9 kg/m^2	0.62 (0.08-4.58)	Age, age at menarche, age at menopause, alcohol, education years, exogenous female hormones, family history of cancer In first degree relatives, height, marital status, parity, physical activity,	Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								smoking, study area	
						≥29 vs 20-23.9 kg/m^2	0.54 (0.07-3.97)		
Fagherazzi, 2012a BRE80539 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W	223/ 63 726 582 144 person-years	Self report verified by medical record and pathology report	Self-reported	Incidence, breast cancer ER+/PR+, premenopausal	≥30 vs ≤19.9 kg/m^2	0.40 (0.16-1.00) Ptrend:0.04	Age at first child birth, age at menarche, age at menopause, alcohol Intake, breastfeeding, educational level, family history of breast cancer, history of benign breast disease, mammography, non-alcohol energy, OC use, parous/nulliparous, smoking status, total physical activity, use of HRT, year of birth	Results by joint hormone receptor defined breast cancer, not analysed; superseded publication
		54/			Incidence, breast cancer ER-/PR-, premenopausal	≥30 vs ≤19.9 kg/m^2	1.45 (0.38-5.59) Ptrend:0.20		
					Incidence, breast cancer ER+/PR-,	≥30 vs ≤19.9 kg/m^2	0.93 (0.26-3.42) Ptrend:0.88		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					premenopausal				
		24/			Incidence, breast cancer ER-/PR+, premenopausal	≥30 vs ≤19.9 kg/m^2	0.37 (0.11-3.86) Ptrend:0.05		
Ritte, 2012 BRE80415 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 25-70 years, W	390/ 314 760 3 399 178 person-years	Cancer and pathology registeries	Measured or self-reported	Incidence, breast cancer ER+/PR+, age <= 49 years	per 5 kg/m^2	0.80 (0.69-0.93)	Age, age at first child birth, age at menarche, age at menopause, alcohol, centre location, educational level, height, menopausal status, oral contraceptive history, parity, smoking	Results by joint hormone receptor defined breast cancer, not analysed; superseded publication
		64/			Incidence, breast cancer ER+/PR-, age <= 49 years	per 5 kg/m^2	1.14 (0.83-1.55)		
		71/			Incidence, breast cancer ER-/PR+, age <= 49 years	per 5 kg/m^2	0.67 (0.46-0.99)		
		147/			Incidence, breast cancer ER-/PR-, age <= 49 years	per 5 kg/m^2	0.90 (0.71-1.13)		
Harris, 2011a BRE80622 USA	NHS I and II, Nested Case Control, Age: 25-55	258/ 563 controls 15 years	Self-reported verified by medical record review	Self-reported body fatness during childhood,	Incidence, premenopausal breast cancer	≥30 vs 20-22.4 kg/m^2	1.28 (0.72-2.30) Ptrend:0.07	Age at menarche, alcohol, breast density, family	Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	years, W			adolescence, BMI at age 18 years, current BMI, self-reported height and weight				history of breast cancer, parity and age at first birth	
Harris, 2011b BRE80317 USA	NHS II, Prospective Cohort, Age: 25-42 years, W, Premenopausal	620/ 45 799 426 164 person-years	Self report verified by medical record	Self-reported	Incidence, premenopausal breast cancer	≥27.5 vs ≤20.5 kg/m^2	0.81 (0.53-1.21) Ptrend:0.32	Age, age at first child birth, age at menarche, alcohol consumption, benign breast disease, BMI, family history of breast cancer, height, hip circumference, oral contraceptive use, parity, physical activity, waist circumference, waist to hip ratio	Superseded publication
Suzuki, 2011b BRE80318 Japan	JPHC I and II, Prospective Cohort, Age: 40-69 years	220/ 41 594 14 years	Hospital records + cancer registry	Self-reported	Incidence, breast cancer, premenopausal	per 5 kg/m^2	1.02 (0.81-1.27)	Age, age at first child birth, age at menarche, alcohol Intake, BMI, leisure time physical activity, parity, smoking, total	Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								energy, total energy, total energy	
						≥24 vs 20-23.9 kg/m^2	0.97 (0.73-1.31) Ptrend:0.89		
Wilson, 2011 BRE80380 USA	NHS, Nested Case Control, W, mothers and daughters	474 cases 1556 controls	Medical record	Self-reported	Incidence, breast cancer, <50y at diagnosis	≥25 vs ≤20 kg/m^2	0.94 (0.64-1.39) Ptrend:0.92	Age, family history of breast cancer, smoking	Excluded, exposure was on pre-pregnancy BMI, superseded publication
Bjorge, 2010 Austria, Norway, Sweden	Me-Can, Pooled study of 6 cohorts, W (NCS; CONOR; 40-y; VHM&PP; VIP, MPP)	3 043/ 11 years follow-up Mean age: 58 years at diagnosis	Record linkage to cancer registries, and death register and population registers	Measured	Incidence, breast cancer Attained age <50 years	≥31.7 vs ≤ 20 kg/m^2	0.70 (0.57-0.85) Ptrend<0.001	Year of birth, age at measurement, smoking, stratified for cohort	Excluded, insufficient data
		414/			Mortality, breast cancer Attained age <50 years	≥31.7 vs ≤ 20 kg/m^2	1.22 (0.64-2.31) Prend:0.3		
Burton, 2010 BRE80315 Scotland	Glasgow Alumni Cohort study, Prospective Cohort, Age: 20 years, M/W, University students	30/ 2 657 49 years	Cancer registry/ death certificate	Measured	Incidence, premenopausal breast cancer	per 1 kg/m^2	1.05 (0.91-1.21)	Age at menarche, height, smoking, social class	Excluded, exposure was on BMI at a younger age

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Parr, 2010 Australia, New Zealand, Asia	APCSC, Pooled study of 35 cohorts* W	Overall 324/ 174 053 Mean age 48 years			Mortality, breast cancer, women <60 years	30-60 vs 18.5-24.9 kg/m^2 Per 5 kg/m^2	Floating absolute risk: 0.93 (0.42-2.09) Ptrend:0.84 1.13 (0.97-1.33)	Attained age, smoking status, stratified by study	Superseded by Whitlock, 2006, PSC
*Busselton; Australian Longitudinal Study of Aging; Melbourne; National Heart Foundation; Newcastle; Perth 1978-1994; Fletcher Challenge; Anzhen; Beijing Aging; CISCH; East Beijing; Fangshan; Guangzhou Occupational; Huashan; Seven Cities Cohorts; Six Cohorts; Tianjin; Yunnan; Hong Kong; CVDFACTS; Kinmen; Aito Town; Akabane; Civil Service Workers; Hisayama; Konan; Miyama; Ohasama; Saitama; Shibata; Shigaraki Town; Tanno/Soubetsu; Singapore NHS92; EGAT; Shirakawa; KMIC; Singapore Heart									
Yang XR, 2011 USA	BCAC, Pooled study, 12 cohorts and population-based case-control studies in case-control analysis*	14 795 cases/ 17 399 controls	Medical records	Self-reported in questionnaire	Incidence, Invasive breast cancer, women ≤50 years	≥30 vs <25 kg/m^2	0.81 (0.69-0.95)	Age, study, age at menarche, nulliparous, age at first birth	Excluded, insufficient data
		10 900 cases/			ER+				
		3 895 cases/			ER-	≥30 vs <25 kg/m^2	1.10 (0.92-1.30)		
*MCCS; MEC; NHS; ABCFS; GENICA; GESBC; MARIE; NC-BCFR; OFBCR; PBCS; SASBAC; UCIBCS									
Cust, 2009 BRE80216 Sweden	NSHDC (VIP and MSP), Nested Case Control, Age: 30- years, W	278 cases 278 controls	Cancer registry	Measured	Incidence, breast cancer TMN >1	Q3 vs Q1	1.44 (0.95-2.18) Ptrend:0.10	Age, date of blood collection, HRT use	Superseded publication
		248 cases 248 controls			Incidence, breast cancer TMN 1	Q3 vs Q1	0.48 (0.30-0.78) Ptrend:0.004		
		218 cases 218 controls			Incidence, breast cancer, premenopausal	Q3 vs Q1	0.90 (0.58-1.40) Ptrend:0.67		
Davey Smith, 2009	SIMS, Prospective	1 018 012	Death record & Swedish cause	Measured	Mortality, breast cancer, died at	per 1 standard deviation	0.92 (0.88-0.97)	Educational level, parental	Excluded, exposure was on

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
BRE80459 Sweden	Cohort, W	50 years	of death register		age <50yrs			age, social class	proxy BMI
Lundqvist, 2007 BRE80003 Sweden, Finland	Sweden,Finland Co-twin study,1975, Nested Case Control, Age: 44 years, W	667 cases 667 controls		Measured	Incidence, breast cancer, younger subjects	≥30 vs 18.5-24.9 kg/m^2	0.60 (0.30-1.50)	Diabetes, educational level, parity/pregnancies, physical activity , smoking habits	Superseded publication
Palmer, 2007 BRE80122 USA	BWHS, Prospective Cohort, Age: 21-69 years, Black women	495/ 59 000 10 years	Death certificate / patient records / self report	Self-reported, validated	Incidence, breast cancer, premenopausal	≥35 vs ≤24	0.72 (0.54-0.96)	Age, age at first child birth, age at menarche, educational level, family history of breast cancer, parity, physical activity	Superseded publication
Silvera, 2006 BRE24118 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W, Participants of a RCT of screening for breast cancer	818/ 38 645 16.4 years	Partially histological - over 80%	Measured	Incidence, breast cancer, premenopausal	≥30 vs ≤24 kg/m^2	1.01 (0.74-1.37) Ptrend:0.82	Age , age at first child, age at menarche, alcohol, breast diseases , energy Intake , family history, HRT use, leisure time physical activity, menopausal status, OC use, other design Issue, parity/pregnanci	Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								es, recruitment center, smoking habits	
Tehard, 2006 BRE80103 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years	212/ 69 116 3.6 years	Patient records/direct contact/health Insurance records	Self-reported	Incidence, breast cancer, premenopausal	≥30 vs 18.5-24.9	0.26 (0.06-1.00) Ptrend:<=0.05	Age at first child, age at menarche, age-underlying cox models, alcohol, benign breast disease, educational level, family history, marital status, parity/pregnancies, physical activity	Superseded study
						≥24.4 vs ≤20.6	0.61 (0.42-0.89) Ptrend:<=0.05		
Kuriyama, 2005 BRE22995 Japan	Miyagi, 1993, Prospective Cohort, Age: 40- years, W	33/ 15 054 9 years	Partially histological - over 80%	Self-reported	Incidence, breast cancer, premenopausal	27.5-29 vs 18.5-24.9 kg/m^2	0.84 (0.24-2.88) Ptrend:0.7	Age , age at first child, age at menarche, alcohol, food, smoking habits	Superseded publication
Tehard, 2004 BRE12173 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W,	692/ 94 805 9.7 years	Not specified + partially self-reported	Self-reported	Incidence, Invasive breast cancer, premenopausal	≥23.5 vs ≤20.2 kg/m^2	0.78 (0.64-0.94)	Age at first child, age at menarche, alcohol, benign breast disease, educational level, family	Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Registered teachers							history, marital status, parity/pregnancies	
Lee, 2003 BRE17745 Korea	KWC, Prospective Cohort, Age: 20- years, W, Premenopausal	360/ 110 604 6 years	Medical records + death certificate	Reported by medical analysis of the Insurance In 1992-1994	Incidence, breast cancer, premenopausal	≥23 vs ≤22.9 kg/m^2	1.00 (0.80-1.30) Ptrend:0.7575	Age , age at first child, age at menarche, BMI, OC use, parity/pregnancies, physical activity , smoking habits	Excluded, insufficient data
Rissanen, 2003 BRE17954 Finland	Mobile Clinic Health Examination Survey, 1973, Nested Case Control, Age: 18-89 years, W	8 196 10 years	Partially histological - over 80%	Measured	Incidence, breast cancer, premenopausal	(mean exposure)			Excluded, mean exposure comparison only
Saadatian-Elahi, 2002 BRE21486 USA	NYUWHS, Nested Case Control, Age: 34-65 years, W	91 cases 91 controls 4.3 years	Partially histological – over 80%	Self-reported	Incidence, breast cancer, premenopausal	(mean exposure)			Superseded publication
Huang, 1997 BRE04117 USA	NHS, Prospective Cohort, Age: 35-55	1 000/ 95 256 16 years	Medical records + self-reported +death certificate	Self-reported	Incidence, Invasive breast cancer, premenopausal	≥31.1 vs ≤20 kg/m^2	0.62 (0.45-0.86) Ptrend:0.001	Age , age at first child, age at menarche, family history,	Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	years, W, Registered nurses							height, parity/pregnancies	
Toniolo, 1994 BRE12398 USA	NYUWHS, Nested Case Control, Age: 35-65 years, W	79 cases 366 controls 7 years	Medical records	Self-reported	Incidence, Invasive breast cancer, premenopausal	≥26.6 vs ≤21.69 kg/m^2	1.52 (0.79-2.92) Ptrend:0.99		Superseded publication
Vatten, 1990c BRE12826 Norway	NNHSS, 1974, Prospective Cohort, Age: 35-51 years, W	137/ 23 826 11.9 years	Partially histological - over 80%	Measured	Incidence, breast cancer, premenopausal	≥2.68 vs ≤2.19 g/cm^2	0.36 (0.20-0.65) Ptrend:0.001	Age	Superseded publication
London, 1989 BRE80626 USA	NHS, Prospective Cohort, W	658/ 507 937 person-years Age 30-55 years	Self-reported in questionnaire and verified by medical notes	Self-reported	Incidence, breast cancer, premenopausal	≥29.0 vs <21 kg/m^2	0.6 (0.4-0.8)	Age, parity, age at birth of first child, age at menarche, history of benign breast disease, family history of breast cancer, smoking	Superseded publication
Le Marchand, 1988 BRE15836 USA	Hawaii 1942, 1960, 1972, Nested Case Control, W	101 cases 444 controls	All histology	From drive licence	Incidence, breast cancer, premenopausal	Q3 vs Q1	0.45 (0.23-0.86) Ptrend:0.016	Husband occupation, other anthropometric Index	Excluded, insufficient data
Tornberg, 1988	Swedish cohort,		Partially	Measured	Incidence, breast	per 1 unit	0.95 (0.91-1.00)	Age , place of	Superseded

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
BRE12418 Sweden	1963, Prospective Cohort, Age: 17-74 years, W	46 570 20 years	histological - over 80%		cancer, premenopausal			residence	study
Willett, 1985 BRE80625 USA	NHS, Prospective Cohort, Age: 30-55 years, W	346/ 103 688 4 years	Self-reported validated by pathology report	Self-reported	Incidence, breast cancer, premenopausal	Q5 vs Q1	0.66 Ptrend:0.005	Age	Superseded publication

Premenopausal breast cancer

Figure 533 RR estimates of premenopausal breast cancer by levels of BMI

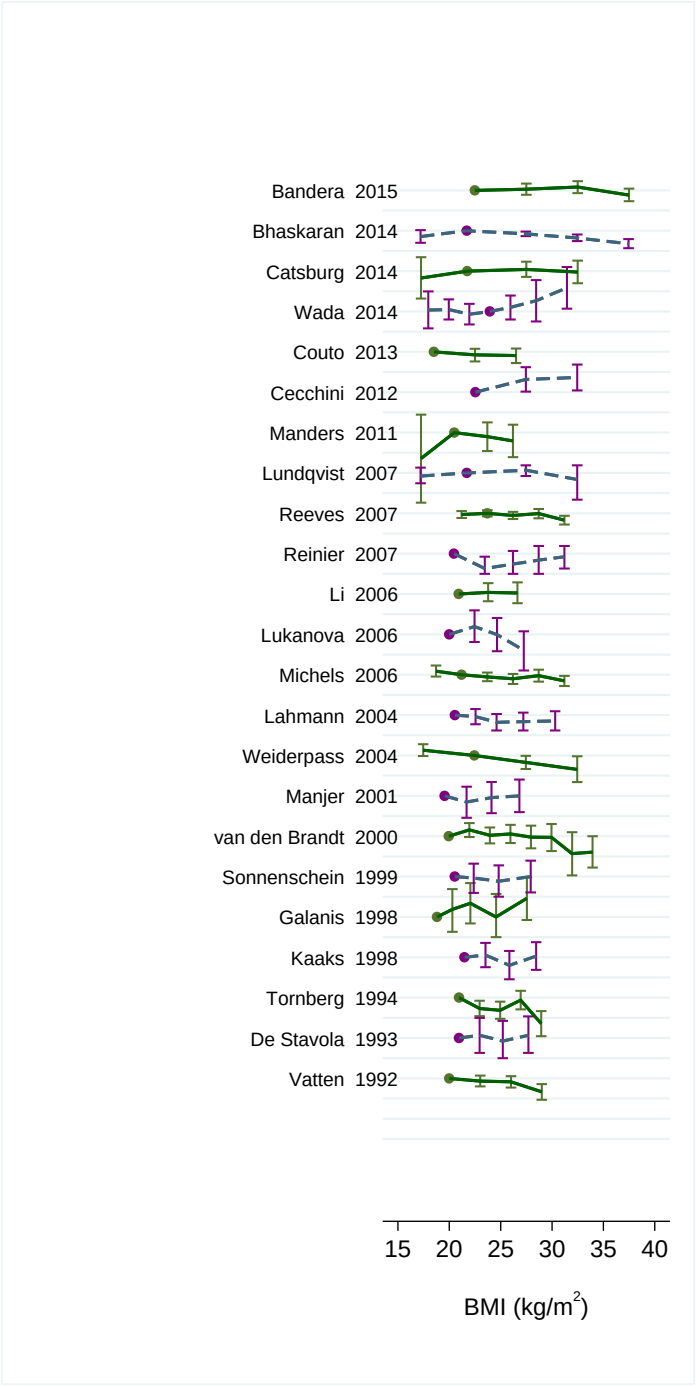


Figure 534 RR (95% CI) of premenopausal breast cancer for the highest compared with the lowest level of BMI

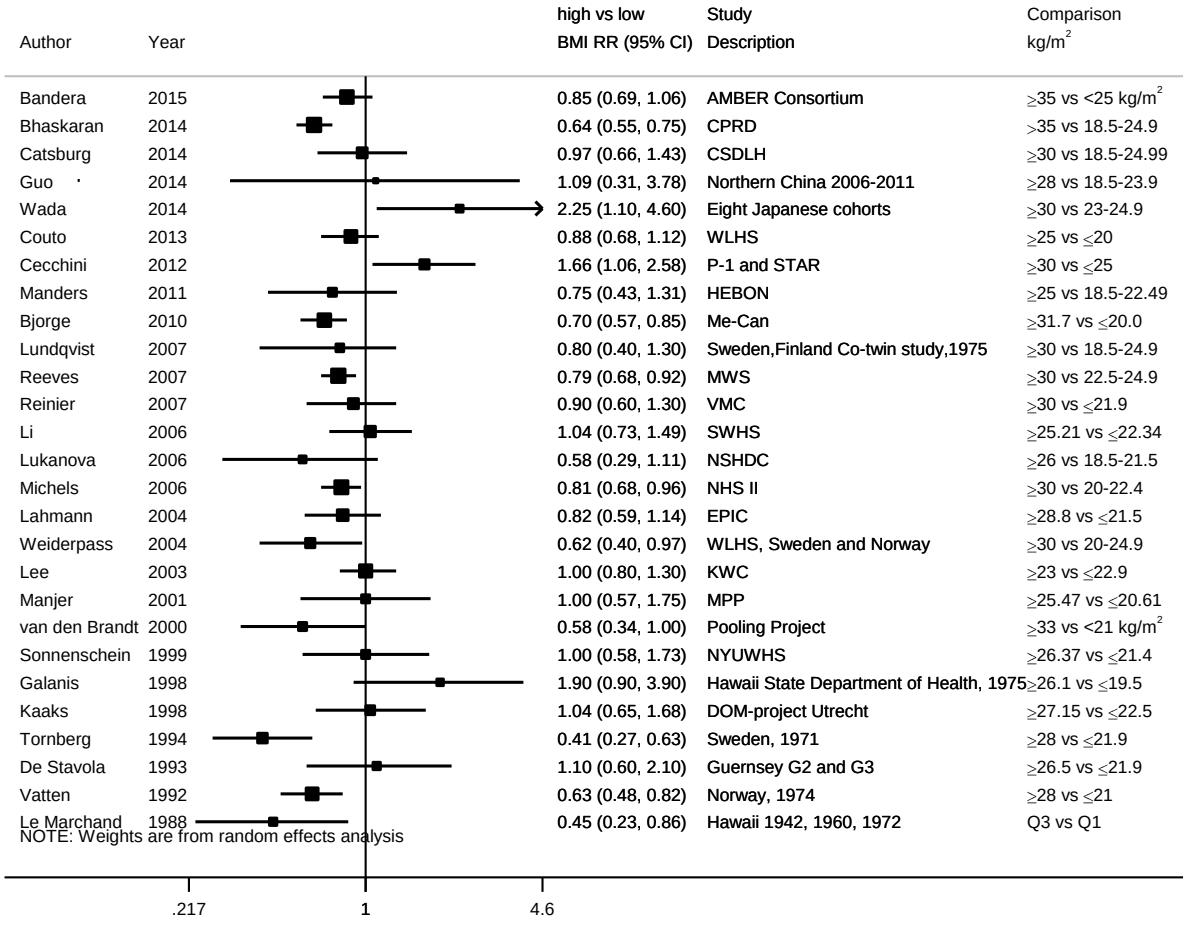


Figure 535 Relative risk of premenopausal breast cancer for 5 kg/m^2 increase of BMI

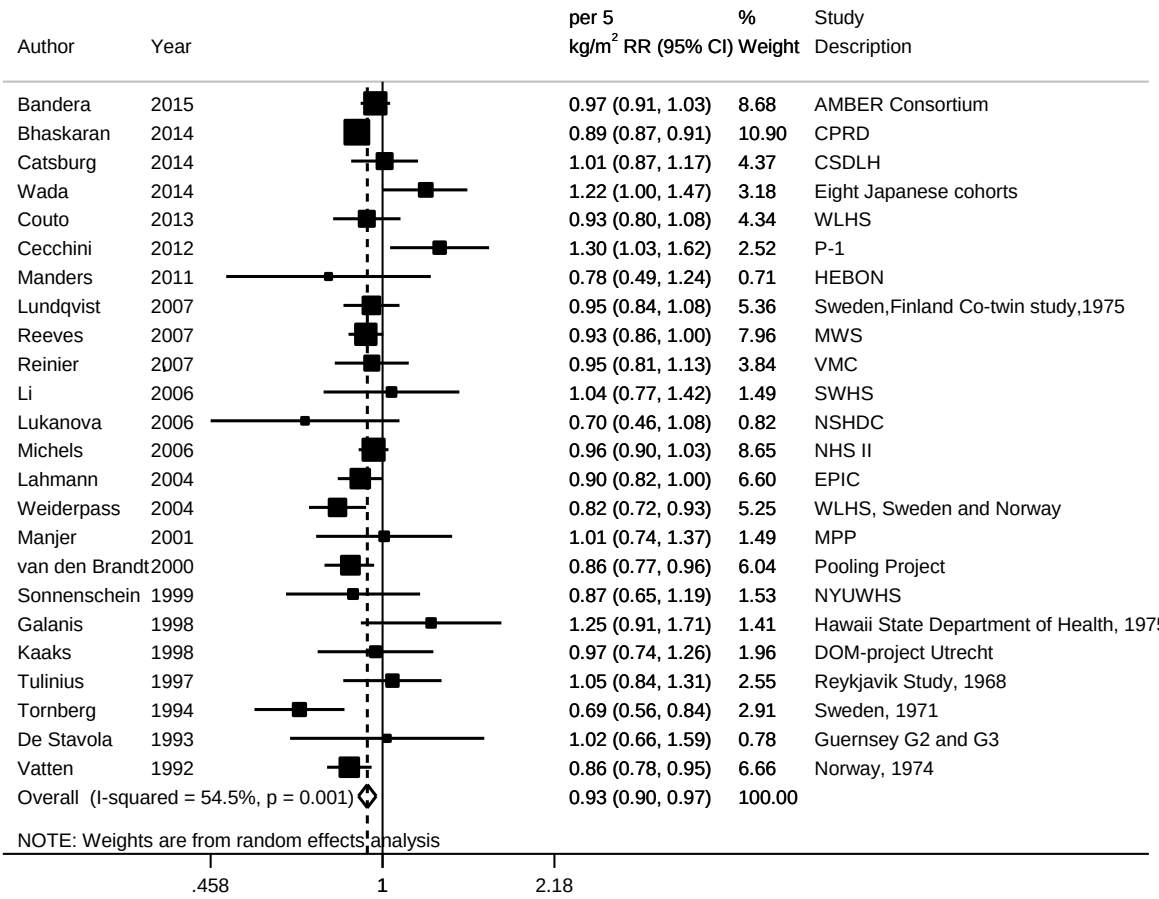


Figure 536 Funnel plot of studies included in the dose response meta-analysis of BMI and premenopausal breast cancer

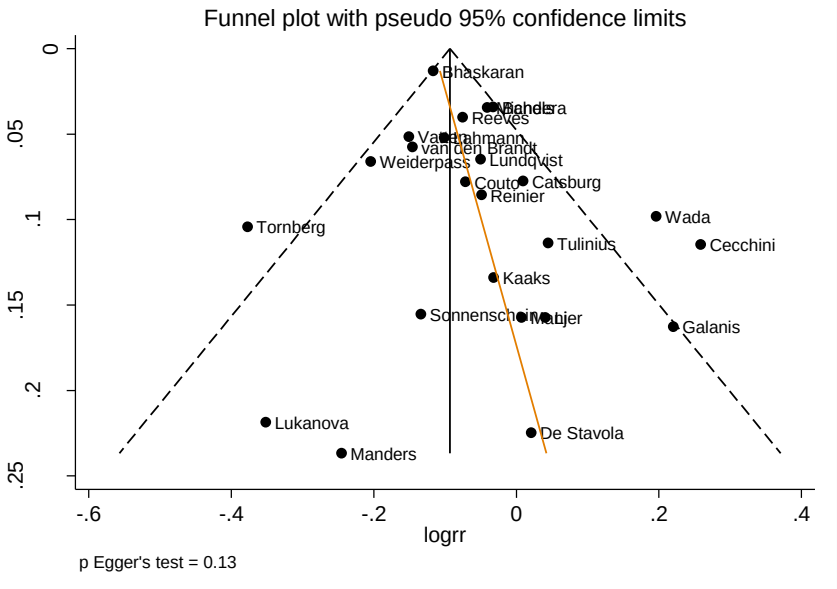
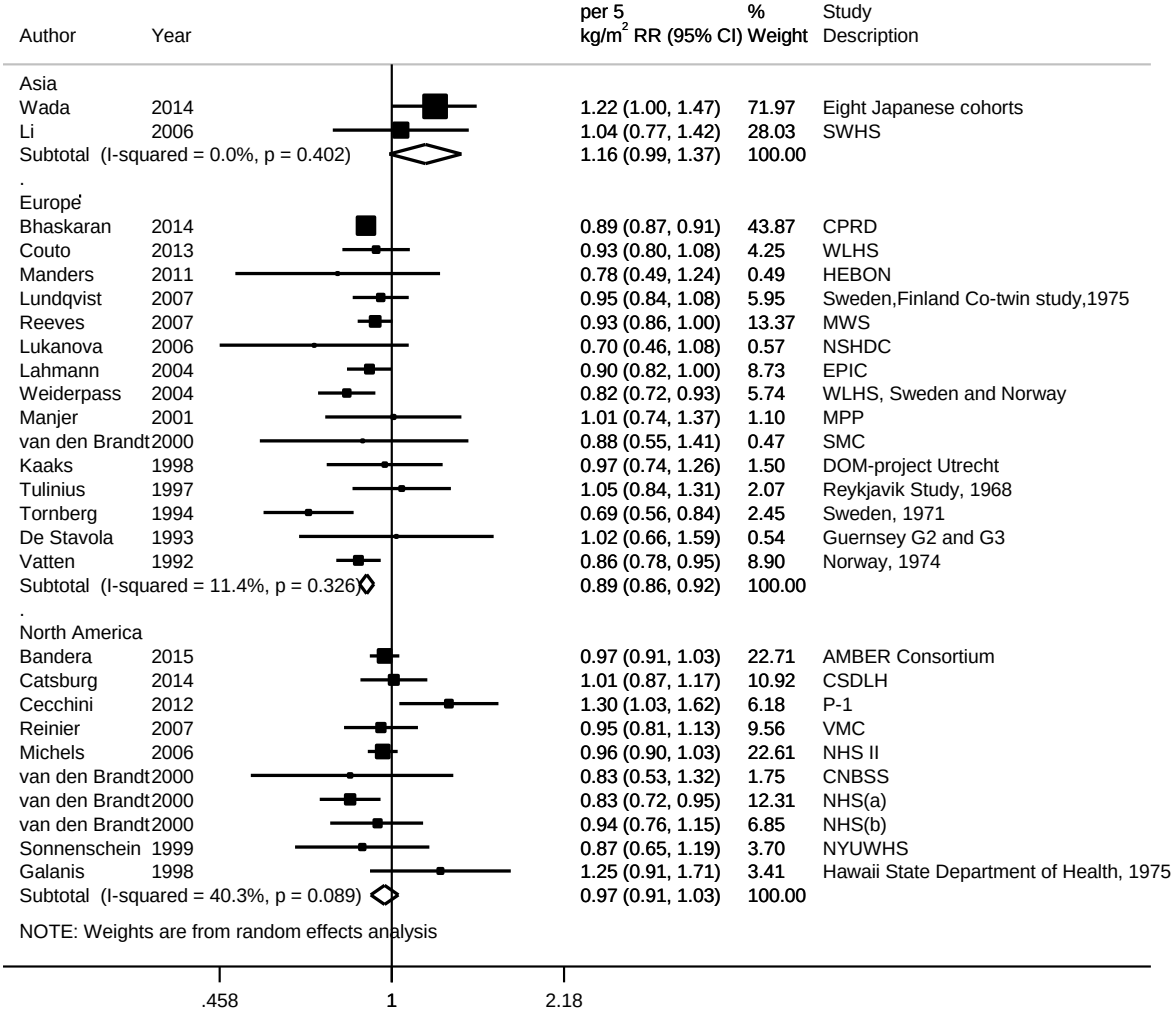


Figure 537 Relative risk of premenopausal breast cancer for 5 kg/m^2 increase of BMI, by geographic location



Note: Individual study results within the Pooling Project (van den Brandt, 2000) were used.

Figure 538 Relative risk of premenopausal breast cancer for 5 kg/m^2 increase of BMI, by anthropometric measurement methods

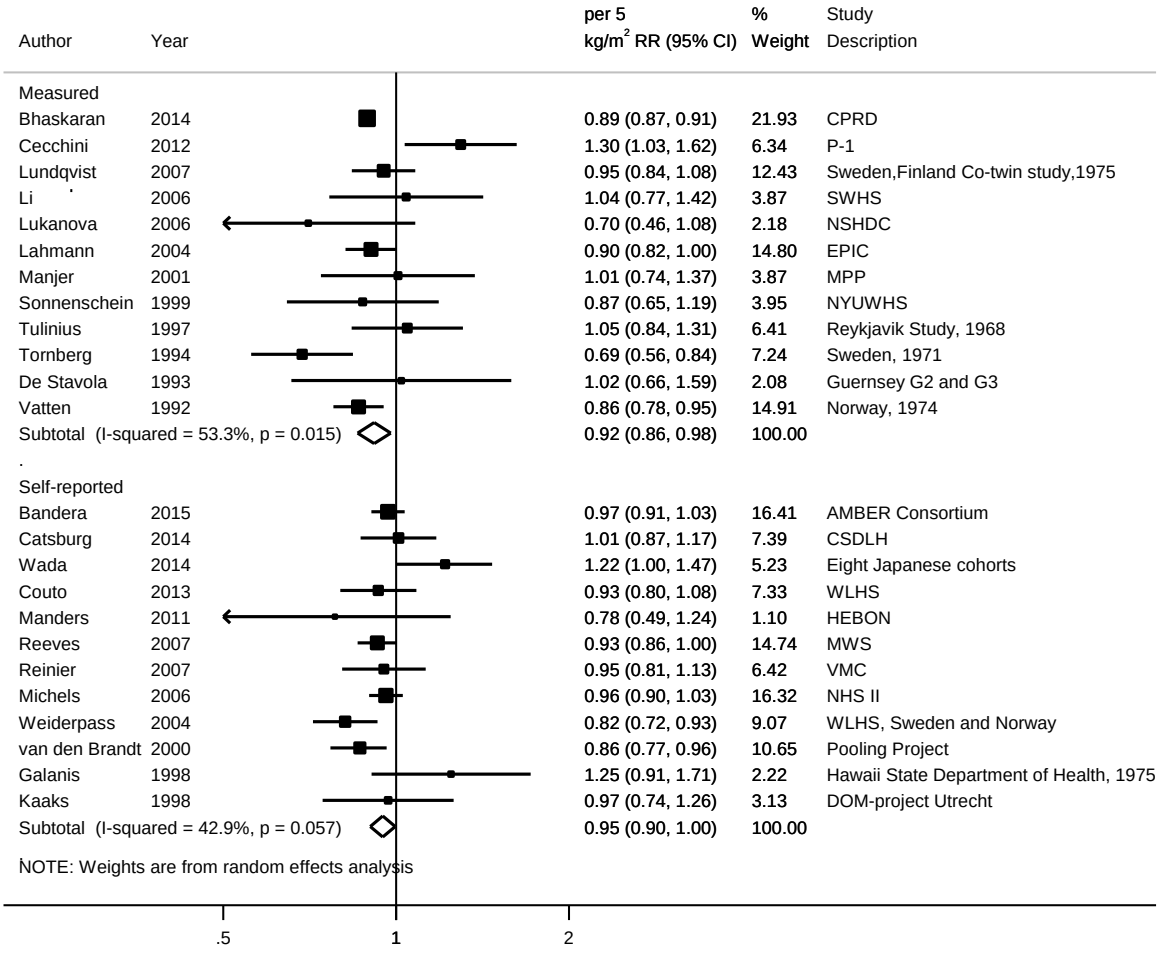
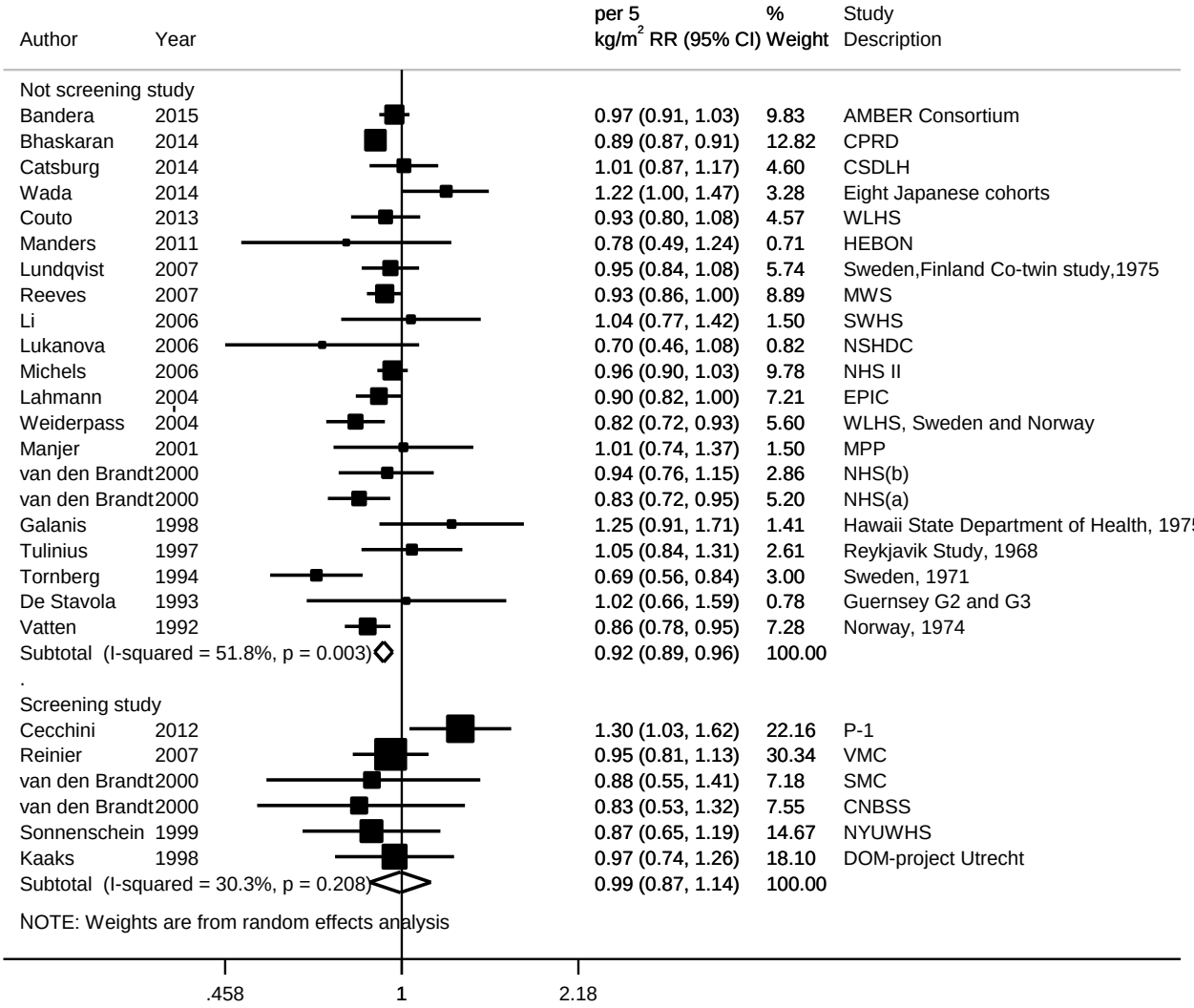


Figure 539 Relative risk of premenopausal breast cancer for 5 kg/m^2 increase of BMI, by study design



Note: Individual study results within the Pooling Project (van den Brandt, 2000) were used

Figure 540 RR (95% CI) of premenopausal breast cancer subtypes for the highest compared with the lowest level of BMI

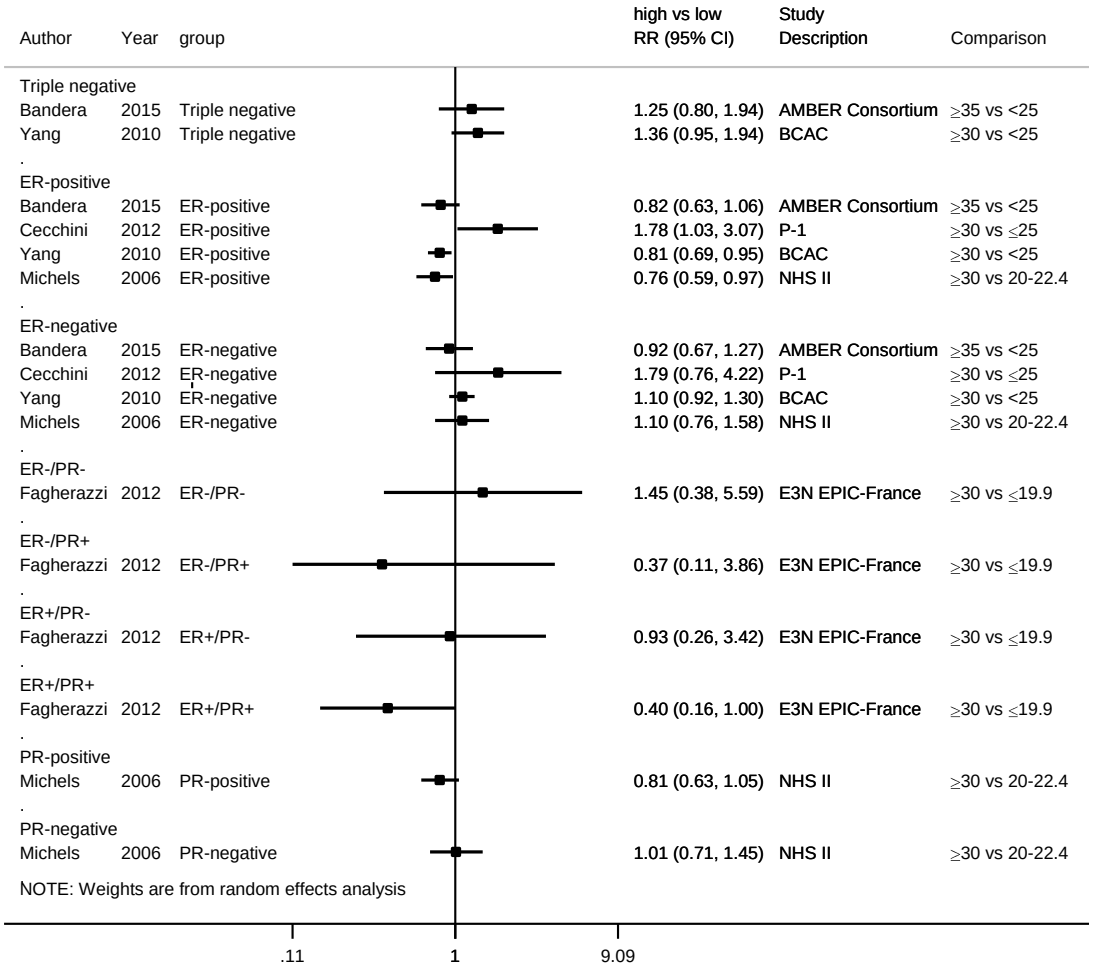


Figure 541 Relative risk of hormone receptor-defined premenopausal breast cancer for 5 kg/m^2 increase of BMI

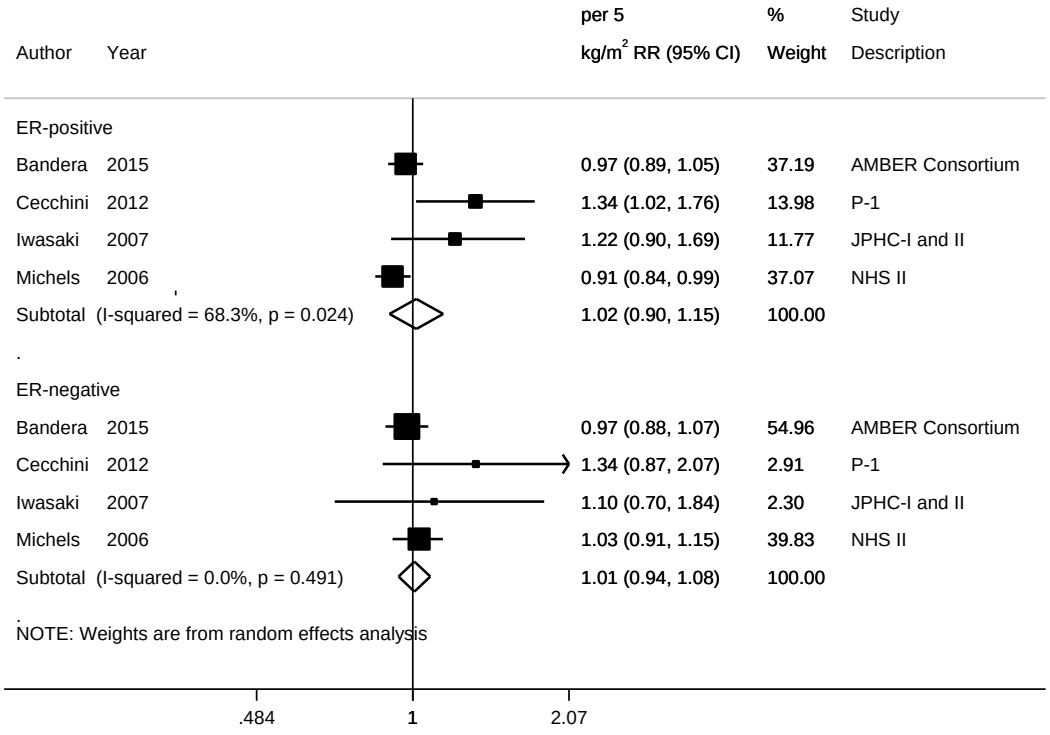


Figure 542 RR (95% CI) of premenopausal breast cancer mortality for the highest compared with the lowest level of BMI

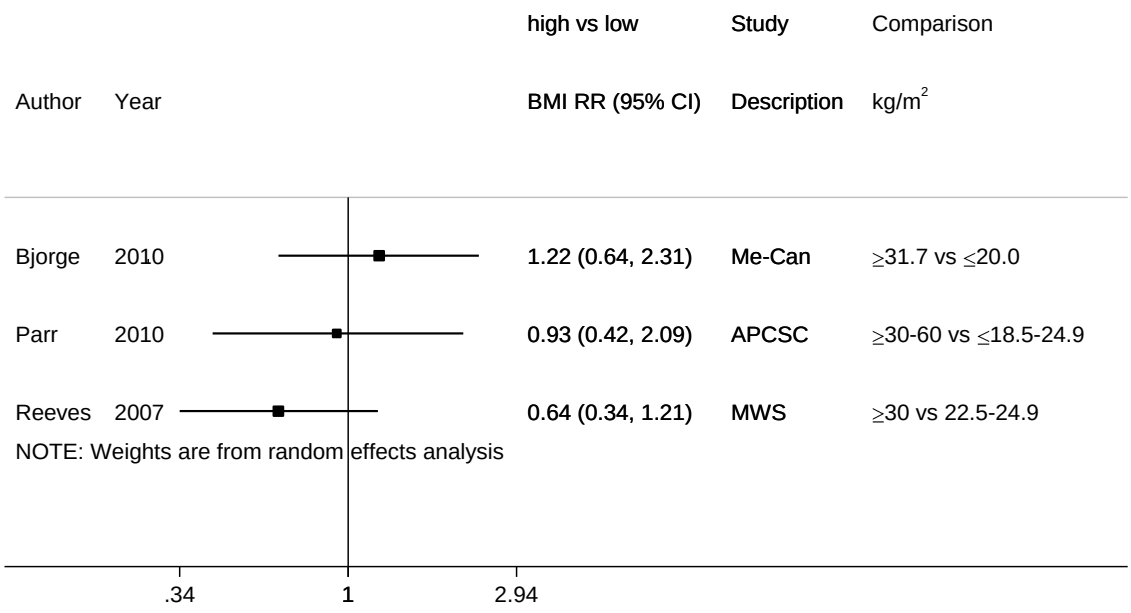
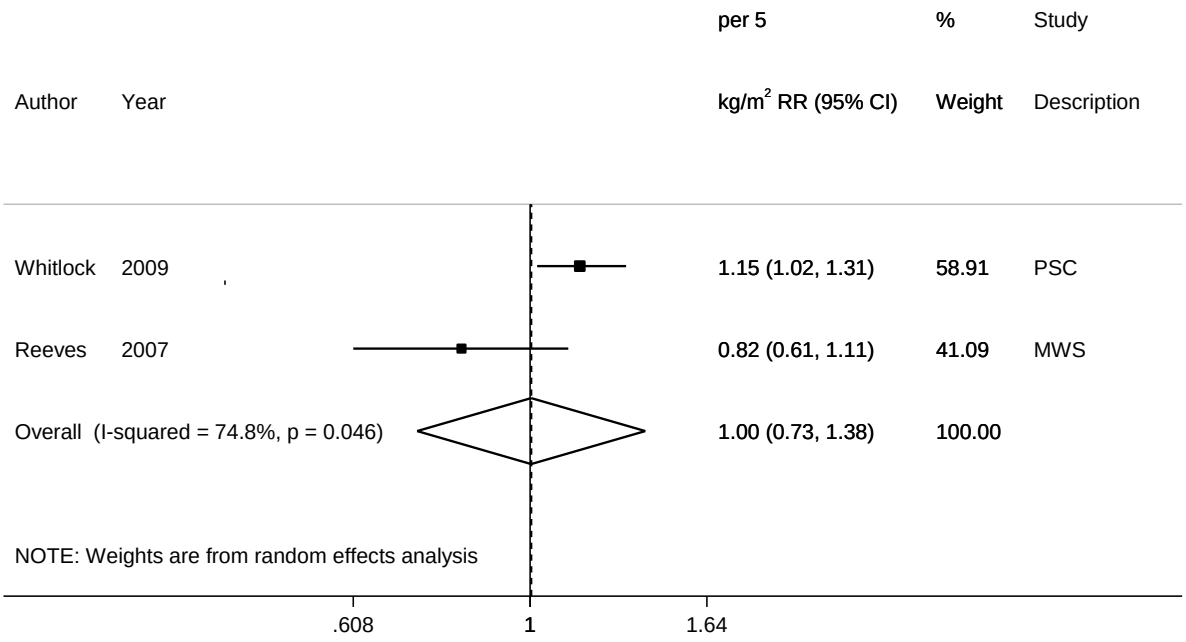


Figure 543 Relative risk of premenopausal breast cancer mortality for 5 kg/m^2 increase of BMI



Postmenopausal breast cancer

Summary

Main results:

Ninety-five out of 156 studies (131 publications) identified could be included in the dose-response meta-analyses. There were 56 studies (35 publications) on BMI and breast cancer risk overall, 20 studies (18 publications) on breast cancer subtypes, and 38 studies (four publications) on breast cancer mortality. Nineteen studies (13 publications) were included in the analysis by MHT use.

BMI was significantly positively associated with postmenopausal breast cancer risk (summary RR per 5 kg/m^2=1.12, 95% CI=1.09-1.15) and mortality (summary RR=1.20, 95% CI=1.13-1.27). There was evidence of high heterogeneity between studies of breast cancer incidence (I^2=74%, P=<0.001), which could partly explained by the geographical locations of the studies. On average, Asian studies (summary RR=1.37, 95% CI=1.24-1.50, I^2=27%, P=0.25) observed stronger positive association compared with European (summary RR=1.10, 95% CI= 1.06-1.15, I^2=75%, P<0.001) and North American studies (summary RR=1.10, 95% CI=1.08-1.12, I^2=30%, P=0.10).

MHT use and proportion of breast cancer subtypes in the studies may also explain the disparity of the results. Significant positive associations were only observed among MHT never users (summary RR per 5 kg/m^2=1.16, 95% CI=1.10-1.23) or never/former users (RR=1.20, 95% CI=1.15-1.25), but not current users (RR=0.98, 95% CI=0.90-1.06) or ever users (RR=1.01, 95% CI=0.96-1.06). BMI was significantly positively associated with ER-positive (summary RR=1.17, 95% CI=1.09-1.25) or ER+PR+ breast cancer (RR=1.29, 95%

CI=1.19-1.40), but not ER-negative (RR=1.00, 95% CI= 0.95-1.06) or other joint hormone receptor-defined breast cancers (ER+PR-: 0.94, 95% CI=0.87-1.01; ER-PR-: RR=0.96, 95% CI=0.87-1.06). Heterogeneity existed in some analyses by MHT use and of breast cancer subtypes (I^2 ranged from 0% - 91%). Positive associations that was only significant in PR-positive but not PR-negative breast cancer were observed (summary RR=1.47, 95% CI=1.36-1.60; RR=1.05, 95% CI=0.93-1.18, respectively).

There was not enough data to conduct a meta-analysis of BMI with hormone receptor-defined breast cancer risk by MHT use. For the highest versus the lowest BMI comparison, among MHT never or never/former users; five studies showed significant positive associations with ER-positive (Gaudet, 2014; Phipps, 2011) and ER+PR+ (Ritte, 2012; Ahn, 2007; Suzuki, 2006) breast cancer, and three studies showed non-significant inverse associations with ER-negative (Gaudet, 2014) and ER-PR- (Ahn, 2007; Suzuki, 2006) breast cancer.

There was evidence of significant publication bias or small study bias (P for Egger's test= 0.03). Visual inspection of the funnel plot shows more large-sized studies publishing positive associations.

Sixty-one studies and 74 publications were excluded from the dose-response meta-analyses. Study populations in five studies (Opdahl, 2011; Vacek, 2011; Benzon Larsen, 2010; Lundqvist, 2007, case-control analysis; Tornberg, 1988) overlapped with other studies that were already included in the analyses. Some studies were common between the two pooled studies on breast cancer mortality (Parr, 2010, APCSC; Whitlock, 2009, PSC) and the one with less number of deaths (Parr, 2010, APCSC, 31 non-overlapping studies) were excluded. One excluded study (Burton, 2010) was on BMI at young adulthood and one (Davey Smith, 2009) used offspring BMI as an indicator of own BMI.

Fourteen studies (five publications) did not report sufficient data to be included in the meta-analysis. Positive associations, which were significant in 11 (Harding, 2015, eight non-overlapping studies; Bjorge, 2010, three non-overlapping studies), and non-significant in one study of BRCA1/2 mutation carriers (Manders, 2011) were reported. One study (Le Marchand, 1988) found a non-significant inverse association. One study (Rissanen, 2003) reported on average similar BMI between the cases and non-cases.

One excluded pooled study (Yang XR, 2011, nine non-overlapping studies) reported that the risk association for BMI among women >50 years was not statistically significantly modified by ER status.

Sensitivity and stratified analyses:

Summary RR did not change materially when studies were omitted in turn in influence analysis and the positive association remained similar when analysis was restricted to invasive breast cancer only.

Subgroup analyses of other a priori defined factors, including anthropometric measurement methods, study design, confounder adjustment, publication year, number of cases, and range of BMI in studies, showed significant positive associations of similar magnitude.

Subgroup analyses restricted to European studies only found similar positive associations with persisting high heterogeneity. Two earlier North American studies, which recruited participants from the breast screening clinic (Sonnenscheini, 1999) and Hawaii (Galanis, 1998) showed slightly stronger results (summary RR per 5 kg/m^2=1.36, 95% CI=1.08-1.72) (results not tabulated).

Nonlinear dose-response meta-analysis:

Postmenopausal breast cancer risk increased monotonically through all ranges of BMI (P for non-linearity=0.08) (graph not shown).

Study quality:

Majority of the studies were from North America or Europe. There was one study each from Hawaii and Australia, and 11 from Asian (eight were from a pooled study of Japanese cohorts). One study (Miao Jonasson, 2014) was a cohort of type 2 diabetic women. NSABP P-1 and STAR (Cecchini, 2012) was a chemoprevention (tamoxifen) trial in women at high risk for developing breast cancer. Participants had bilateral mammograms annually during follow-up. SOF (Krebs, 2006) was a study of older subjects (mean age 73.5 years). Gaudet, 2014 (CPS-II) included only women not currently using MHT and Reeves, 2007, (MWS) included only never MHT user. All these studies did not have a strong influence in the summary RR.

Case ascertainment was through cancer registries or confirmed through medical records. Seven studies (five publications) (Cecchini, 2012, P-1 and STAR; Kerlikowske, 2008; van den Brandt, 2000, CNBSS and SMC; Sonnenschein, 1999; Kaaks, 1998) involved cancer screening. All observed positive associations, apart from the non-significant inverse association in the DOM-project (Kaaks, 1998). About half of the studies were simultaneously adjusted for age, alcohol intake, reproductive factors, and MHT use. On average, studies that involved breast screening or not, used measured or self-reported anthropometric data, or adjusted for confounding factors or not found similar positive associations on average.

Table 530 BMI and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified[1]	156 (131 publications)
Studies included in forest plot of highest compared with lowest exposure	62 (36 publications) breast cancer risk 16 (16 publications) breast cancer subtypes 47 (6 publications) breast cancer mortality 12 (12 publications) breast cancer risk by MHT use
Studies included in linear dose-response meta-analysis[2]	56 (35 publications) breast cancer risk 20 (18 publications) breast cancer subtypes 38 (4 publications) breast cancer mortality 19 (13 publications) breast cancer risk by MHT use
Studies included in non-linear dose-response meta-analysis	38 (29 publications) breast cancer risk

Note: Included cohorts, case-cohort, and nested case-control designs. AMBER Consortium (Bandera, 2015) included two cohorts and two case-control studies. [1]Included nine pooled studies (Bandera, 2015, AMBER Consortium, four studies; Harding, 2015, ANZDCC, 10 studies; Wada, 2014, Eight Japanese studies; Schonfeld, 2011, four US studies; Bjorge, 2010, Me-Can, six studies; Parr, 2010, APCSC, 37 studies; Yang XR, 2011, BCAC, 12 studies in case-control analysis; Whitlock, 2009, PSC, 35 studies; van den Brandt, 2000, the Pooling Project, seven studies). [2]In total, 95 studies (57 publications) were included in the dose-response meta-analyses.

Table 531 BMI and postmenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2008 SLR and CUP SLR

	2008 SLR	**CUP**
Increment unit used	2 kg/m^2	5 kg/m^2
Studies (n)	19	56
Cases	17 459	80 404
RR (95%CI)	1.05 (1.03-1.07)	1.12 (1.09-1.15)

Heterogeneity (I^2, p-value)	60%, <0.001	74%, <0.001	
P value Egger test	-	0.03	
Stratified analyses in the CUP			
Geographic area[1]	**Asia**	**Europe**	**North America**
Studies (n)	11	19	25
Cases	2 362	44 265	33 109
RR (95%CI)	1.37 (1.24-1.50)	1.10 (1.06-1.15)	1.10 (1.08-1.12)
Heterogeneity (I^2, p-value)	27%, 0.25	75%, <0.001	30%, 0.10
Anthropometric measurement methods[2]	**Measured**	**Self-reported**	**From records**
Studies (n)	19	35	1
Cases	42 021	34 099	263
RR (95%CI)	1.14 (1.09-1.19)	1.11 (1.08-1.14)	1.19 (1.07-1.33)
Heterogeneity (I^2, p-value)	79%, <0.001	62%, 0.001	-
Screening studies	**Yes**	**No**	
Studies (n)	7	49	
Cases	5 838	74 566	
RR (95%CI)	1.12 (1.03-1.22)	1.12 (1.09-1.14)	
Heterogeneity (I^2, p-value)	52%, 0.06	72%, <0.001	
Adjustment for age, alcohol intake, reproductive factors, and MHT use	**Adjusted**	**Not adjusted**	
Studies (n)	27	29	
Cases	35 777	43 145	
RR (95%CI)	1.12 (1.09-1.15)	1.12 (1.08-1.16)	
Heterogeneity (I^2, p-value)	64%, 0.001	69%, <0.001	
Publication year	<2000	2000-<2010	≥2010
Studies (n)	8	16	32
Cases	2 148	17 566	60 690
RR (95%CI)	1.13 (1.01-1.26)	1.15 (1.10-1.21)	1.10 (1.07-1.13)
Heterogeneity (I^2, p-value)	50%, 0.06	77, <0.001	68%, <0.001
Number of cases in study	≤350 cases	350-≤1500 cases	>1500 cases

Studies (n)	15	20	21
Cases	2 757	8 910	68 737
RR (95%CI)	1.14 (1.05-1.23)	1.15 (1.09-1.20)	1.10 (1.07-1.13)
Heterogeneity (I^2, p-value)	50%, 0.02	60%, 0.005	86%, <0.001
Difference in BMI between the highest and the lowest mean of category	<10 kg/m^2	≥10 kg/m^2	
Studies (n)	24	32	
Cases	5 732	72 190	
RR (95%CI)	1.14 (1.06-1.23)	1.11 (1.09-1.14)	
Heterogeneity (I^2, p-value)	57%, 0.003	79%, <0.001	
Other analyses in the CUP			
	Invasive breast cancer	**Breast cancer mortality**	
Studies (n)	29	38	
Cases	57 624	4 131	
RR (95%CI)	1.13 (1.09-1.17)	1.20 (1.13-1.27)	
Heterogeneity (I^2, p-value)	81%, <0.001	49%, 0.12	

[1]One study (Krishnan, 2013) was from Australia and New Zealand (RR per 5 kg/m^2=1.12, 95% CI=1.03-1.21, 668 cases); [2]One study (Emaus, 2014) used self-reported or measured height and weight (RR=1.05, 95% CI=1.01-1.11, 4 021 cases)

Table 532 BMI and postmenopausal breast cancer risk by menopausal hormone therapy use. Summary of the linear dose-response meta-analysis in the CUP SLR[3]

MHT use[4]	**Current**	**Ever**	**Never**	**Never/former**
Increment unit used	5 kg/m^2	5 kg/m^2	5 kg/m^2	5 kg/m^2
Studies (n)	5	13	15	4
Cases	3 940	>3 004	>10 487	3 369
RR (95%CI)	0.98 (0.90-1.06)	1.01 (0.96-1.06)	1.16 (1.10-1.23)	1.20 (1.15-1.25)
Heterogeneity (I^2, p-value)	69%, 0.01	0%, 0.66	72%, 0.001	0%, 0.62
Stratified analyses among MHT never users				
Geographic area	**Asia**	**Europe**	**North America**	
Studies (n)	1	2	4	
RR (95%CI)	1.38 (1.10-1.73)	1.16 (1.09-1.22)	1.16 (1.00-1.35)	
Heterogeneity (I^2, p-value)	-	62%, 0.11	83%, 0.001	

[3]In the 2008 SLR, among HRT-non-users, summary RR was 1.06 (95% CI=1.05-1.08, I^2=15%, p=0.31, 3 studies) per 2 kg/m^2. [4]One study (White, 2012) reported results on MHT former users (RR per 5 kg/m^2=1.27, 95% CI= 1.13-1.42, 546 cases)

Table 533 BMI and risk of postmenopausal breast cancer subtypes. Summary of the linear dose-response meta-analysis in the CUP SLR

ER-status	**ER-positive**	**ER-negative**	
Increment unit used	5 kg/m^2	5 kg/m^2	
Studies (n)	14	13	
Cases	9 587	2 180	
RR (95%CI)	1.17 (1.09-1.25)	1.00 (0.95-1.06)	
Heterogeneity (I^2, p-value)	91%, <0.001	7%, 0.38	
PR-status	**PR-positive**	**PR-negative**	
Studies (n)	5	5	
Cases	1 314	654	
RR (95%CI)	1.47 (1.36-1.60)	1.05 (0.93-1.18)	
Heterogeneity (I^2, p-value)	0%, 0.86	0%, 0.95	
Joint ER/PR-status[5]	**ER+PR+**	**ER+PR-**	**ER-PR-**
Studies (n)	9	6	9

Cases	>4 487	1 206	>1 131
RR (95%CI)	1.29 (1.19-1.40)	0.94 (0.87-1.01)	0.96 (0.87-1.06)
Heterogeneity (I^2, p-value)	78%, <0.001	0%, 0.71	33%, 0.17
Triple negative breast cancer			
Studies (n)	6		
Cases	608		
RR (95%CI)	1.05 (0.88-1.25)		
Heterogeneity (I^2, p-value)	64%, 0.06		

[5]One study (Fagherazzi, 2012a) reported results on ER-PR+ breast cancer (RR per 5 kg/m^2=0.86, 95% CI=0.58-1.28, 52 cases)

Table 534 BMI and postmenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies[1]	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Munsell, 2014	12 cohort studies, 27 case-control studies	59 185	Sweden, USA, Europe	Incidence, postmenopausal breast cancer (12 cohort studies, 16 180 cases)	25-29.9 vs <25 kg/m^2	1.13 (1.09-1.18)		6%, 0.39
					≥30 vs <25 kg/m^2	1.20 (1.11 1.31)		64%, <0.01
					Never MHT users ≥30 vs <25 kg/m^2	1.37 (1.10-1.71)		69%, 0.07
					Ever MHT users (2 cohort studies)	1.26 (1.02-1.56)		62%, 0.11
				ER+PR+ (8 cohort or case-control studies, 6 733 cases)	25-29.9 vs <25 kg/m^2	1.17 (1.01-1.36)		74%, <0.01
					≥30 vs <25 kg/m^2	1.39 (1.14-1.70)		81%, <0.01
				ER-PR- (9 studies, 2 302 cases)	25-29.9 vs <25 kg/m^2	1.06 (0.95-1.18)		0%, 0.99
					≥30 vs <25 kg/m^2	0.98 (0.78-1.22)		57%, 0.02
				ER+PR unknown (6 studies, 7 965 cases)	25-29.9 vs <25 kg/m^2	1.08 (1.02-1.15)		48%, 0.09
					≥30 vs <25 kg/m^2	1.22 (1.03-1.45)		74%, <0.01
				ER-PR unknown	25-29.9 vs	0.96 (0.78-1.17)		22%, 0.28

				(3 studies, 831 cases)	<25 kg/m^2 ≥30 vs <25 kg/m^2	1.27 (1.05-1.55)		0%, 0.77
Xia, 2014[2]	25 estimates from 20 prospective studies and 1 pooled analysis of 8 cohorts	22 809	China, France, Japan, The Netherlands, Norway, Sweden, North America	Incidence, postmenopausal breast cancer	25 vs 21.75 kg/m^2 30 vs 21.75 kg/m^2 35 vs 21.75 kg/m^2	1.02 (0.98-1.06) 1.12 (1.01-1.24) 1.26 (1.07-1.50) Significant non-linear relationship per 1 kg/m^2 increase in BMI		<0.001 P for non-linearity <0.001
Esposito, 2013	8 studies (5 cohorts, 2 case-control studies, 1 pooled study of 6 cohorts)	6 207	Italy, Japan, Sweden, Switzerland, Norway, Uruguay, USA	Incidence, postmenopausal breast cancer	High BMI/WC vs low	1.12 (0.99-1.27)	0.07	61%, 0.01
Pierobon, 2013[3]	6 case-case or case-control studies	-	USA	Incidence, postmenopausal triple-negative breast cancer	>30 vs <30 kg/m^2	0.99 (0.79-1.24)		69%, <0.01
Cheraghi, 2012[4]	8 cohort studies	9 878	France, USA, Sweden and	Incidence, postmenopausal	Overweight vs normal	1.12 (1.06-1.18)		56%, 0.03

			Norway	breast cancer	weight Obese vs normal weight	1.16 (1.08-1.25)		65%, <0.01
Suzuki, 2009	11 cohort and case-control studies	5 469 ER+PR+ cases, 1 523 ER-PR- cases, 999 ER+PR- cases, 138 ER-PR+ cases	Asia, Australia, Canada, USA, Europe	Incidence, premenopausal breast cancer ER+PR+ ER-PR- ER+PR- ER-PR+ ER+ ER- PR+ PR- ER+PR+ Overall, 8 studies (4 267 cases) MHT never users (4 studies)	Highest vs lowest Per 5 kg/m^2	 1.82 (1.55-2.14) 1.06 (0.84-1.33) 0.93 (0.72-1.21) 2.01 (1.22-3.32) 1.78 (1.50-2.11) 1.19 (1.03-1.36) 1.99 (1.74-2.28) 1.07 (0.94-1.23) 1.33 (1.20-1.48) 1.40 (1.22-1.60)		 <0.1 0.13 0.15 0.76 <0.0001 0.47 <0.06 0.40

[1]All cohort studies and RCTs identified in the published meta-analyses were included in the present review unless otherwise specified.

[2]Four studies (Cecchini, 2012, P-1; Cecchini, 2012, STAR; Opdahl, 2011; Li, 2006) included in Xia, 2014 had insufficient BMI categories and one study (Canchola, 2012) reported results only by hormone receptor subtype; these studies were not included in the non-linear analysis of the present report (36 studies, 13 studies not in Xia, 2014).

[3]Analysis used raw data from published studies and no adjustments were applied to analyses.

[4]Two studies (Barlow, 2006; Lee, 2006) included in Cheraghi, 2012 were not included in the present review. Barlow, 2006 (Breast Cancer Surveillance Consortium) estimated the risk of developing breast cancer within a year of mammography screening and no relevant data could be found in Lee, 2006.

Table 535 BMI and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Bandera, 2015 USA	AMBER Consortium, Pooled study, 2 cohorts and 2 case-control studies*, W African American (*CBCS; WCHS; BWHS; MEC)	2025/	Record linkage to cancer registries, identified through hospitals, self-reported and verified with medical records and cancer registry data	Self-reported or measured	Incidence, postmenopausal breast cancer	≥ 35 vs < 25 kg/m^2	1.14 (0.96-1.34) Ptrend; 0.08	Age, education, study, time period, geographical region, family history of breast cancer, age at menarche, parity, breastfeeding, age at first birth, hormone therapy use, OC use, age at menopause	
		1413/			ER+	≥ 35 vs < 25 kg/m^2	1.32 (1.09-1.60) Ptrend: 0.002		
		612/			ER-	≥ 35 vs < 25 kg/m^2	0.82 (0.63-1.08) Ptrend: 0.09		
		264/			Triple-negative	≥ 35 vs < 25 kg/m^2	0.68 (0.46-1.02) Ptrend: 0.25		
Kabat, 2015b BRE80526 USA	Womens Health Initiative (WHI), Prospective Cohort, Age: 50-79 years, W, Postmenopausal	7 039/ 143 901 12.7 years	Self report verified by medical record and pathology report	Measured	Incidence, invasive breast cancer	Q5 vs Q1	1.41 (1.31-1.53) Ptrend:<0.0001	Age, age at menarche, alcohol, aspirin use, diabetes, educational level, ethnicity, family history of colon cancer,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								HRT use, met-hours per week, parity, smoking, treatment allocation	
					Never HRT users	Q5 vs Q1	1.39 (1.13-1.72) Ptrend:0.001		
					Ever used HRT	Q5 vs Q1	1.12 (0.95-1.33) Ptrend:0.15		
					Never used HRT	Q2 vs Q1	1.70 (1.50-1.94)	Waist circumference	
Bhaskaran, 2014 BRE80518 UK	CPRD, Prospective Cohort, Age: 16- years, W	28 409/ 2 864 658 25 years	Medical record	Measured	Incidence, invasive postmenopausal breast cancer	per 5 kg/m^2	1.05, 99% CI:(1.03-1.07)	Age, sex, alcohol, calendar year, diabetes, smoking, socio-economic status	
						>35 vs 18.5-24.9 kg/m^2	1.10, 99% CI:(1.03-1.17)		
					Never smokers	per 5 kg/m^2	1.05, 99% CI:(1.03-1.08)		
Catsburg, 2014b BRE80529 Canada	CSDLH, Case Cohort, W	541/ 2 210 15 years	Cancer registry	Self-reported	Incidence, Invasive breast cancer, Postmenopausal	≥30 vs 18.5-24.99 kg/m^2	1.24 (0.90-1.71) Ptrend:0.08	Age at first child birth, age at menarche, alcohol Intake, family history of breast cancer, menopausal status, number of childbirths,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								OC use, physical activity, HRT use	
					HRT ever	≥30 vs 18.5-24.99 kg/m^2	1.20 (0.79-1.83) Ptrend:0.24		
					HRT never	≥30 vs 18.5-24.99 kg/m^2	0.99 (0.73-1.34) Ptrend:0.68		
Emaus, 2014 BRE80540 Europe	EPIC-PANACEA, Prospective Cohort, Age: 25-70 years, W	2 370/ 205 723 1 396 538 person-years	Active follow up and cancer registry	Self-reported or measured	Incidence, Invasive breast cancer, HRT never, >50y	28.1-59.7 vs 16-21.3 kg/m^2	1.24 (1.07-1.43) Ptrend:0.00	Age, age at first child birth, age at menarche, alcohol consumption, alcohol drinking, BMI at baseline, educational level, energy Intake, physical activity, smoking, study center, time between measurements, use of oral contraception	
		1 651/			HRT ever, >50y	28.1-59.7 vs 16-21.3 kg/m^2	0.95 (0.80-1.14) Ptrend:0.46		
Gaudet, 2014 BRE80533 USA	CPS II, Prospective Cohort, W,	1 088/ 28 965 11.58 years	Self report verified by medical records or by linkage	Self-reported	Incidence, Invasive breast cancer, HRT - no	per 1 kg/m^2	1.04 (1.03-1.05)	Age, age at first child birth, age at menopause, alcohol Intake,	Included in the analysis by hormone receptor-defined

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Postmenopausal		with state cancer registries					benign breast disease, diabetes, educational level, exercise, family history of breast cancer, height, mammography, oral contraceptive use, parity, postmenopausal hormone use, race, smoking	breast cancer
						≥30 vs ≤24.9 kg/m^2	1.60 (1.36-1.89)		
		791/			Incidence, breast cancer ER+, HRT - no	per 1 kg/m^2	1.04 (1.01-1.06)	Waist circumference	
						≥30 vs ≤24.9 kg/m^2	1.41 (1.08-1.85)		
		128/			Incidence, breast cancer ER-, HRT - no	per 1 kg/m^2	0.99 (0.95-1.04)		
						≥30 vs ≤24.9 kg/m^2	0.61 (0.35-1.08)		
Guo, 2014 BRE80541 China	Northern China 2006-2011, Prospective Cohort, Age: 18- years, W	57/ 26 643 4.28 years	Self report, next of kin, medical and pathological records	Measured	Incidence, breast cancer, postmenopausal	≥28 vs 18.5-23.9	1.97 (1.01-3.82)	Age, alcohol consumption, educational level, smoking	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Horn, 2014b BRE80564 Norway	NNTHS, Prospective Cohort, Age: 55 years, W, Postmenopausal	1 069/ 18 562 409 377 person-years	Cancer registry	Measured	Incidence, invasive breast cancer, postmenopausal	≥30 vs ≤24 kg/m^2	1.44 (1.22-1.70) Ptrend:<0.001	Age, birth cohort	
						per 5 kg/m^2	1.16 (1.09-1.25)		
		734/			Incidence, breast cancer subtype classified, postmenopausal	≥30 vs ≤24 kg/m^2	1.49 (1.23-1.81) Ptrend:<0.001		
						per 5 kg/m^2	1.19 (1.10-1.29)		
		235/			Incidence, breast cancer unclassified subtype, postmenopausal	≥30 vs ≤24 kg/m^2	1.27 (0.91-1.77) Ptrend:0.13		
						per 5 kg/m^2	1.08 (0.93-1.24)		
		614/			Incidence, luminal breast cancer, postmenopausal	≥30 vs ≤24 kg/m^2	1.58 (1.28-1.95) Ptrend:<0.001		
						per 5 kg/m^2	1.22 (1.12-1.33)		
		120/			Incidence, non-luminal breast cancer, postmenopausal	≥30 vs ≤24 kg/m^2	1.14 (0.71-1.83) Ptrend:0.59		
						per 5 kg/m^2	1.06 (0.86-1.30)		
		361/			Incidence, luminal A breast cancer, postmenopausal	≥30 vs ≤24 kg/m^2	1.55 (1.18-2.05) Ptrend:0.002		
						per 5 kg/m^2	1.20 (1.07-1.34)		
		205/			Incidence, luminal B (HER2-) breast cancer, postmenopausal	≥30 vs ≤24 kg/m^2	1.53 (1.06-2.21) Ptrend:0.02		
						per 5 kg/m^2	1.21 (1.05-1.40)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		48/			Incidence, luminal B (HER2+) breast cancer, postmenopausal	≥30 vs ≤24 kg/m^2	1.96 (0.94-4.09) Ptrend:0.06		
						per 5 kg/m^2	1.42 (1.07-1.88)		
		40/			Incidence, non-luminal (HER2+) breast cancer, postmenopausal	≥30 vs ≤24 kg/m^2	2.21 (1.01-4.83) Ptrend:0.04		
						per 5 kg/m^2	1.25 (0.90-1.73)		
		50/			Incidence, basal-like breast cancer, postmenopausal	≥30 vs ≤24 kg/m^2	1.09 (0.49-2.39) Ptrend:0.82		
						per 5 kg/m^2	1.14 (0.84-1.55)		
		30/			Incidence, five negative phenotype, postmenopausal	≥30 vs ≤24 kg/m^2	0.44 (0.16-1.24) Ptrend:0.10		
						per 5 kg/m^2	0.69 (0.43-1.10)		
Miao Jonasson, 2014 BRE80530 Sweden	Swedish National Diabetes Register Cohort Study, Prospective Cohort, Age: 30-90 years, W, Type 2 diabetic patients	263/ 11 093 8.6 years	Swedish cancer registry & record linkage with Swedish cause-of-death registry	From registry records	Incidence, invasive breast cancer, postmenopausal	≥30 vs 18.5-24.9 kg/m^2	1.39 (1.00-1.91)	Age, diabetes, diabetes medication use, hba1c, smoking	
						per 5 kg/m^2	1.19 (1.07-1.33)		
Wada, 2014,	Eight Japanese	1 482/	Through cancer	Self-reported	Incidence,	≥30 vs 23-24.9	1.34 (0.99-1.81)	Age, area,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Japan	cohorts, Pooled study (JPHC-I and II, JACC, OHSAKI, MIYAGI-I and II, AICHI, TAKAYAMA) W	1 860 389 person-years Mean age 55.3 years 11.93 years of follow-up	registries and/or active patient notification from hospitals	height and weight in questionnaire	invasive postmenopausal breast cancer	kg/m^2 Per 1 kg/m^2	Ptrend:0.34 1.05 (1.04-1.07)	smoking status, alcohol consumption, age at menarche, menopausal status, age at first delivery, parity number	
Couto, 2013 BRE80454 Sweden	WLHS, Prospective Cohort, Age: 30-49 years, W	448/ 49 258 16 years	Cancer registry		Incidence, breast cancer, postmenopausal	≥25 vs ≤20 kg/m^2	1.24 (0.85-1.80)	Age at first child birth, age at menarche, alcohol, benign breast disease, contraception, educational level, energy Intake, height, history of breast cancer, hormone use, number of childbirths, smoking	
Krishnan, 2013 BRE80482 Australia	MCCS, Prospective Cohort, Age: 39-76 years, W, Postmenopausal	668/ 14 441 16.5 years	Cancer registry / database / pathology reports	Measured by trained nurses	Incidence, invasive breast cancer	≥30 vs ≤24.9 kg/m^2	1.20 (0.98-1.48)	Age at menarche, age-underlying cox models, alcohol, breastfeeding, country of birth, educational level, energy Intake, HRT use, ocp use,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								parity, phyisical activity, smoking	
						per 5 kg/m^2	1.12 (1.03-1.21)		
		327/			<=69 years	per 5 kg/m^2	1.07 (0.95-1.21)	BMI at age 18 years	
		341/			>69 years	per 5 kg/m^2	1.26 (1.12-1.41)		
		428/			Never HRT users	per 5 kg/m^2	1.20 (1.09-1.33)		
		240/			HRT users	per 5 kg/m^2	1.07 (0.92-1.24)		
		38/			Incidence, triple negative breast cancer	per 5 kg/m^2	1.13 (0.86-1.49)		
		68/			Incidence, luminal B breast cancer	per 5 kg/m^2	1.13 (0.87-1.48)		
		190/			Incidence, luminal A breast cancer	per 5 kg/m^2	1.39 (1.20-1.61)		
		234/			Incidence, breast cancer HER-2 -	per 5 kg/m^2	1.31 (1.15-1.50)		
		86/			Incidence, breast cancer HER-2 +	per 5 kg/m^2	1.13 (0.89-1.44)		
		106/			Incidence, poorly differentiated breast cancer	per 5 kg/m^2	1.22 (0.98-1.52)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		147/			Incidence, moderate differentiated breast cancer	per 5 kg/m^2	1.33 (1.13-1.56)		
		63/			Incidence, well differentiated breast cancer	per 5 kg/m^2	1.29 (1.01-1.66)		
		52/			Incidence, breast cancer ER-/PR-	per 5 kg/m^2	1.13 (0.87-1.47)		
		77/			Incidence, breast cancer ER+/PR-	per 5 kg/m^2	0.93 (0.72-1.20)		
		168/			Incidence, breast cancer ER+/PR+	per 5 kg/m^2	1.51 (1.31-1.74)		
		129/			Incidence, breast cancer PR-	per 5 kg/m^2	1.01 (0.84-1.22)		
		175/			Incidence, breast cancer PR+	per 5 kg/m^2	1.49 (1.29-1.72)		
		59/			Incidence, breast cancer ER-	per 5 kg/m^2	1.11 (0.86-1.43)		
		261/			Incidence, breast cancer ER+	per 5 kg/m^2	1.31 (1.16-1.49)		
Canchola, 2012 BRE80401 USA	CTS, Prospective Cohort, Age: 56-70 years, W, Postmenopausal	1 371/ 56 542 12.1 years	Cancer registry and national death Index	Self-reported	Incidence, breast cancer ER+/PR+	≥30 vs <25 kg/m^2	1.20 (1.03-1.40) Ptrend:0.01	Age at baseline, age at first child birth, age at menarche, alcohol, breast biopsies, family history of breast cancer, height,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								HRT use, parity	
						per 1 kg/m^2	1.02 (1.01-1.03)		
		287/			Incidence, breast cancer ER+/PR-	≥30 vs <25 kg/m^2	0.84 (0.58-1.21) Ptrend:0.27		
						per 1 kg/m^2	0.99 (0.96-1.01)		
		280/			Incidence, breast cancer ER-/PR-	≥30 vs <25 kg/m^2	0.77 (0.53-1.12) Ptrend:0.36		
						per 1 kg/m^2	1.00 (0.97-1.02)		
Cecchini, 2012 BRE80405 USA	P-1 and STAR, Prospective Cohort, W, Women at high risk for developing breast cancer, involved mammography screening	650/ 31 731	Mammography screening program	Measured	Incidence, invasive breast cancer, postmenopausal	≥30 vs ≤25	1.12 (0.92-1.36) Ptrend:0.25	Age, diabetes, estrogen use, gail score, oral contraceptive history, smoking	
		557/				≥30 vs ≤25	1.16 (0.94-1.42) Ptrend:0.16		
		127/				≥30 vs ≤25	1.09 (0.70-1.69) Ptrend:0.68		
		293/			Raloxifene	≥30 vs ≤25	1.07 (0.81-1.42) Ptrend:0.61		
		276/			Tamoxifen	≥30 vs ≤25	1.18 (0.88-1.58) Ptrend:0.26		
		84/			Placebo-group	≥30 vs ≤25	1.28 (0.72-2.28) Ptrend:0.36		
		472/			Incidence, breast cancer ER+, postmenopausal	≥30 vs ≤25	1.23 (0.98-1.55) Ptrend:0.07		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		154/			Incidence, breast cancer ER-, postmenopausal	≥30 vs ≤25	1.03 (0.70-1.52) Ptrend:0.88		
Fagherazzi, 2012a BRE80539 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W	944/ 63 726 582 144 person-years	Self report verified by medical record and pathology report	Self-reported	Incidence, breast cancer ER+/PR+, postmenopausal	≥30 vs ≤19.9 kg/m^2	1.63 (1.17-2.28) Ptrend:<0.01	Age at first child birth, age at menarche, age at menopause, alcohol Intake, breastfeeding, educational level, family history of breast cancer, history of benign breast disease, mammography, non-alcohol energy, OC use, parous/nulliparous, smoking status, total physical activity, use of HRT, year of birth	
		243/			Incidence, breast cancer ER-/PR-, postmenopausal	≥30 vs ≤19.9 kg/m^2	0.77 (0.36-1.66) Ptrend:0.35		
		302/			Incidence, breast cancer ER+/PR-, postmenopausal	≥30 vs ≤19.9 kg/m^2	0.68 (0.35-1.33) Ptrend:0.57		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		52/			Incidence, breast cancer ER-/PR+, postmenopausal	≥30 vs ≤19.9 kg/m^2	0.86 (0.23-3.25) Ptrend:0.44		
Harlid, 2012 BRE80422 Sweden	NSHDC (VIP and MSP), Prospective Cohort, Age: 27-95 years, W	850/ 3 994	Cancer registry	Self-reported	Incidence, invasive breast cancer, >50 years	≥30 vs 18.5-25	1.10 (0.85-1.41)	Age	
Ritte, 2012 BRE80415 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 25-70 years, W	698/ 314 760 3 399 178 person-years	Cancer and pathology registeries	Self-reported or measured	Incidence, breast cancer, ER+PR+ Age 50-54 yrs	per 5 kg/m^2	0.90 (0.81-1.01)	Age, age at first child birth, age at menarche, age at menopause, alcohol, centre location, educational level, height, menopausal status, oral contraceptive history, parity, smoking	
		830/			Age 55-59 yrs	per 5 kg/m^2	1.11 (1.01-1.21)		
		806/			Age 60-64 yrs	per 5 kg/m^2	1.10 (1.01-1.20)		
		862/			Age >=65 yr	per 5 kg/m^2	1.32 (1.22-1.43)		
		180/			Incidence, breast cancer, ER+PR- Age 50-54 yrs	per 5 kg/m^2	0.90 (0.72-1.12)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		306/			Age 55-59 yrs	per 5 kg/m^2	0.90 (0.76-1.05)		
		280/			Age 60-64 yrs	per 5 kg/m^2	0.88 (0.75-1.03)		
		256/ 57/			Age >=65 yr Incidence, breast cancer, ER-PR+ Age 50-54 yrs	per 5 kg/m^2	0.97 (0.82-1.14)		
						per 5 kg/m^2	0.98 (0.68-1.40)		
		37/ 31/			Age 55-59 yrs Age 60-64 yrs	per 5 kg/m^2	0.57 (0.32-1.01)		
						per 5 kg/m^2	0.84 (0.50-1.43)		
		17/ 217/			Age >=65 yr Incidence, breast cancer, ER-PR- Age 50-54 yrs	per 5 kg/m^2	0.79 (0.37-1.68)		
						per 5 kg/m^2	1.09 (0.92-1.29)		
		244/ 217/			Age 55-59 yrs Age 60-64 yrs	per 5 kg/m^2	1.00 (0.84-1.18)		
						per 5 kg/m^2	0.97 (0.81-1.16)		
		196/ 350/			Age >=65 yr Incidence, breast cancer, ER+PR+ HRT never, age 55-59 yrs	per 5 kg/m^2	0.97 (0.81-1.17)		
						per 5 kg/m^2	1.11 (0.97-1.27)		
		348/			HRT never, age 60-64yrs	per 5 kg/m^2	1.13 (1.00-1.28)		
		441/			HRT never, age >=65yrs	per 5 kg/m^2	1.38 (1.25-1.52)		
		135/			Incidence, breast	per 5 kg/m^2	0.91 (0.72-1.15)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					cancer ER+/PR-, HRT never, age 55-59 yrs				
		118/			HRT never, age 60-64yrs	per 5 kg/m^2	0.96 (0.76-1.21)		
		138/			HRT never, age >=65yrs	per 5 kg/m^2	1.02 (0.83-1.25)		
		16/			Incidence, breast cancer ER-/PR+, HRT never, age 55-59 yrs	per 5 kg/m^2	0.62 (0.26-1.49)		
		10/			HRT never, age 60-64yrs	per 5 kg/m^2	0.63 (0.24-1.67)		
		8/			HRT never, age >=65yrs	per 5 kg/m^2	1.06 (0.37-3.03)		
		95/			Incidence, breast cancer ER-/PR-, HRT never, age 55-59 yrs	per 5 kg/m^2	1.19 (0.93-1.54)		
		90/			HRT never, age 60-64yrs	per 5 kg/m^2	1.09 (0.85-1.40)		
		105/			HRT never, age >=65yrs	per 5 kg/m^2	1.11 (0.88-1.39)		
		765/			Incidence, breast cancer ER+/PR+, Never HRT users	≥25.9 vs ≤22.5 kg/m^2	1.90 (1.53-2.35)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
						per 5 kg/m^2	1.28 (1.18-1.38)		
		225/			Past HRT users	≥25.9 vs ≤22.5 kg/m^2	1.89 (1.29-2.77)		
						per 5 kg/m^2	1.47 (1.26-1.72)		
		808/			Current HRT users	≥25.9 vs ≤22.5 kg/m^2	0.95 (0.78-1.15)		
						per 5 kg/m^2	1.01 (0.91-1.12)		
		224/			Incidence, breast cancer ER-/PR-, Never HRT users	≥25.9 vs ≤22.5 kg/m^2	1.59 (1.08-2.34)		
						per 5 kg/m^2	1.12 (0.96-1.31)		
		117/			Past HRT users	≥25.9 vs ≤22.5 kg/m^2	0.76 (0.37-1.56)		
						per 5 kg/m^2	0.82 (0.58-1.16)		
		193/			HRT current users	≥25.9 vs ≤22.5 kg/m^2	0.77 (0.52-1.14)		
						per 5 kg/m^2	0.80 (0.64-1.01)		
Sczaniecka, 2012 BRE80434 USA	VITAL, Prospective Cohort, Age: 50-76 years, W, Postmenopausal	741/ 30 252 6 years	Seer registry	Self-reported	Incidence, invasive breast cancer	≥30 vs ≤25 kg/m^2	1.13 (0.96-1.34) Ptrend:0.070	Age	
White, 2012 BRE80396	MEC, Prospective	3 080/ 82 971	Cancer registry and national	Self-reported compared with	Incidence, breast cancer	≥30 vs 20-24.9 kg/m^2	1.38 (1.24-1.53) Ptrend:0.0001	Age, age at first child birth, age	Excluded, overlapped with

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Hawai, California	Cohort, Age: 45-75 years, Postmenopausal	9 years	death Index	the driving license				at menarche, age at menopause, alcohol Intake, energy, family history of breast cancer, height, HRT use, number of childbirths, physical activity, smoking status, type of menopause	Bandera, 2015
						per 5 kg/m^2	1.11 (1.07-1.15)		
		465/			Latina	≥30 vs 20-24.9 kg/m^2	1.27 (0.99-1.61) Ptrend:0.11		Included, combined with other racial/ethnicity groups using a random effect model
						per 5 kg/m^2	1.04 (0.95-1.14)		
		835/			White	≥30 vs 20-24.9 kg/m^2	1.33 (1.10-1.62) Ptrend:0.018		Included, combined with other racial/ethnicity groups using a random effect model
						per 5 kg/m^2	1.06 (1.00-1.14)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		921/			Japanese	≥30 vs 20-24.9 kg/m^2	1.59 (1.24-2.05) Ptrend:0.001		Included, combined with other racial/ethnicity groups using a random effect model
						per 5 kg/m^2	1.25 (1.15-1.36)		
		598/			African American	≥30 vs 20-24.9 kg/m^2	1.21 (0.97-1.50) Ptrend:0.068		Excluded, overlapped with Bandera, 2015
						per 5 kg/m^2	1.08 (1.01-1.16)		
		261/			Native HawaIIan	≥30 vs 20-24.9 kg/m^2	1.82 (1.31-2.54) Ptrend:0.001		Included, combined with other racial/ethnicity groups using a random effect model
						per 5 kg/m^2	1.15 (1.04-1.27)		
		1 308/			HRT current users	≥30 vs 20-24.9 kg/m^2	1.14 (0.97-1.35) Ptrend:0.18		
		546/			HRT former users	≥30 vs 20-24.9 kg/m^2	1.60 (1.27-2.01) Ptrend:0.0001		
		1 104/			HRT non-users	≥30 vs 20-24.9 kg/m^2	1.60 (1.36-1.87) Ptrend:0.0001		
		947/			Incidence, advanced breast cancer	≥30 vs 20-24.9 kg/m^2	1.82 (1.53-2.17) Ptrend:0.001		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		2 133/			Incidence, localized breast cancer	≥30 vs 20-24.9 kg/m^2	1.22 (1.08-1.38) Ptrend:0.0008		
Bessonova, 2011 BRE80306 USA	CTS, Prospective Cohort, Age: 53 years, W, teachers	159/ 115 1 322 634 person-years	Teacher's retirement system	Self-reported	Mortality, breast cancer, HRT ever	≥30 vs 18.5-24.9 kg/m^2	1.42 (1.16-1.75)	Age, alcohol consumption, calories derived from fat, HRT use, morbidity, physical activity, smoking, weight change	
		63/			HRT never	≥30 vs 18.5-24.9 kg/m^2	2.27 (0.97-5.29)		
Grenier, 2011 BRE80337 Canada	Manitoba Cancer Registry Study, Prospective Cohort, Age: 50- years, W, Postmenopausal	484/ 37 860 5.4 years	Cancer registry	Measured	Incidence, breast cancer ER+	per 5.26 kg/m^2	1.02 (1.00-1.04)	Age, age, lumbar spine bone mass density	
Phipps, 2011 BRE80343 USA	WHI, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	2 592/ 155 723 7.9 years	Mail or telephone questionnaires verified by trained physician adjudicators	Measured	Incidence, breast cancer ER+	≥31.05 vs ≤23.75 kg/m^2	1.39 (1.22-1.58) Ptrend:<0.01	Age, educational level, family history of breast cancer, Income, mammography, mammography, race, recreational activity	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
						≥30 vs ≤24.9 kg/m^2	1.35 (1.20-1.51) Ptrend:<0.01		
		1 427/				≥24.15 vs ≤20.83 kg/m^2	0.79 (0.64-0.97) Ptrend:0.01	BMI	
		1 116/			HRT never	≥30 vs ≤25 kg/m^2	1.59 (1.33-1.89) Ptrend:<0.01		
						≥31.05 vs ≤23.75 kg/m^2	1.71 (1.39-2.10) Ptrend:<0.01		
		155/			Incidence, triple negative breast cancer, HRT never	≥30 vs ≤25 kg/m^2	1.47 (0.91-2.38) Ptrend:0.12		
						≥31.05 vs ≤23.75 kg/m^2	1.50 (0.85-2.67) Ptrend:0.11		
		306/				≥30 vs ≤24.9 kg/m^2	1.37 (0.98-1.93) Ptrend:0.06		
						≥31.05 vs ≤23.75 kg/m^2	1.35 (0.92-1.99) Ptrend:0.07		
		177/				≥24.15 vs ≤20.83 kg/m^2	1.03 (0.57-1.87) Ptrend:0.77		
Schonfeld, 2011 USA	Four NCI cohorts, Pooled study (NIH-AAPR; BCDDP; PLCO; USRT) W Caucasian	9 792/ 236 911 Mean age 60.8 years 1562 /32 641	Record linkage to cancer registries and death registry; self-report with or without verification by medical records	Self-reported	Incidence, breast cancer Postmenopausal Nulliparous women	≥30 vs <25 kg/m^2	1.10 (0.95-1.27)	Birth year, calendar year of entry, OC use, study	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		4982 /139 255			Parous women aged <25 years at first birth		1.22 (1.13-1.32)	Birth year, calendar year of entry, OC use, study, live births	
		3000 /65 015			Parous women aged ≥25 years at first birth		1.11 (1.00-1.24)		
Suzuki, 2011b BRE80318 Japan	JPHC I and II, Prospective Cohort, Age: 40-69 years	232/ 41 594 14 years	Hospital records + cancer registry	Self-reported	Incidence, breast cancer, postmenopausal	≥24 vs 20-23.9 kg/m^2	1.23 (0.93-1.63) Ptrend:0.008	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, BMI, leisure time physical activity, parity, smoking, total energy, total energy, total energy	
		167/			HRT never	≥24 vs 20-24 kg/m^2	1.31 (0.95-1.82) Ptrend:0.006		
						per 5 kg/m^3	1.38 (1.10-1.72)		
		65/			HRT ever	≥24 vs 20-24 kg/m^2	1.19 (0.68-2.07) Ptrend:0.85		
						per 5 kg/m^3	1.04 (0.69-1.56)		
		64/			Incidence, postmenopausal breast cancer,	≥24 vs 20-24 kg/m^2	1.19 (0.67-2.13) Ptrend:0.59		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					BMI at 20y < 20				
		168/			BMI 20y >=20	≥24 vs 20-24 kg/m^2	1.22 (0.89-1.69) Ptrend:0.016		
Gaudet, 2010 BRE80339 USA	Columbia, MO cohort, Nested Case Control, W, Postmenopausal	229/ 227 controls 25 years	Histology	Self-reported	Incidence, breast cancer	≥30 vs ≤25 kg/m^2	0.77 (0.47-1.28)	Age, time of blood collection	
Torio, 2010 BRE80277 USA	CLUE II, Prospective Cohort, Age: 63 years, W, Postmenopausal	172/ 5 642	Cancer registry	Self-reported	Incidence, invasive breast cancer, complete data available	per 1 kg/m^2	1.02 (0.99-1.06)	Age, age at first child birth, breastfeeding, educational level, HRT use, parity, social class	
Borgquist, 2009 BRE80214 Sweden	MDCS, Prospective Cohort, Age: 61 years, W, Postmenopausal	231/ 9 685 10.3 years	Cancer registry	Measured	Incidence, breast cancer, peri/postmenopausal	≥28 vs ≤22.9 kg/m^2	1.53 (1.05-2.24) Ptrend:<0.01	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, educational level, marital status, occupation, oophorectomy/hysterectomy, oral contraceptive use, parity,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								smoking habits	
		162/			Incidence, ductal carcinomas, peri/postmenopausal	≥28 vs ≤22.9 kg/m^2	1.68 (1.06-2.68) Ptrend:0.02		
		45/			Incidence, lobular carcinoma, peri/postmenopausal	≥28 vs ≤22.9 kg/m^2	1.88 (0.83-4.26) Ptrend:0.04		
		58/			Incidence, grade 1 breast cancer, peri/postmenopausal	≥28 vs ≤22.9 kg/m^2	0.95 (0.44-2.06) Ptrend:0.97		
		112/			Incidence, grade 2 breast cancer, peri/postmenopausal	≥28 vs ≤22.9 kg/m^2	1.97 (1.15-3.37) Ptrend:<0.01		
		63/			Incidence, grade 3 breast cancer, peri/postmenopausal	≥28 vs ≤22.9 kg/m^2	1.34 (0.62-2.01) Ptrend:0.29		
		154/			Incidence, breast cancer ki67 <=10%, peri/postmenopausal	≥28 vs ≤22.9 kg/m^2	1.60 (1.01-2.54) Ptrend:0.03		
		59/			Incidence, breast cancer ki67	≥28 vs ≤22.9 kg/m^2	1.36 (0.63-2.93) Ptrend:0.24		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					>10%, peri/postmenopausal				
					Incidence, breast cancer HER-2 -, peri/postmenopausal	≥28 vs ≤22.9 kg/m^2	1.53 (0.99-2.36) Ptrend:0.03		
		24/			Incidence, breast cancer HER-2 +, peri/postmenopausal	≥28 vs ≤22.9 kg/m^2	1.62 (0.48-5.42) Ptrend:0.34		
		26/			Incidence, breast cancer ERα-, peri/postmenopausal	≥28 vs ≤22.9 kg/m^2	1.01 (0.30-3.42) Ptrend:0.86		
		194/			Incidence, breast cancer ERα+, peri/postmenopausal	≥28 vs ≤22.9 kg/m^2	1.63 (1.08-2.47) Ptrend:0.01		
		90/				≥28 vs ≤22.9 kg/m^2	1.22 (0.68-2.18)		
		98/				≥28 vs ≤22.9 kg/m^2	2.10 (1.12-3.93)		
		93/			Incidence, breast cancer ERβ-, peri/postmenopausal	≥28 vs ≤22.9 kg/m^2	2.17 (1.16-4.06) Ptrend:<0.01		
		83/			Incidence, breast cancer ERβ+, peri/postmenopausal	≥28 vs ≤22.9 kg/m^2	1.15 (0.63-2.07) Ptrend:0.62		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		108/			Incidence, breast cancer PR-, peri/postmenopausal	≥28 vs ≤22.9 kg/m^2	1.12 (0.66-1.92) Ptrend:0.51		
		100/			Incidence, breast cancer PR+, peri/postmenopausal	≥28 vs ≤22.9 kg/m^2	2.19 (1.18-4.07) Ptrend:<0.01		
		165/			Incidence, breast cancer cyclind1 <=10%, peri/postmenopausal	≥28 vs ≤22.9 kg/m^2	1.48 (0.94-2.35) Ptrend:0.04		
		49/			Incidence, breast cancer cyclind1 >10%, peri/postmenopausal	≥28 vs ≤22.9 kg/m^2	1.93 (0.86-4.33) Ptrend:0.10		
		81/			Incidence, breast cancer p27 <=10%, peri/postmenopausal	≥28 vs ≤22.9 kg/m^2	1.19 (0.59-2.41) Ptrend:0.47		
		130/			Incidence, breast cancer p27 >10%, peri/postmenopausal	≥28 vs ≤22.9 kg/m^2	1.79 (1.10-2.91) Ptrend:<0.01		
		80/			Incidence, breast cancer	≥28 vs ≤22.9 kg/m^2	2.21 (1.12-4.33)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					ERα+/ERβ-, peri/postmenopausal				
		73/			Incidence, breast cancer ERα+/ERβ+, peri/postmenopausal	≥28 vs ≤22.9 kg/m^2	1.28 (0.68-2.40)		
Gunter, 2009 BRE80245 USA	WHI-OS, Case Cohort, Age: 50-79 years, W, Postmenopausal	831/ 1 651 77 months	Self report verified by medical record	Measured	Incidence, breast cancer	30.0 vs 18.5 kg/m^2	1.13 (0.83-1.55) Ptrend:0.31	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, educational level, estrogen use, family history of cancer, hormonal variables, HRT use, nsaid use, ocp use, parity, physical activity, race, smoking habits	
		211/			Estrogen users	30.0 vs 18.5 kg/m^2	1.42 (0.64-3.14) Ptrend:0.97		
		224/			HRT users	30.0 vs 18.5 kg/m^2	0.41 (0.17-1.00) Ptrend:0.21		
Rod, 2009 BRE80270	CCHS, Prospective	263/ 5 054	Cancer registry	Measured wearing light	Incidence, invasive breast	≥30.1 vs 18.5-25 kg/m^2	1.50 (1.02-2.22)	Age, alcohol consumption,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Denmark	Cohort, Age: 62 years, W, Postmenopausal	20 years		clothes without shoes	cancer			BMI, educational level, height, marital status, parity, physical activity, postmenopausal hormone use, psychological distress	
Setiawan, 2009 BRE80272 USA	MEC, Prospective Cohort, Age: 45-75 years, W	1 182/ 84 427 10.4 years	Seer registry	Self-reported	Incidence, breast cancer ER+/PR+, postmenopausal	30.0 vs ≥24.9	1.53 (1.29-1.81) Ptrend:<0.001	Age, age at first child birth, age at menarche, alcohol consumption, ethnicity, family history of cancer, HRT use, menopausal status, parity, study center, year of recruitment	
		217/			Incidence, breast cancer ER+/PR-, postmenopausal	30.0 vs ≥24.9	0.98 (0.63-1.52) Ptrend:0.82		
		327/			Incidence, breast cancer ER-/PR-, postmenopausal	30.0 vs ≥24.9	0.69 (0.49-0.98) Ptrend:0.04		
Whitlock, 2009	Prospective Studies	Overall 353 124 women, mean	Death certificates,	Self-reported, or measured	Mortality, breast cancer,				

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Collaboration (PSC), Pooled study*, W,	age: 46 years, 8 years of follow-up 420/	medical records and autopsy findings		Women ≥60 years, excluding first 5 years of follow-up	Per 5 kg/m^2 In range of 15-50 kg/m^2	1.15 (1.02-1.31)	Age at risk, study, smoking status	
		192/				Per 5 kg/m^2 In range of 15-25 kg/m^2	1.06 (0.66-1.70)		
		228/				Per 5 kg/m^2 In range of 25-50 kg/m^2	1.11 (0.91-1.36)		
Kerlikowske, 2008 BRE80200 USA	BCSC, Prospective Cohort, Age: 40- years, W, Postmenopausal, underwent mammography screening	4 446/ 287 115	Cancer registry	Self-reported	Incidence, breast cancer, postmenopausal	≥35 vs 18.5-24.9 kg/m^2	1.30 (1.17-1.45) Ptrend:<0.001	Age, centre location, mammography, race	
						≥35 vs 18.5-24.9 kg/m^2	2.13 (1.37-3.31) Ptrend:0.001		
						≥35 vs 18.5-24.9 kg/m^2	1.42 (0.88-2.30) Ptrend:0.1		
						≥35 vs 18.5-24.9 kg/m^2	3.15 (1.82-5.44) Ptrend:<0.001		
		1 571/			Incidence, large Invasive breast cancer, postmenopausal	≥35 vs 18.5-24.9 kg/m^2	1.42 (1.19-1.69) Ptrend:<0.001		
		616/			Incidence, advanced breast cancer,	≥35 vs 18.5-24.9 kg/m^2	1.82 (1.40-2.37) Ptrend:<0.001		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					postmenopausal				
		1 004/			Incidence, high grade disease, postmenopausal	≥35 vs 18.5-24.9 kg/m^2	1.21 (0.97-1.51) Ptrend:0.10		
		2 466/			Incidence, breast cancer ER+, postmenopausal	≥35 vs 18.5-24.9 kg/m^2	1.34 (1.16-1.54) Ptrend:<0.001		
		495/			Incidence, breast cancer ER-, postmenopausal	≥35 vs 18.5-24.9 kg/m^2	0.95 (0.68-1.32) Ptrend:0.8		
		737/			Incidence, breast cancer stage 0, postmenopausal	≥35 vs 18.5-24.9 kg/m^2	1.46 (1.14-1.87) Ptrend:0.005		
		2 039/			Incidence, breast cancer stage I, postmenopausal	≥35 vs 18.5-24.9 kg/m^2	1.18 (1.00-1.38) Ptrend:0.03		
		789/			Incidence, breast cancer stage Iia, postmenopausal	≥35 vs 18.5-24.9 kg/m^2	1.13 (0.82-1.40) Ptrend:0.8		
		318/			Incidence, breast cancer stage Iib, postmenopausal	≥35 vs 18.5-24.9 kg/m^2	1.70 (1.17-2.45) Ptrend:0.003		
		298/			Incidence, breast cancer stage Iv, postmenopausal	≥35 vs 18.5-24.9 kg/m^2	1.95 (1.35-2.83) Ptrend:<0.001		
Song, 2008 BRE80198 Korea	KNHIC, Prospective Cohort, Age: 40-64	612/ 170 481 8.75 years	Cancer registry and national Insurance health database	Measured	Incidence, invasive breast cancer	≥30 vs 21-22.9 kg/m^2	1.86 (1.25-2.76)	Age, alcohol consumption, height, Income, physical	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	years, W, Postmenopausal							activity, smoking status	
						per 1 kg/m^2	1.07 (1.05-1.10)		
		322/			Follow-up for >5 yr	per 1 kg/m^2	1.08 (1.04-1.12)		
						≥30 vs 21-22.9 kg/m^2	1.64 (0.91-2.97)		
Ahn, 2007 BRE80139 USA	NIH-AARP, Prospective Cohort, Age: 50- years, W, Postmenopausal	1 162/ 99 039 4 years	Cancer registry	Self-reported	Incidence, breast cancer, current MHT users	≥40 vs 18.5-22.4	1.10 (0.64-1.88) Ptrend:0.22	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, BMI, educational level, family history of cancer, fat Intake, oophorectomy/hysterectomy, parity, physical activity, race, smoking habits	
		948/			Non MHT users	≥40 vs 18.5-22.4	2.08 (1.44-2.99) Ptrend:<0.001		
		57/			MHT nonusers & age at menarche <=10yrs	≥35 vs ≤24.9	1.43 (0.57-3.58) Ptrend:0.83	Weight	
		420/			MHT nonusers	≥35 vs ≤24.9	1.52 (1.07-2.15)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					& age at menarche 11-12y		Ptrend:<0.001		
		382/			MHT nonusers & age at menarche 13-14y	≥35 vs ≤24.9	1.97 (1.33-2.91) Ptrend:<0.001		
		75/			MHT nonusers & age at menarche >=15yrs	≥35 vs ≤24.9	3.25 (1.44-7.36) Ptrend:<0.001		
		700/			Incidence, In situ or localised breast cancer, non MHT users	≥35 vs ≤24.9	1.44 (1.09-1.91) Ptrend:0.002		
		248/			Incidence, regional or distant metastases, non MHT users	≥35 vs ≤24.9	3.05 (1.97-4.71) Ptrend:<0.001		
		201/			Incidence, breast cancer ER+/PR+, non MHT users	≥35 vs ≤24.9	2.69 (1.62-4.46) Ptrend:<0.001		
		44/			Incidence, breast cancer ER+/PR-, non MHT users	≥35 vs ≤24.9	0.75 (0.20-2.75) Ptrend:0.39		
		53/			Incidence, breast cancer ER-/PR-, non MHT users	≥35 vs ≤24.9	0.33 (0.09-1.19) Ptrend:0.06		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		189/			Incidence, breast cancer unknown ER/PR status, non MHT users	≥35 vs ≤24.9	2.08 (1.25-3.45) Ptrend:0.003		
Chlebowski, 2007 BRE80607 USA	WHI-CT and OS, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	2 391/ 147 916 5 years	Self-reported validated by pathology report	Self-reported	Incidence, breast cancer ER+, postmenopausal	≥30 vs ≤24.9 kg/m^2	1.26 (1.12-1.43)	Age at first child birth, age at menarche, age at menopause, age at screening, alcohol consumption, breast biopsies, breastfeeding, estrogen use, ethnicity, family history of breast cancer, parity, physical activity, progestin + estrogen use, smoking	
		459/			Incidence, breast cancer ER-, postmenopausal	≥30 vs ≤24.9 kg/m^2	1.21 (0.92-1.60)		
Iwasaki, 2007b BRE20027 Japan	JPHC I and II, Prospective Cohort, Age: 40-69 years, W	229/ 53 857 9.9 years	Cancer registry	Self-reported	Incidence, breast cancer, postmenopausal	≥30 vs ≤18 kg/m^2	2.28 (0.94-5.53) Ptrend:0.08	Age , age at first child, area, height, parity/pregnancies	Excluded, superseded by Wada, 2014
		65/			Incidence, breast	per 1 kg/m^2	1.08 (1.01-1.15)		Included in the

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					cancer ER+, postmenopausal				analysis by hormone receptor-defined breast cancer
		41/			Incidence, breast cancer ER-, postmenopausal	per 1 kg/m^2	0.95 (0.84-1.06)		
		46/			Incidence, breast cancer PR+, postmenopausal	per 1 kg/m^2	1.07 (0.98-1.16)		
		55/			Incidence, breast cancer PR-, postmenopausal	per 1 kg/m^2	1.01 (0.93-1.10)		
					Incidence, breast cancer ER+/PR+, postmenopausal	per 1 kg/m^2	1.10 (1.01-1.18)		
					Incidence, breast cancer ER-/PR-, postmenopausal	per 1 kg/m^2	0.98 (0.87-1.10)		
Lundqvist, 2007 BRE80002 Sweden, Finland	Sweden,Finland Co-twin study,1975, cohort analysis Prospective Cohort, Age: 44 years, W	756/ 36 490 25.2 years	Cancer registry	Measured	Incidence, breast cancer, older subjects	≥30 vs 18.5-24.9 kg/m^2	1.30 (1.00-1.70)	Age , country of birth, diabetes, educational level, physical activity , smoking habits	
						per 1 kg/m^2	1.03 (1.01-1.05)	Parity	
Palmer, 2007 BRE80122	BWHS, Prospective	454/ 59 000	Death certificate / patient records	Self-reported, validated	Incidence, breast cancer,	≥35 vs ≤24	0.78 (0.58-1.05)	Age, age at first child birth, age	Excluded, superseded by

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
USA	Cohort, Age: 21-69 years, Black women	10 years	/ self report		postmenopausal			at menarche, age at menopause, educational level, family history of cancer, parity, physical activity	Bandera, 2015
		165/			Postmenopausal and HRT nonusers	≥35 vs ≤24	1.12 (0.66-1.90)	BMI	Included in the analysis by hormone therapy use
		84/			Incidence, breast cancer ER+/PR+, postmenopausal	≥30 vs ≤24	1.66 (0.86-3.21)		Included in the analysis by hormone receptor-defined breast cancer
		36/			Incidence, breast cancer ER+/PR- or ER-/PR+, postmenopausal	≥30 vs ≤24	0.39 (0.14-1.07)		
		52/			Incidence, breast cancer ER-/PR-, postmenopausal	≥30 vs ≤24	0.88 (0.39-1.97)		
Reeves, 2007 BRE80146 UK	MWS, Prospective Cohort, Age: 50-64 years, W	637/ 1 222 630 5.4 years	National health records	Self-reported	Mortality, breast cancer, postmenopausal and HRT nonusers	per 10 kg/m^2	1.36 (1.12-1.66)	Age, alcohol consumption, geographic area, physical activity, reproductive factors, smoking habits, socio-economic status,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								time since menopause	
						≥30 vs 22.5-24.9 kg/m^2	1.49 (1.27-1.75)		
		5 629/			Incidence, invasive breast cancer, postmenopausal and HRT nonusers	per 10 kg/m^2	1.40 (1.31-1.49)		
						≥30 vs 22.5-24.9 kg/m^2	1.29 (1.22-1.36)		
		2 855/			Never smokers	per 10 units	1.41 (1.28-1.55)		
Krebs, 2006 BRE80106 USA	SOF, Prospective Cohort, Mean age: 73.5 years, Postmenopausal	350/ 9 704 11.3 years	Self report verified by medical record	Measured	Incidence, Invasive breast cancer, postmenopausal	≥29 vs ≤23	1.29 (0.92-1.81) Ptrend:0.06	Age , age at menarche, age at menopause, anthropometry, benign breast disease, educational level, family history, HRT use, parity/pregnancies, physical activity , smoking habits	
						≥30 vs ≤24.9	1.55 (1.13-2.13)		
					Age >=70 years	≥29 vs ≤23	1.33 (0.90-1.98)		
Li, 2006 BRE80166 China	SWHS, Prospective Cohort,	211/ 73 410 5.66 years	Medical records	Measured by trained Interviewers	Incidence, breast cancer, postmenopausal	≥25.21 vs ≤22.34	1.77 (1.23-2.56) Ptrend:0.001	Age, age at first child birth, age at menopause,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Age: 40-70 years, W							breastfeeding, educational level, energy Intake, family history, family history of cancer	
Suzuki, 2006 BRE80116 Sweden	SMC, Prospective Cohort, Age: -70 years, W, Postmenopausal	1 284/ 51 823 8.3 years	Cancer registry	Self-reported	Incidence, Invasive breast cancer, postmenopausal	≥30 vs 18.5-24.9	1.28 (1.07-1.52) Ptrend:0.0046	Age at first child, age at menarche, age at menopause, age-underlying cox models, alcohol, benign breast disease, educational level, energy Intake , family history, food, height, HRT use, menopausal status, nutrients, OC use, parity/pregnancies	Excluded, superseded by van den Brandt, 2000
		528/			Postmenopausal and HRT nonusers	≥30 vs ≤24.9	1.38 (1.07-1.77) Ptrend:0.009		Excluded, superseded by van den Brandt, 2000
		446/			Postmenopausal and HRT users	≥30 vs ≤24.9	1.04 (0.75-1.45) Ptrend:0.55		Excluded, superseded by van den Brandt, 2000

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		299/			Incidence, breast cancer ER+/PR+, postmenopausal and HRT nonusers	≥30 vs ≤24.9	1.90 (1.38-2.61) Ptrend:<0.0001		Included in the analysis by hormone receptor-defined breast cancer
		243/			Postmenopausal and HRT users	≥30 vs ≤24.9	1.18 (0.78-1.81) Ptrend:0.32		
		716/			Postmenopausal	≥30 vs 18.5-24.9	1.67 (1.34-2.07) Ptrend:<0.0001		
		102/			Incidence, breast cancer ER+/PR-, postmenopausal and HRT nonusers	≥30 vs ≤24.9	0.92 (0.50-1.69) Ptrend:0.61		Included in the analysis by hormone receptor-defined breast cancer
		123/			Postmenopausal and HRT users	≥30 vs ≤24.9	0.59 (0.27-1.29) Ptrend:0.14	Nutritional factors	
		279/			Postmenopausal	≥30 vs 18.5-24.9	0.76 (0.49-1.17) Ptrend:.096		
		66/			Incidence, breast cancer ER-/PR-, postmenopausal and HRT nonusers	≥30 vs ≤24.9	0.43 (0.15-1.23) Ptrend:0.15		Included in the analysis by hormone receptor-defined breast cancer
		34/			Postmenopausal and HRT users	≥30 vs ≤24.9	0.84 (0.24-2.87) Ptrend:0.77		
		143/			Postmenopausal	≥30 vs 18.5-24.9	0.52 (0.26-1.04) Ptrend:0.099		
Feigelson, 2004	CPS II,	1 182/	Medical records	Self-reported	Incidence,	≥35 vs ≤21	1.61 (1.22-2.12)	Age , age at first	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
BRE02721 USA	Prospective Cohort, Age: 50-74 years, W, Postmenopausal	62 756 9 years	+ self-reported +death certificate		invasive breast cancer, HRT - no	kg/m^2	Ptrend:0.0001	child, age at menarche, age at menopause, alcohol, benign breast disease, educational level, ethnicity, family history, height, mammography, OC use, parity/pregnancies, physical activity	
		752/			HRT - yes	≥35 vs ≤21 kg/m^2	1.09 (0.70-1.69) Ptrend:0.12		
Lahmann, 2004a BRE15804 Europe	EPIC, Prospective Cohort, Age: 18-80 years, W	911/ 176 886 4.7 years	Partially histological - over 80%	Measurements performed by trained personnel	Incidence, breast cancer, HRT - no	per 1 unit	1.03 (1.01-1.05)	Age , age at first child, age at menarche, alcohol, educational level, parity/pregnancies, smoking habits	Included in the analysis by MHT use
						≥30 vs ≤24.9 kg/m^2	1.31 (1.08-1.59) Ptrend:0.0012	Recruitment center	
						≥28.8 vs ≤21.5 kg/m^2	1.36 (1.06-1.75) Ptrend:0.002		
		494/			HRT - yes	per 1 unit	0.99 (0.96-1.01)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
						≥30 vs ≤24.9 kg/m^2	0.66 (0.45-0.98) Ptrend:0.064		
						≥28.8 vs ≤21.5 kg/m^2	0.71 (0.50-1.01) Ptrend:0.073		
Morimoto, 2002 BRE20457	WHI-OS, Prospective Cohort, Age: 50-79 years, Postmenopausal	704/ 85 917 34.8 months	Medical records + self-reported	Measurements performed by clinical staff	Incidence, breast cancer, HRT - yes	≥31.11 vs ≤22.6 kg/m^2	0.96 (0.73-1.27) Ptrend:0.75	Age , age at first child, age at menarche, age at menopause, alcohol, educational level, energy Intake , ethnicity, family history, leisure time physical activity, parity/pregnancies, smoking habits	Included in the analysis by MHT use
		315/			HRT - no	≥31.11 vs ≤22.6 kg/m^2	2.52 (1.62-3.93) Ptrend:0.001		
Petrelli, 2002 BRE20653 USA	CPS II, Prospective Cohort, Age: 30- years, W	2 852/ 424 168 14 years	Partially histological - over 80%	Self-reported	Mortality, breast cancer, postmenopausal	≥30 vs ≤24.99 kg/m^2	1.60 (1.42-1.79) Ptrend:<0.0001	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, educational level, ethnicity, family history, height, HRT	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								use, menopausal status, OC use, parity/pregnancies, physical activity , smoking habits	
						≥40 vs 18.5-20.49 kg/m^2	3.08 (2.09-4.51) Ptrend:<0.0001		
Sellers, 2002 BRE20892 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	1 368/ 37 105 13 years	Partially histological - over 80%	Self-reported	Incidence, breast cancer, family history breast cancer - no and postmenopausal	≥30.7 vs ≤22.89 kg/m^2	1.93 (1.57-2.36) Ptrend:0.001	Age at first child, age at menarche, age at menopause, alcohol, BMI, body weight, educational level, family history, HRT use, OC use, parity/pregnancies, physical activity , smoking habits, whr	Excluded, superseded by van den Brandt, 2000
		282/			Family history breast cancer - yes and postmenopausal	≥30.7 vs ≤22.89 kg/m^2	1.47 (0.99-2.17) Ptrend:0.05		
		1 043/			Incidence, breast cancer ER+, postmenopausal	≥30.7 vs ≤22.89 kg/m^2	2.00 (1.58-2.53)		Included in the analysis by hormone receptor-defined
		232/			Incidence, breast	≥30.7 vs ≤22.89	1.38 (0.78-2.43)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					cancer ER-, postmenopausal	kg/m^2			breast cancer
		993/			Incidence, breast cancer PR+, postmenopausal	≥30.7 vs ≤22.89 kg/m^2	2.24 (1.72-2.91)		
		362/			Incidence, breast cancer PR-, postmenopausal	≥30.7 vs ≤22.89 kg/m^2	0.96 (0.62-1.49)		
Manjer, 2001b BRE17790 Sweden	MPP, Prospective Cohort, Age: 55 years, W	157/ 9 738 13.1 years	Partially histological - over 80%	Measured by trained personnel	Incidence, Invasive breast cancer, postmenopausal	≥26.55 vs ≤21.98 kg/m^2	0.79 (0.51-1.23) Ptrend:0.46	Age	
van den Brandt, 2000 North America and Europe	The Pooling Project, Pooled study of 7 cohorts*, W (*AHS; CNBSS; IWHS; NLCS; NYSC; NHS(a); NHS(b); SMC)	3 208/	Follow-up questionnaires and inspection of medical records and/or tumour registry linkage	Self-reported	Incidence, postmenopausal breast cancer	≥33 vs <21 kg/m^2	1.27 (1.03-1.55) Ptrend:0.001	Age at menarche, parity, age at birth of first child, postmenopausal hormone use, oral contraceptive use, history of benign breast disease, maternal history of breast cancer, history of breast cancer in a sister, smoking status,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								education, fat intake, fibre intake, energy intake, alcohol intake	
						per 4 kg/m^2	1.07 (1.02-1.11)		
	ANS	87/				per 4 kg/m^2	1.21 (0.98-1.50)		
	CNBSS (RCT of screening for breast cancer)	242/				per 4 kg/m^2	1.11 (0.91-1.36)		
	IWHS	643/				per 4 kg/m^2	1.11 (1.04-1.19)		
	NLCS	420/				per 4 kg/m^2	0.99 (0.86-1.13)		
	NYSC	358/				per 4 kg/m^2	1.05 (0.95-1.16)		
	NHS(a)	571/				per 4 kg/m^2	1.01 (0.93-1.10)		
	NHS(b)	613/				per 4 kg/m^2	1.04 (0.97-1.12)		
	SMC (mammography screening cohort)	274/				per 4 kg/m^2	1.15 (1.01-1.32)		
					HRT never users	per 4 kg/m^2	1.09 (1.04-1.14)		
					HRT ever users	per 4 kg/m^2	1.04 (0.92-1.18)		
Sonnenschein, 1999 BRE11604 USA	NYUWHS, Prospective Cohort, Age: 35-65	150/ 8 416 6.6 years	All histology	Measured	Incidence, breast cancer, postmenopausal	≥27.47 vs ≤22.31 kg/m^2	2.36 (1.43-3.91)	Age , age at first child, age at menarche, breast biopsies, family	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	years, W, Participants identified through breast cancer screening centres							history	
Galanis, 1998 BRE03058 hawaii	Hawaii State Department of Health, 1975, Prospective Cohort, Age: 43 years, W	292/ 17 628 14.9 years	Partially histological - over 80%	Self-reported	Incidence, invasive breast cancer, postmenopausal	≥26.1 vs ≤19.5 kg/m^2	1.50 (1.00-2.30) Ptrend:0.01	Age , alcohol, educational level, ethnicity	
Kaaks, 1998 BRE04522 Netherlands	DOM-project Utrecht, Prospective Cohort, Age: 39-73 years, W, Mammography screening study	76/ 11 480 7.1 years	Partially histological – over 80%	Self-reported	Incidence, breast cancer, postmenopausal	≥27.15 vs ≤22.5 kg/m^2	0.81 (0.43-1.51) Ptrend:0.59	Age , age at first child, age at menarche, menopausal status, parity/pregnancies	
Tulinius, 1997 BRE12565 Iceland	Reykjavik Study, 1968, Prospective Cohort, Age: 45-59 years, W	343/ 11 580 27 years	Partially histological - over 80%	Measured	Incidence, breast cancer, postmenopausal	per 1 kg/m^2	1.02 (1.00-1.05)	Age	
Potter, 1995	IWHS,	414/	National cancer	Self-reported	Incidence, breast	≥30 vs ≤29.9	1.38 (1.12-1.71)	Age	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
BRE80164 USA	Prospective Cohort, Age: 55-69 years, W, Postmenopausal	37 105 7 years	registers		cancer ER+/PR+, postmenopausal				
		99/			Incidence, breast cancer ER+/PR-, postmenopausal	≥30 vs ≤29.9	0.49 (0.27-0.88)		
		17/			Incidence, breast cancer ER-/PR+, postmenopausal	≥30 vs ≤29.9	2.88 (1.11-7.46)		
		80/			Incidence, breast cancer ER-/PR-, postmenopausal	≥30 vs ≤29.9	0.75 (0.43-1.31)		
		329/			Incidence, breast cancer unknown ER/PR status, postmenopausal	≥30 vs ≤29.9	1.26 (0.99-1.60)		
Tornberg, 1994 BRE12417 Sweden	Sweden, 1971, Prospective Cohort, Age: 25-75 years, W	1 093/ 47 003 25 years	Partially histological - over 80%	Measured	Incidence, breast cancer, postmenopausal	≥28 vs ≤21.9 kg/m^2	1.13 Ptrend:0.021	Age	
						per 2 kg/m^2	1.05 (1.01-1.10)		
De Stavola, 1993 BRE02122 UK (One publication, two studies)	Guernsey G2 and G3, Prospective Cohort, W	95/ 4 528 15 years	Partially histological - over 80%	Measurements performed by trained personnel	Incidence, breast cancer, postmenopausal	≥26.5 vs ≤21.9 kg/m^2	1.10 (0.60-2.20) Ptrend:0.74	Age	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Vatten, 1990c BRE12826 Norway	NNHSS, 1974, Prospective Cohort, Age: 35-51 years, W	99/ 23 826 11.9 years	Partially histological - over 80%	Measured	Incidence, breast cancer, postmenopausal	≥2.68 vs ≤2.19 g/cm^2	0.73 (0.41-1.29) Ptrend:0.52	Age	

Table 536 BMI and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Harding, 2015 Australia and New Zealand	ANZDCC, Pooled study of 11 cohorts* W	1 323/ 38 724 Mean age: 54.3 years 16 years of follow-up	Cancer database and National death index	Measured	Incidence, breast cancer, diagnosed ≥ 50 years	Per 1 SD	1.06 (1.01-1.12)	Smoking status, education, study cohort, age as timescale in model	Excluded, insufficient data
		901/			Never smokers	Per 1 SD	1.07 (1.01-1.15)		
		422/			Ever smokers	Per 1 SD	1.04 (0.94-1.15)		
*Current analysis used data from 10 cohorts - Australian National Blood Pressure Trial; Australian Longitudinal Study of Aging; Australian Diabetes Obesity and Lifestyle Study; Crossroads Undiagnosed Study; Fremantle Diabetes Study; Geelong Osteoporosis Study; Melbourne Collaborative Cohort Study; North West Adelaide Health Study; Perth Risk Factor Prevalence Cohort Study 1989; Perth Risk Factor Prevalence Cohort Study 1994									
Heo, 2015 BRE80581 USA	Women's Health Initiative, Prospective	6 798/ 144 701 12 years	Self report verified by medical record	Measured	Incidence, breast cancer	≥30 vs ≤29.9 kg/m^2	1.25 (1.18-1.32)	Age, age at first child birth, age at menopause,	Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Cohort, Age: 50-79 years, W, Postmenopausal		and pathology report					alcohol, breast biopsies, educational level, ethnicity, family history of breast cancer In first degree relatives, height, hormone use, pack years of smoking, parity, randomisation	
					HRT ever	≥33 vs ≤32.9 kg/m^2	1.19 (1.10-1.29)		
					HRT never	≥28 vs ≤27.9 kg/m^2	1.34 (1.23-1.45)		
McKenzie, 2015 BRE80534 Europe	EPIC, Prospective Cohort, Age: 25-70 years, W, Postmenopausal	7 756/ 242 918 10.9 years	Record linkage with population-based In 6 countries, Insurance, cancer records & self-report verified by med.records In the rest	Measured or self-reported	Incidence, Invasive breast cancer, postmenopausal	≤21.9 vs ≥29 kg/m^2	0.81 (0.74-0.87) Ptrend:<0.001	Age, age at first child, age at menarche, alcohol, breastfeeding, centre location, combined food score Index, educational level, height, HRT use, non-alcohol energy, OC use, physical activity Index, smoking	Excluded, exposure was on obesity guideline adherence, superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Zhang X, 2015 BRE80578 USA	NHS, Prospective Cohort, Age: 30-55 years, W	5 953/ 103 577 26 years	Self report verified by medical record	Self-reported In questionnaire	Incidence, Invasive breast cancer, postmenopausal women	≥30 vs ≤22.9 kg/m^2	1.47 (1.35-1.59) Ptrend:<0.0001	Age at menarche, age at menopause, alcohol Intake, BMI at age 18 years, family history of breast cancer, height, history of benign breast disease, parity and age at first birth, postmenopausal hormone use	Superseded publication
						per 5 kg/m^2	1.16 (1.13-1.20)		
		1 701/			Incidence, breast cancer AR+, postmenopausal women	≥30 vs ≤22.9 kg/m^2	1.17 (1.00-1.37) Ptrend:0.12		
						per 5 kg/m^2	1.07 (1.01-1.13)		
		497/			Incidence, breast cancer AR-, postmenopausal women	≥30 vs ≤22.9 kg/m^2	1.64 (1.21-2.24) Ptrend:0.09		
						per 5 kg/m^2	1.16 (1.05-1.29)		
		1 163/			Incidence, breast cancer ER+PR+AR+, postmenopausal women	per 5 kg/m^2	1.15 (1.08-1.23)		
		181/			Incidence, breast cancer	per 5 kg/m^2	1.23 (1.04-1.45)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					ER+PR+AR-, postmenopausal women				
		260/			Incidence, breast cancer ER+PR-AR+, postmenopausal women	per 5 kg/m^2	0.88 (0.75-1.03)		
		75/			Incidence, breast cancer ER+PR-AR-, postmenopausal women	per 5 kg/m^2	0.92 (0.70-1.22)		
		197/			Incidence, breast cancer ER-PR-AR+, postmenopausal women	per 5 kg/m^2	1.08 (0.92-1.28)		
		205/			Incidence, breast cancer ER-PR-AR-, postmenopausal women	per 5 kg/m^2	1.19 (1.01-1.39)		
Brinton, 2014 BRE80579 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W, Postmenopausal	7 158/ 190 872 9.3 years	Cancer registry	Self-reported	Incidence, Invasive breast cancer	35 vs 18.5 kg/m^2	1.39 (1.27-1.52) Ptrend:<0.0001	Age at menarche, alcohol Intake, breast biopsies, educational level, family history of breast cancer In first	Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								degree relatives, marital status, menopausal age, menopausal status, parity and age at first birth, postmenopausal hormone use, race	
		793/			Age of follow-up 50-59 years	35 vs 18.5 kg/m^2	1.24 (0.97-1.58) Ptrend:0.14		
		3 743/			Age of follow-up 60-69 years	35 vs 18.5 kg/m^2	1.39 (1.24-1.57) Ptrend:<0.0001		
		2 622/			Age of follow-up >=70 years	35 vs 18.5 kg/m^2	1.46 (1.26-1.70) Ptrend:<0.0001		
		1 604/			Incidence, breast cancer ER+, age of follow-up 60-69 years	35 vs 18.5 kg/m^2	1.33 (1.10-1.60) Ptrend:<0.0001		
		306/			Age of follow-up 50-59 years	35 vs 18.5 kg/m^2	1.06 (0.71-1.57) Ptrend:0.78		
		1 126/			Age of follow-up >=70 years	35 vs 18.5 kg/m^2	1.46 (1.15-1.84) Ptrend:<0.0001		
		297/			Incidence, breast cancer ER-, age of follow-up 60-69 years	35 vs 18.5 kg/m^2	1.27 (0.83-1.95) Ptrend:0.27		
		94/			Age of follow-up 50-59 years	35 vs 18.5 kg/m^2	1.47 (0.75-2.89) Ptrend:0.44		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		208/			Age of follow-up >=70 years	35 vs 18.5 kg/m^2	1.41 (0.83-2.41) Ptrend:0.08		
		2 607/			Incidence, ductal carcinomas, age of follow-up 60-69 years	35 vs 18.5 kg/m^2	1.47 (1.28-1.70) Ptrend:<0.0001		
		585/			Age of follow-up 50-59 years	35 vs 18.5 kg/m^2	1.31 (0.99-1.73) Ptrend:0.08		
		1 773/			Age of follow-up >=70 years	35 vs 18.5 kg/m^2	1.43 (1.19-1.72) Ptrend:<0.0001		
		386/			Incidence, lobular carcinoma, age of follow-up 60-69 years	35 vs 18.5 kg/m^2	1.18 (0.79-1.77) Ptrend:0.12		
		66/			Age of follow-up 50-59 years	35 vs 18.5 kg/m^2	1.40 (0.62-3.14) Ptrend:0.73		
		323/			Age of follow-up >=70 years	35 vs 18.5 kg/m^2	1.22 (0.76-1.95) Ptrend:0.04		
Gaudet, 2013 BRE80493 USA	CPS II, Nested Case Control, Age: 50-74 years, W, Postmenopausal	273/ 267 controls	Self report verified by medical record	Self-reported	Incidence, breast cancer, HRT - no	≥30 vs ≤24.9 kg/m^2	1.43 (0.88-2.32) Ptrend:0.21	Age, age at first child birth, age at menarche, age at menopause, alcohol, educational level, family history of breast cancer, history of breast cyst,	Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								mammography, parity, smoking	
						per 1 kg/m^2	1.02 (0.99-1.06)		
Hastert, 2013 BRE80481 USA	VITAL, Prospective Cohort, Age: 50-76 years, W, Postmenopausal	899/ 30 797 6.7 years	Seer registry	Self-reported	Incidence, breast cancer	met vs not met	0.85 (0.74-0.98)	Age, age at first child birth, age at menarche, age at menopause, educational level, energy Intake, family history of breast cancer, mammography, other factors , race, years of HRT use	Excluded, exposure was on obesity guideline adherence, superseded publication
Loft, 2013 BRE80484 Denmark	DCH, Nested Case Control, Age: 50-64 years, W, Postmenopausal	336/ 336 controls 7 years	Cancer registry	Health professionals obtained anthropometrical measurements and BMI	Incidence, breast cancer	per 5 kg/m^2	1.09 (0.90-1.32)	Age at first child birth, alcohol, education years, HRT use, number of childbirths, parity, smoking	Superseded publication
Nyante, 2013 BRE80496 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W, Postmenopausal	5 137/ 192 076 9.6 years	Cancer registry	Self-reported	Incidence, ductal carcinomas	≥30 vs 18.5-24.9 kg/m^2	1.29 (1.19-1.39) Ptrend:<0.01	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, breast biopsies, educational level, family	Results by specific breast cancer subtype, not analysed

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								history of breast cancer, height, HRT use, marital status, OC use, parity, race, type of menopause, vigorous activity, weight	
		2 113/			Mht never	≥30 vs 18.5-24.9 kg/m^2	1.46 (1.30-1.65) Ptrend:<0.01		
		234/			Incidence, ductal-lobular breast cancer, mht never	≥30 vs 18.5-24.9 kg/m^2	1.28 (0.88-1.86) Ptrend:0.13		
		617/				≥30 vs 18.5-24.9 kg/m^2	1.18 (0.94-1.50) Ptrend:0.03		
		83/			Incidence, mucinous breast cancer, MHT never	≥30 vs 18.5-24.9 kg/m^2	2.60 (1.44-4.71) Ptrend:<0.01		
		204/				≥30 vs 18.5-24.9 kg/m^2	1.74 (1.20-2.52) Ptrend:<0.01		
		30/			Incidence, tubular breast cancer, MHT never	≥30 vs 18.5-24.9 kg/m^2	1.35 (0.48-3.80) Ptrend:0.74		
		130/				≥30 vs 18.5-24.9 kg/m^2	0.72 (0.41-1.26) Ptrend:0.29		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		340/			Incidence, lobular carcinoma, MHT never	≥30 vs 18.5-24.9 kg/m^2	1.49 (1.11-2.01) Ptrend:<0.01		
		805/				≥30 vs 18.5-24.9 kg/m^2	1.23 (1.01-1.51) Ptrend:0.01		
Poynter, 2013 BRE80453 USA	IWHS, Prospective Cohort, Age: 55-71 years, Postmenopausal	1 593/ 37 459 22 years	Health registers	Self-reported	Incidence, breast cancer, age <75y	≥30 vs <25 kg/m^2	1.35 (1.17-1.55) Ptrend:<0.0001	Age at baseline, age at first child birth, age at menarche, age at menopause, alcohol, number of childbirths, physical activity, smoking, waist hip ratio	Superseded publication, subgroup by age only
		1 071/			Age >=75y	≥30 vs <25 kg/m^2	1.35 (1.13-1.62) Ptrend:0.001		
Rohan, 2013 BRE80478 USA	Women's Health Initiative, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	502/ 10 960 12.9 years	Self report verified by medical record and pathology report	Measured	Incidence, Invasive breast cancer	Q5 vs Q1	1.97 (1.45-2.68) Ptrend:<0.0001	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, breast biopsies, educational level, energy Intake, ethnicity, family history of breast cancer,	Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								HRT use, OC use, pack-years smoking, parity, physical activity, randomisation	
						Q5 vs Q1	1.74 (1.27-2.40) Ptrend:0.0004		
						Q5 vs Q1	1.64 (1.08-2.49) Ptrend:0.02		
Schairer, 2013 BRE80568 USA	BCSC, Nested Case Control, W	5 856/ 93 654	Seer registry/hospital records/pathology	Self-reported	Incidence, non-inflammatory breast cancer, postmenopausal HRT current users	≥30 vs ≤24.9 kg/m^2	1.23 (0.89-1.68)	Age at first child birth, breast biopsies, educational level, family history of breast cancer In first degree relatives, height, mammographic density, parous/nulliparous, race/ethnicity	BC type only, superseded publication
						≥30 vs ≤24.9 kg/m^2	1.21 (0.88-1.65)		
		5 856/			Postmenopausal never/past HRT users	≥30 vs ≤24.9 kg/m^2	1.41 (1.08-1.84)		
						≥30 vs ≤24.9 kg/m^2	1.36 (1.05-1.77)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		896/			Incidence, non-inflammatory locally advanced breast cancer, postmenopausal never/past HRT users	≥30 vs ≤24.9 kg/m^2	1.34 (0.76-2.36)		
						≥30 vs ≤24.9 kg/m^2	1.33 (0.74-2.37)		
		896/			Postmenopausal HRT current users	≥30 vs ≤24.9 kg/m^2	1.19 (0.70-2.03)		
						≥30 vs ≤24.9 kg/m^2	1.22 (0.74-2.00)		
		435/			Incidence, Inflammatory breast cancer, postmenopausal never/past HRT users	≥30 vs ≤24.9 kg/m^2	3.75 (1.92-7.34)		
						≥30 vs ≤24.9 kg/m^2	3.70 (1.98-6.94)		
		435/			Postmenopausal HRTcurrent users	≥30 vs ≤24.9 kg/m^2	3.20 (1.27-8.03)		
						≥30 vs ≤24.9 kg/m^2	2.94 (1.10-7.90)		
					Incidence, Inflammatory breast cancer ER+, postmenopausal never/past HRT users	≥30 vs ≤24.9 kg/m^2	4.21 (1.91-9.28)		
					Postmenopausal HRT current	≥30 vs ≤24.9 kg/m^2	2.48 (0.79-7.84)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					users				
					Incidence, LABC ER+, postmenopausal never/past HRT users	≥30 vs ≤24.9 kg/m^2	1.44 (0.91-2.27)		
					Postmenopausal HRT current users	≥30 vs ≤24.9 kg/m^2	1.11 (0.61-2.04)		
					Incidence, non-inflammatory breast cancer ER+, postmenopausal never/past HRT users	≥30 vs ≤24.9 kg/m^2	1.40 (1.11-1.76)		
					Postmenopausal HRT current users	≥30 vs ≤24.9 kg/m^2	1.18 (0.84-1.67)		
					Incidence, Inflammatory breast cancer ER-, postmenopausal never/past HRT users	≥30 vs ≤24.9 kg/m^2	3.35 (1.73-6.49)		
					Postmenopausal HRT current users	≥30 vs ≤24.9 kg/m^2	3.70 (1.24-11.00)		
					Incidence,	≥30 vs ≤24.9	1.06 (0.35-3.21)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					LABC ER-, postmenopausal never/past HRT users	kg/m^2			
					Postmenopausal HRT current users	≥30 vs ≤24.9 kg/m^2	1.58 (0.70-3.60)		
					Incidence, non-inflammatory breast cancer ER-, postmenopausal never/past HRT users	≥30 vs ≤24.9 kg/m^2	1.22 (0.75-1.98)		
					Postmenopausal HRT current users	≥30 vs ≤24.9 kg/m^2	1.36 (0.88-2.12)		
Suzuki, 2013 BRE80452 Japan	JACC, Prospective Cohort, Age: 40-79 years, W	172/ 36 164 12.3 years	Cancer registry	Self-reported	Incidence, breast cancer, postmenopausal women	≥29 vs 20-23.9 kg/m^2	2.13 (1.09-4.16)	Age, age at menarche, age at menopause, alcohol, education years, exogenous female hormones, family history of cancer In first degree relatives, height, marital status, parity, physical	Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								activity, smoking, study area	
						≥29 vs 20-23.9 kg/m^2	2.00 (1.03-3.89)		
Harlid, 2012 BRE80421 Sweden	MDCS, Prospective Cohort, Age: 45-84 years, W	649/ 17 035 16 years	Cancer registry	Measured	Incidence, breast cancer, >50 years	≥30 vs 18.5-25 kg/m^2	1.26 (0.94-1.68)	Age	Superseded publication
Hartz, 2012 BRE80400 USA	Women's Health Initiative, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	6 052/ 141 652 8 years		Measured	Incidence, breast cancer	per 1 sd units	1.10	Age, alcohol, educational level, Income, physical activity, race, region, smoking, treatment allocation	Superseded publication
Manders, 2011 BRE80314 Netherlands	HEBON, Historical Cohort, W, Subjects with BRCA1/2 mutation	63/ 719 10 years	Cancer registry	Self-reported	Incidence, breast cancer, postmenopausal	≥25 vs ≤24 kg/m^2	1.46 (0.86-2.51)	HRT use, parity, physical activity, type of menopause	Excluded, two exposure categories only
Opdahl, 2011 BRE80600 Norway	Norwegian Screening Programme for Tuberculosis, Prospective	1 165/ 58 191 24.1 years	Cancer registry	Measured height and weight during health examination	Incidence, breast cancer, parous, followed from age >=70 y	≥30 vs ≤24.9 kg/m^2	1.56 (1.33-1.83) Ptrend:<0.0001	Age, age at menarche, birth cohort, county of residence, marital status,	Superseded study by Horn, 2014b, BRE80564

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Cohort, W, Postmenopausal							occupation, urban/rural	
		306/			Nulliparous, followed from age >=70 y	≥30 vs ≤24.9 kg/m^2	1.76 (1.27-2.44) Ptrend:<0.001		
		581/			Parous, followed from age 55-69 y	≥30 vs ≤24.9 kg/m^2	1.17 (0.93-1.49) Ptrend:0.14		
		126/			Nulliparous, followed from age 55-69 y	≥30 vs ≤24.9 kg/m^2	1.09 (0.64-1.85) Ptrend:0.99		
Vacek, 2011 BRE80377 USA	VMC, Prospective Cohort, Age: 70- years, W, Postmenopausal	821/ 19 779 7.1 years	Pathology		Incidence, breast cancer	30 vs ≥22 kg/m^2	1.49 (1.06-2.98)	Age, age at first child birth, age at menarche, breast biopsies, density, family history of breast cancer, HRT use, other, surgical menopause	Superseded study
Wilson, 2011 BRE80380 USA	NHS, Nested Case Control, W, mothers and daughters	239/ 1556 controls	Medical record	Self-reported	Incidence, breast cancer, >=50y at diagnosis	≥25 vs ≤20 kg/m^2	1.15 (0.70-1.89) Ptrend:0.51	Age, family history of breast cancer, smoking	Excluded, exposure was on pre-pregnancy BMI and risk of BC in daughters, superseded publication
Andreotti, 2010 BRE80313	AHS, Prospective	464/ 28 319	Cancer registry	Self-reported	Incidence, breast cancer,	per 1 kg/m^2	1.03 (1.01-1.05)	Diabetes, family history of breast	superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
USA	Cohort, M/W, Spouse of pesticide applicator	10 years			postmenopausal			cancer, parity, vitamin supplement	
						≥35 vs 18.5-24.9 kg/m^2	1.07 (0.61-1.87)		
					Incidence, postmenopausal breast cancer, no alcohol consumption	per 1 kg/m^2	1.05 (1.02-1.08)		
					Ever drank	per 1 kg/m^2	1.00 (0.95-1.04)		
Benzon Larsen S, 2010 BRE80302 Denmark	DCH, Nested Case Control, Age: 50-64 years, W, Postmenopausal	809/ 809 controls 13 years	Cancer registry		Incidence, breast cancer	per 1 kg/m^2	1.02 (0.99-1.04)	Age, age at first child birth, alcohol Intake, duration of HRT use, educational level, HRT use, menopausal status, nsaid use, parity	Superseded study
Bjorge, 2010 Sweden, Norway	Me-Can, Pooled study, 6 cohorts W	1 106/ 11 years follow-up Mean age: 58 years at diagnosis	Record linkage to cancer registries, and death register and population registers	Measured	Incidence, breast cancer Attained age 50-59 years	≥31.7 vs ≤ 20 kg/m^2	0.87 (0.71-1.07) Ptrend:0.2	Year of birth, age at measurement, smoking, stratified for cohort	
		713/			Attained age ≥60 years	≥31.7 vs ≤ 20 kg/m^2	1.21 (1.01-1.43) Ptrend:0.003		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		219/			Mortality, breast cancer Attained age ≥50 years	≥31.7 vs ≤ 20 kg/m^2	0.92 (0.66-1.27) Ptrend:0.80		
Burton, 2010 BRE80315 Scotland	Glasgow Alumni Cohort study, Prospective Cohort, Age: 20 years, M/W, University students	69/ 2 657 49 years	Cancer registry/ death certificate	Measured	Incidence, postmenopausal breast cancer	per 1 kg/m^2	0.97 (0.88-1.08)	Age at menarche, height, smoking, social class	Excluded, exposure was on BMI at a younger age
Kabat, 2010 BRE80312 USA	Women's Health Initiative, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	450/ 58 8 years	Pathology and medical record	Measured	Incidence, ductal In situ breast cancer	≥33.8 vs ≤23.9 kg/m^2	1.13 (0.68-1.87) Ptrend:0.97	Age, age at first child birth, age at menarche, age at menopause, BMI, breast biopsies, educational level, ethnicity, family history of breast cancer, HRT use, mammogram In the past 2 years, oral contraceptive history, randomisation, smoking, waist circumference	BC type only, superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Kawai, 2010b BRE80316 Japan	MCS, Prospective Cohort, Age: 40-64 years, M/W, Postmenopausal	108/ 10 106 129 891 person-years	Cancer registry	Self-reported	Incidence, breast cancer	≥25.9 vs ≤20.4 kg/m^2	2.54 (1.16-5.55) Ptrend:0.02	Age, age at menarche, age at menopause, alcohol Intake, BMI, educational level, family history of breast cancer, HRT use, occupation, parity, smoking, walking	Superseded publication
Kotsopoulos, 2010 BRE80335 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Postmenopausal	4 566/ 107 759 26 years	Self report (provided evidence of treatment), medical records and pathology reports, national death Index	Self-reported	Incidence, ductal carcinomas	≥30 vs ≤20.99 kg/m^2	1.60 (1.42-1.80)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, benign breast disease, BMI, BMI at age 18 years, family history of breast cancer, menopausal age, menopausal type, parity, postmenopausal hormone use	BC type only, superseded publication
						per 1 kg/m^2	1.14		
		645/			Incidence, lobular	≥30 vs ≤20.99 kg/m^2	1.47 (1.08-2.00)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					carcinoma	per 1 kg/m^2	1.12		
					Incidence, Invasive ER+PR+ ductal cancer	per 1 kg/m^2	1.23		
		1 918/				≥30 vs ≤20.99 kg/m^2	2.00 (1.67-2.39)		
		279/			Incidence, Invasive ER+PR+ lobular cancer	≥30 vs ≤20.99 kg/m^2	1.87 (1.16-3.01)		
						per 1 kg/m^2	1.25		
Parr, 2010 Australia, New Zealand, Asia	APCSC, Pooled study, 35 cohorts* W	Overall 324/ 174 053 Mean age 48 years			Mortality, breast cancer, women ≥60 years	30-60 vs 18.5-24.9 kg/m^2 Per 5 kg/m^2	Floating absolute risk: 1.63 (1.13-2.35) Ptrend:0.03 1.19 (1.03-1.38)	Attained age, smoking status, stratified by study	Superseded by Whitlock, 2006, PSC
*Busselton; Australian Longitudinal Study of Aging; Melbourne; National Heart Foundation; Newcastle; Perth 1978-1994; Fletcher Challenge; Anzhen; Beijing Aging; CISCH; East Beijing; Fangshan; Guangzhou Occupational; Huashan; Seven Cities Cohorts; Six Cohorts; Tianjin; Yunnan; Hong Kong; CVDFACTS; Kinmen; Aito Town; Akabane; Civil Service Workers; Hisayama; Konan; Miyama; Ohasama; Saitama; Shibata; Shigaraki Town; Tanno/Soubetsu; Singapore NHS92; EGAT; Shirakawa; KMIC; Singapore Heart									
Yang XR, 2011	BCAC, Pooled study, 12 population-based case-control studies in case-control analysis*		Medical records	Self-reported	Incidence, Invasive breast cancer, women ≤50 years ER+	≥30 vs <25 kg/m^2	BMI did not significantly modify the associations	Age, study, age at menarche, nulliparous, age at first birth	Excluded, insufficient data
					ER-	≥30 vs <25 kg/m^2			
*MCCS; MEC; NHS; ABCFS; GENICA; GESBC; MARIE; NC-BCFR; OFBCR; PBCS; SASBAC; UCIBCS									
Cust, 2009 BRE80216	NSHDC, Nested Case	315/ 315 controls	Cancer registry	Measured	Incidence, breast cancer,	≥27.5 vs ≤24.1	0.86 (0.57-1.30) Ptrend:0.45	Age, date of blood collection,	Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Sweden	Control, Age: 30- years, W				postmenopausal			HRT use	
Davey Smith G, 2009 BRE80459 Sweden	SIMS, Prospective Cohort, W	1 018 012 50 years	Death record & Swedish cause of death register	Measured	Mortality, breast cancer, died at age >=60yrs	per 1 standard deviation	1.02 (0.98-1.07)	Educational level, parental age, social class	Excluded, exposure was on proxy BMI
					Died at age 50-59yrs	per 1 standard deviation	0.95 (0.90-0.99)		
Lacey JV Jr, 2009 BRE80247 USA	PLCO, Prospective Cohort, Age: 55-74 years, W, Postmenopausal	2 063/ 70 575 4.98 years	Self reported/death certificate/ medical records	Self-reported	Incidence, breast cancer	≥35 vs 18.5-24.9 kg/m^2	1.21 (1.02-1.43)	Age, age at first child birth, age at menarche, age at menopause, benign breast disease, calendar period, family history of cancer, height, HRT use, study center	Superseded publication
Sue, 2009 BRE80282 USA	PLCO, Prospective Cohort, Age: 55-75 years, W, Postmenopausal	1 319/ 29 170 8.7 years	Self report verified by medical record		Incidence, breast cancer	obese vs normal	1.18 (1.00-1.38) Ptrend:0.06	Age, age at first child birth, age at menarche, age at menopause, benign breast disease, duration of HRT use, educational level, family history of cancer, height, mammography,	Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								parity, race, study center	
Prentice, 2009 BRE80301 USA	WHI, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	1 703/ 80 816 12 years	Self report verified by medical record	Measured	Incidence, breast cancer	per 10 units	1.10 (0.86-1.40)	Age, alcohol, educational level, energy Intake, estrogen use, family history of cancer, gail model risk, hormone use, physical activity, race, smoking status	Superseded publication
Jee, 2008 BRE80195 Korea	KNHIC, Prospective Cohort, Age: 30-95 years, W	443 273 10.8 years	Cancer registry and hospital records	Measured In light clothing at physical examination	Incidence, breast cancer, postmenopausal	per 1 kg/m^2	1.05	Age, smoking status	Superseded publication
					Age >= 50 years	≥30 vs ≤29.9 kg/m^2	1.00		
Ericson, 2007 BRE80128 Sweden	MDCS, Prospective Cohort, Age: 50- years, Postmenopausal	392/ 11 699 9.5 years	Cancer registry	Measured by nurse at screening centre	Incidence, Invasive breast cancer, postmenopausal	≥30.1 vs ≤25	1.19 (0.89-1.59) Ptrend:0.41	Age	Superseded publication
Gallicchio, 2007 BRE80006 USA	BBD cohort-CLUE II, Prospective Cohort, Age: 59 years, W,	50/ 994 14 years	Clue Ii cohort/patholog y report/self-reported	Self-reported	Incidence, Invasive & In situ breast cancer,	≥25 vs ≤24.9	-	Age	Excluded, association between genotypes, BMI and postmenopausal

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Postmenopausal Benign breast disease								breast cancer risk, superseded publication
Lundqvist, 2007 BRE80003 Sweden, Finland	Sweden,Finland Co-twin study,1975, Nested Case Control, Age: 44 years, W	503/ 503 controls		Measured	Incidence, breast cancer, older subjects	≥30 vs 18.5-24.9 kg/m^2	2.50 (1.30-4.50)	Diabetes, educational level, parity/pregnancies, physical activity , smoking habits	Superseded study
Reinier, 2007 BRE80038 USA	VMC, Prospective Cohort, W	572/ 61 844 3.1 years	Screening examinations	Self-reported	Incidence, Invasive breast cancer, postmenopausal women	≥30 vs ≤21.9 kg/m^2	1.90 (1.40-2.50)	Age, age at first child birth, breast density, family history of cancer, postmenopausal hormone use	Superseded publication
		176/			Incidence, In situ breast cancer, postmenopausal women	≥30 vs ≤21.9 kg/m^2	0.80 (0.50-1.40)		
Vogel, 2007 BRE80150 Denmark	DCH, Nested Case Control, Age: 50-64 years, Postmenopausal	361/ 361 controls	Cancer registry	Recorded by technician	Incidence, breast cancer, postmenopausal	per 1 kg/m^2	1.01 (0.97-1.05)	Age at first child birth, alcohol consumption, benign breast disease, educational level, HRT use, nsaid use,	Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								parity/pregnancies, smoking habits	
Chang, 2006 BRE80110 USA	PLCO, Prospective Cohort, Age: 55-74 years, W, participants of a RCT	764/ 38 660 4.9 years	Cancer screening programme	Self-reported	Incidence, breast cancer, postmenopausal	≥30 vs ≤22.4	1.35 (1.06-1.70) Ptrend:0.014	Age at first child, age at menarche, age at menopause, benign breast disease, educational level, ethnicity, family history, height, HRT use, parity/pregnancies, recruitment center	Superseded publication
Lukanova, 2006 BRE80100 Sweden	NSHDC, Prospective Cohort, Age: 29-61 years, W	422/ 74 207 8.2 years	Medical records	Measured	Incidence, breast cancer, postmenopausal	≥27.9 vs 18.5-22.7	1.04 (0.80-1.36) Ptrend:0.83	Age , calendar year, smoking habits	Superseded publication
Mellemkjaer, 2006 BRE80039 Denmark	DCH, Prospective Cohort, Age: 50-65 years, Postmenopausal	416/ 23 788 6.1 years	Cancer registry	Recorded by trained technician.	Incidence, breast cancer, HRT ever	per 4 kg/m^2	0.98 (0.89-1.09)	Age, age at first child birth, alcohol consumption, benign breast disease, duration of HRT use, educational level, HRT use,	Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								parity	
						≥30 vs 18.5-24.9 kg/m^2	0.94 (0.67-1.31)		
		217/			HRT never	per 4 kg/m^2	1.06 (0.95-1.19)		
						≥30 vs 18.5-24.9 kg/m^2	1.17 (0.79-1.73)		
Modugno, 2006 BRE80137 USA	Women's Health Initiative - Observational study, Nested Case Control, Age: 50-79 years, Postmenopausal	96/ 96 controls 7 years	Self report verified by medical record	Measured at clinic	Incidence, Invasive breast cancer, postmenopausal and HRT users	Q3 vs Q1	1.47 (0.67-3.22) Ptrend:0.36	Age, menarche status, smoking habits	Superseded publication
		94/ 94 controls			Postmenopausal and HRT nonusers	Q3 vs Q1	3.27 (1.40-8.40) Ptrend:0.006	Alcohol consumption, educational level, marital status	
Ravn-Haren, 2006 BRE80151 Denmark	DCH, Nested Case Control, Age: 50-64 years, Postmenopausal	377/ 377 controls	Cancer registry	Self-reported In questionnaire	Incidence, breast cancer, postmenopausal	per 1 kg/m^2	1.02 (0.99-1.06)	Age at first child birth, alcohol consumption, benign breast disease, educational level, fruits and vegetables Intake, HRT use, number of children, parity, selenium Intake, smoking habits	Superseded publication
Rinaldi, 2006	EPIC,	613/	Population	Measured and	Incidence,	per 5 kg/m^2	1.11 (0.99-1.25)	Age at first	Superseded

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
BRE80101 The Netherlands, UK, Germany, Spain, Italy, Greece, France	Nested Case Control, W, Postmenopausal	1139 controls	cancer registries and other procedures	self-report	Invasive & In situ breast cancer, postmenopausal			child, parity/pregnancies	publication
						≥30.3 vs ≤22.9	1.22 (0.86-1.72) Ptrend:0.03		
Silvera, 2006 BRE24118 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	662/ 38 645 16.4 years	Partially histological - over 80%	Weight and height measured at baseline	Incidence, breast cancer, postmenopausal	≥30 vs ≤24 kg/m^2	1.26 (0.95-1.67) Ptrend:0.08	Age , age at first child, age at menarche, alcohol, breast diseases , energy Intake , family history, HRT use, leisure time physical activity, menopausal status, OC use, other design Issue, parity/pregnancies, recruitment center, smoking habits	superseded publication
Tehard, 2006 BRE80103 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years	1 037/ 69 116 3.6 years	Patient records/direct contact/health Insurance records	Self-reported In questionnaire	Incidence, breast cancer, postmenopausal	≥30 vs 18.5-24.9	1.44 (1.04-1.99) Ptrend:>0.05	Age at first child, age at menarche, age-underlying cox models, alcohol, benign breast disease, educational	superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								level, family history, marital status, parity/pregnancies, physical activity	
						≥25.1 vs ≤19.9	1.21 (0.96-1.52) Ptrend:>0.05		
		271/			Postmenopausal and HRT nonusers	≥25.1 vs ≤19.9	1.07 (0.80-1.43) Ptrend:>0.05		
						≥30 vs 18.5-24.9	1.40 (0.91-2.17) Ptrend:>0.05		
		472/			Postmenopausal and HRT users	≥30 vs 18.5-24.9	1.45 (0.90-2.33) Ptrend:>0.05		
						≥25 vs ≤19.9	1.16 (0.90-1.49) Ptrend:>0.05		
		147/			Postmenopausal and transdermal HRT users	≥25.1 vs ≤19.9	1.16 (0.71-1.78) Ptrend:>0.05		
Kuriyama, 2005 BRE22995 Japan	Miyagi, 1993, Prospective Cohort, Age: 40- years, W	65/ 15 054 9 years	Partially histological - over 80%	Self-reported	Incidence, breast cancer, postmenopausal	≥30 vs 18.5-24.9 kg/m^2	2.67 (1.03-6.92) Ptrend:0.01	Age , age at first child, age at menarche, alcohol, food, smoking habits	Superseded publication
Wirfält, 2005 BRE11111 Sweden	MDCS, Nested Case Control, Age: 50- years, Postmenopausal	237/ 673 controls	Cancer registry	Measured	Incidence, breast cancer	(mean exposure)			Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
MacInnis, 2004 BRE80159 Australia	MCCS, Prospective Cohort, Age: 27-75 years, W, Postmenopausal	357/ 13 598 9.1 years	Medical records	Measured	Incidence, Invasive breast cancer, postmenopausal	≥30 vs ≤24 kg/m^2	1.40 (1.00-1.90)	Age, birthplace, educational level, HRT use, physical activity	superseded publication
						per 5 kg/m^2	1.14 (1.02-1.27)		
		36/			Incidence, well differentiated breast cancer, postmenopausal	per 5 kg/m^2	1.00 (0.74-1.36)		
		59/			Incidence, moderate differentiated breast cancer, postmenopausal	per 5 kg/m^2	1.21 (0.97-1.52)		
		44/			Incidence, poorly differentiated breast cancer, postmenopausal	per 5 kg/m^2	1.50 (1.17-1.93)		
		97/			Incidence, breast cancer ER+, >=15 years postmenopausal	per 5 kg/m^2	1.25 (1.05-1.49)		
		29/			Incidence, breast cancer ER-, >=15 years postmenopausal	per 5 kg/m^2	0.82 (0.55-1.24)		
		84/			Incidence, breast cancer PR+, >=15 years	per 5 kg/m^2	1.17 (0.95-1.44)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					postmenopausal				
		42/			Incidence, breast cancer PR-, >=15 years postmenopausal	per 5 kg/m^2	1.11 (0.86-1.45)		
Sweeney, 2004 BRE80599 USA	IWHS, Prospective Cohort, Age: 61 years, W, Postmenopausal	1 297/ 36 658 16 years	Seer registry	Self-reported	Incidence, breast cancer, age 65-74 years	≥29.6 vs ≤23.4 kg/m^2	1.48 (1.26-1.73) Ptrend:<0.0001	Age at baseline, age at first child birth, age at menarche, age at menopause, educational level, family history of breast cancer, height, parity	Superseded publication, subgroup by age only
		428/			Age 55 - 64 years	≥29.6 vs ≤23.4 kg/m^2	1.34 (1.03-1.75) Ptrend:0.004		
		561/			Age 75-84 years	≥29.6 vs ≤23.4 kg/m^2	1.44 (1.12-1.84) Ptrend:0.001		
Tehard, 2004 BRE12173 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W, Registered teachers	1 311/ 94 805 9.7 years	Not specified + partially self-reported	Self-reported	Incidence, Invasive breast cancer, postmenopausal	≥26.3 vs ≤20.6 kg/m^2	1.15 (1.00-1.34)	Age at first child, age at menarche, alcohol, benign breast disease, educational level, family history, marital status, parity/pregnancies	superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		680/			HRT - yes	reference error: no min from refernce	1.00		
		631/			HRT - no	reference error: no min from refernce	1.00		
Wirfalt, 2004 BRE17083 Sweden	MDCS, Nested Case Control, Age: 50- years, W, Postmenopausal	12 803 8 years	Partially histological - over 80%		Incidence, breast cancer, postmenopausal	(mean exposure)			Superseded publication
Calle, 2003 BRE01340 USA	CPS II, Prospective Cohort, Age: 30- years, W, Postmenopausal	2 755/ 495 477 16 years	Cancer registry + death certificate	Self-reported	Mortality, breast cancer	≥40 vs 18.5-24.9 kg/m^2	2.12 (1.41-3.19) Ptrend:0.001	Age , alcohol, educational level, ethnicity, HRT use, marital status, other nutritional factors, other nutritional factors, other specified factor, physical activity , smoking habits, smoking habits	Superseded publication
Chang, 2003 BRE18295 USA	BCDDP, 1973, Prospective Cohort, Age: 55-74 years,	27 534 7 years	Partially histological - over 80%	Self-reported	Incidence, breast cancer	≥1 vs ≥-1	1.26 (0.99-1.60) Ptrend:0.06		Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	W, Screening Program								
Lahmann, 2003 BRE20119 Sweden	MDCS, Prospective Cohort, Age: 50-73 years, W, Postmenopausal	236/ 12 159 5.7 years	Cancer registry + death certificate		Incidence, Invasive & In situ breast cancer	≥28.6 vs ≤21.9 kg/m^2	1.54 (1.01-2.35) Ptrend:0.023	Age , age at first child, age at menarche, alcohol, height, marital status, OC use, occupation, other anthropometric Index, parity/pregnancies, smoking habits	Superseded publication
Rissanen, 2003 BRE17954 Finland	Mobile Clinic Health Examination Survey, 1973, Nested Case Control, Age: 18-89 years, W	8 196 10 years	Partially histological - over 80%	Weight and height were measured	Incidence, breast cancer, postmenopausal	(mean exposure)			Excluded, mean exposure comparison only
Saadatian-Elahi, 2002 BRE21486 USA	NYUWHS, Nested Case Control, Age: 34-65 years, W	106/ 106 controls 4.3 years	Partially histological - over 80%		Incidence, breast cancer, postmenopausal	(mean exposure)			Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Wirfalt, 2002 BRE13504 Sweden	MDCS, Nested Case Control, Age: 50- years, W, Postmenopausal	237/ 673 controls 8 years	Partially histological - over 80%		Incidence, breast cancer, postmenopausal	(mean exposure)			Superseded publication
Manjer, 2001a BRE80623 Sweden	MPP, Prospective Cohort, Age: 49.9 years, W, Non smokers	50/ 2 082 13.3 years	Cancer registry	Measured	Incidence, Invasive & In situ breast cancer, peri/postmenopause	per 1 kg/m^2	1.01 (0.95-1.08)	Age, cholesterol, HRT use, OC use, triglyceride	Superseded publication
Folsom, 2000 BRE80610 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	1 299/ 31 702 10 years	Active follow up, cancer registry, death certificate and national death Index	Tape measure sent to participants Instructing them to have a friend take the measurements, self-reported height and weight	Incidence, breast cancer	≥30.21 vs ≤22.8 kg/m^2	1.60 (1.30-1.90)	Age, age at first child, alcohol Intake, educational level, energy, fish Intake, fruits and vegetables Intake, keys score, pack years of smoking, phyisical activity, red meat Intake, smoking status, vitamin use, whole grains, oestrogen use	Superseded publication
Jumaan, 1999	SMC,	273/	Not specified	Self-reported	Incidence,	≥30 vs ≤24.9	0.76 (0.45-1.30)	Age , other	Superseded

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
BRE04514 Sweden	Nested Case Control, Age: 40-70 years, W, Postmenopausal	371 controls 2 years			Invasive breast cancer, postmenopausal	kg/m^2		design Issue, place of residence	publication
Huang, 1997 BRE04117 USA	NHS, Prospective Cohort, Age: 35-55 years, W, Registered nurses	1 517/ 95 256 16 years	Medical records + self-reported +death certificate	Self-reported	Incidence, Invasive breast cancer, postmenopausal	≥31.1 vs ≤20 kg/m^2	1.13 (0.87-1.46) Ptrend:0.53	Age , age at first child, age at menarche, age at menopause, family history, height, HRT use, parity/pregnancies	superseded publication
van den Brandt, 1997 BRE12717 Netherlands	NLCS, Case Cohort, Age: 55-69 years, W, Postmenopausal	553/ 4.3 years	All histology	Self-reported	Incidence, Invasive breast cancer, postmenopausal	≥30 vs ≤22.9 kg/m^2	0.98 (0.66-1.45) Ptrend:0.46	Age , age at first child, age at menarche, alcohol, parity/pregnancies	superseded publication
						per 8 kg/m^2	1.11 (0.88-1.39)		
Den Tonkelaar, 1995 BRE02224 Netherlands	DOM-project Utrecht, Prospective Cohort, Age: 40-73 years, W, Screening Program	38/ 9 491 4 years	Not specified	Measurements performed by trained personnel	Incidence, breast cancer, postmenopausal	≥27 vs ≤24.09 kg/m^2	1.45 (0.62-3.38) Ptrend:0.82	Age	Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Toniolo, 1994 BRE12398 USA	NYUWHS, Nested Case Control, Age: 35-65 years, W	101/ 465 controls 7 years	Medical records	Self-reported	Incidence, Invasive breast cancer, postmenopausal	≥26.6 vs ≤21.69 kg/m^2	2.10 (1.05-4.17)		Superseded publication
den Tonkelaar, 1994 BRE02222 Netherlands	DOM-project Utrecht, Prospective Cohort, Age: 49-66 years, W, Postmenopausal	9 746 12.5 years	Partially histological - over 80%	Direct measures by trained assistants	Incidence, breast cancer, postmenopausal	≥28 vs ≤22.9	1.20 (0.86-1.67) Ptrend:0.99	Age	Superseded publication
						≥29 vs ≤22 kg/m^2	1.64 (1.00-2.69)		
Barrett-Connor, 1993 BRE00581 USA	Rancho Bernardo, 1972, Prospective Cohort, Age: 40-79 years, W	15/ 590 15 years	Medical records + death certificate	Height and weight measured with subjects In light clothing without shoes.	Incidence, breast cancer, postmenopausal	(mean exposure)		Age	Excluded, mean exposure comparison only
Van den Brandt, 1993 BRE16919 Netherlands	NLCS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	448/ 1 598 3.3 years	All histology		Incidence, Invasive breast cancer	≥27 vs ≤22.9 kg/m^2	0.90 (0.67-1.20) Ptrend:0.44	Age	superseded publication
Gapstur, 1992 BRE03101 USA	IWHS, Prospective Cohort,	493/ 37 105 4 years	Partially histological - over 80%	Self-report	Incidence, breast cancer, postmenopausal	≥30.71 vs ≤22.89 kg/m^2	1.65 (1.24-2.19) Ptrend:0.0001	Age	Superseded publication

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Age: 55-69 years, W, Postmenopausal								
Graham, 1992 BRE03424 USA	New York State Cohort, 1980, Prospective Cohort, Age: 50-107 years, W, Postmenopausal	359/ 18 586 8 years	Partially histological - over 80%	Self-reported	Incidence, breast cancer, postmenopausal	24-59 vs 13-23 kg/m^2	1.09 (0.88-1.35) Ptrend:0.418	Age , educational level	superseded publication
Folsom, 1990 BRE02836 USA	IWHS, Nested Case Control, Age: 55-69 years, W, Postmenopausal	226/ 1784 controls 2 years	All histology	Self-reported	Incidence, breast cancer, postmenopausal	≥28.36 vs ≤24.39 kg/m^2	1.06 (0.76-1.49) Ptrend:0.69	Age	Superseded publication
London, 1989 BRE80626 USA	NHS, Prospective Cohort, Age: 30-55 years, W	420/ 115 534 743 716 person-years	Self-report verified by medical record	Self-reported	Incidence, Invasive breast cancer, postmenopausal	Q5 vs Q1	1.1 (0.8-1.5) Ptrend:0.62	Age, parity, age at birth of first child, age at menarche, history of benign breast disease, family history of breast cancer, smoking	Superseded publication
Le Marchand, 1988 BRE15836	Hawaii 1942, 1960, 1972, Nested Case	39/ 172 controls	All histology	From drive licence	Incidence, breast cancer, postmenopausal	Q3 vs Q1	0.72 (0.24-2.19) Ptrend:0.99	Husband occupation, other	Excluded, insufficient data

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
USA	Control, W							anthropometric Index	
Tornberg, 1988 BRE12418 sweden	Swedish cohort, 1963, Prospective Cohort, Age: 17-74 years, W, Screening Program	46 570 20 years	Partially histological - over 80%	Measured	Incidence, breast cancer, postmenopausal	per 1 unit	1.02 (1.00-1.04)	Age , place of residence	Superseded study, by Tornberg, 1994
Willett, 1985 BRE80625 USA	NHS, Prospective Cohort, Age: 30-55 years, W	97/ 103 688 4 years	Self-reported validated by pathology report	Self-reported	Incidence, breast cancer, natural menopause	Q5 vs Q1	1.02 Ptrend:0.944	Age	Superseded publication
		80/			Incidence, breast cancer, hysterectomy	Q5 vs Q1	0.62 Ptrend:0.046		
		47/			Incidence, breast cancer, oophorectomy	Q5 vs Q1	1.68 Ptrend:0.013		

Figure 544 RR estimates of postmenopausal breast cancer by levels of BMI

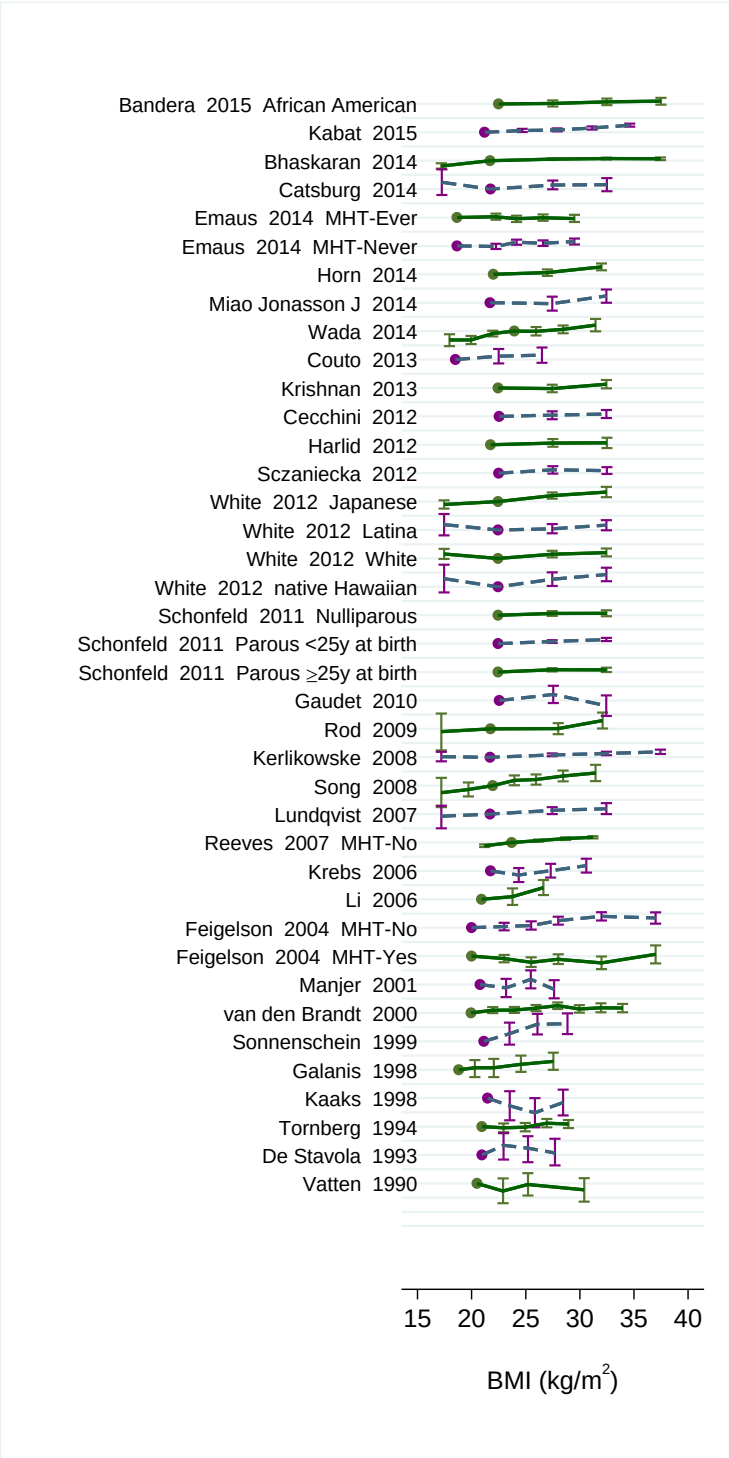


Figure 545 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest level of BMI

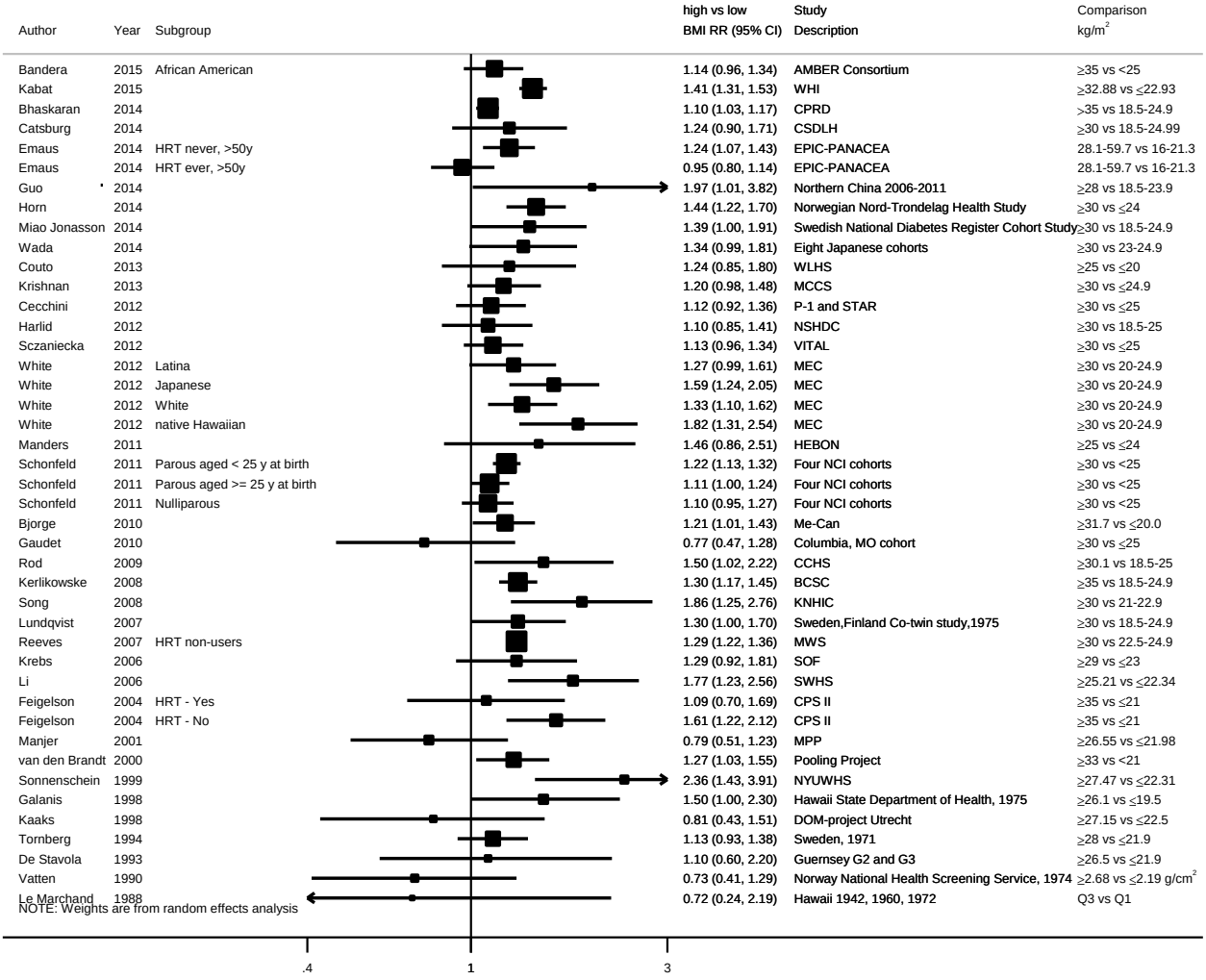


Figure 546 Relative risk of postmenopausal breast cancer for 5 kg/m^2 increase of BMI

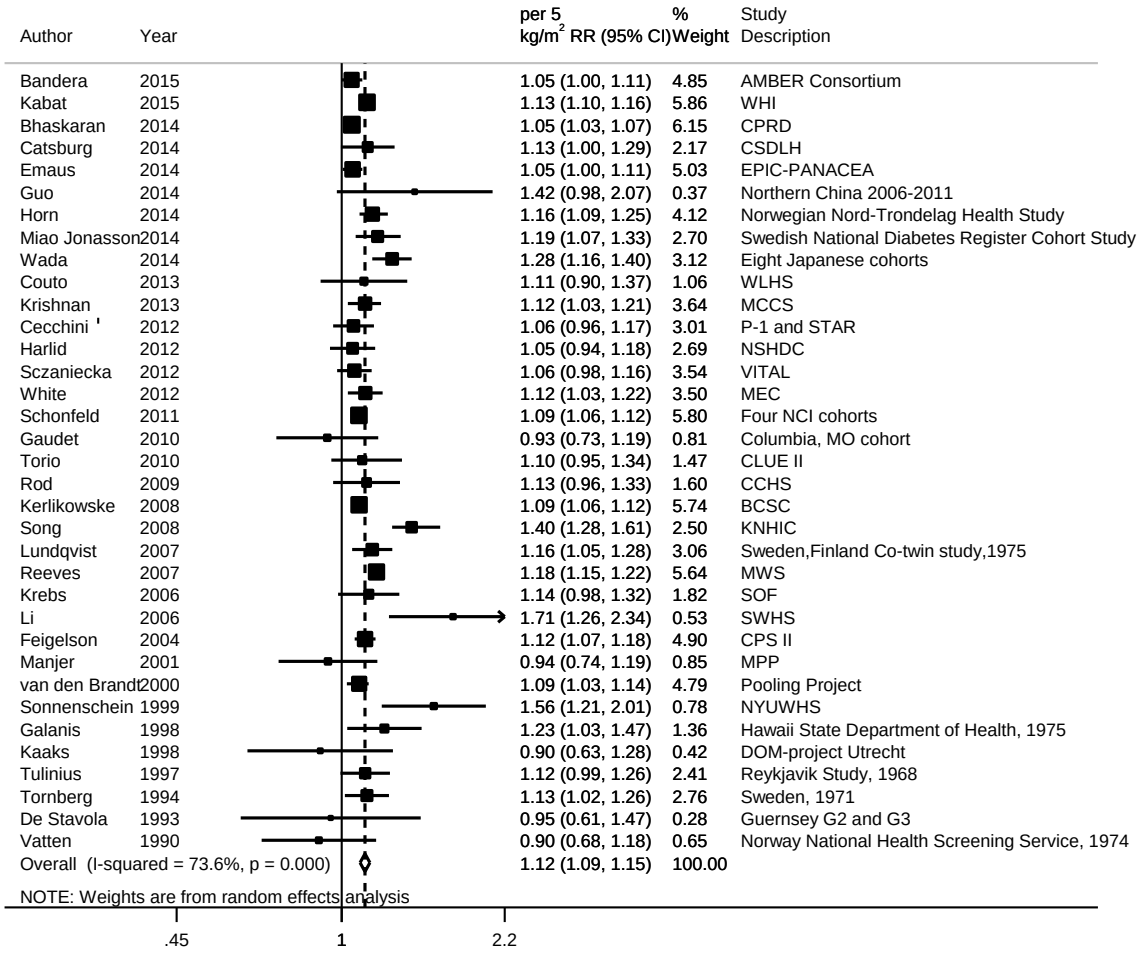


Figure 547 Funnel plot of studies included in the dose response meta-analysis of BMI and postmenopausal breast cancer

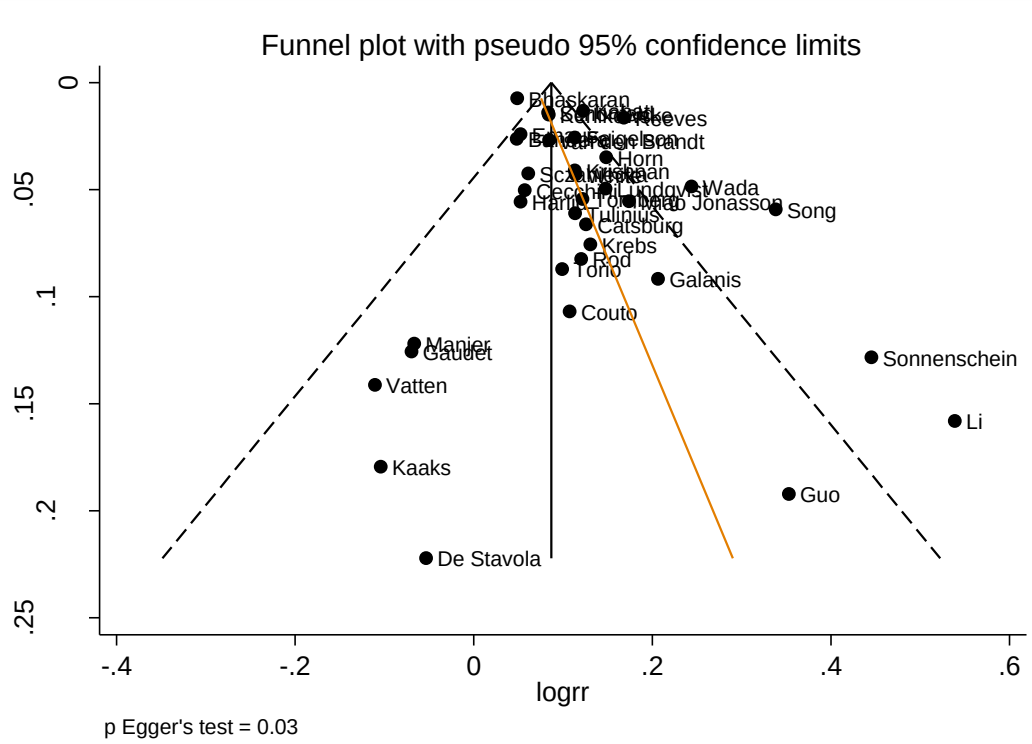
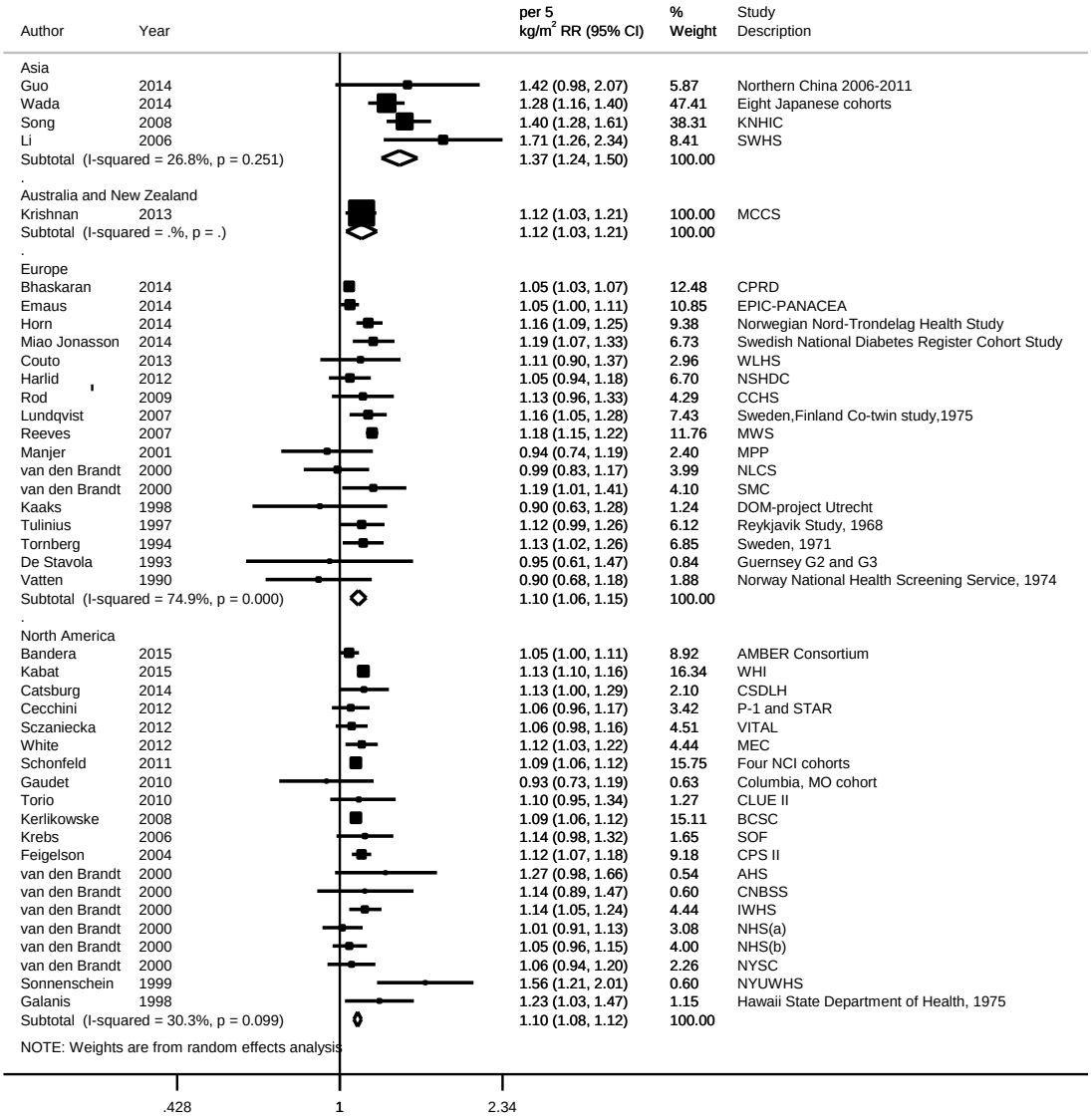


Figure 548 Relative risk of postmenopausal breast cancer for 5 kg/m^2 increase of BMI, by geographic location



Note: Individual study results within the Pooling Project (van den Brandt, 2000) were used

Figure 549 Relative risk of postmenopausal breast cancer for 5 kg/m^2 increase of BMI, by anthropometric measurement methods

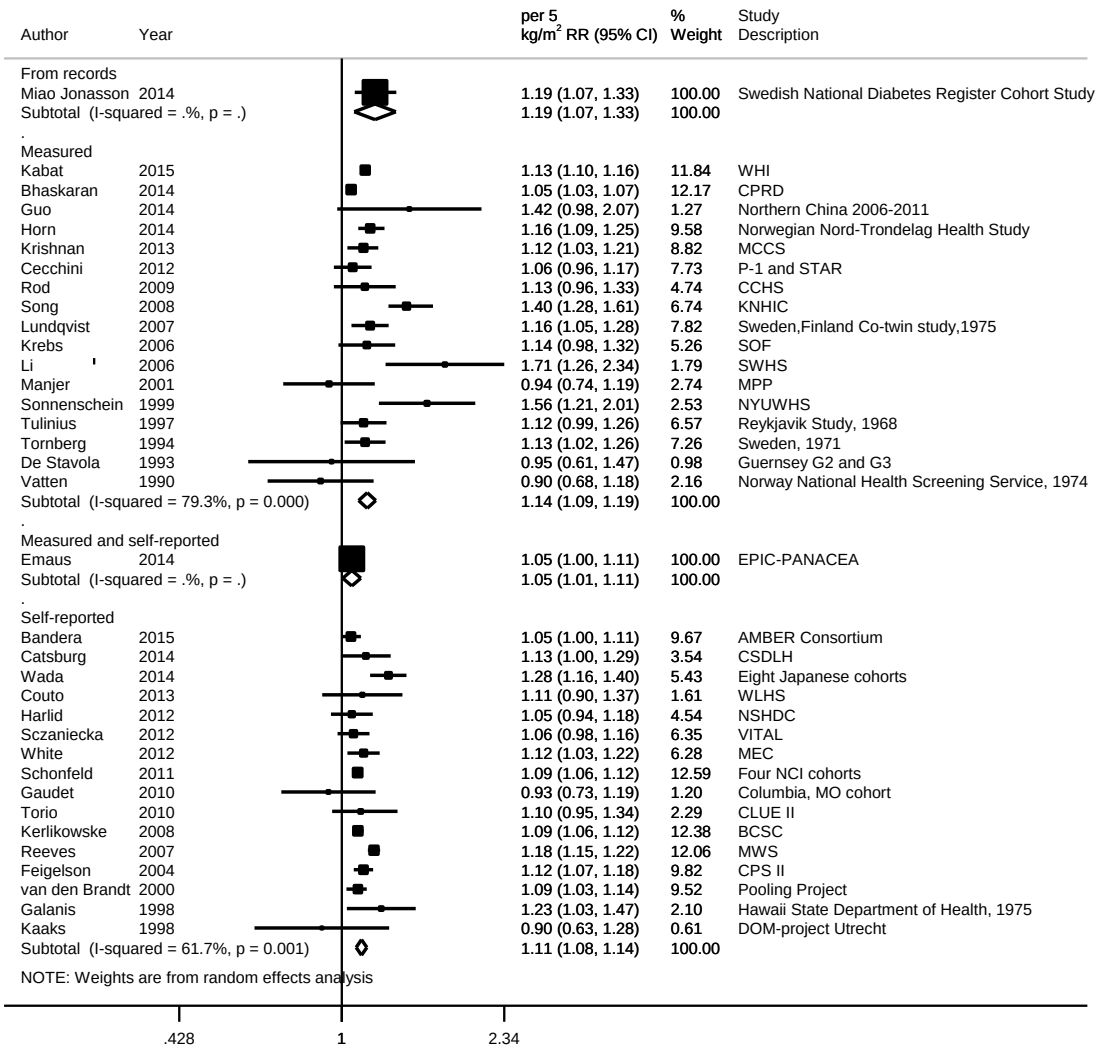
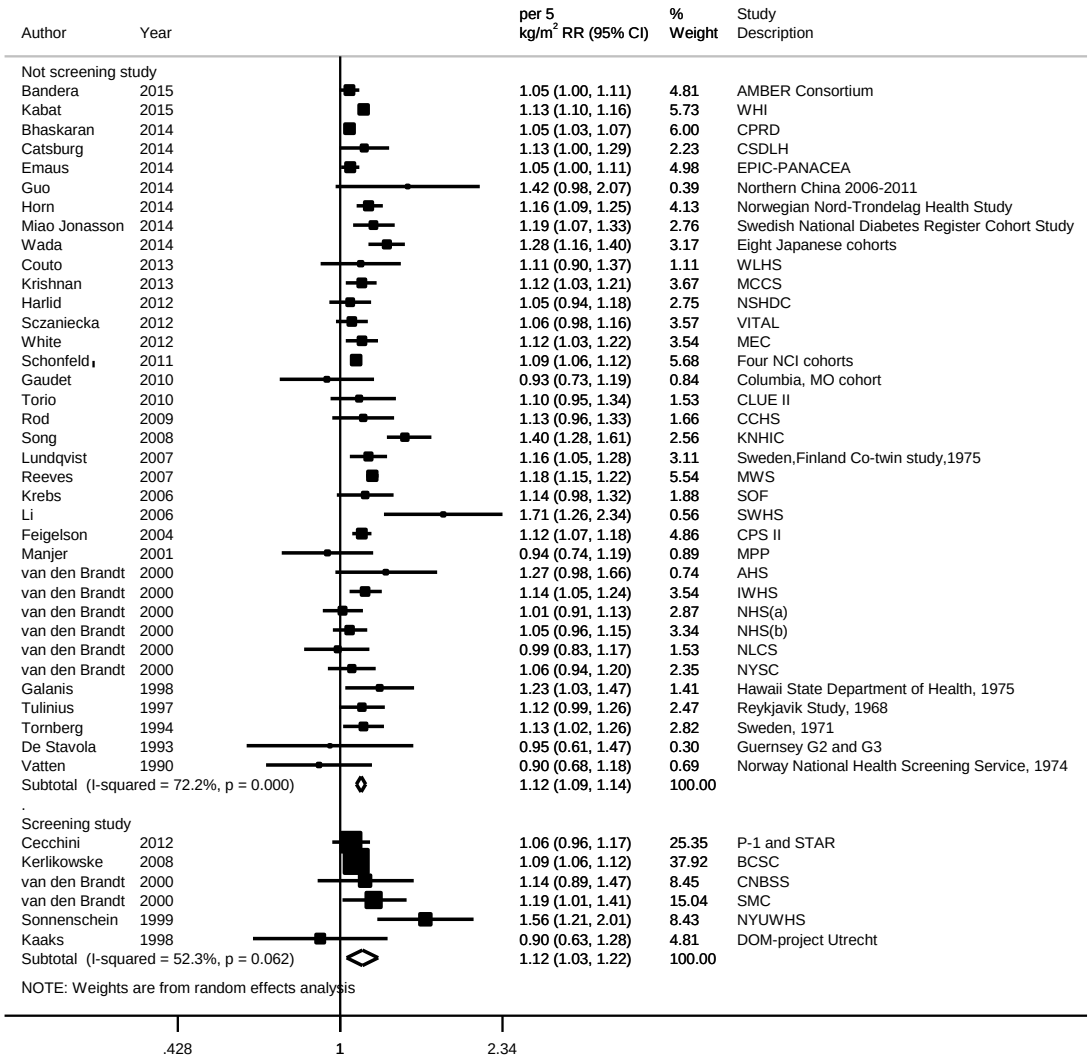


Figure 550 Relative risk of postmenopausal breast cancer for 5 kg/m^2 increase of BMI, by study design



Note: Individual study results within the Pooling Project (van den Brandt, 2000) were used.

Figure 551 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest level of BMI, by menopausal hormone therapy use

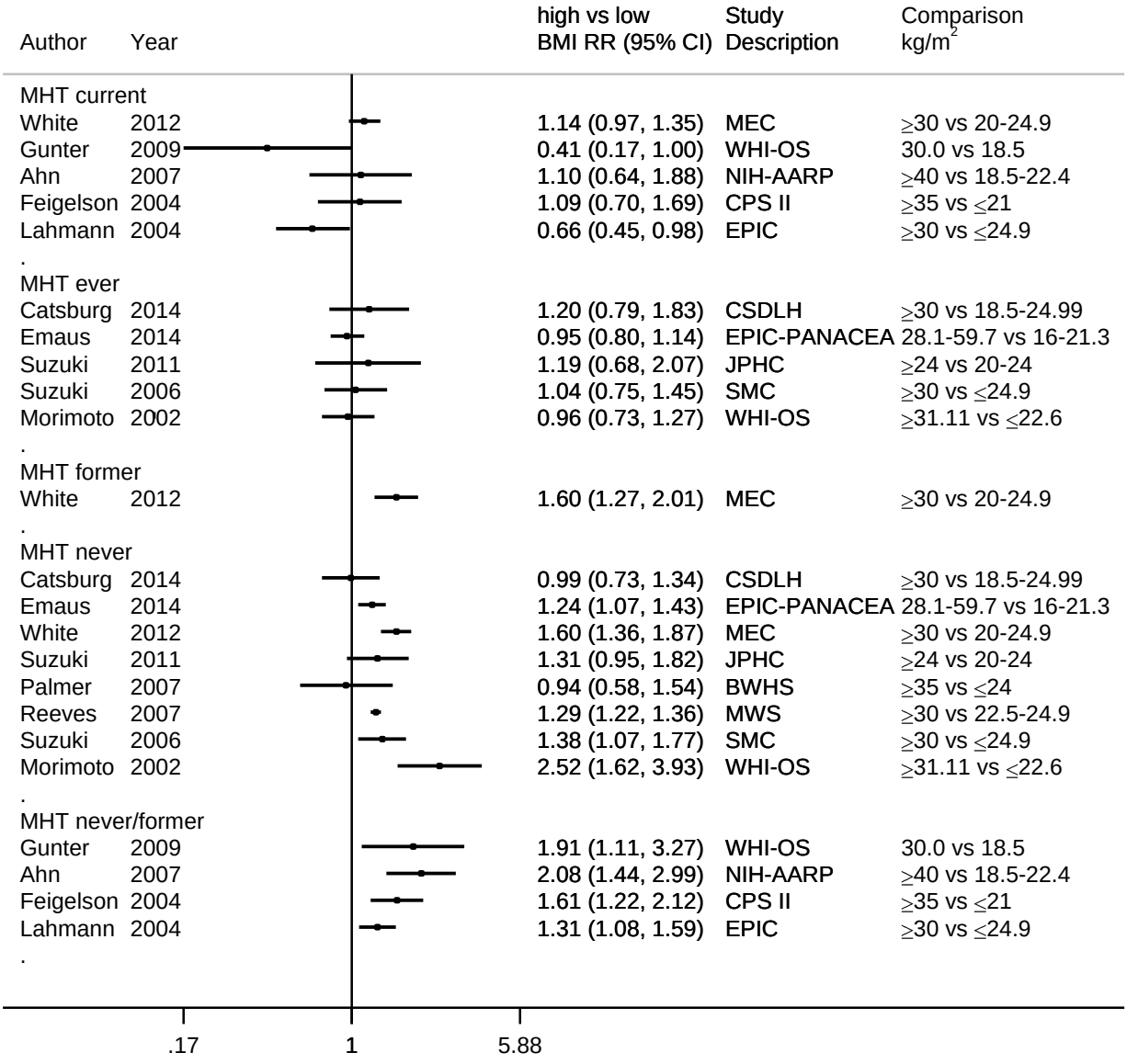


Figure 552 Relative risk of postmenopausal breast cancer for 5 kg/m^2 increase of BMI, by menopausal hormone therapy use

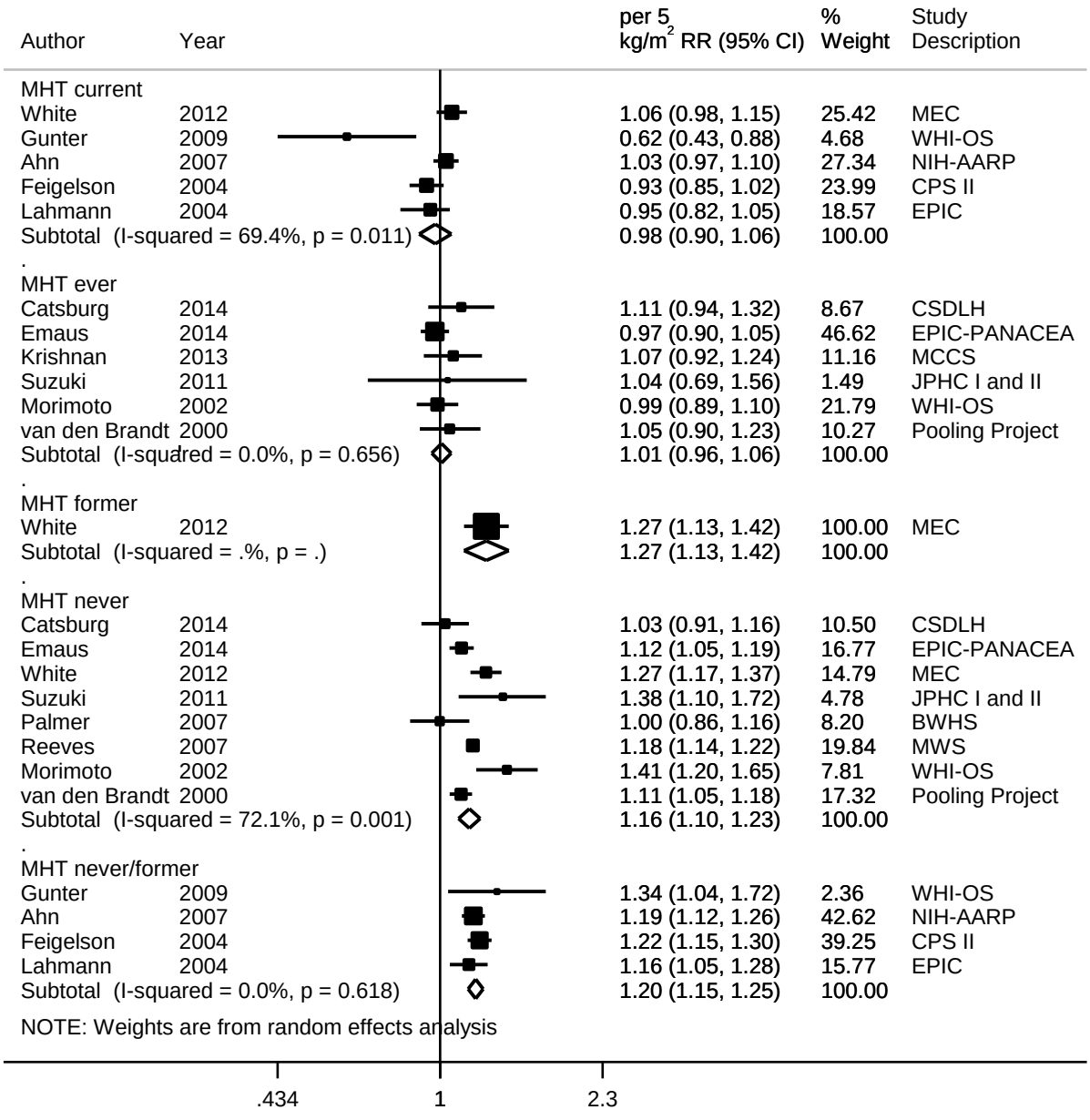


Figure 553 RR (95% CI) of hormone receptor-defined postmenopausal breast cancer for the highest compared with the lowest level of BMI

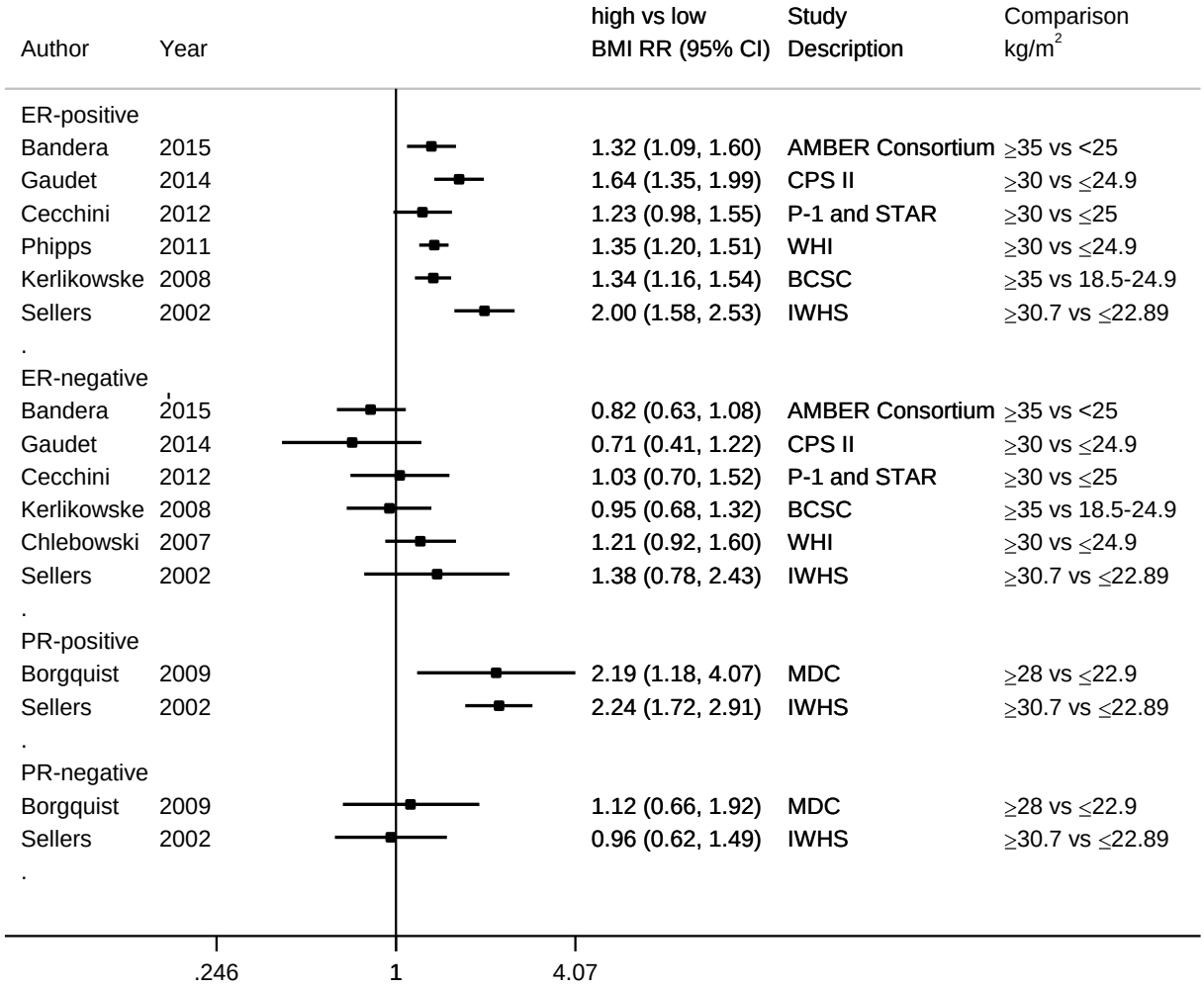


Figure 554 Relative risk of hormone receptor-defined postmenopausal breast cancer for 5 kg/m^2 increase of BMI

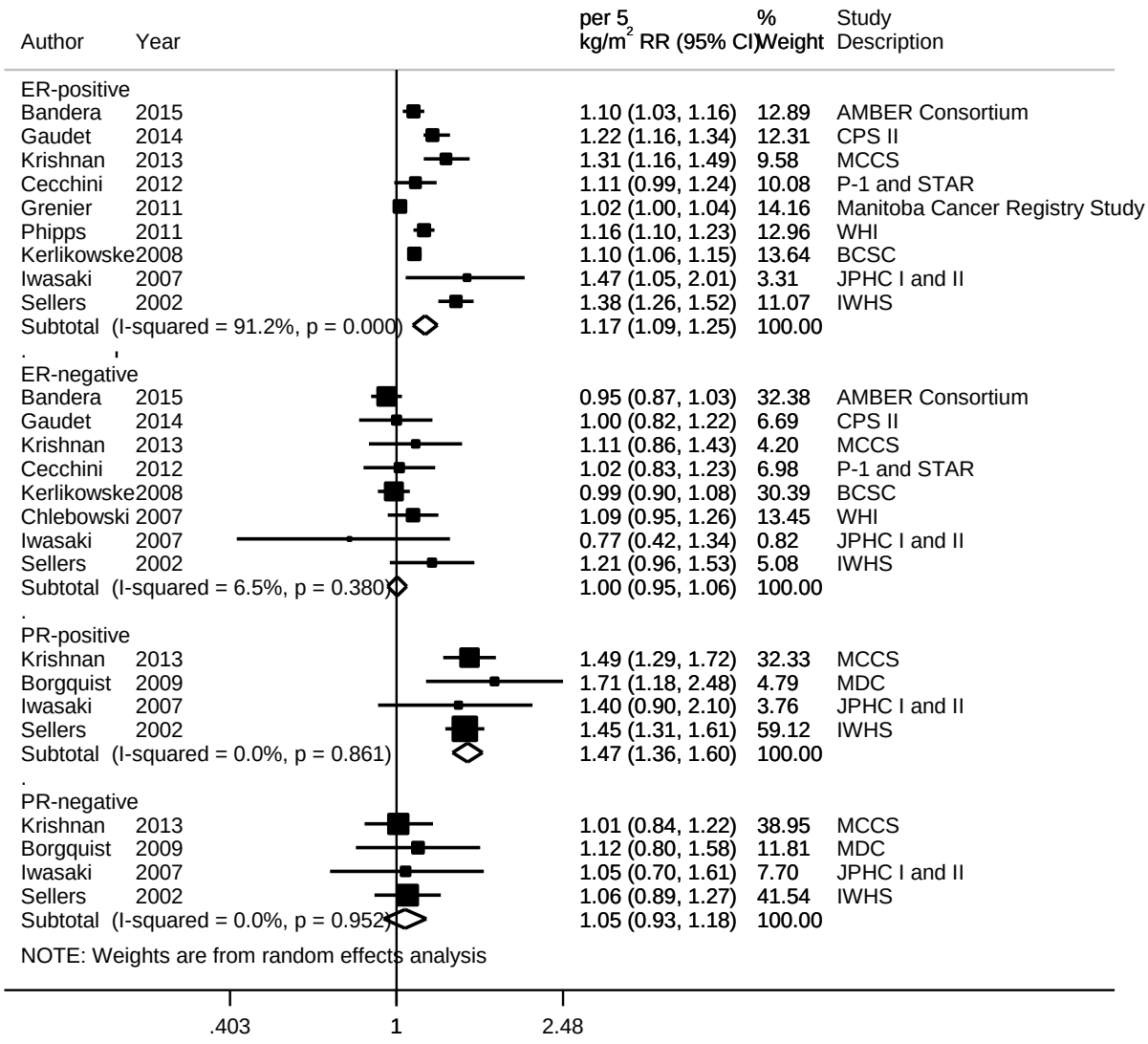


Figure 555 RR (95% CI) of joint hormone receptor-defined postmenopausal breast cancer for the highest compared with the lowest level of BMI

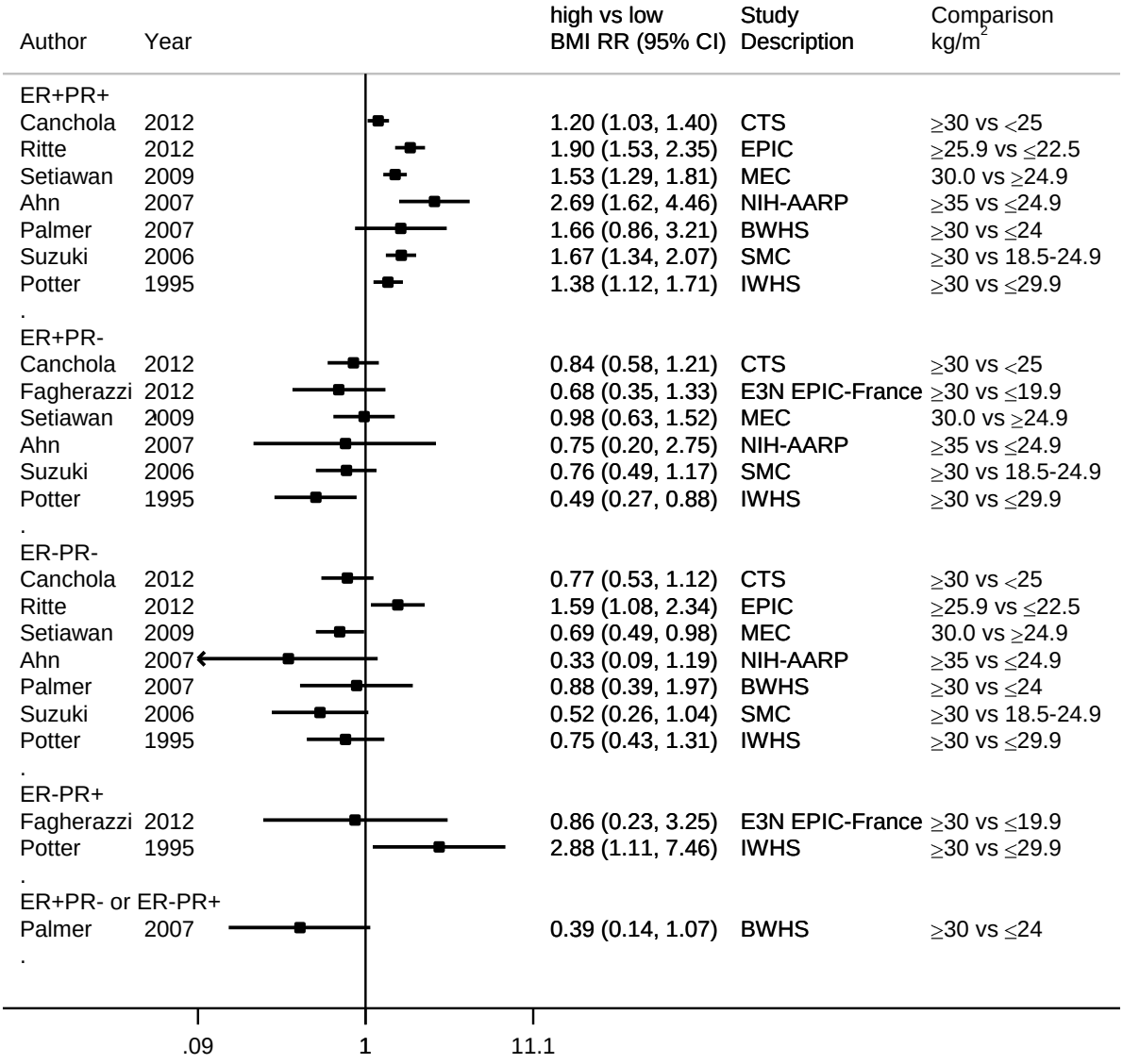


Figure 556 Relative risk of joint hormone receptor-defined postmenopausal breast cancer for 5 kg/m^2 increase of BMI

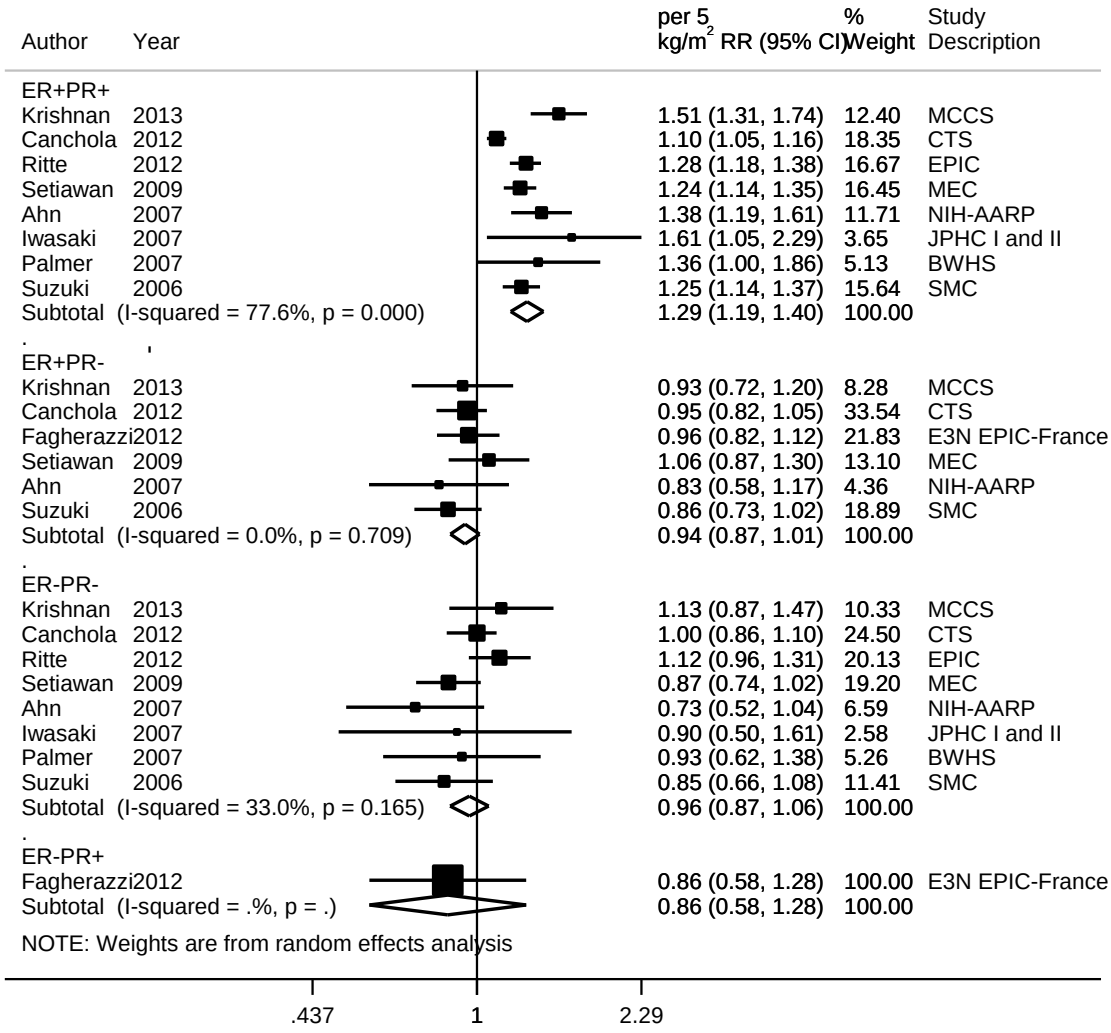
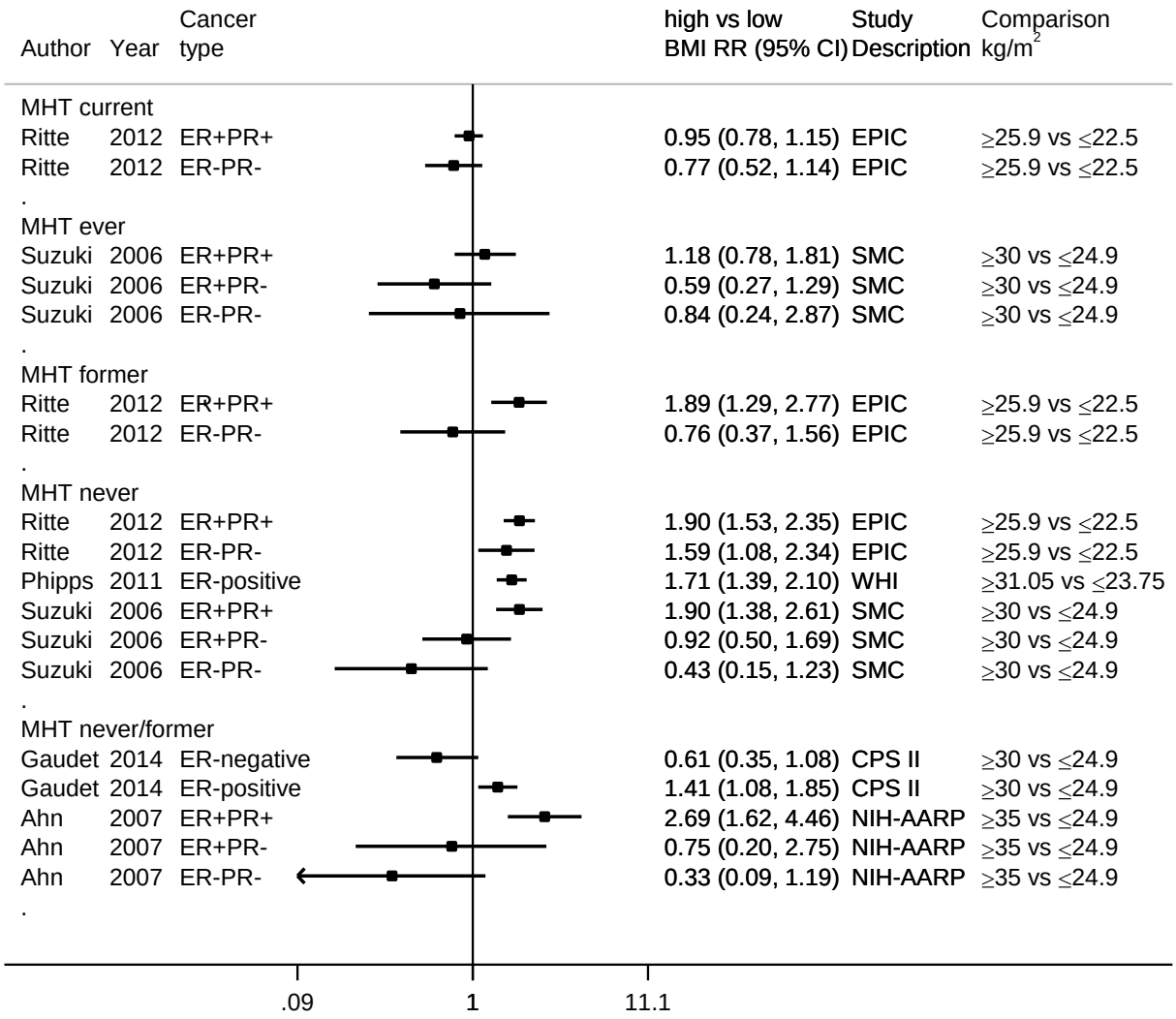


Figure 557 RR (95% CI) of hormone receptor-defined postmenopausal breast cancer for the highest compared with the lowest level of BMI, by menopausal hormone therapy use



Note: Insufficient data to conduct a dose-response meta-analysis, results for the highest versus the lowest BMI comparison are presented in a forest plot to aid interpretation.

Figure 558 RR (95% CI) of triple negative breast cancer for the highest compared with the lowest level of BMI in postmenopausal women

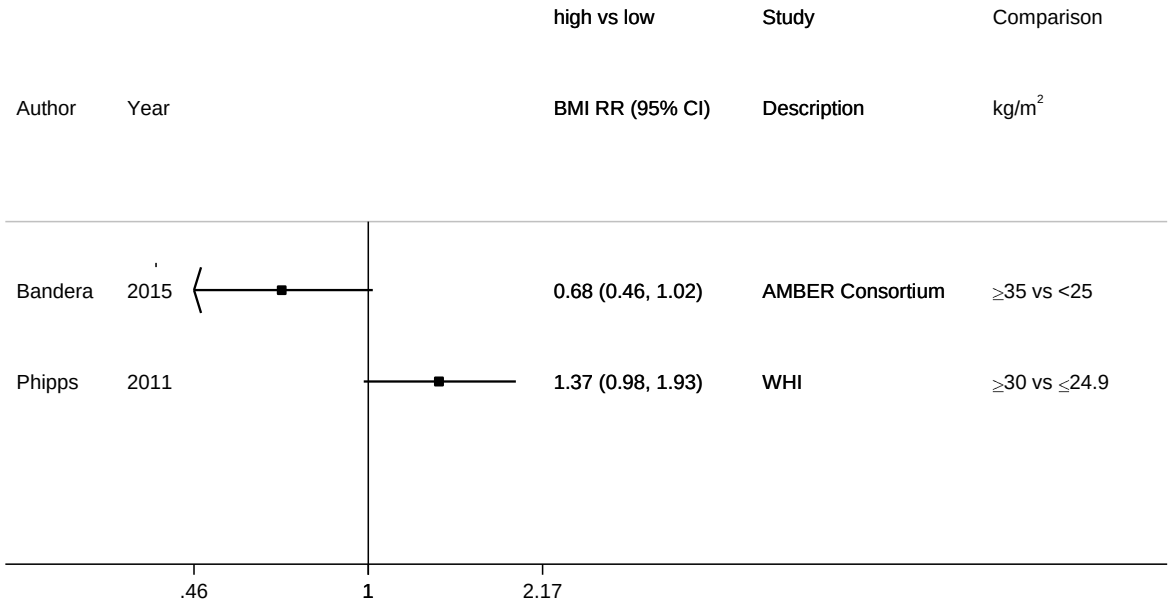


Figure 559 Relative risk of triple negative breast cancer for 5 kg/m^2 increase of BMI in postmenopausal women

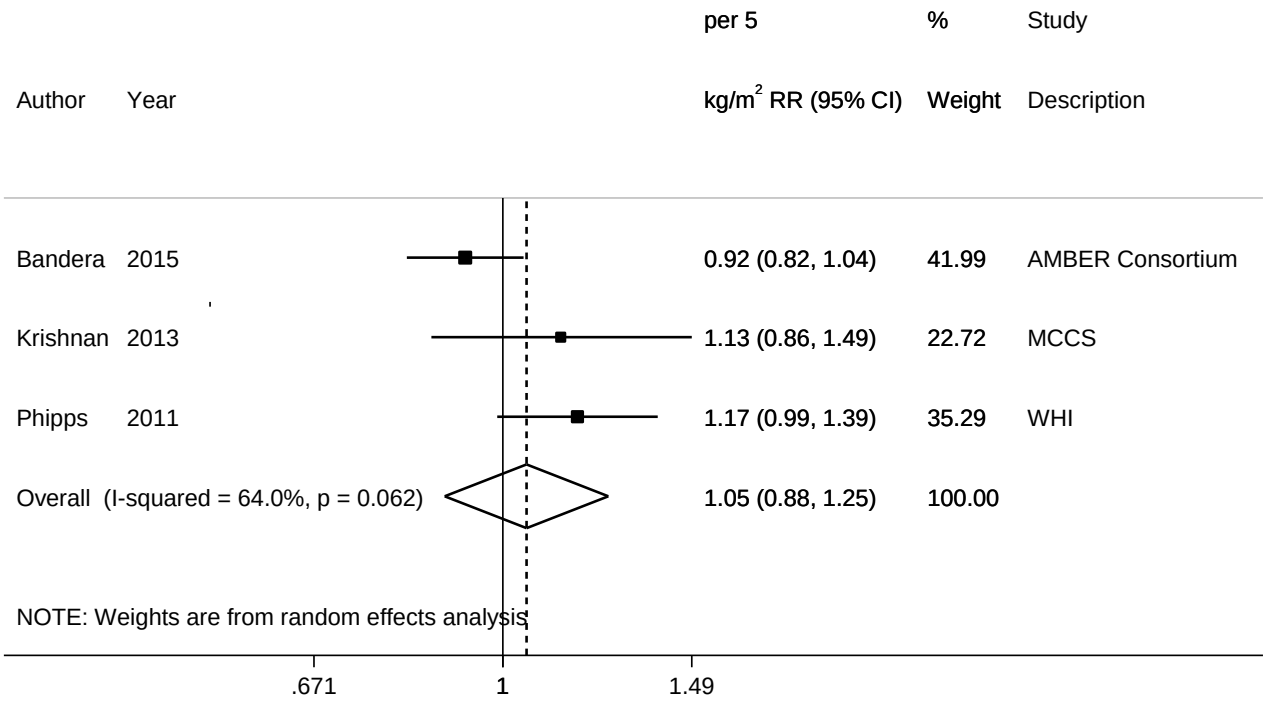


Figure 560 RR (95% CI) of postmenopausal breast cancer mortality for the highest compared with the lowest level of BMI

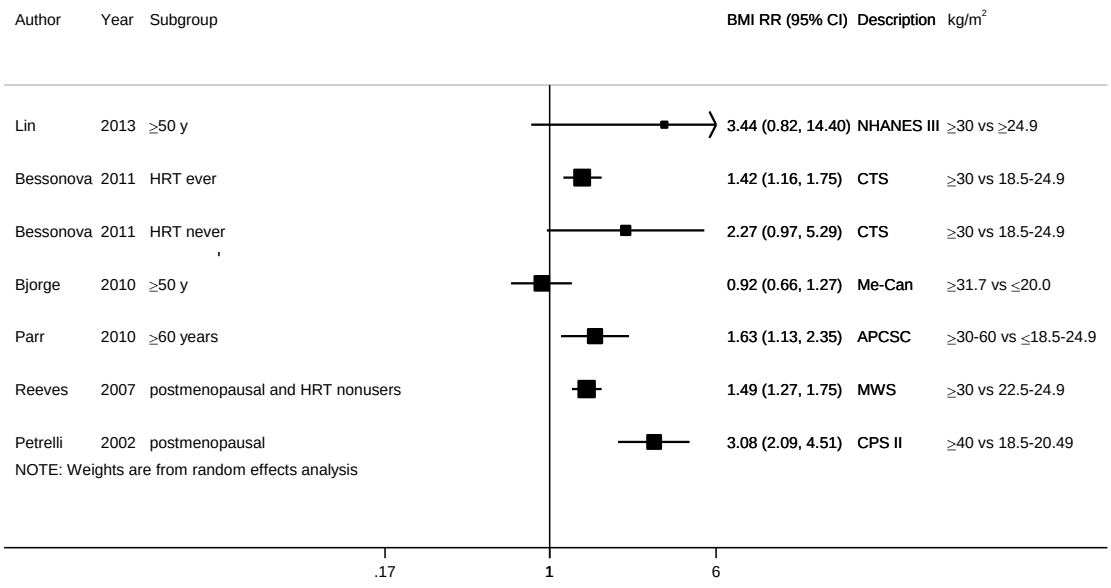
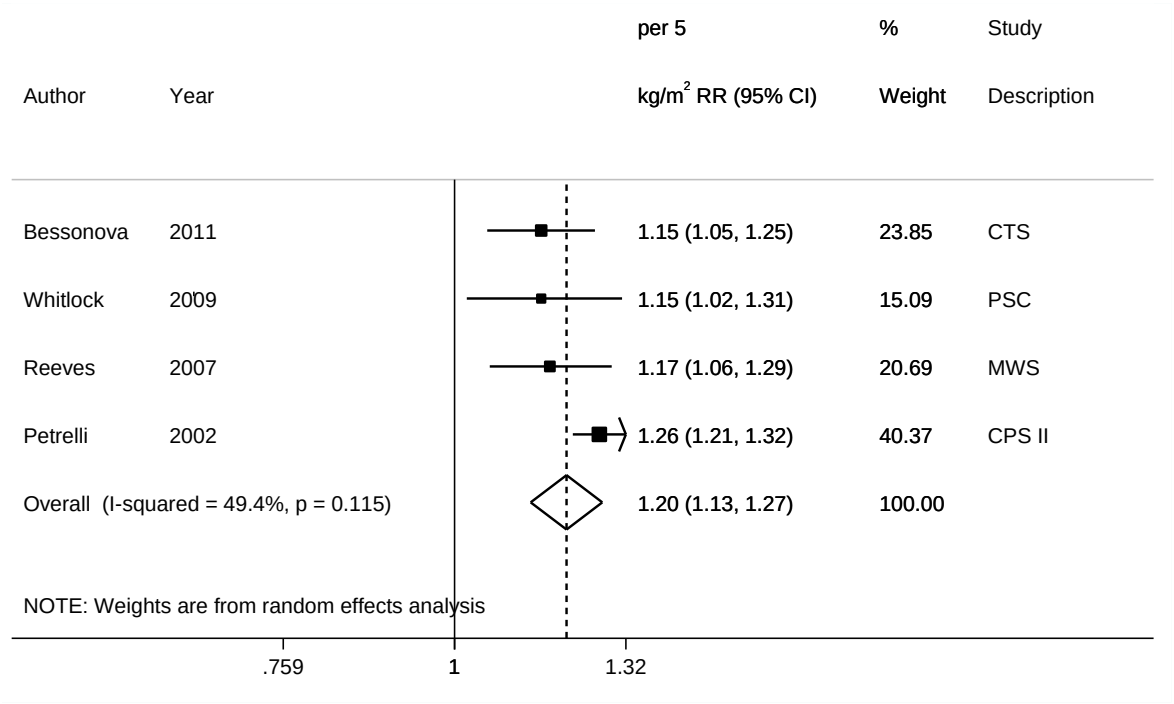


Figure 561 Relative risk of postmenopausal breast cancer mortality for 5 kg/m2 increase of BMI



8.1.1 BMI at early adulthood

Cohort studies

Overall summary

Thirty-six publications from 27 studies that examined BMI at early adulthood (age 18-<30 years) were identified. This included one pooled study (Bandera, 2015). No published meta-analysis was identified.

Dose-response meta-analyses were conducted to examine the associations of BMI at early adulthood with risk of breast cancer, and pre- and postmenopausal breast cancer.

Notes on methods:

Results that were adjusted for multiple confounding factors as reported by the studies were pooled in the meta-analysis. This included the adjustment for weight change during adulthood, adult BMI or other obesity indicators if studies reported such results.

Table 537 Summary of results of the dose-response meta-analysis in the 2016 CUP SLR

	Breast cancer	Premenopausal breast cancer	Postmenopausal breast cancer
BMI at early adulthood Increment unit used	Per 5 kg/m^2	Per 5 kg/m^2	Per 5 kg/m^2
Studies (n)	8	12[1]	17[1]
Cases	4 116	4 953	10 229
RR (95%CI)	0.85 (0.78-0.93)	0.82 (0.76-0.89)	0.82 (0.76-0.88)
Heterogeneity (I^2, p-value)	11%, 0.34	15%, 0.31	44%, 0.04
P value Egger test	0.22	0.75	0.28

[1]Included one pooled study (Bandera, 2015), in which three studies were pooled in the analysis of premenopausal breast cancer and four studies in postmenopausal breast cancer.

Breast cancer

Summary

Main results:

Eight out of 11 studies (12 publications) on BMI at early adulthood could be included in the dose-response meta-analysis.

BMI at early adulthood was significantly inversely associated with any breast cancer risk (summary RR per 5 kg/m^2=0.85, 95% CI= 0.78-0.93). There was low heterogeneity between studies (I^2=11%, P=0.34).

There was no evidence of significant publication or small studies bias (P for Egger's test=0.22) but the number of studies was low. Visual inspection of the funnel plot shows asymmetry which could be explained by a small study with a positive association (Cerhan, 2004).

Three studies were excluded from the dose-response meta-analysis. Two studies did not have sufficient data to be included. For high versus low BMI at early adulthood, one study (Jonsson, 2003) observed a significant inverse association and the other (Whittemore, 1985) reported a significant positive association. One excluded study reported results on breast cancer mortality only. A non-significant positive association was reported (Ma, 2011).

One study (Suzuki, 2011b) reported results on breast cancer subtypes and observed a non-significant positive association of ER+PR+ breast cancer, a non-significant inverse association of ER+PR- breast cancer, and a significant inverse association of ER-PR- breast cancer with the increase of BMI at 20 years.

Sensitivity analyses:

The summary RR became non-significant when Boggs, 2015 (47% weight) was omitted in influence analysis (RR per 5 kg/m^2=0.87, 95% CI=0.75-1.01). Inverse associations were observed in the stratified analysis by geographic locations and in studies adjusted for major confounding factors.

Non-linear dose-response meta-analysis:

Non-linear dose-response meta-analysis was not conducted due to insufficient number of studies.

Study quality:

There were one European study, two Asian studies (one publication), and five North American studies. Boggs, 2015 was of black women. Cerhan, 2004 was a historical cohort study of family members of breast cancer cases. Increased risk of breast cancer with higher compared with lower BMI at 18 years were observed in sisters and daughters, and granddaughters and nieces, and not in marry-ins relatives.

Participants were asked to recall their weight at age 18 years (Boggs, 2015; Harris, 2011a; Cerhan, 2004) or 20 years (Catsburg, 2014b; Suzuki, 2011b) in all studies apart from Burton, 2010 where body measurements were taken at college physical examination. Case ascertainment was through cancer registries or confirmed through medical records. Most studies were adjusted for major confounding factors. Burton, 2010 did not adjust for alcohol consumption and Cerhan, 2004 did not adjust for reproductive factors.

Table 538 BMI at early adulthood and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	11 (12 publications)
Studies included in forest plot of highest compared with lowest exposure	10 (8 publications)
Studies included in linear dose-response meta-analysis	8 (6 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 539 BMI at early adulthood and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and 2016 CUP

	2005 SLR[1]	**CUP**
Increment unit used	-	**Per 5 kg/m^2**
Studies (n)	-	8
Cases	-	4 116

RR (95%CI)	-		0.85 (0.78-0.93)
Heterogeneity (I^2, p-value)	-		11%, 0.34
P value Egger test	-		0.22
Stratified analysis in the CUP			
Geographic locations	**Asia**	**Europe**	**North America**
Studies (n)	2	1	5
Cases	452	95	3 569
RR (95%CI)	0.75 (0.61-0.92)	0.95 (0.62-1.47)	0.88 (0.78-0.99)
Heterogeneity (I^2, p-value)	-	-	22%, 0.28
Adjustment for age, alcohol intake, reproductive factors	**Adjusted**		**Not adjusted**
Studies (n)	6		2
Cases	3 864		252
RR (95%CI)	0.83 (0.76-0.90)		1.11 (0.80-1.53)
Heterogeneity (I^2, p-value)	0%, 0.66		5%, 0.31

[1]Meta-analysis was not conducted in the 2005 and 2008 SLR.

Table 540 BMI at early adulthood and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Boggs, 2015 BRE80582 USA	BWHS, Prospective Cohort, Age: 30-69 years, W	896/ 55 093 10 years	Cancer registry, national death Index, self-report, pathology reports	Self-reported, weight at 18 years	Incidence, Invasive breast cancer	<20 vs 25 kg/m^2	1.50 (1.17-1.92)	Age, age at first child birth, age at menarche, benign breast disease, estrogen plus progesterone use, family history, height, oophorectomy/hysterectomy, oral contraceptive use	
Catsburg, 2014b BRE80529 Canada	CSDLH, Case Cohort, W, alumnae	1 064/ 4 417 15 years	Cancer registry	Self-reported, weight at 20 years	Incidence, Invasive breast cancer	≥30 vs 18.5-24.99 kg/m^2	0.59 (0.24-1.45) Ptrend:0.11	Age at first child birth, age at menarche, alcohol Intake, family history of breast cancer, HRT use, menopausal status, number of childbirths, OC use, physical activity	
Harris, 2011a BRE80622 USA	NHS I and II, Nested Case Control, Age: 25-55 years,	1 452/ 2731 controls 15 years	Self-reported verified by medical record review	Self-reported body fatness during childhood and adolescence,	Incidence, breast cancer	≥25 vs 20-22.4 kg/m^2	0.84 (0.65-1.09) Ptrend:0.78	Age at menarche, alcohol, breast density, family history of breast	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	W			BMI at age 18 years				cancer, parity and age at first birth; matched by age, menopausal status, MHT use, race/ethnicity, time and fasting status of blood draw	
Suzuki, 2011b BRE80318 Japan	JPHC I and II, Prospective Cohort, Age: 40-69 years	452/ 41 594 14 years	Hospital records + cancer registry	Self-reported, weight at 20 years	Incidence, breast cancer	≥24 vs 20-24 kg/m^2	0.82 (0.61-1.11) Ptrend:0.005	Age, age at first child birth, age at menarche, parity, menopausal status, use of exogenous female hormones, smoking status, leisure-time physical activity, alcohol intake, green-yellow vegetables, meat and meat products, isoflavones intake, change in BMI from age 20 years	
						per 5 kg/m^2	0.75 (0.61-0.92)		Included in meta-analysis
		241/			Incidence, unknown ER/PR status	per 5 kg/m^2	0.79 (0.59-1.05)		
		94/			Incidence, breast cancer ER+/PR+	per 5 kg/m^2	1.10 (0.71-1.70)		
		60/			Incidence, breast cancer ER-/PR-	per 5 kg/m^2	0.49 (0.27-0.88)		
		45/			Incidence, breast cancer ER+/PR-	per 5 kg/m^2	0.64 (0.32-1.24)		
		452/			Incidence, breast	≥24 vs 20-24	0.75 (0.56-1.00)	As above, with	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
					cancer	kg/m^2	Ptrend:<0.0001	change in BMI from age 20 years replaced by recent BMI	
						per 5 kg/m^2	0.68 (0.56-0.82)		
Burton, 2010 BRE80315 Scotland	Glasgow Alumni Cohort study, Prospective Cohort, Age: 20 years, M/W, University students	95/ 2 657 49 years	Cancer registry/ death certificate	Measured at college physical examination, weight at 18 years	Incidence, breast cancer	per 1 kg/m^2	0.99 (0.91-1.08)	Age as time axis in Cox proportional hazard model, age at menarche, height, smoking, social class	
						>25 vs 19-23 kg/m^2	0.85 (0.37-1.96)		
		51/			Mortality, breast cancer	per 1 kg/m^2	0.98 (0.87-1.10)		
						>25 vs 19-23 kg/m^2	1.09 (0.38-3.08)		
Cerhan, 2004 BRE01495 USA	Minesota, 1944, Prospective Cohort, W	31/ 4 633 5 years	Partially histological - over 80%	Self reported, weight at 18 years and adult height	Incidence, breast cancer, Sisters and daughters of cases	≥21.9 vs ≤19.6 kg/m^2	1.60 (0.65-3.91) Ptrend:0.31	Age, birth cohort, non-independence of observations within a family, adult BMI	
		72/			Granddaughters and nieces of cases	≥21.9 vs ≤19.6 kg/m^2	1.60 (0.86-2.98) Ptrend:0.14		
		54/			Marry-ins of cases	≥21.9 vs ≤19.6 kg/m^2	0.86 (0.43-1.74) Ptrend:0.66		

Table 541 BMI at early adulthood and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Ma, 2011 BRE80629 USA	National Health Interview Survey (NHIS), Prospective Cohort, Age: 18-39 years, W	142/ 63 582 16.1 years	National death Index	Self-reported (74.1%), reported by family member (25.9%), weight between 18-39 years	Mortality, breast cancer	≥35 vs 18.5-24.9 kg/m^2	1.31 (0.60-2.87)	Age, educational level, race/ethnicity, smoking status	Breast cancer mortality, not analysed
		80/			BMI 15 to <25kg/m^2	per 5 kg/m^2	0.62 (0.35-1.10)		
		62/			BMI >=25 kg/m^2	per 5 kg/m^2	1.07 (0.82-1.39)		
		72/			Never smoker	≥35 vs 18.5-24.9 kg/m^2	1.75 (0.62-4.89)		
		35/			Never smokers, BMI 15-<25 kg/m^2	per 5 kg/m^2	0.44 (0.18-1.05)		
		37/			Never smokers, BMI>=25 kg/m^2	per 5 kg/m^2	1.17 (0.87-1.56)		
Jonsson, 2003 BRE04482 Sweden	Swedish twin cohort, 1969, Prospective Cohort, Age: 44-83 years, W, Twins	421/ 11 598 29 years	Partially histological - over 80%	Self-report (questionnaire).repeated measures (at the time they answered the questionnaire, at ages 25 and 40.	Incidence, breast cancer	≥25 vs 18.5-24.99 kg	0.50 (0.30-0.80)	Age , BMI at baseline	Excluded, two exposure categories only
Zhang, 2003	NHS,		Medical records	Self-reported,	Incidence, breast	(mean			Superseded by

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
BRE13958 USA	Nested Case Control, Age: 43-69 years, W, Registered nurses	32 826 40 months	+ self-reported +death certificate	weight at 18 years	cancer	exposure)			Harris, 2011a
Okasha, 2002a BRE80631 UK	Glasgow Alumni Cohort study, Historical Cohort, W	32/ 2 340 41 years	NHS central registry	Measured at student health service	Mortality, breast cancer	22.8-35.08 vs 11.77-19.71 kg/m^2	3.61 (1.00-12.94)	Age	Breast cancer mortality, not analysed (same study as Burton, 2010)
Okasha, 2002b BRE17887 UK	Glasgow cohort, 1948, Prospective Cohort, Age: 20 years, W, College alumnae	113/ 2 528 53 years	Partially histological - over 80%	Measured by physician.	Incidence, breast cancer	≥25 vs 19-22.9	0.89 (0.42-1.87)	Age	Superseded by Burton, 2010, BRE80315
Whittemore, 1985 BRE80630 USA	CAHS, Nested Case Control, Age: 17- years, W	67/ 276 50 years	Self-report and/or death certificate	At college physical examination	Incidence, breast cancer	High vs low lb*1000/inch^2 High vs low kg/m^2	2.30 (1.10-4.90) 1.80 (1.07-3.06)	Matched by year of birth	Excluded, two exposure categories only; BMI measured in imperial units, converted to kg/m^2 (lb*703/inch^2)

Figure 562 RR estimates of breast cancer by BMI at early adulthood

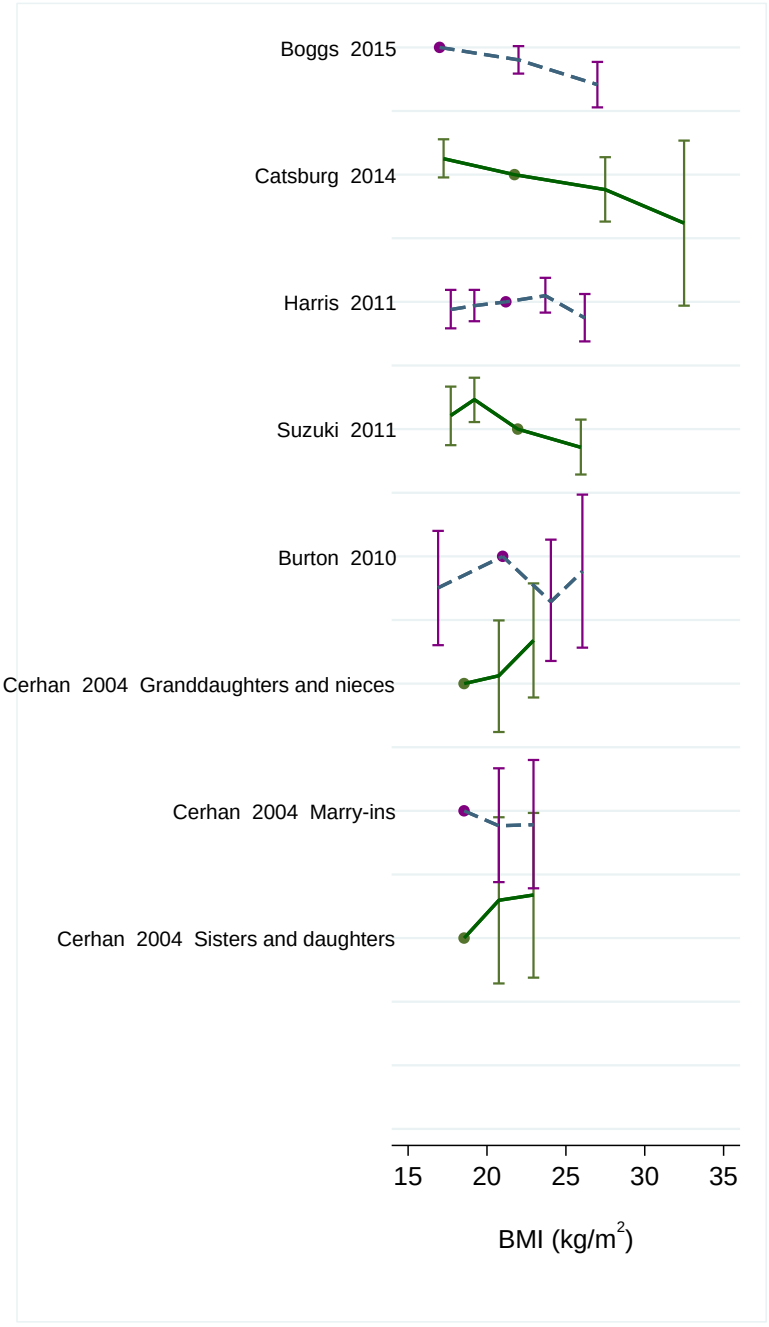


Figure 563 RR (95% CI) of breast cancer for the highest compared with the lowest level of BMI at early adulthood

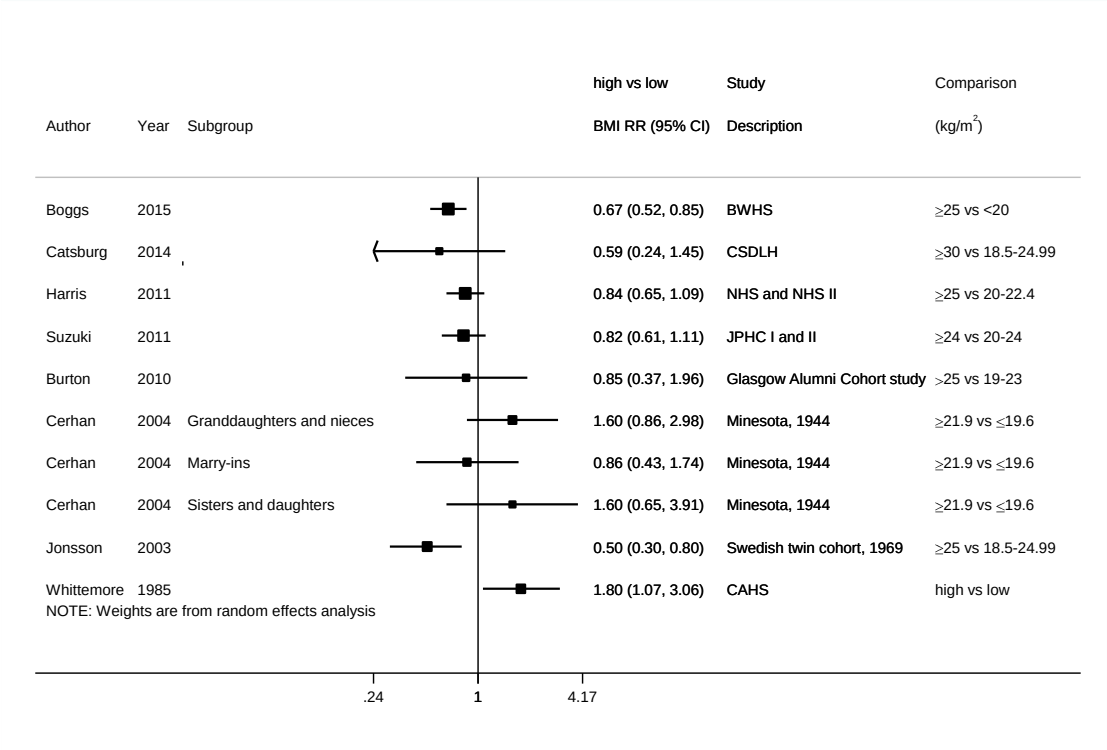


Figure 564 Relative risk of breast cancer for 5 kg/m^2 increase of BMI at early adulthood

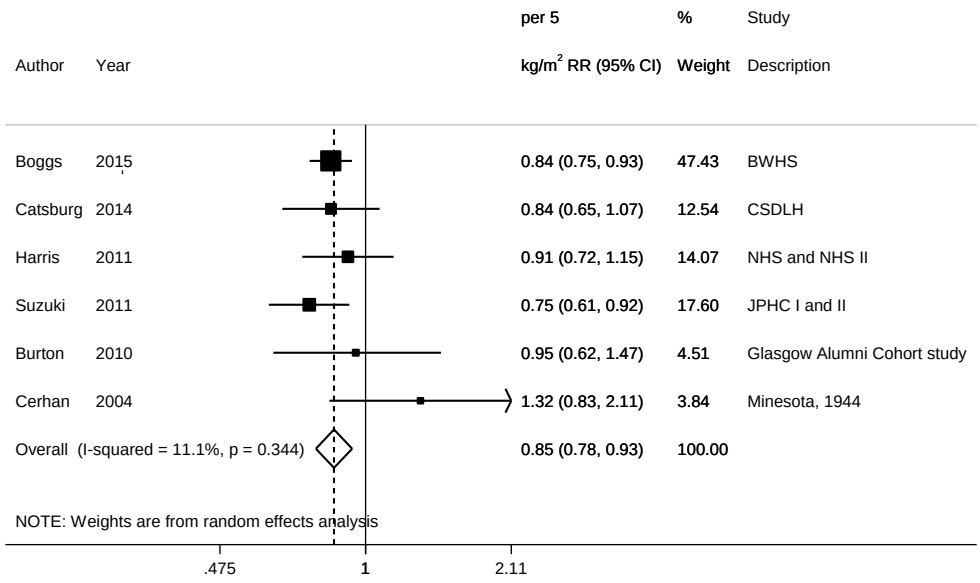


Figure 565 Funnel plot of studies included in the dose response meta-analysis of BMI at early adulthood and breast cancer

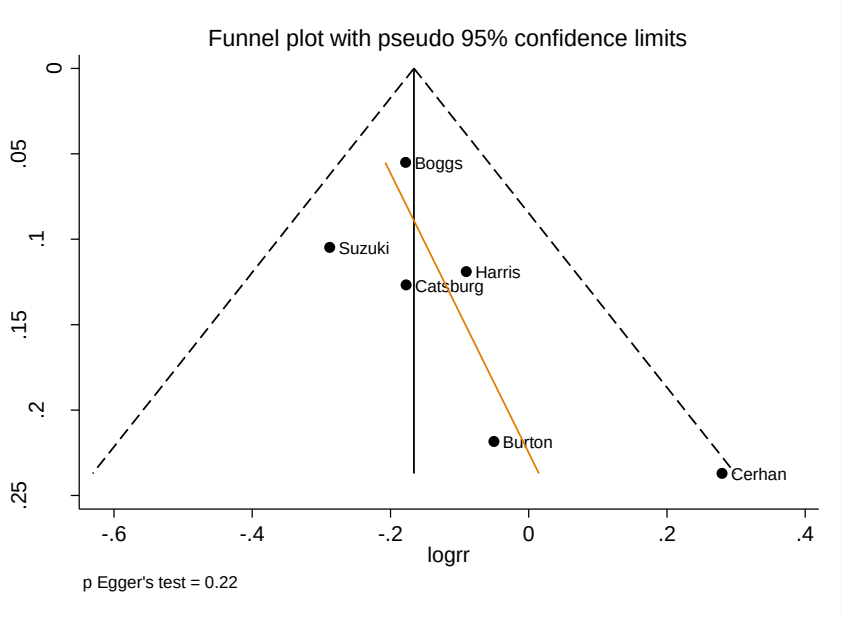
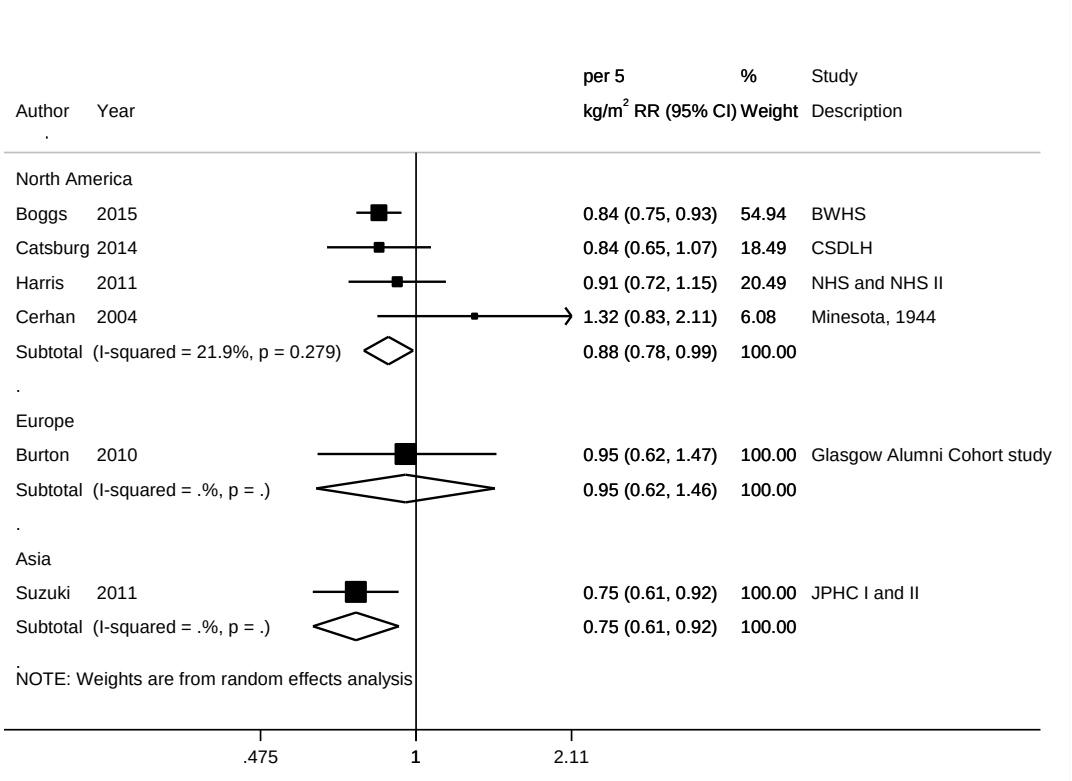


Figure 566 Relative risk of breast cancer for 5 kg/m^2 increase of BMI at early adulthood, by geographic location



Premenopausal breast cancer

Summary

Main results:

All twelve studies on BMI at early adulthood could be included in the dose-response meta-analysis.

BMI at early adulthood was significantly inversely associated with premenopausal breast cancer risk (summary RR per 5 kg/m^2=0.82, 95% CI= 0.76-0.89). There was low heterogeneity between studies (I^2=15%, P=0.31). There was no evidence of significant publication or small studies bias (P for Egger's test=0.75).

Four studies (two publications) (Bandera, 2015, three studies; Michels, 2006a) reported results by breast cancer oestrogen receptor status. For the highest versus the lowest BMI at early adulthood, non-significant inverse associations of ER-positive breast cancer were reported in all studies. For ER-negative breast cancer, one study (Michels, 2006a) reported a non-significant inverse association and the other pooled study (Bandera, 2015) reported no significant association.

Sensitivity analyses:

Summary RR remained significant when studies were omitted in turn in influence analysis. When the pooled study (Bandera, 2015) that included one cohort and two case-control studies were excluded, the summary RR was 0.81 (95% CI=0.73-0.89) (I^2=20%, p=0.27).

Inverse associations were observed in the stratified analysis by geographic locations, which was significant among North American studies (summary RR per 5 kg/m^2=0.80, 95% CI= 0.71-0.90) (six studies, moderate heterogeneity) and not European (RR=0.90, 95% CI=0.73-1.11) (three studies, low heterogeneity) or Asian studies (RR=0.82, 95% CI= 0.64-1.05) (three studies, low heterogeneity).

Significant inverse association (summary RR=0.77, 95% CI=0.70-0.85) was observed in studies adjusted for major confounding factors. When restricted to the seven studies (Bandera, 2015, three studies; Weiderpass, 2004; Suzuki, 2011b, two studies; Michels, 2006a) that adjusted for weight change, adult BMI or WHR, the summary RR was 0.85 (95% CI=0.79-0.92).

Non-linear dose-response meta-analysis:

There was no evidence of non-linear relationship between BMI at early adulthood and premenopausal breast cancer (P for non-linearity=0.09). Premenopausal breast cancer risk decreased monotonically through all ranges of BMI (graph not shown).

Study quality:

There were three European studies, three Asian studies, and six North American studies. Bandera, 2015 was of black women. Manders, 2011 included BRCA1/2 carriers. The non-

significant inverse association observed in this study (Manders, 2011) was similar to other studies.

Participants were asked to recall their weight at early adulthood in all studies apart from Burton, 2010 where body measurements were taken at college physical examination. A non-significant positive association was reported but there were only 30 premenopausal breast cancer cases in this study (Burton, 2010). Seven studies assessed weight at age 18 years (Bandera, 2015, BWHS and CBCS; Manders, 2011; Burton, 2010; Michels, 2006a; Weiderpass, 2004; London, 1989), and five studies at 20 years (Bandera, 2015, WCHS; Catsburg, 2014b; Suzuki, 2011b, JPHC I and II; Li, 2006).

Case ascertainment was through cancer registries or confirmed through medical records. Most studies were adjusted for major confounding factors. Bandera, 2015, Burton, 2010, Li, 2006, and Weiderpass, 2004 did not adjust for alcohol consumption. Not all studies accounted for weight change or obesity during adulthood. When restricted to the seven studies that adjusted for this factor (Bandera, 2015, three studies; Weiderpass, 2004; Suzuki, 2011b, two studies; Michels, 2006a), the significant inverse association remained.

Table 542 BMI at early adulthood and premenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	12 (12 publications)
Studies included in forest plot of highest compared with lowest exposure	11 (8 publications)
Studies included in linear dose-response meta-analysis	12 (9 publications)
Studies included in non-linear dose-response meta-analysis	8 (6 publications)

Table 543 BMI at early adulthood and premenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and 2016 CUP

	2005 SLR[1]	**CUP**
Increment unit used	-	**Per 5 kg/m^2**
Studies (n)	-	12
Cases	-	4 953
RR (95%CI)	-	0.82 (0.76-0.89)
Heterogeneity (I^2, p-value)	-	15%, 0.31

P value Egger test	-		0.75
Stratified analysis in the CUP			
Geographic locations	**Asia**	**Europe**	**North America**
Studies (n)	3	3	6
Cases	432	874	3 647
RR (95%CI)	0.82 (0.64-1.05)	0.90 (0.73-1.11)	0.80 (0.71-0.90)
Heterogeneity (I^2, p-value)	0%, 0.59	8%, 0.34	45%, 0.14
Adjustment for age, alcohol intake, reproductive factors	**Adjusted**		**Not adjusted**
Studies (n)	6		6
Cases	2 897		2 056
RR (95%CI)	0.77 (0.70-0.85)		0.89 (0.80-0.99)
Heterogeneity (I^2, p-value)	12%, 0.34		0%, 0.77
Adjusted for weight change or adult BMI/WHR			
Studies (n)	7		
Cases	3 413		
RR (95%CI)	0.85 (0.79-0.92)		
Heterogeneity (I^2, p-value)	0%, 0.81		

[1]Meta-analysis was not conducted in the 2005 and 2008 SLR.

Table 544 BMI at early adulthood and premenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Bandera, 2015 USA	AMBER Consortium, Pooled study, 1 cohort and 2 case-control studies* W African American (*CBCS; WCHS; BWHS)	1 125 cases 4053 controls	Record linkage to cancer registries, identified through hospitals, self-reported and verified with medical records and cancer registry data	Self-reported, weight at 18 (BWHS, CBCS) or 20 (WCHS)	Incidence, premenopausal breast cancer	≥ 30 vs 20-24.9 kg/m^2	0.78 (0.55-1.10) Prend: 0.06	Age, education, study, time period, geographical region, family history of breast cancer, age at menarche, parity, breastfeeding, age at first birth, hormone therapy use, OC use, recent WHR	Included in meta-analysis
		674 cases			ER+	≥ 30 vs 20-24.9 kg/m^2	0.65 (0.42-1.01) Ptrend: 0.02		
		451 cases			ER-	≥ 30 vs 20-24.9 kg/m^2	1.00 (0.63-1.58) Ptrend: 0.69		
		224 cases			Triple-negative	≥ 30 vs 20-24.9 kg/m^2	1.08 (0.59-1.98) Ptrend: 0.31		
		1 125 cases 4053 controls			Incidence, premenopausal breast cancer	≥ 30 vs 20-24.9 kg/m^2	0.77 (0.55-1.07) Ptrend: 0.02	As above, without recent WHR	
		674 cases			ER+	≥ 30 vs 20-24.9 kg/m^2	0.65 (0.42-0.99) Ptrend: 0.005		
		451 cases			ER-	≥ 30 vs 20-24.9 kg/m^2	0.97 (0.62-1.51) Ptrend: 0.58		
		224 cases			Triple-negative	≥ 30 vs 20-24.9 kg/m^2	1.08 (0.60-1.95) Ptrend: 0.30		
Catsburg, 2014b BRE80529 Canada	CSDLH, Case Cohort, W, alumnae	545/ 4 417 15 years	Cancer registry	Self-reported, weight at 20 years	Incidence, Invasive breast cancer, premenopausal	≥30 vs 18.5-24.99 kg/m^2	0.96 (0.33-2.81) Ptrend:0.36	Age at first child birth, age at menarche, alcohol Intake, family history of breast cancer,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								HRT use, menopausal status, number of childbirths, OC use, physical activity	
Manders, 2011 BRE80314 Netherlands	HEBON, Historical Cohort, W, Subjects with BRCA1/2 mutation	155/ 719 10 years	Cancer registry	Self-reported, weight at 18 years	Incidence, breast cancer, premenopausal	≥25 vs 18.50-22.49 kg/m^2	0.41 (0.13-1.27)	Age as time axis in Cox proportional hazard model, stratified for birth cohort and genes, clustered on family, adjusted for lifetime spots activity	
Suzuki, 2011b BRE80318 Japan	JPHC I and II Prospective Cohort, Age: 40-69 years	220/ 41 594 14 years	Hospital records + cancer registry	Self-reported, weight at 20 years	Incidence, breast cancer, premenopausal	≥24 vs 20-24 kg/m^2	1.01 (0.63-1.61) Ptrend:0.11	Age, age at first child birth, age at menarche, parity, use of exogenous female hormones, smoking status, leisure-time physical activity, alcohol intake, green-yellow vegetables, meat and meat products, isoflavones	
						per 5 kg/m^2	0.78 (0.57-1.06)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								intake, change in BMI from age 20 years	
Burton, 2010 BRE80315 Scotland	Glasgow Alumni Cohort study, Prospective Cohort, Age: 20 years, M/W, University students	30/ 2 657 49 years	Cancer registry/ death certificate	Measured at college physical examination, weight at 18 years	Incidence, premenopausal breast cancer	per 1 kg/m^2	1.05 (0.91-1.21)	Age at menarche, height, smoking, social class	
Li, 2006 BRE80166 China	SWHS, Prospective Cohort, Age: 40-70 years, W	212/ 73 410 5.66 years	Medical records	Self-reported, weight at 20 years	Incidence, breast cancer, premenopausal	≥20.46 vs ≤18.36	0.87 (0.61-1.24) Ptrend:0.55	Age, age at first child birth, breastfeeding, educational level, energy intake, family history of breast disease, family history of breast cancer	
Michels, 2006a BRE80033 USA	NHS II, Prospective Cohort, Age: 25-42 years, Premenopausal	1 379/ 116 609 14 years	Self-report verified by medical record	Self-reported, weight at 18 years	Incidence, breast cancer, premenopausal	per 5 units	0.83 (0.74-0.94)	Age , age at first child, age at menarche, alcohol, benign breast disease, family history, height, OC use, parity/pregnancies, physical activity, current BMI	Included in meta-analysis
						≥27.5 vs 20-22.4 kg/m^2	0.61 (0.42-0.87) Ptrend:0.01		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
						per 5 units	0.81 (0.73-0.89)		
						≥27.5 vs 20-22.4 kg/m^2	0.57 (0.41-0.81) Ptrend:<0.001		
		663/			ER-positive	per 5 units	0.87 (0.75-1.00)		
						≥25.0 vs 20-22.4 kg/m^2	0.76 (0.56-1.03)		
		282/			ER-negative	per 5 units	0.93 (0.75-1.15)	As above, without current BMI	
						≥25.0 vs 20-22.4 kg/m^2	0.94 (0.60-1.49)		
		630/			PR-positive	per 5 units	0.87 (0.75-1.00)		
						≥25.0 vs 20-22.4 kg/m^2	0.84 (0.62-1.14)		
		298/			PR-negative	per 5 units	0.90 (0.73-1.11)		
						≥25.0 vs 20-22.4 kg/m^2	0.76 (0.48-1.21)		
Weiderpass, 2004 BRE18151 Sweden, Norway	WLHS, Sweden and Norway, Prospective Cohort, Age: 30-49 years, W, Premenopausal	689/ 99 717 8 years	Partially histological - over 80%	Self-reported, weight at 18 years	Incidence, premenopausal breast cancer	per 1 kg/m^2	0.98 (0.95-1.02)	Age, age at first child, age at menarche, duration of breastfeeding, family history of breast cancer, OC use, parity, place of residence, adult BMI	Rescaled to per 5 kg/m^2, included in meta-analysis
						≥25 vs 20-24.59 kg/m^2	0.90 (0.66-1.24) Ptrend:0.60		
						per 1 kg/m^2	0.96 (0.93-0.99)	As above,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
						≥25 vs 20-24.59 kg/m^2	0.74 (0.59-0.91)	without adult BMI	
London, 1989 BRE80626 USA	NHS, Prospective Cohort, Age: 30-55 years, W	598/ 115 534 743 716 person-years	Self-report verified by medical record	Self-reported, weight at 18 years	Incidence, Invasive breast cancer, premenopausal	≥25 vs ≤19.9 kg/m^2	0.60 (0.50-0.80) Ptrend:0.0005	Age, age at first child, age at menarche, family history of breast cancer, history of benign breast disease, parity, smoking	

Table 545 BMI at early adulthood and premenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Palmer, 2007 BRE80122 USA	BWHS, Prospective Cohort, Age: 21-69 years	491/ 59 000 10 years	Death certificate / patient records / self report	Self-reported, weight at 18 years	Incidence, breast cancer, premenopausal	≥25 vs ≤19	0.63 (0.46-0.87)	Age, age at first child birth, age at menarche, educational level, parity, physical activity	Superseded by Bandera, 2015
						≥25 vs ≤19	0.68 (0.46-0.98)	Current BMI	
Huang, 1997 BRE04117 USA	NHS, Prospective Cohort, Age: 35-55 years, W,	1 000/ 95 256 16 years	Medical records + self-reported +death certificate	Self-reported, weight at 18 years	Incidence, Invasive breast cancer, premenopausal	≥25 vs ≤18.2 kg/m^2	0.61 (0.45-0.83) Ptrend:<0.001	Age , age at first child, age at menarche, family history, height, parity/pregnanci	Superseded by London, 1989

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	Registered nurses							es	
Willett, 1985 BRE80625 USA	NHS, Prospective Cohort, Age: 30-55 years, W	310/ 103 688 4 years	Self-reported validated by pathology report	Self-reported, weight at 18 years	Incidence, breast cancer, premenopausal	70.4 vs 47 kg	0.55 Ptrend:0.0001	Age	Superseded by London, 1989

Figure 567 RR estimates of premenopausal breast cancer by BMI at early adulthood

Figure 568 RR (95% CI) of premenopausal breast cancer for the highest compared with the lowest level of BMI at early adulthood

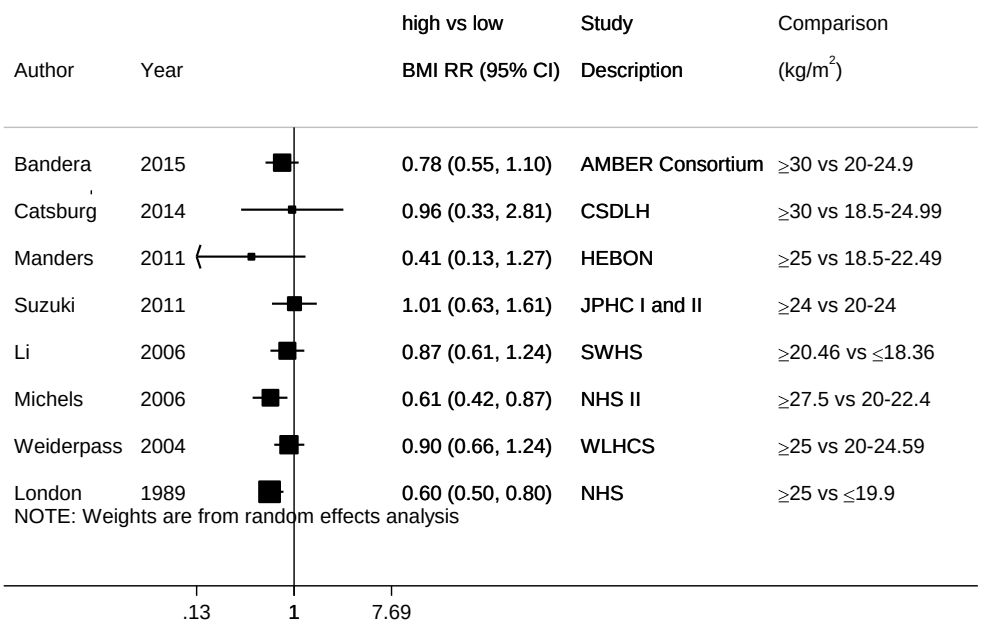


Figure 569 Relative risk of premenopausal breast cancer for 5 kg/m^2 increase of BMI at early adulthood

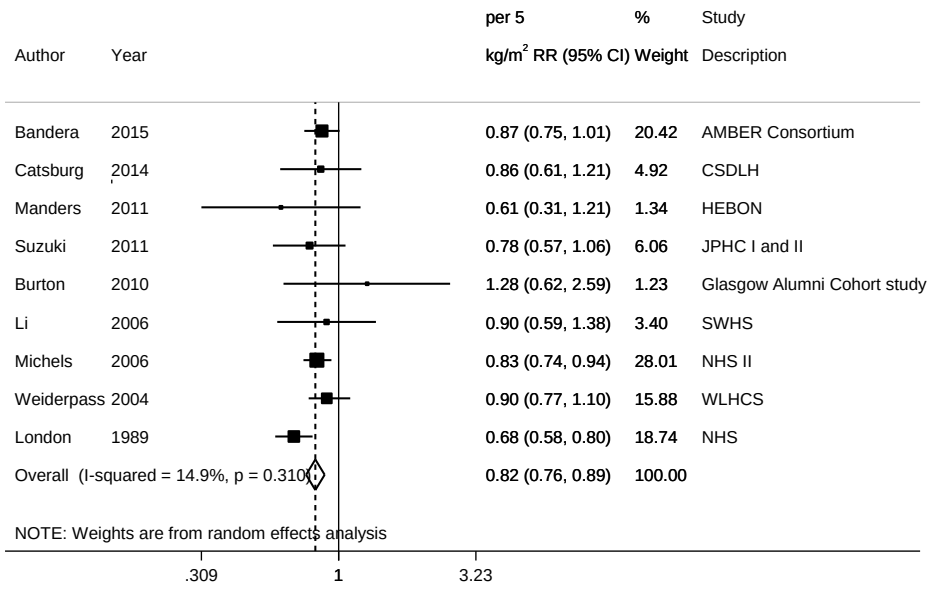


Figure 570 Funnel plot of studies included in the dose response meta-analysis of BMI at early adulthood and premenopausal breast cancer

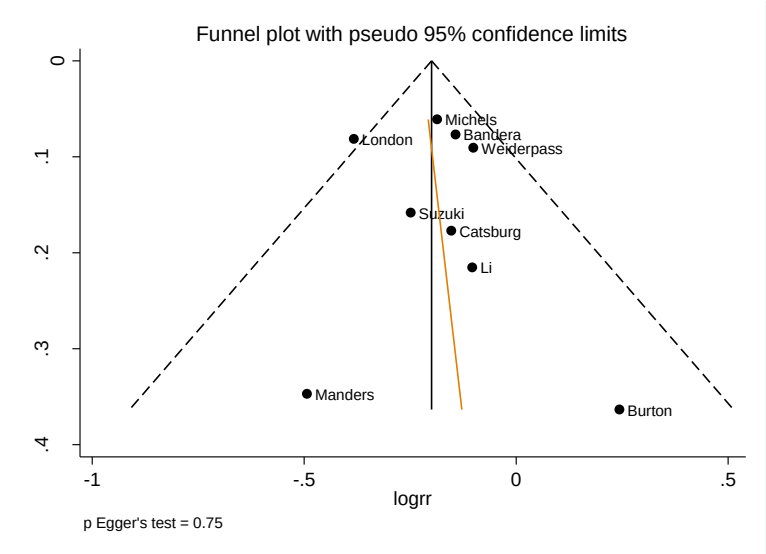
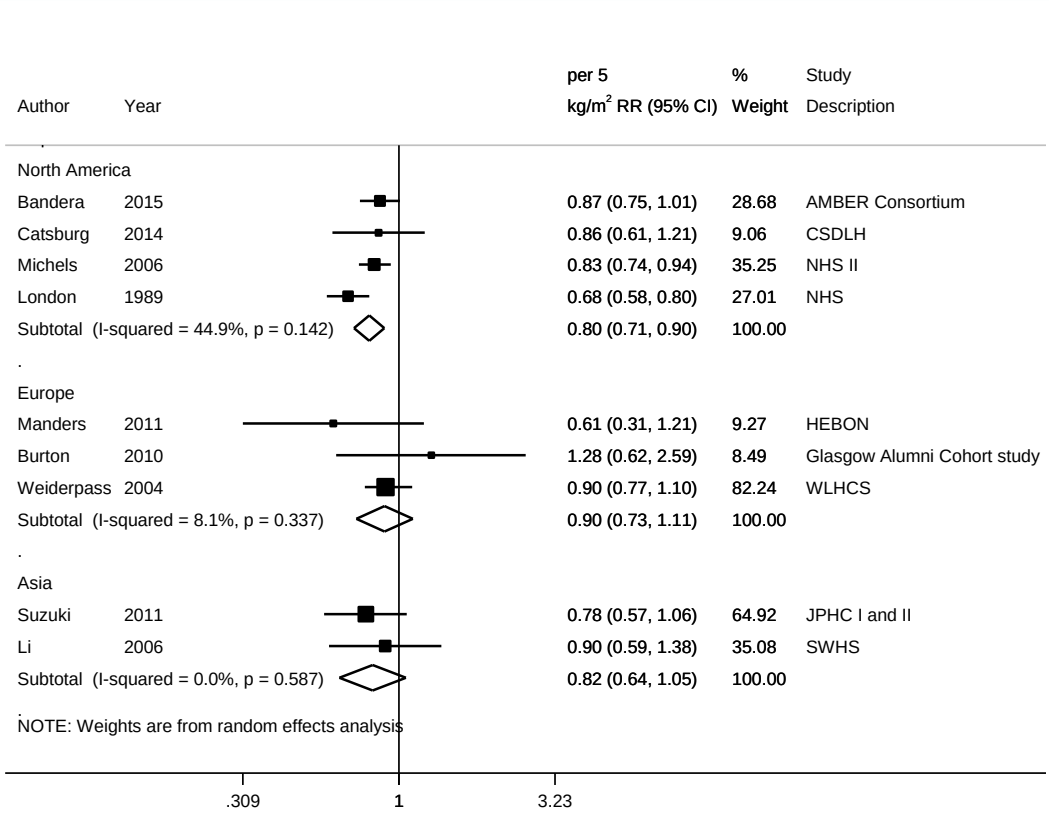


Figure 571 Relative risk of premenopausal breast cancer for 5 kg/m^2 increase of BMI at early adulthood, by geographic location



Postmenopausal breast cancer

Summary

Main results:

Seventeen out of 21 studies (24 publications) on BMI at early adulthood could be included in the dose-response meta-analysis.

BMI at early adulthood was significantly inversely associated with postmenopausal breast cancer risk (summary RR per 5 kg/m^2=0.82, 95% CI= 0.76-0.88). There was moderate heterogeneity between studies (I^2=44%, P=0.04). There was no evidence of significant publication or small studies bias (P for Egger's test=0.28)

Four studies were excluded from the dose-response meta-analysis. Two studies did not have sufficient data to be included. Inverse associations were reported, which was not significant overall (Manders, 2011) or among current MHT users (Ahn, 2007) and significant among MHT non-users (Ahn, 2007).

Two excluded studies reported results by hormone receptor-defined breast cancer only (Canchola, 2012; Phipps, 2011). Meta-analysis was not conducted as only a total of four studies (five publications) reported results. Significant inverse association with ER-positive (Phipps, 2011; Sellers, 2002), PR-positive (Sellers, 2002), ER+PR+ (Potter, 1995), and ER+PR- (Canchola, 2012) breast cancers were reported. Non-significant inverse associations were observed for other breast cancer subtypes, apart from ER-PR- breast cancer, where a non-significant positive association was reported (Potter, 1995). A highest versus the lowest forest plot was constructed to display the results.

Three studies (Suzuki, 2011b; Ahn, 2007; Palmer, 2007) reported results by MHT use. Inverse associations for the highest compared with the lowest BMI at early adulthood were observed regardless of the MHT status.

Sensitivity analyses:

Summary RR remained significant when studies were omitted in turn in influence analysis. When the pooled study (Bandera, 2015) that included two cohorts and two case-control studies were excluded, the summary RR was 0.81 (95% CI=0.75-0.88) (I^2=47%, p=0.03).

Inverse associations were observed in the stratified analysis by geographic locations, which were significant among North American studies (RR per 5 kg/m^2=0.82, 95% CI= 0.75-0.90) (10 studies, high heterogeneity) and Asian studies (RR=0.68, 95% CI= 0.51-0.92) (four studies, moderate heterogeneity), and not European studies (RR=0.86, 95% CI=0.72-1.03) (two studies, low heterogeneity). One study from Australia and New Zealand also reported a non-significant inverse association (RR=0.90, 95% CI=0.79-1.04).

Significant inverse association (RR=0.81, 95% CI=0.74-0.88) was observed in studies adjusted for major confounding factors. When restricted to the nine studies (Bandera, 2015, four studies;

Han, 2014; Suzuki, 2011b, two studies; Kawai, 2010b; Sellers, 2002) that adjusted for weight change, adult BMI or WHR, the summary RR was 0.76 (95% CI=0.64-0.91).

Non-linear dose-response meta-analysis:

There was no evidence of non-linear relationship between BMI at early adulthood and postmenopausal breast cancer (P for non-linearity=0.07). Postmenopausal breast cancer risk decreased monotonically through all ranges of BMI (graph not shown).

Study quality:

There were two European studies, four Asian studies, one study from Australia and New Zealand, and 10 North American studies. Bandera, 2015 was of black women. White, 2012 was a multi-ethnic study. Manders, 2011 that was excluded from the dose-response meta-analysis included BRCA1/2 carriers. The study (Manders, 2011) reported a non-significant inverse association for high versus low BMI at 18 years that was similar to other studies.

Participants were asked to recall their weight at early adulthood in all studies apart from Burton, 2010 where body measurements were taken at college physical examination. Similar inverse associations were observed in this study and other studies that used self-reported data.

Six studies assessed weight at age 18 years (Bandera, 2015, BWHS and CBCS; Burton, 2010; Morimoto, 2002; Sellers, 2002; London, 1989), seven studies at 20 years (Bandera, 2015, WCHS; Catsburg, 2014b; Suzuki, 2011b, JPHC I and II; Kawai, 2010b; Li, 2006; van den Brandt, 1997), two studies at 21 years (Bandera, 2015, MEC African American, Torio, 2010; White, 2012 MEC non-African American), one study at 25 years (Han, 2014), and one study assessed weight between 18-21 years (Krishnan, 2013).

Case ascertainment was through cancer registries or confirmed through medical records. Most studies adjusted for major confounding factors. This included the MEC (White, 2012), where results from non-African American women were pooled and included in the present meta-analysis. Bandera, 2015 (four studies, including African American women from MEC), Burton, 2010, Li, 2006, and Weiderpass, 2004 did not adjust for alcohol consumption. Stratified analysis by adjustment showed significant inverse associations. Not all studies accounted for weight change or obesity during adulthood. When restricted to the nine studies that adjusted for this factor (Bandera, 2015, four studies; Han, 2014; Suzuki, 2011b, two studies; Kawai, 2010b; Sellers, 2002), the significant inverse association remained.

Table 546 BMI at early adulthood and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	21 (24 publications)
Studies included in forest plot of highest compared with lowest exposure	17 (14 publications)

Studies included in linear dose-response meta-analysis	17 (14 publications)
Studies included in non-linear dose-response meta-analysis	13 (10 publications)

Table 547 BMI at early adulthood and postmenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and 2016 CUP

	2005 SLR[1]		**CUP**
Increment unit used	-		**Per 5 kg/m^2**
Studies (n)	-		17
Cases	-		10 229
RR (95%CI)	-		0.82 (0.76-0.88)
Heterogeneity (I^2, p-value)	-		44%, 0.04
P value Egger test	-		0.28
Stratified analysis in the CUP			
Geographic locations[2]	**Asia**	**Europe**	**North America**
Studies (n)	4	2	10
Cases	509	569	8 483
RR (95%CI)	0.68 (0.51-0.92)	0.86 (0.72-1.03)	0.82 (0.75-0.90)
Heterogeneity (I^2, p-value)	39%, 0.19	0%, 0.99	57%, 0.02
Adjustment for age, alcohol intake, reproductive factors	**Adjusted**		**Not adjusted**
Studies (n)	11		7
Cases	7 796		2 433
RR (95%CI)	0.81 (0.74-0.88)		0.87 (0.77-0.99)
Heterogeneity (I^2, p-value)	59%, 0.01		0%, 0.93
Adjusted for weight change or adult BMI/WHR			
Studies (n)	9		
Cases	4 285		
RR (95%CI)	0.76 (0.64-0.91)		
Heterogeneity (I^2, p-value)	70%, 0.01		

[1]Meta-analysis was not conducted in the 2005 and 2008 SLR.

[2]Also one study from Australia and New Zealand (Krishnan, 2013) (RR per 5 kg/m^2=0.90, 95% CI=0.79-1.04)

Table 548 BMI at early adulthood and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Bandera, 2015 USA	AMBER Consortium, Pooled study, 2 cohorts and 2 case-control studies* W African American (*CBCS; WCHS; BWHS; MEC)	1 923 cases 7 465 controls	Record linkage to cancer registries, identified through hospitals, self-reported and verified with medical records and cancer registry data	Self-reported, weight at 18 (BWHS, CBCS), 20 (WCHS), or 21 (MEC)	Incidence, postmenopausal breast cancer	≥ 30 vs 20-24.9 kg/m^2	0.67 (0.45-1.01) Prend: 0.02	Age, education, study, time period, geographical region, family history of breast cancer, age at menarche, parity, breastfeeding, age at first birth, hormone therapy use, OC use, age at menopause, recent WHR	Included in meta-analysis
		1338 cases			ER+	≥ 30 vs 20-24.9 kg/m^2	0.62 (0.38-1.01) Ptrend: 0.12		
		585 cases			ER-	≥ 30 vs 20-24.9 kg/m^2	0.78 (0.44-1.41) Ptrend: 0.04		
		255 cases			Triple-negative	≥ 30 vs 20-24.9 kg/m^2	0.68 (0.29-1.56) Ptrend: 0.06		
		1 923 cases 7 465 controls			Incidence, postmenopausal breast cancer	≥ 30 vs 20-24.9 kg/m^2	0.71 (0.50-1.01) Ptrend: 0.01	As above, without recent WHR	
		1338 cases			ER+	≥ 30 vs 20-24.9 kg/m^2	0.68 (0.45-1.03) Ptrend:0.05		
		585 cases			ER-	≥ 30 vs 20-24.9 kg/m^2	0.78 (0.46-1.34) Ptrend:0.02		
		255 cases			Triple-negative	≥ 30 vs 20-24.9 kg/m^2	0.77 (0.35-1.66) Ptrend: 0.03		
Catsburg, 2014b BRE80529 Canada	CSDLH, Case Cohort, W, alumnae	519/ 4 417 15 years	Cancer registry	Self-reported, weight at 20 years	Incidence, Invasive breast cancer, postmenopausal	≥30 vs 18.5-24.99 kg/m^2	0.21 (0.03-1.59) Ptrend:0.21	Age at first child birth, age at menarche, alcohol Intake, family history of	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								breast cancer, HRT use, menopausal status, number of childbirths, OC use, physical activity	
Han, 2014 BRE80525 USA	ARIC, Prospective Cohort, Age: 45-64 years, W, Postmenopausal	372/ 7 569 20 years	Cancer registry and hospital records	Self-reported, weight at 25 years	Incidence, postmenopausal breast cancer	≥30 vs 18.5-24.9 kg/m^2	0.87 (0.45-1.66)	Age, menopause status at baseline, age at menarche, age at menopause, alcohol consumption, smoking status, cigarette smoking status, education, height, physical activity, race-center, weight change from age 25 to baseline	Included in meta-analysis, estimated dose-response slope
		36/			Mortality, postmenopausal breast cancer	per 5 kg/m^2	0.90 (0.54-1.51)		
						≥25 vs 18.5-24.9 kg/m^2	0.74 (0.25-2.19)		
		372/			Incidence, postmenopausal breast cancer	≥30 vs 18.5-24.9 kg/m^2	0.79 (0.42-1.49)	As above, without weight change from age 25 to baseline	
		36/			Mortality, postmenopausal breast cancer	per 5 kg/m^2	0.88 (0.53-1.45)		
						≥25 vs 18.5-24.9 kg/m^2	0.71 (0.25-2.06)		
Krishnan, 2013 BRE80482 Australia	MCCS, Prospective Cohort,	668/ 14 441 16.5 years	Cancer registry / database / pathology	Self-reported weight at 18-21 years	Incidence, postmenopausal breast cancer	≥25 vs 18.5-24.9 kg/m^2	0.81 (0.61-1.07)	Age-underlying Cox proportional	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	Age: 39-76 years, W, Postmenopausal		reports					hazards model, age at menarche, alcohol, breastfeeding, country of birth, educational level, energy Intake, HRT use, OC use, parity, physical activity, smoking	
						per 5 kg/m^2	0.90 (0.79-1.04)		
White, 2012 BRE80396 Hawaii, California	MEC, Prospective Cohort, Age: 45-75 years, Postmenopausal	2 872/ 82 971 9 years	Cancer registry and national death Index	Self-reported weight at 21 years	Incidence, breast cancer	per 5 kg/m^2	0.90 (0.84-0.96)	Age, age at first child birth, age at menarche, age and type of menopause, alcohol Intake, energy intake, family history of breast cancer, height, HRT use, number of children, physical activity, smoking status	Excluded, overlapped with Bandera, 2015
						≥30 vs 20-24.9 kg/m^2	0.63 (0.43-0.91) Ptrend:0.009		
		893/			Japanese	≥30 vs 20-24.9 kg/m^2	0.20 (0.03-1.42) Ptrend:0.15		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
						per 5 kg/m^2	0.85 (0.74-0.98)		Included, pooled results with other ethnicity/race subgroups using fixed effect model
		790/			White	per 5 kg/m^2	0.82 (0.72-0.95)		
						≥30 vs 20-24.9 kg/m^2	0.47 (0.19-1.13) Ptrend:0.036		
		523/			African American	per 5 kg/m^2	0.91 (0.79-1.04)		Excluded, overlapped with Bandera, 2015
						≥30 vs 20-24.9 kg/m^2	0.73 (0.36-1.48) Ptrend:0.14		
		420/			Latina	≥30 vs 20-24.9 kg/m^2	0.70 (0.33-1.49) Ptrend:0.49		
						per 5 kg/m^2	0.92 (0.80-1.07)		Included, pooled results with other ethnicity/race subgroups using fixed effect model
		246/			Native Hawaiian	per 5 kg/m^2	1.01 (0.84-1.21)		
						≥30 vs 20-24.9 kg/m^2	0.91 (0.43-1.96) Ptrend:0.76		
Suzuki, 2011b BRE80318 Japan	JPHC I and II, Prospective Cohort, Age: 40-69 years	232/ 41 594 14 years	Hospital records + cancer registry	Self-reported, weight at 20 years	Incidence, breast cancer, postmenopausal	≥24 vs 20-24 kg/m^2	0.77 (0.52-1.14) Ptrend:0.07	Age, age at first child birth, age at menarche, parity, age at menopause, use of exogenous female hormones,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
						per 5 kg/m^2	0.77 (0.59-1.02)	smoking status, leisure-time physical activity, alcohol intake, green-yellow vegetables, meat and meat products, isoflavones intake, change in BMI from age 20 years	
		167/			HRT never	≥24 vs 20-24 kg/m^2	0.77 (0.48-1.23) Ptrend:0.22		
						per 5 kg/m^2	0.82 (0.59-1.13)		
		65/			HRT ever	≥24 vs 20-24 kg/m^2	0.76 (0.35-1.62) Ptrend:0.14		
						per 5 kg/m^2	0.67 (0.40-1.13)		
Burton, 2010 BRE80315 Scotland	Glasgow Alumni Cohort study, Prospective Cohort, Age: 20 years, M/W, University students	69/ 2 657 49 years	Cancer registry/ death certificate	Measured at college physical examination, weight at 18 years	Incidence, postmenopausal breast cancer	per 1 kg/m^2	0.97 (0.88-1.08)	Age at menarche, height, smoking, social class	
Kawai, 2010b BRE80316 Japan	MCS, Prospective Cohort, Age: 40-64	108/ 10 106 129 891 person-years	Cancer registry	Self-reported, weight at 20 years	Incidence, postmenopausal breast cancer	≥23.8 vs ≤20.4 kg/m^2	0.38 (0.20-0.70) Ptrend:0.002	Age, age at menarche, age at menopause, alcohol Intake,	Included in meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	years, M/W, Postmenopausal							educational level, family history of breast cancer, exogenous female hormone use, occupation, parity, smoking, walking, current BMI	
						≥23.8 vs ≤20.4 kg/m^2	0.44 (0.24-0.81)	As above, without current BMI	
Torio, 2010 BRE80277 USA	CLUE II, Prospective Cohort, Age: 63 years, W, Postmenopausal	172/ 5 642	Cancer registry	Self-reported, weight at 21 years	Incidence, breast cancer, complete data available	per 1 kg/m^2	0.98 (0.93-1.04)	Age, age at first child birth, breastfeeding, educational level, HRT use, parity, social class	
Li, 2006 BRE80166 China	SWHS, Prospective Cohort, Age: 40-70 years, W	169/ 73 410 5.66 years	Medical records	Self-reported, weight at 20 years	Incidence, breast cancer, postmenopausal	≥20.46 vs ≤18.36	0.79 (0.55-1.13) Ptrend:0.14	Age, age at first child birth, age at menopause, breastfeeding, educational level, energy Intake, family history of benign breast disease, family history of breast cancer	
Morimoto, 2002	WHI-OS,	1 014/	Medical records	Self-reported	Incidence, breast	≥22.32 vs ≤18.6	0.70 (0.56-0.87)	Age, age at first	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
BRE20457	Prospective Cohort, Age: 50-79 years, Postmenopausal	85 917 34.8 months	+ self-reported	weight and height at 18 years	cancer, postmenopausal	kg/m^2	Ptrend:0.005	child, age at menarche, age at menopause, alcohol, educational level, energy Intake , race, family history of breast cancer, leisure time physical activity, parity/pregnancies, smoking status	
Sellers, 2002 BRE20892 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	1 368/ 37 105 13 years	Partially histological - over 80%	Self-reported weight at 18 years	Incidence, postmenopausal breast cancer, No family history of breast cancer	≥22.91 vs ≤18.6 kg/m^2	0.61 (0.50-0.73) Ptrend:0.0001	Age as time axis in Cox proportional hazard model, age at first child, age at menarche, age at menopause, alcohol, educational level, family history of breast cancer, HRT use, OC use, parity, physical activity , smoking habits, height, WHR, BMI	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
		282/			Incidence, postmenopausal breast cancer, Yes family history of breast cancer	≥22.91 vs ≤18.6 kg/m^2	0.55 (0.37-0.81) Ptrend:0.0001		
		1 043/			Incidence, breast cancer ER+, postmenopausal	≥22.91 vs ≤18.6 kg/m^2	0.61 (0.49-0.76)		
		232/			Incidence, breast cancer ER-, postmenopausal	≥22.91 vs ≤18.6 kg/m^2	0.91 (0.58-1.44)		
		993/			Incidence, breast cancer PR+, postmenopausal	≥22.91 vs ≤18.6 kg/m^2	0.57 (0.45-0.73)		
		362/			Incidence, breast cancer PR-, postmenopausal	≥22.91 vs ≤18.6 kg/m^2	0.85 (0.57-1.26)		
van den Brandt, 1997 BRE12717 Netherlands	NLCS, Case Cohort, Age: 55-69 years, W, Postmenopausal	500/ 4.3 years	All histology	Self-reported, weight at 20 years	Incidence, Invasive breast cancer, postmenopausal	≥27 vs ≤19.9 kg/m^2	0.99 (0.52-1.87) Ptrend:0.03	Age , age at first child, age at menarche, alcohol, parity	
						per 8 kg/m^2	0.79 (0.58-1.08)		
London, 1989 BRE80626 USA	NHS, Prospective Cohort, Age: 30-55 years, W	384/ 115 534 743 716 person-years	Self-report verified by medical record	Self-reported, weight at 18 years	Incidence, Invasive breast cancer, postmenopausal	≥25 vs ≤19.9 kg/m^2	0.80 (0.60-1.20)	Age, age at first child, age at menarche, family history of breast cancer, history of benign breast disease, parity,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								smoking, years since menopause	

Table 549 BMI at early adulthood and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Canchola, 2012 BRE80401 USA	CTS, Prospective Cohort, Age: 56-70 years, W, Postmenopausal	1 348/ 56 542 12.1 years	Cancer registry and national death Index	Self-reported, weight and height at 18 years	Incidence, breast cancer ER+/PR+	≥25 vs <20 kg/m^2	0.98 (0.80-1.19) Ptrend:0.76	Age at baseline, age at first child birth, age at menarche, alcohol, breast biopsies, family history of breast cancer, height, HRT use, parity	Results by breast cancer type only, not analysed
						per 1 kg/m^2	1.00 (0.98-1.02)		
		280/			Incidence, breast cancer ER+/PR-	≥25 vs <20 kg/m^2	0.41 (0.23-0.73) Ptrend:<0.01		
						per 1 kg/m^2	0.93 (0.88-0.97)		
		276/			Incidence, breast cancer ER-/PR-	≥25 vs <20 kg/m^2	0.89 (0.58-1.35) Ptrend:0.34		
						per 1 kg/m^2	0.97 (0.94-1.02)		
Manders, 2011 BRE80314 Netherlands	HEBON, Historical Cohort, W,	63/ 719 10 years	Cancer registry	Self-reported, weight at 18 years	Incidence, breast cancer, postmenopausal	≥22.5 vs ≤22.4 kg/m^2	0.94 (0.37-2.39)	HRT use, parity, physical activity, type of menopause	Excluded, two exposure categories only

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	Subjects with BRCA1/2 mutation								
Phipps, 2011 BRE80343 USA	WHI-CT-OS, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	1 426/ 155 723 7.9 years	Mail or telephone questionnaires verified by trained physician adjudicators	Self-reported weight at 18 years, height measured at study baseline	Incidence, breast cancer ER+	≥22.42 vs ≤19.33 kg/m^2	0.83 (0.69-0.98) Ptrend:<0.01	Age, educational level, family history of breast cancer, income, mammography at baseline, and during follow-up, race, recreational activity, BMI at baseline	Results by breast cancer type only, not analysed
		177/			Incidence, triple negative breast cancer	≥22.42 vs ≤19.33 kg/m^2	0.94 (0.56-1.56) Ptrend:0.59		
Kotsopoulos, 2010 BRE80335 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Postmenopausal	4 048/ 107 759 26 years	Self-report (provided evidence of treatment), medical records and pathology reports, national death Index	Self-reported, weight at 18 years	Incidence, ductal carcinomas	≥23 vs 19-<21 kg/m^2	0.74 (0.67-0.81)	Age, age at first child birth, age at menarche, age at menopause, alcohol intake, benign breast disease, family history of breast cancer, menopausal type, parity, postmenopausal hormone use, BMI	Results by breast cancer type only, not analysed (publication from the same study (London, 1989) on overall breast cancer was included)
						per 5 kg/m^2	0.77 Ptrend:<0.001		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
		582/			Incidence, lobular carcinomas	≥23 vs 19-<21 kg/m^2	0.69 (0.54-0.88)		
						per 5 kg/m^2	0.78 Ptrend: 0.003		
		1701/			ER+PR+ ductal carcinomas	≥23 vs 19-<21 kg/m^2	0.81 (0.71-0.93)		
						per 5 kg/m^2	0.80 Ptrend:<0.001		
		247/			ER+PR+ lobular carcinomas	≥23 vs 19-<21 kg/m^2	0.89 (0.61-1.30)		
						per 5 kg/m^2	0.81 Ptrend:0.08		
Ahn, 2007 BRE80139 USA	NIH-AARP, Prospective Cohort, Age: 50- years, W, Postmenopausal	1 162/ 99 039 4 years	Cancer registry	Self-reported, weight at 18 years	Incidence, breast cancer, current MHT users	≥30 vs 18.5-22.4	0.65 (0.35-1.23) Ptrend:0.01	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, educational level, family history of cancer, fat intake, oophorectomy/hysterectomy, parity, physical activity, race, smoking habits, current BMI,	Excluded, missing non-cases per category in subgroups
		948/			Non MHT users	≥30 vs 18.5-22.4	0.48 (0.27-0.86) Ptrend:<0.001		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Palmer, 2007 BRE80122 USA	BWHS, Prospective Cohort, Age: 21-69 years	442/ 59 000 10 years	Death certificate / patient records / self report	Self-reported, weight at 18 years	Incidence, breast cancer, postmenopausal	≥25 vs ≤19	0.55 (0.37-0.82)	Age, age at first child birth, age at menarche, age at menopause, educational level, family history of cancer, parity, physical activity	Superseded by Bandera, 2015
		160/			Postmenopausal and HRT nonusers	≥25 vs ≤19	0.74 (0.43-1.27)		
		442/			Incidence, breast cancer, postmenopausal	≥25 vs ≤19	0.53 (0.35-0.81)	As above, and current BMI	
		160/			Postmenopausal and HRT nonusers	≥25 vs ≤19	0.63 (0.34-1.16)		
Huang, 1997 BRE04117 USA	NHS, Prospective Cohort, Age: 35-55 years, W, Registered nurses	1 517/ 95 256 16 years	Medical records + self-reported +death certificate	Self-reported, weight at 18 years	Incidence, Invasive breast cancer, postmenopausal	≥25 vs ≤18.2 kg/m^2	0.72 (0.56-0.91) Ptrend:<0.001	Age , age at first child, age at menarche, age at menopause, family history, height, HRT use, parity/pregnancies	Superseded by London, 1989
Barnes-Josiah, 1995 BRE00566 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	623/ 37 105 6 years	Partially histological - over 80%	Self-reported, weight at 18 years	Incidence, breast cancer, postmenopausal	lower half vs upper half of BMI distribution at age 18	1.41 (1.20-1.66)	Age , age at first child, age at menarche, age at menopause, alcohol, educational level, family history, HRT use, OC use,	Superseded by Sellers, 2002

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								parity/pregnancies, smoking habits, weight at enrollment	
							1.23 (1.05-1.45)	As above, with weight at enrolment replaced by weight change	
Potter, 1995 BRE80164 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	411/ 37 105 7 years	National cancer registers	Self-reported, weight at 18 years	Incidence, breast cancer ER+/PR+, postmenopausal	≥23 vs ≤22.9	0.62 (0.47-0.81)	Age at menarche, parity, age at first live birth, age at menopause, type of menopause, contraceptive/noncontraceptive estrogen use, history of bilateral oophorectomy, family history of breast cancer, alcohol consumption, BMI, WHR	Results by breast cancer type only, not analysed (publication from the same study (Sellers, 2002) on overall breast cancer was included)
		327/			Incidence, breast cancer unknown ER/PR status, postmenopausal	≥23 vs ≤22.9	0.62 (0.45-0.83)		
		97/			Incidence, breast cancer ER+/PR-, postmenopausal	≥23 vs ≤22.9	0.89 (0.53-1.50)		
		79/			Incidence, breast cancer ER-/PR-, postmenopausal	≥23 vs ≤22.9	1.38 (0.82-2.31)		
		16/			Incidence, breast cancer ER-/PR+,	≥23 vs ≤22.9	0.41 (0.09-1.80)	Age adjusted only	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
					postmenopausal				
Gapstur, 1992 BRE03101 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	493/ 37 105 4 years	Partially histological - over 80%	Self-reported, weight at 18 years	Incidence, breast cancer, postmenopausal	≥24.6 vs ≤19.34 kg/m^2	0.68 (0.48-0.95) Ptrend:0.003	Age	Superseded by Sellers, 2002

Figure 572 RR estimates of postmenopausal breast cancer by BMI at early adulthood

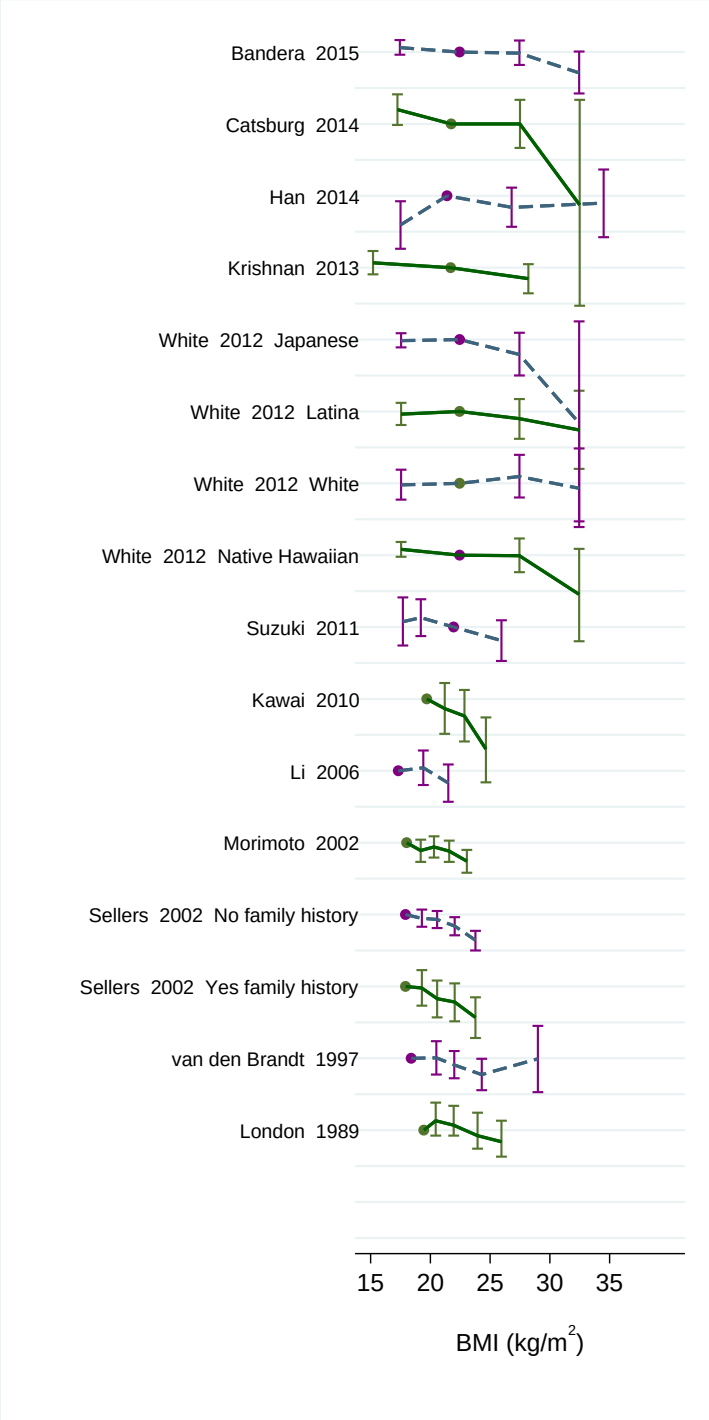


Figure 573 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest level of BMI at early adulthood

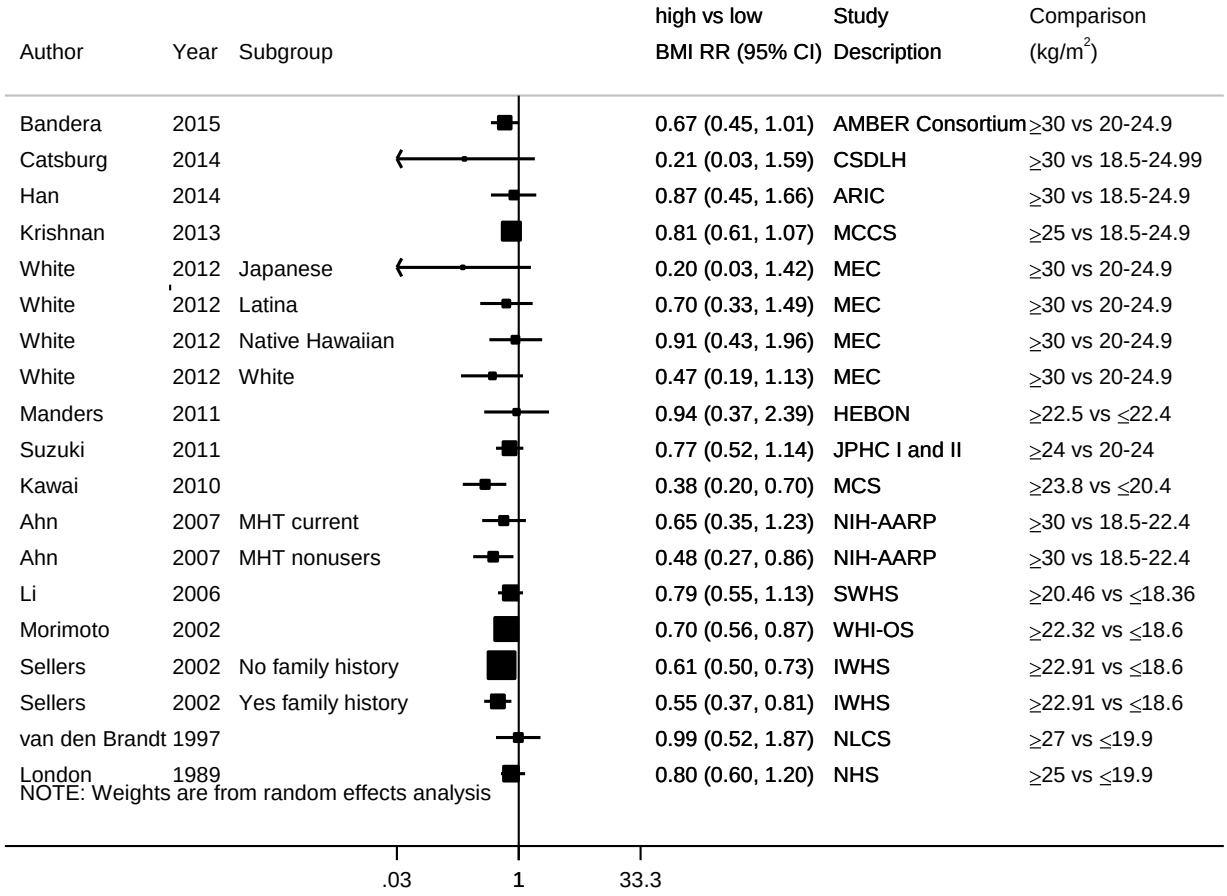


Figure 574 Relative risk of postmenopausal breast cancer for 5 kg/m^2 increase of BMI at early adulthood

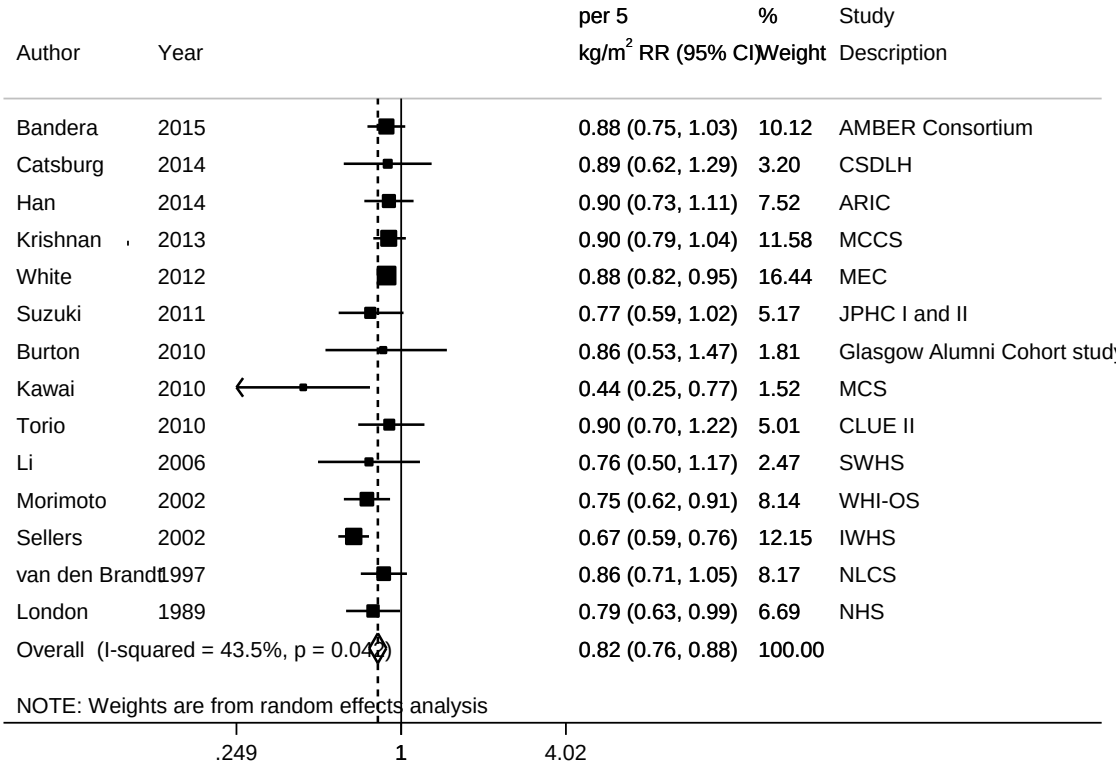


Figure 575 Funnel plot of studies included in the dose response meta-analysis of BMI at early adulthood and postmenopausal breast cancer

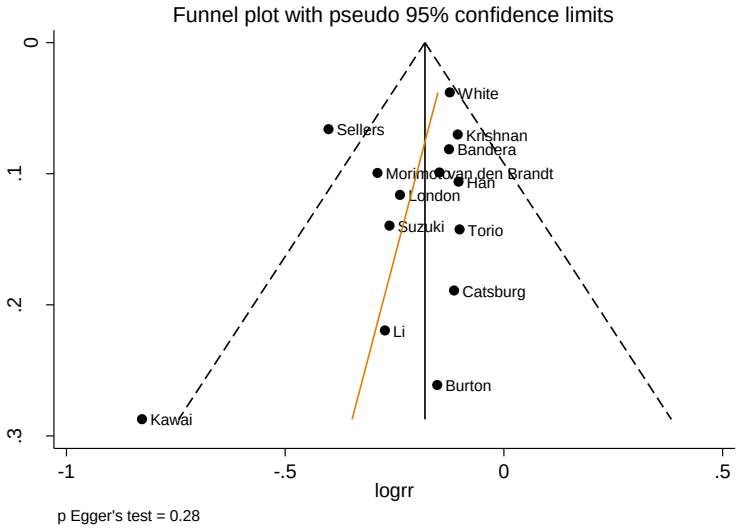


Figure 576 Relative risk of postmenopausal breast cancer for 5 kg/m^2 increase of BMI at early adulthood, by geographic location

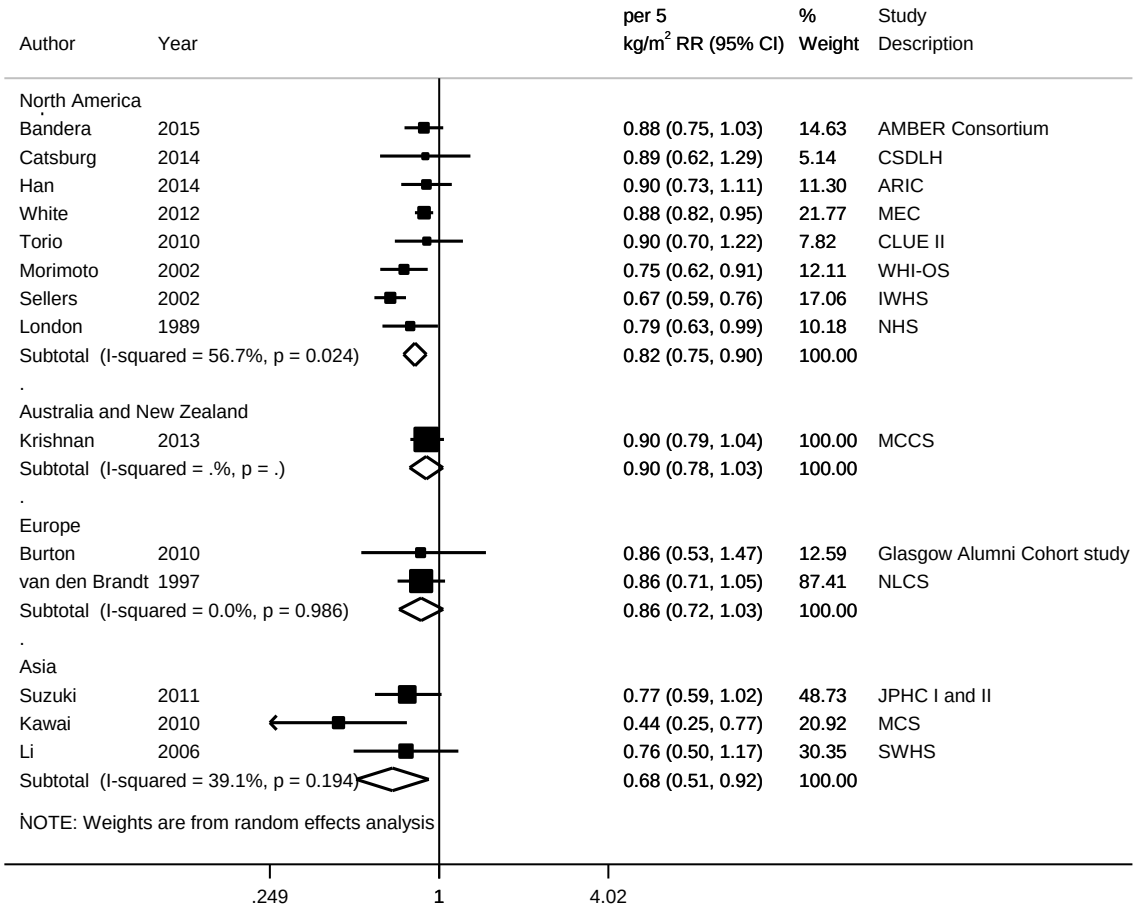
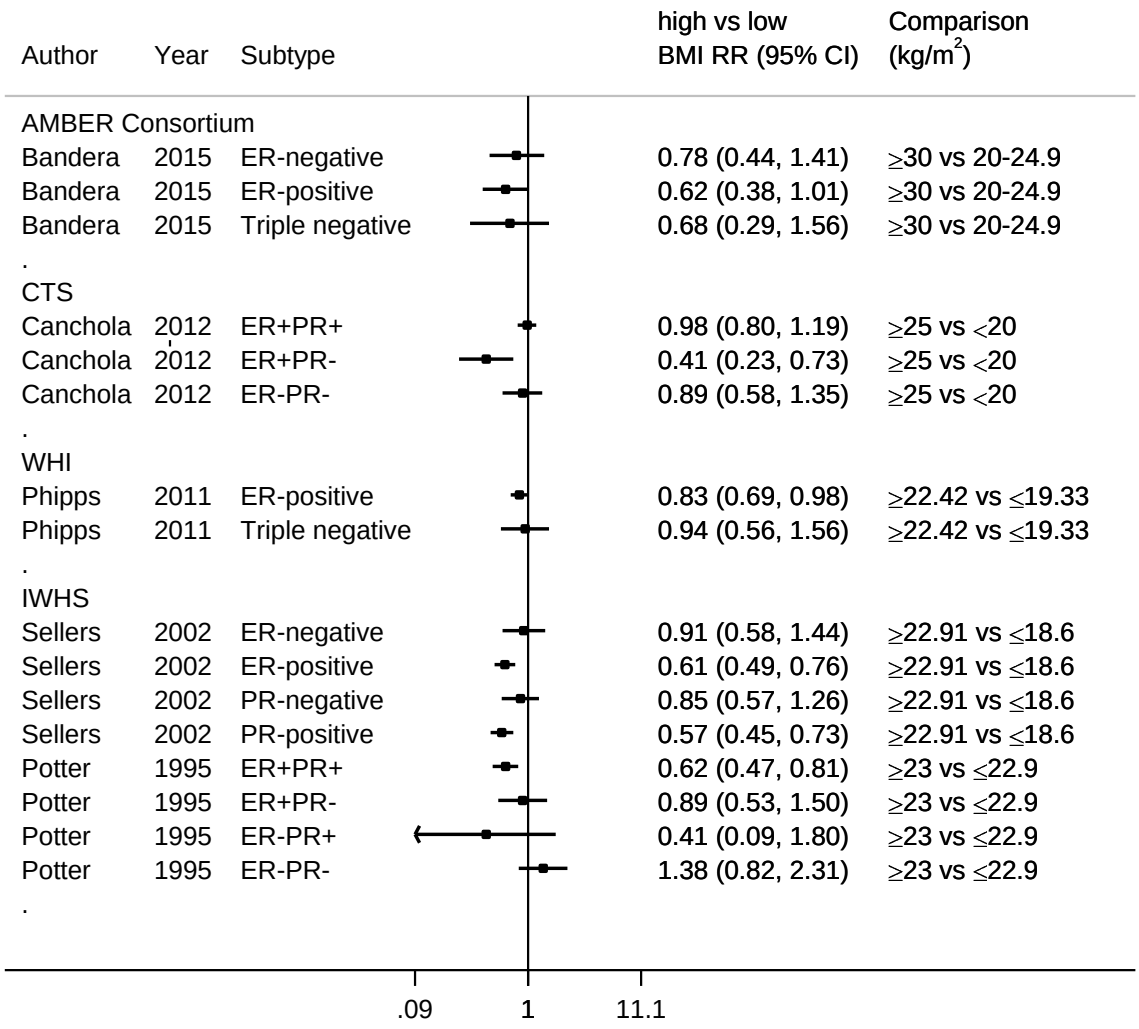


Figure 577 RR (95% CI) of hormone receptor-defined postmenopausal breast cancer for the highest compared with the lowest level of BMI at early adulthood



Note: Insufficient data to conduct a dose-response meta-analysis, results for the highest versus the lowest BMI at early adulthood comparison are presented in a forest plot to aid interpretation.

8.1.6 Weight change

8.1.6 Weight gain

Cohort studies

Overall summary

Thirty-eight publications from 27 studies that examined long or short-term weight gain during adulthood or specifically during early, middle, or late adulthood were identified. No pooled analysis was identified.

Long-term adult weight gain, as examined in most studies of weight change, is the weight change between an earlier age (for example, age 18 years or early 20s) and study baseline or the recent follow-up.

Short-term adult weight gain is the weight change that occurs recently, for example, over past four years in the Nurses' Health Study (Rosner, 2015) and on average 7 years after baseline in the VHM&PP study (Rapp, 2008).

Fewer numbers of studies examined weight change for a specific period during adulthood and the definition varies between the studies, for example, the three periods were <45 years, ≥45–< 55 years, and ≥55 years in the HUNT study (Alsaker, 2013) and 18–<35 years, 35–<50 years, and 50 years–current age in the NIH-AARP study (Ahn, 2007).

Details on the exposures are provided in the results table. Dose-response meta-analyses were conducted to examine the associations of long-term adult weight gain with the risk of premenopausal and postmenopausal breast cancer. Weight gain during the specific periods in adulthood was reviewed in the text.

Notes on method:

The reference weight and weight gain categories were defined differently between the studies. To estimate a dose-response slope through the weight categories, we estimated the midpoints. For stable weight ±3 kg, midpoint was set as zero; otherwise, zero was used as the lowest boundary – as used in the meta-analysis conducted by Keum, 2015.

Results selected for inclusion in the meta-analysis were those adjusted for multiple confounding factors by the studies, which could include initial body weight. Some studies further reported results that were adjusted for current body weight. These results were pooled separately.

Table 550 Summary of results of the dose-response meta-analysis in the CUP SLR

	Breast cancer (any)	Premenopausal breast cancer	Postmenopausal breast cancer
Weight gain Increment unit used		5 kg	5 kg

Studies (n)	-	8	15
Cases	-	3 512	16 600
RR (95%CI)	-	0.99 (0.96-1.03)	1.06 (1.05-1.08)
Heterogeneity (I^2, p-value)	-	13%, 0.33	38%, 0.07
P value Egger test	-	0.28	0.10

Breast cancer (any)

Seven studies (9 publications) were identified. Dose-response meta-analysis was not conducted due to insufficient data.

For the five studies (Catsburg, 2014b; Jonsson, 2003; Breslow, 2001; Manger, 2001; Colditz, 2000) on adult weight gain (age 18 – 30 years to current weight) and breast cancer risk, positive associations, two being significant (Jonsson, 2003; Colditz, 2000), were reported. EPIC-PANACEA (Emaus, 2014) observed a significant positive association with the highest weight gain during middle adulthood (age 40 – 50 years) compared with stable weight.

One publication from NHS (Rosner, 2015) reported a significant positive association with breast cancer risk for the highest short-term (4 years) weight gain compared with stable weight. The association remained borderline significant for ER+PR+ breast cancer, and significant among women with initial BMI < 25 or ≥25 kg/m^2. Another publication of the same study (Wilson, 2011) reported a non-significant inverse association for the highest weight gain during pregnancy compared with reference weight category.

Framingham-Offspring cohort (Makarem, 2015) reported a non-significant positive association for each point scored for adhering to the WCRF/AICR guideline on foods that promote weight gain.

Table 551 Weight gain and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Vrieling, 2010	11 studies (3 cohorts, 8 population-based case-control studies)	4144 ER+PR+, 1266 ER-PR- breast cancer	USA, Sweden	ER+PR+ breast cancer ER-PR- breast cancer	Highest vs lowest adult weight gain, in women of any menopausal status (11 studies)	2.03 (1.62-2.45) 1.36 (1.14-1.58)	- -	91%, <0.0001 32%, 0.14

*All cohort studies identified were of postmenopausal women only and were included in the present review (see section on weight gain and postmenopausal breast cancer)

Premenopausal breast cancer

Summary

Main results:

Eight out of nine studies (12 publications) identified could be included in the dose-response meta-analysis of adult weight gain (age 18-25 years to study baseline/recent follow-up).

No significant association was observed for premenopausal breast cancer overall, and in subgroup analyses. Low heterogeneity was observed between studies. There was no evidence of significant publication or small study bias; however funnel plot shows that small studies with an inverse association could be missing.

One study (Emaus, 2014, EPIC-PANACEA) on weight gain during middle adulthood (age 40 – 50 years) was excluded from the analysis. A significant positive association for high weight gain versus stable weight was reported in women who were premenopausal at first assessment and aged ≤ 50 years at both second assessment and diagnosis.

NHS also published results on short-term (4 years) weight gain (Rosner, 2015) and weight gain during pregnancy (Wilson, 2011). Compared with stable weight, highest weight gain was associated with significant increased risks in premenopausal breast cancer and ER-PR- breast cancer, and non-significant positive associations were observed with ER+PR+ and ER+PR- breast cancers (Rosner, 2015). A non-significant inverse association was reported for the highest versus reference weight gain during pregnancy (Wilson, 2011).

Summary RRs for studies adjusted (Michels, 2012, NHS and NHS II; Palmer, 2007; Lahmann, 2005a; Breslow, 2001) or not adjusted (Catsburg, 2014b; Manders, 2011; Li, 2006) for initial body weight were similar (data not shown). None of the studies adjusted for current weight.

Three studies reported results by initial weight/BMI. A significant positive association with short-term weight gain was observed in women with lower initial BMI (RR for the highest vs the lowest gain=1.42, 95% CI=1.09-1.85, P trend<0.001) but not higher initial BMI (RR=1.02, 95% CI=0.83-1.25, P trend=0.84) (Rosner, 2015). The same differential association was not observed in the other two studies. One reported non-significant positive associations with weight gain during middle adulthood among BMI ≤25 kg/m^2 and >25 kg/m^2 (RRs=1.23, 95% CI=0.87-1.72 and 1.42, 95% CI=0.76-2.65, respectively) (Emaus, 2014) and the other, inverse associations with weight gain from 18 years among BMI ≤21 kg/m^2 and >21 kg/m^2 (RRs=0.82, 95% CI=0.40-1.68 and 0.68, 95% CI=0.48-0.96, respectively) (Michels, 2012).

Sensitivity analyses:

The summary RR did not change materially when studies were omitted in turn in influence analysis.

Non-linear dose-response meta-analysis:

There was evidence of significant non-linearity. The curve shows that premenopausal breast cancer risk increased with adult weight gain to 12 kg and dropped thereafter.

Study quality:

HEBON (Manders, 2011) consisted of BRCA1/2 carriers only. BWHS (Palmer, 2007) is a cohort of black women and there is one Chinese study (Li, 2006). Change of body weight was measured from age 18-25 years to baseline/most recent follow-up in the studies. Michels, 2012 and Palmer, 2007 assessed adult weight change since age 18 years; Catsburg, 2014, Li, 2006, and Lahmann, 2005, since age 20 years; Breslow, 2001, since age 25 years; and Manders, 2011 did not specify period of change during adulthood. NHS updated body weight data overtime. Influence analysis shows non-significant associations when each study was excluded in turn from the meta-analysis.

Similar RRs were observed in studies that used either self-reported or self-reported and measured body weight data, and in studies that adjusted or not adjusted for major confounding factors (age, alcohol, and reproductive factors).

Table 552 Weight change and premenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	9 (12 publications)
Studies included in forest plot of highest compared with lowest exposure	8 (7 publications)
Studies included in linear dose-response meta-analysis	8 (7 publications)
Studies included in non-linear dose-response meta-analysis	7 (6 publications)

Note: Include cohort, case-cohort, and nested case-control designs

Table 553 Weight gain and premenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR[1]	CUP SLR	
Increment unit used	5 kg	5 kg	
Studies (n)	2	8	
Cases	1 041	3 512	
RR (95%CI)	0.99 (0.95-1.03)	0.99 (0.96-1.03)	
Heterogeneity (I^2, p-value)	67%	13%, 0.33	
P value Egger test	-	0.28	
Stratified analyses in CUP SLR			
Geographic location	**Asia**	**Europe**	**North America**
Studies (n)	1	2	5
RR (95%CI)	1.01 (0.90-1.13)	0.98 (0.90-1.06)	1.00 (0.95-1.06)
Heterogeneity (I^2, p-value)	-	0%, 0.69	54%, 0.09
Weight change measurement methods[2]	**Both self-reported**	**Self-reported then measured**	
Studies (n)	5	3	
RR (95%CI)	0.99 (0.95-1.03)	1.02 (0.94-1.11)	
Heterogeneity (I^2, p-value)	20%, 0.29	23%, 0.27	
Adjustment for age, alcohol intake, reproductive factors	**Adjusted**	**Not adjusted**	
Studies (n)	4	4	
RR (95%CI)	0.97 (0.94-1.01)	1.02 (0.98-1.07)	
Heterogeneity (I^2, p-value)	0%, 0.58	0%, 0.44	

[2]Self-reported initial and current weight; Self-reported initial weight and measured current weight.

Table 554 Weight gain and premenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Keum, 2015	4 prospective studies on premenopausal breast cancer	2 409 premenopausal breast cancer	Europe, North America	Incidence, Premenopausal breast cancer	Adult weight gain Per 5 kg (3 studies) Highest vs lowest (4 studies)	 0.99 (0.95-1.03) 0.99 (0.82-1.21)	 - -	 36%, 0.21 17%, 0.31

*All cohort studies identified were included in the present review.

Table 555 Weight change and premenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Catsburg, 2014b BRE80529 Canada	CSDLH, Case Cohort, W, alumnae	548/ 4 417 15 years	Cancer registry	Self-reported weight at age 20 years and study baseline	Incidence, Invasive breast cancer, premenopausal	≥16 vs ≤0 kg	1.05 (0.71-1.56)	Age at first child birth, age at menarche, alcohol Intake, family history of breast cancer, HRT use, menopausal status, number of childbirths, oc use, physical activity
Michels, 2012 BRE80354 USA	NHS I and II, Prospective Cohort, W, Premenopausal	1 811/ 165 608 1 014 175 person-years	Questionnaire, medical records or pathology reports, death certificate, physician, family member	Self-reported weight at age 18 years and recent follow-up	Incidence, breast cancer	gained ≥25 vs stable kg	0.78 (0.55-1.11)	Age, age at first child birth, age at menarche, alcohol, contraception, family history of breast cancer, height, history of breast disease, parity, physical activity, weight at 18 yrs
					BMI at 18y <=21	gained ≥25 vs stable kg	0.82 (0.40-1.68) Ptrend:0.68	
					BMI at 18y >21	gained ≥25 vs stable kg	0.68 (0.48-0.96) Ptrend:0.02	
Manders, 2011 BRE80314 Netherlands	HEBON, Historical Cohort, W, Subjects with BRCA1/2	155/ 719 10 years	Cancer registry	Self-reported weight change during adulthood	Incidence, breast cancer, premenopausal	≥25 vs 4-12.9 %	0.85 (0.48-1.51)	Age as time axis in Cox proportional hazards model,stratified for genes, birth cohort, clustered on family, adjusted for lifetime sports activity
						≥15gain vs <5loss/<5gain kg	0.77 (0.41-1.45)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	mutation							
Palmer, 2007 BRE80122 USA	BWHS, Prospective Cohort, Age: 21-69 years	490/ 59 000 10 years	Death certificate / patient records / self-report	Self-reported weight at age 18 years and at last follow-up	Incidence, breast cancer, premenopausal	≥25 vs ≤9 kg	1.17 (0.90-1.52)	Age, age at first child birth, age at menarche, educational level, family history of breast cancer, parity, physical activity, BMI at 18 years
Li, 2006 BRE80166 China	SWHS, Prospective Cohort, Age: 40-70 years, Mean age: 52 years W	213/ 73 410 5.66 years	Medical records	Self-reported weight at age 20 years; height and weight measured by trained interviewers at study baseline	Incidence, breast cancer, premenopausal	≥13.6 vs ≤6 kg	1.02 (0.73-1.42)	Age, age at first child birth, breastfeeding, educational level, energy Intake, family history, family history of cancer
						≥13.6 vs ≤6 kg	0.89 (0.59-1.35)	
Lahmann, 2005a BRE23014 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 25-70 years, W	254/ 98 352 5.8 years	Partially histological - over 80%	Self-reported weight at age 20 years, measurements obtained at the time of enrolment (1992-2000)	Incidence, Invasive breast cancer, premenopausal	> 20 kg vs +/- 2 kg	0.87 (0.51-1.49)	Age at first child, age at menarche, age-underlying cox models, alcohol, body weight, educational level, height, leisure time physical activity, oc use, smoking habits, stratified by age, and study centre
Breslow, 2001 BRE01123 USA	NHEFS, Prospective Cohort, Age: 24-75 years,	41/ 6 160 9.2 years	Medical records + self-reported	Self-reported weight at age 25 years; measured by skilled personnel in	Incidence, breast cancer, premenopausal	≥20 vs +/-4.9 kg	1.88 (0.73-4.88)	Age , ethnicity, height, Income, physical activity , socio-economic status, BMI at 25 years

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	W			1982-1984				

Table 556 Weight change and premenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Rosner, 2015 BRE80548 USA	NHS, Prospective Cohort, W	736/ 77 232 1 445 578 person-years	Self-report verified by medical record	Self-reported since 1980, weight change over past 4 years	Incidence, breast cancer, premenopause	≥15 vs 0-5 lb	1.38 (1.13-1.69)	Age, age at menarche, age at first birth, parity, birth index, height, alcohol intake, benign breast disease, family history of breast cancer, weight at 18 years, current weight
						per 25 lb	1.26 (1.08-1.48)	
		316/			Incidence, breast cancer ER+/PR+, premenopause	per 25 lb	1.13 (0.89-1.43)	
						≥15 vs 0-5 lb	1.27 (0.93-1.73)	
		100/			Incidence, breast cancer ER-/PR-, premenopause	≥15 vs 0-5 lb	2.06 (1.21-3.51)	
						per 25 lb	1.61 (1.09-2.38)	
		42/			Incidence, breast cancer ER+/PR-, premenopause	≥15 vs 0-5 lb	1.77 (0.80-3.89)	
						per 25 lb	2.19 (1.33-3.61)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Emaus, 2014 BRE80540 Europe	EPIC-PANACEA, Prospective Cohort, Age: 25-70 years, Mean age: 51.9 years W	283/ 205 723 1 396 538 person-years	Active follow up and cancer registry	Most study centres measured the initial weight and used self-reported data from the second weight assessment; weight change between age 40-50 years	Incidence, Invasive breast cancer, premenopausal at 1st assess, <= 50 years at 2nd assess, <= 50 years at diagnosis	0.84-4.98 vs ≤0.36 kg/year	1.37 (1.02-1.85)	Age, age at first child birth, age at menarche, alcohol consumption, alcohol drinking, BMI at baseline, educational level, energy Intake, HRT use, physical activity, smoking, study center, time between measurements, use of oral contraception
		218/			BMI<=25, age <=50y	0.84-4.98 vs ≤0.36 kg/year	1.23 (0.87-1.72)	
		80/			BMI>25, age <=50y	0.84-4.98 vs ≤0.36 kg/year	1.42 (0.76-2.65)	
Wilson, 2011 BRE80380 USA	NHS, Nested Case Control, W, mothers and daughters	458/ 1413 controls	Medical record	Self-reported weight during pregnancy	Incidence, breast cancer, <50y at diagnosis	≥40 vs 20-29 lbs	0.90 (0.57-1.42)	Age, family history of breast cancer, smoking
Huang, 1997 BRE04117 USA	NHS, Prospective Cohort, Age: 35-55 years, W, Registered	1 000/ 95 256 16 years	Medical records + self-reported +death certificate	Self-reported weight at age 18 years and in follow-ups	Incidence, Invasive breast cancer, premenopausal	≥25 vs +/-2 kg	0.74 (0.54-1.03)	Age , age at first child, age at menarche, family history, height, parity/pregnancies

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	nurses							
London, 1989 BRE80626 USA	NHS, Prospective Cohort, Age: 30-55 years, W	598/ 115 534 743 716 person-years	Self-report verified by medical record	Self-reported weight at age 18 years and most recent follow-up	Incidence, Invasive breast cancer, premenopausal	≥30 vs +/-3 kg	0.60 (0.40-0.90)	Age, parity, age at birth of first child, family history of breast cancer, age at menarche, smoking, history of benign breast disease, Quetelet's index at 18 years

Figure 578 RR estimates of premenopausal breast cancer by levels of weight gain

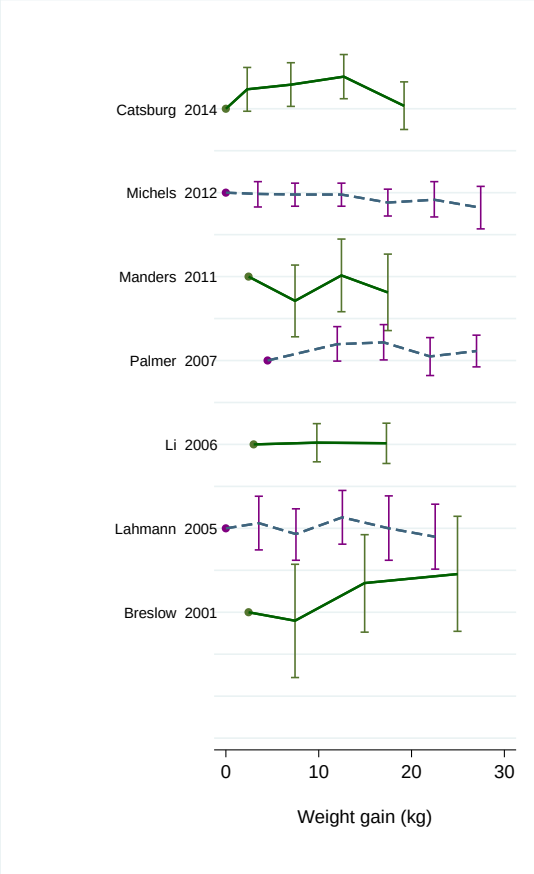


Figure 579 RR (95% CI) of premenopausal breast cancer for the highest weight gain compared with reference category

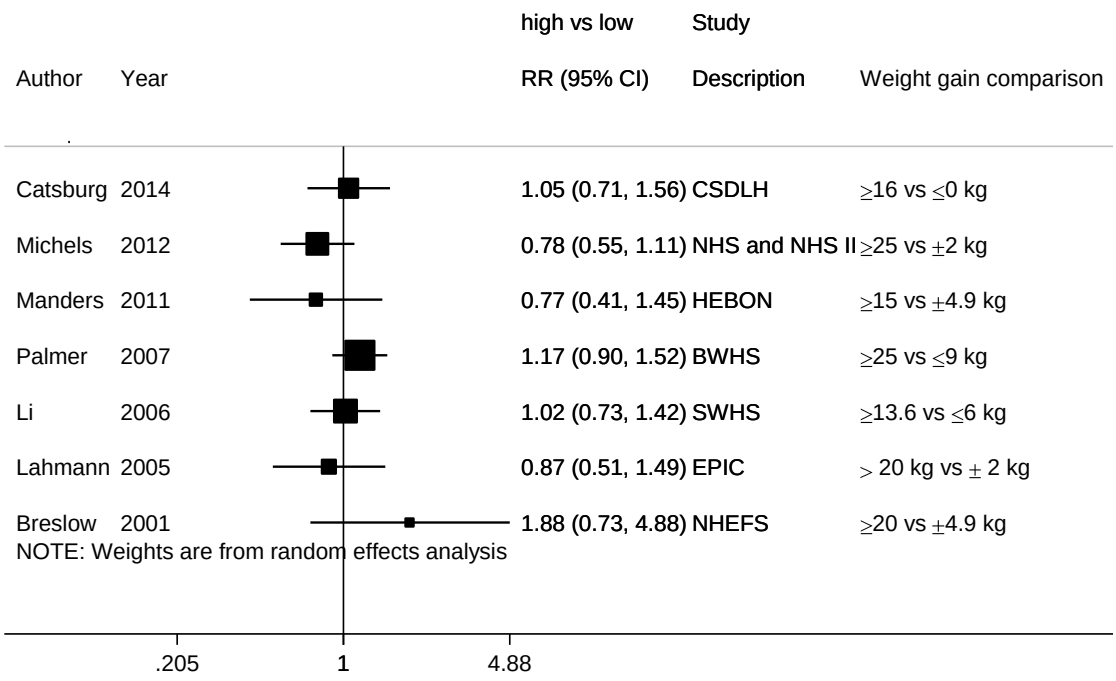


Figure 580 Relative risk of premenopausal breast cancer for 5 kg increase of weight gain

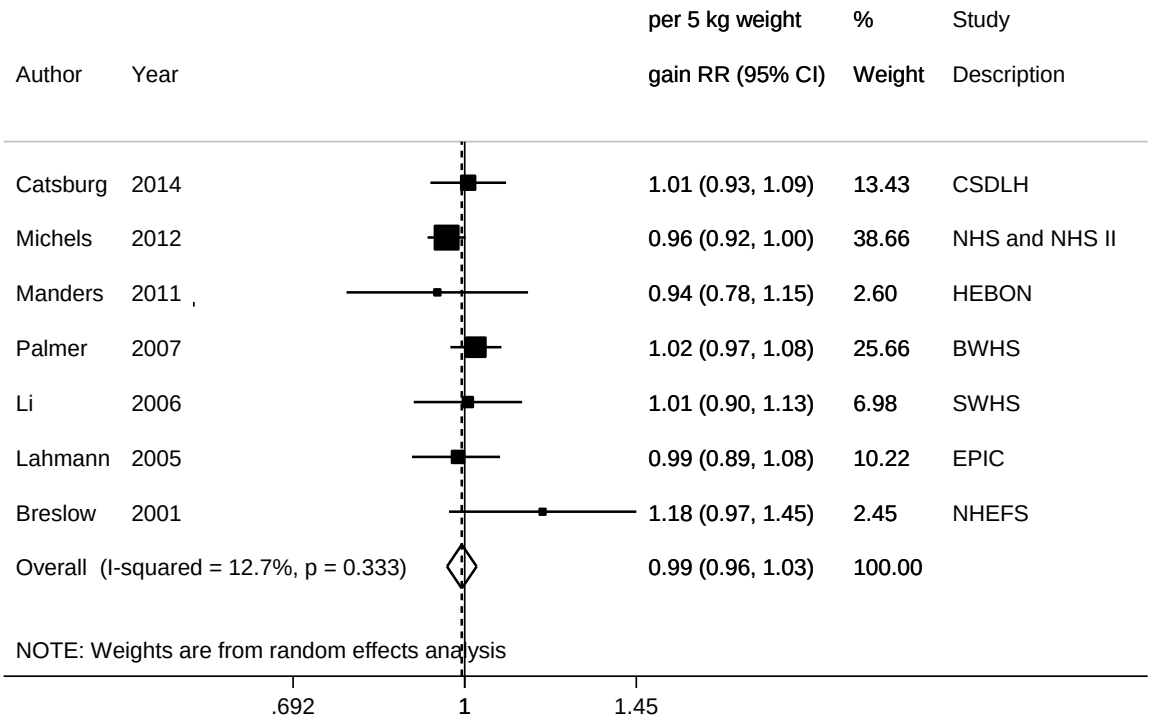


Figure 581 Funnel plot of studies included in the dose response meta-analysis of weight gain and premenopausal breast cancer

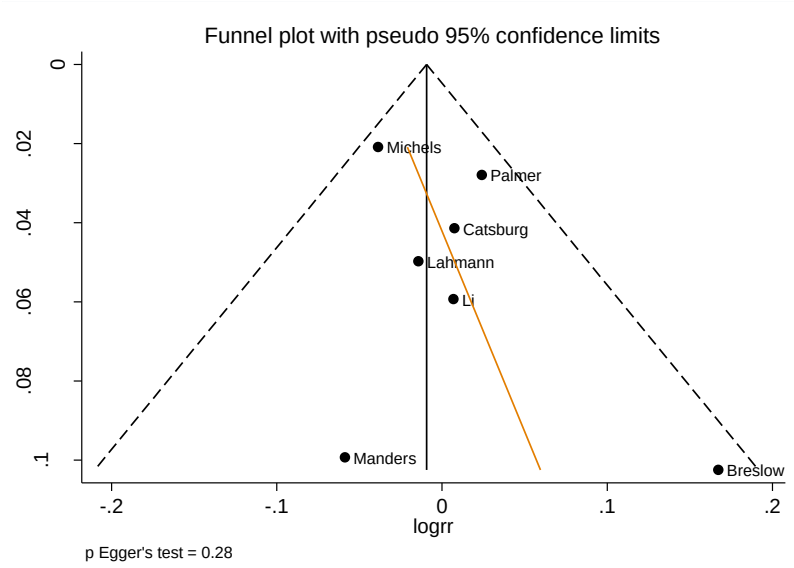


Figure 582 Relative risk of premenopausal breast cancer for 5 kg increase of weight gain, by geographic location

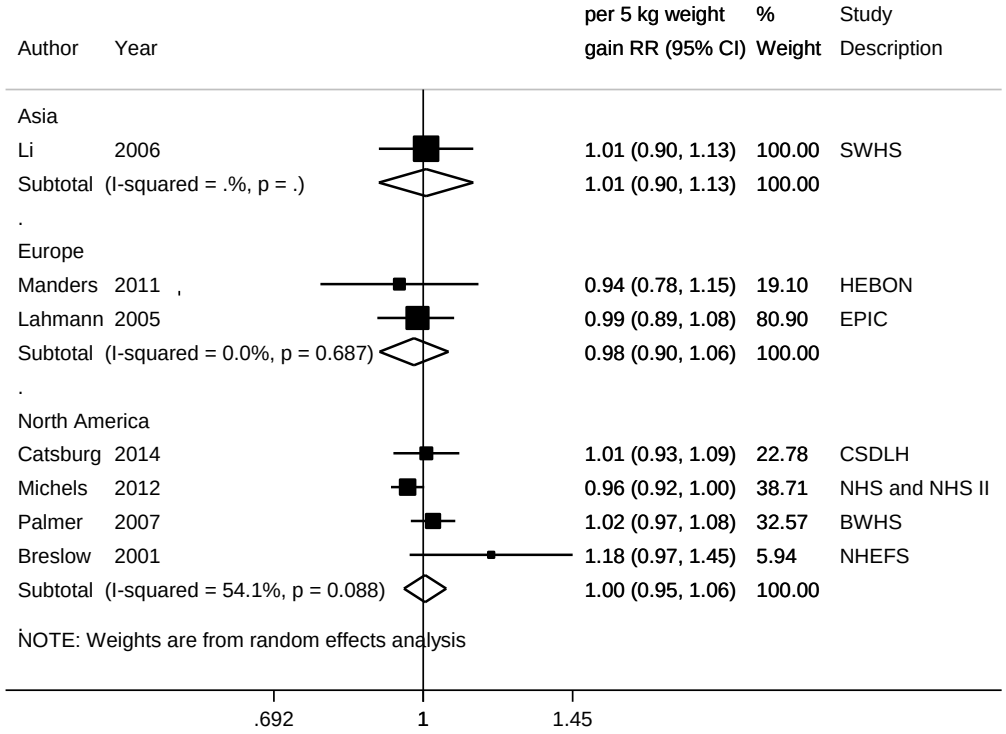


Figure 583 Relative risk of premenopausal breast cancer for 5 kg increase of weight gain, by weight change measurement methods

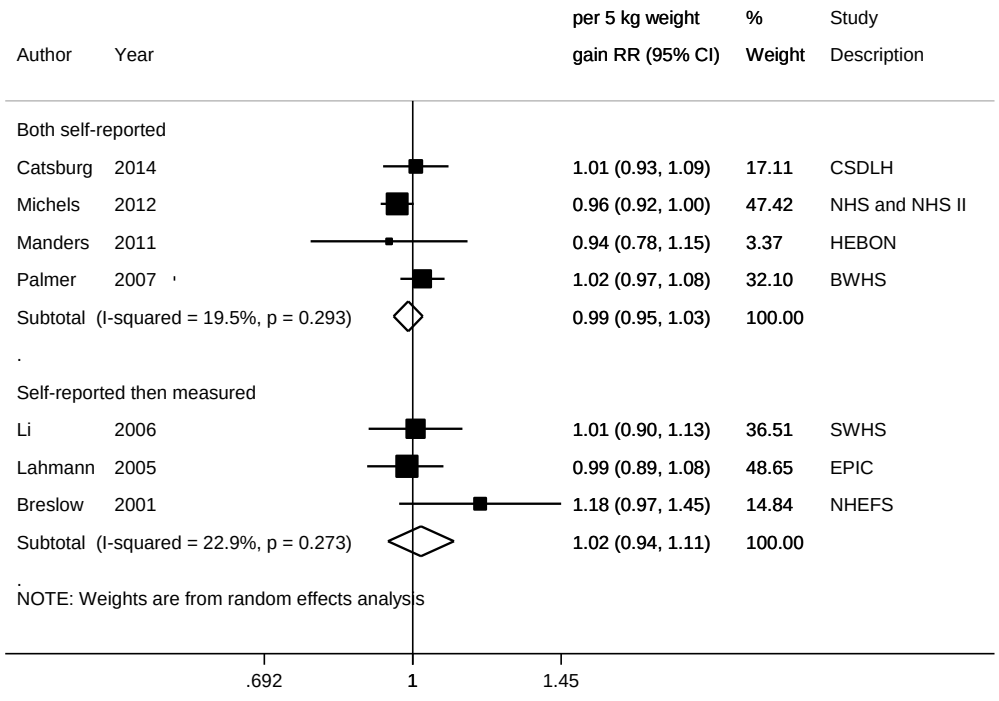


Figure 584 Non-linear dose-response meta-analysis of weight gain and premenopausal breast cancer

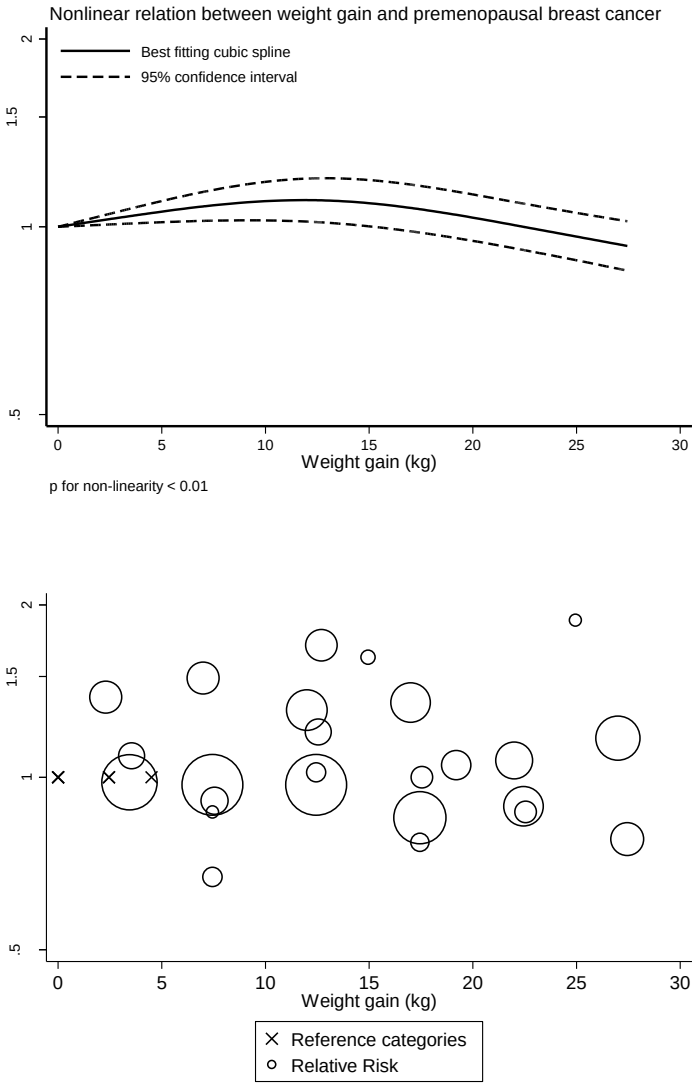


Table 557 Relative risk of premenopausal breast cancer and weight gain estimated using non-linear models

Weight gain (kg)	RR (95%CI)
0	1.00
4.5	1.05 (1.02-1.09)
12.0	1.10 (1.02-1.19)
19.0	1.05 (0.96-1.14)
27.0	0.94 (0.86-1.03)

Postmenopausal breast cancer

Summary

Main results:

Fifteen out of 24 studies (34 publications) identified could be included in the dose-response meta-analysis of adult weight gain (age 18-25 years to study baseline/recent follow-up).

Significant positive association was observed with postmenopausal breast cancer overall, and in subgroup analyses. Moderate heterogeneity was observed between studies. There was no evidence of significant publication or small study bias; however funnel plot shows that small studies with an inverse association could be missing.

The association appeared stronger in Asian countries than European or North American countries, although there were only two Asian studies and contributed little weight to the overall meta-analysis. Significant positive associations were observed among MHT never users (no heterogeneity, four studies) or never/former users (moderate heterogeneity, three studies), but not current users (low heterogeneity, three studies). Increasing adult weight gain was significantly associated with risk of ER+PR+ breast cancer (high heterogeneity, five studies), but not ER+PR- (no heterogeneity, three studies) nor ER-PR- breast cancers (low heterogeneity, five studies) in postmenopausal women.

Summary RRs for studies adjusted (Zhang X, 2015; Alsaker, 2013; Krishnan, 2013; Kawai, 2010b; Ahn, 2007; Palmer, 2007; Lahmann, 2005a; Radimer, 2004; Breslow, 2001) or not adjusted (Catsburg, 2014b; White, 2012; Li, 2006; Feigelson, 2004; van den Brandt 1997; Folsom, 1990) for initial body weight were similar (data not shown). Three studies (White, 2012; Li, 2006; Feigelson, 2004) further reported results adjusted for current body weight. Significant positive association remained when these results were pooled (data not shown).

Nine studies (Emaus, 2014; Han, 2014; Alsaker, 2013, HUNT; Hartz, 2013; Canchola, 2012; Manders, 2011; Krebs, 2006; Manjer, 2001a; Lahmann, 2003) were excluded from the analysis of adult weight gain. Alsaker, 2013, HUNT overlapped with HUNT 2 and Lahmann, 2003 is a component study of EPIC, which were included in the meta-analysis. Canchola, 2012 reported results by breast cancer type only. Emaus, 2014, EPIC-PANACEA examined specifically weight change during middle adulthood (between age 40-50 years).

Positive associations (two significant, two non-significant, and one with P>0.01) were reported in five excluded studies on adult weight gain and postmenopausal breast cancer risk (Han, 2014; Hartz, 2013; Manders, 2011; Krebs, 2006; Manjer, 2001a); and in one study on breast cancer mortality (Han, 2014).

Meta-analysis of weight gain during early, middle, or late adulthood was not conducted due to insufficient data in the six studies identified (Emaus, 2014 (between age 40–50 years); Alsaker, 2013 (<45, ≥45–55, and ≥55 years of age); Ahn, 2007 (18–<35, 35–<50, and 50–current age); Eliassen, 2006 (age 18 years to menopause, and since menopause); Harvie, 2005 (age 30 years to menopause, and menopause to study baseline); Radimer, 2004 (25-44, 45-55, and 56–current age). Most studies reported positive associations, but the findings were not as consistent as those reported above for long-term adult weight gain.

For weight gain during earlier years, two studies reported significant (Ahn, 2007, MHT non-users) or borderline significant positive associations (Alsaker, 2013) and one study observed a non-significant inverse association (Radimer, 2004). For weight gain during middle adulthood, four studies reported positive associations (three significant (Alsaker, 2013; Ahn, 2007, MHT non-users; Eliassen, 2006); one non-significant (Emaus, 2014)) and one study reported null association (Radimer, 2004). For weight gain during later years/since menopause, three studies observed positive associations (two significant (Ahn, 2007, MHT non-users; Eliassen, 2006, overall); one non-significant (Radimer, 2004)) and one study reported a non-significant inverse association (Alsaker, 2013). One further study, Harvie, 2005, reported that compared to those who consistently gained weight throughout different periods of life, those who maintained/loss weight during age 30 years to menopause and maintained weight since menopause, and those who maintained/loss weight during age 18 to 30 years and maintained weight during age 30 years to menopause showed significant reduction in risk.

Publications from NHS reported positive associations between short-term (4 years) weight gain and postmenopausal breast cancer and other subtypes apart from ER+PR- breast cancer (Rosner, 2015), and non-significant inverse association with weight gain during pregnancy (Wilson, 2011).

Two studies (three publications) reported results by initial weight/BMI and found differential association. EPIC-PANACEA reported a significant positive association with weight gain during middle ages in women with lower initial BMI (RR for the highest vs the lowest gain=1.12, 95% CI=1.01-1.24, P trend=0.18) but not higher initial BMI (RR=1.03, 95% CI=0.90-1.19, P trend=0.88) (Emaus, 2014). NHS also reported stronger positive associations with weight gain since menopause among initially lighter women compared with heavier women at 18 years and at menopause (Eliassen, 2006). For weight gain from age 18 to menopause, significant positive associations that was stronger among initially lighter women were observed (Eliassen, 2006). Similar non-significant positive associations were reported with short-term weight gain regardless of initial BMI (Rosner, 2015).

Sensitivity analyses:

The summary RR did not change materially when studies were omitted in turn in influence analysis. Similar significant positive associations were observed in the stratified analysis by the starting age of weight change assessed in the studies (from age 18, 20, 21, or 25 years) (results not shown).

Non-linear dose-response meta-analysis:

There was evidence of non-linearity (P = 0.04), however postmenopausal breast cancer risk appeared to increase linearly with increasing weight gain.

Study quality:

BWHS (Palmer, 2007) is a cohort of black women

Change of body weight was measured from age 18-25 years to baseline/most recent follow-up in the studies. Zhang, 2015, Alsaker, 2013, Ahn, 2007, Palmer, 2007, Feigelson, 2004, and Folsom, 1990 assessed adult weight change since age 18 years; Catsburg, 2014, Kawai, 2010, Li, 2006, Lahmann, 2005, and van Den Brandy, 1997, since age 20 years; Krishnan, 2013 since age 18-21 years; White, 2012 since age 21 years; Radimer, 2004, and Breslow, 2001, since age 25 years. NHS updated body weight data overtime. Influence analysis shows non-significant associations when each study was excluded in turn from the meta-analysis.

Similar RRs were observed in studies that used either self-reported or self-reported and measured body weight data, and in studies that adjusted or not adjusted for major confounding factors (age, alcohol, and reproductive factors).

Summary RR was attenuated but remained significant among studies that adjusted for age, alcohol intake, and reproductive factors and MHT use.

MHT use and other reproductive factors were only available in HUNT2 (Alsaker, 2013) and when restricted to MHT never users only, increased risk with weight gain remained Feigelson, 2006, CPS II included only women not currently using MHT.

Summary RR remained significant when each study was omitted in turn in influence analysis.

Table 558 Weight gain and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	24 (34 publications)
Studies included in forest plot of highest compared with lowest exposure	19 (19 publications)
Studies included in linear dose-response meta-analysis	15 (15 publications)
Studies included in non-linear dose-response meta-analysis	13 (13 publications)

Note: Include cohort, case-cohort, and nested case-control designs

Table 559 Weight gain and postmenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR[1]	**CUP SLR**
Weight gain Increment unit used	5 kg	5 kg
Studies (n)	4	15
Cases	2 459	16 600
RR (95%CI)	1.03 (1.02-1.04)	1.06 (1.05-1.08)
Heterogeneity (I^2, p-value)	59%	38%, 0.07
P value Egger test	-	0.10

Stratified analyses in CUP SLR			
Geographic location[2]	**Asia**	**Europe**	**North America**
Studies (n)	2	3	9
RR (95%CI)	1.26 (1.14-1.39)	1.06 (1.03-1.10)	1.06 (1.05-1.07)
Heterogeneity (I^2, p-value)	0%, 0.98	0%, 0.48	19%, 0.28
Weight change measurement methods[3]	**Both measured**	**Both self-reported**	**Self-reported then measured**
Studies (n)	1	9	5
RR (95%CI)	1.10 (1.03-1.18)	1.06 (1.05-1.07)	1.10 (1.04-1.16)
Heterogeneity (I^2, p-value)	-	20%, 0.27	64%, 0.03
Adjustment for age, alcohol intake, reproductive factors	**Adjusted**	**Further adjusted for MHT use**	**Not adjusted**
Studies (n)	2	9	4
RR (95%CI)	1.08 (1.03-1.13)	1.06 (1.05-1.07)	1.12 (1.01-1.25)
Heterogeneity (I^2, p-value)	0%, 0.39	0%, 0.65	80%, <0.01

[1]No meta-analysis in the 2008 SLR

[2]Also one study from Australia (Krishnan, 2013) (RR per 5 kg gain = 1.06, 95% CI=1.03-1.10)

[3]Measured or self-reported initial and current weight; self-reported initial weight and measured current weight

Table 560 Weight gain and postmenopausal breast cancer risk by menopausal hormone therapy use. Summary of the linear dose-response meta-analysis in the CUP SLR

MHT use[4]	Current	Ever	Never	Never/former
Weight gain Increment unit used	5 kg	5 kg	5 kg	5 kg
Studies (n)	3	3	4	3
Cases	2 370	33 13	2 825	2 756
RR (95%CI)	1.00 (0.98-1.03)	1.08 (1.00-1.16)	1.06 (1.03-1.09)	1.09 (1.07-1.12)
Heterogeneity (I^2, p-value)	19%, 0.29	44%, 0.17	0%, 0.69	37%, 0.20

[4]Also one study (Rosner, 2015, NHS) reported results on short-term weight gain. Among current MHT users, RR per 25 lb=1.07 (95% CI=0.97-1.19) and never MHT users RR=1.10 (95% CI=0.95-1.28)

Table 561 Weight gain and hormone receptor-defined postmenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the CUP SLR

Joint ER/PR-status[5]	ER+PR+	ER+PR-	ER-PR-
Studies (n)	5	3	5
Cases	2 252	403	534
RR (95%CI)	1.13 (1.04-1.22)	1.00 (0.95-1.04)	1.02 (0.98-1.06)
Heterogeneity (I^2, p-value)	91%, <0.01	0%, 0.94	4%, 0.38

[5]Also one study (Rosner, 2015, NHS) reported results on short-term weight gain. RRs per 25 lb=1.05 (95% CI=0.94-1.16) for ER+PR+, 1.25 (95% CI=1.01-1.54) for ER+PR-, and 0.99 (0.80-1.23) for ER-PR- breast cancers

Table 562 Weight gain and postmenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Keum, 2015	7 prospective studies on postmenopausal breast cancer	4 570 postmenopausal breast cancer	Australia, Japan, Europe, North America	Incidence, postmenopausal breast cancer, no or low HRT users	Adult weight gain Per 5 kg Highest vs lowest (7 studies)	 1.11 (1.08-1.13) 1.75 (1.54-2.00)	 - 	 22%, 0.26 0%, 0.55
				No HRT users	Per 5 kg Highest vs lowest (5 studies)	1.11 (1.08-1.13) 1.83 (1.58-2.13)	- 	39%, 0.17 0%, 0.50
				HRT users	Per 5 kg (4 studies) Highest vs lowest (5 studies)	1.01 (0.99-1.02) 1.14 (1.00-1.30)	- 	0%, 0.43 0%, 0.58
Vrieling, 2010	11 studies (3 cohorts, 8 population-based case-control studies)	2698 ER+PR+, 787 ER-PR- postmenopausal breast cancer	USA, Sweden	ER+PR+ postmenopausal breast cancer	Highest vs lowest adult weight gain	2.33 (2.05-2.60)	-	71%, <0.01
				ER-PR- postmenopausal breast cancer		1.34 (1.06-1.63)	-	17%, 0.30

*All cohort studies identified were included in the present review

Table 563 Weight change and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Zhang X, 2015 BRE80578 USA	NHS, Prospective Cohort, Age: 30-55 years, Mean age: 62 years W	5 191/ 103 577 26 years	Self-report verified by medical record	Self-reported weight at age 18 years and study baseline in questionnaire	Incidence, Invasive breast cancer, postmenopause	10-19.9 vs ±1.9 kg	1.23 (1.10-1.39)	Age at menarche, age at menopause, alcohol Intake, BMI at age 18 years, family history of breast cancer, height, history of benign breast disease, parity and age at first birth, postmenopausal hormone use	
						per 5 kg	1.06 (1.05-1.08)		
Catsburg, 2014b BRE80529 Canada	CSDLH, Case Cohort, W, alumnae	724/ 4 417 15 years	Cancer registry	Self-reported weight at age 20 years and study baseline	Incidence, Invasive breast cancer, HRT never	≥16 vs ≤0 kg	1.16 (0.85-1.59)	Age at first child birth, age at menarche, alcohol Intake, family history of breast cancer, menopausal status, number of childbirths, oc	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								use, physical activity	
		524/			Postmenopausal	≥16 vs ≤0 kg	1.39 (0.98-1.98)	HRT use	
						per 5 kg	1.06 (1.01-1.11)		
		336/			HRT ever	≥16 vs ≤0 kg	1.44 (0.88-2.36)		
Alsaker, 2013 BRE80497 Norway	HUNT2, Prospective Cohort, Age: 55- years, W, Postmenopausal	471/ 28 153 12.8 years	Cancer registry	Measured at clinical examinations at different periods during adulthood Adulthood weight change	Incidence, breast cancer, age >=55 year	≥7.5 vs ±2.5 kg/10 years	1.49 (1.11-2.01)	Age at menarche, alcohol, attained age, educational level, exercise, height, parity and age at first birth, smoking status, year of birth	
						per 1 kg/year	1.50 (1.20-1.88)		
	HUNT	281/		Weight change <45 years	Age >=55 year	≥7.5 vs ±2.5 kg/10 years	1.41 (1.00-1.99)	Age, height, stratified by year of birth	
						per 1 kg/year	1.38 (1.09-1.75)		
		278/		Weight change between >=45 and <55 years	Age >=55 year	≥7.5 vs ±2.5 kg/10 years	2.09 (1.48-2.95)		
						per 1 kg/year	1.69 (1.32-2.16)		
		341/		Weight change >=55 years	Age >=55 year	≥7.5 vs ±2.5 kg/10 years	0.87 (0.44-1.71)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
						per 1 kg/year	0.92 (0.73-1.18)		
Krishnan, 2013 BRE80482 Australia	MCCS, Prospective Cohort, Age: 39-76 years, Mean age: 60 years W, Postmenopausal	668/ 14 441 16.5 years	Cancer registry / database / pathology reports	Self-reported weight at 18-21 years; weight and height at study baseline was measured by trained nurses	Incidence, breast cancer	per 5 kg	1.06 (1.03-1.10)	Age at menarche, age-underlying cox models, alcohol, breastfeeding, country of birth, educational level, energy Intake, HRT use, ocp use, parity, physical activity, smoking, weight at 18 yrs	
						per 5 kg	1.06 (1.03-1.10)		
		631/				≥18.7 vs 0-10 kg	1.17 (0.96-1.42)		
						≥18.7 vs 0-10 kg	1.17 (0.96-1.42)		
		428/			Never HRT users	per 5 kg	1.07 (1.03-1.11)		
		341/			>69 years	per 5 kg	1.09 (1.04-1.14)		
		327/			<=69 years	per 5 kg	1.03 (0.99-1.08)		
		261/			Incidence, breast	per 5 kg	1.10 (1.04-1.16)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					cancer ER+				
		240/			Incidence, breast cancer, HRT users	per 5 kg	1.04 (0.98-1.10)		
		234/			Incidence, breast cancer hER-2 -	per 5 kg	1.11 (1.05-1.17)		
		190/			Incidence, luminal a breast cancer	per 5 kg	1.13 (1.06-1.20)		
		175/			Incidence, breast cancer PR+	per 5 kg	1.15 (1.08-1.22)		
		168/			Incidence, breast cancer ER+/PR+	per 5 kg	1.16 (1.09-1.23)		
		147/			Incidence, moderate differentiated breast cancer	per 5 kg	1.11 (1.04-1.19)		
		129/			Incidence, breast cancer PR-	per 5 kg	1.02 (0.94-1.09)		
		106/			Incidence, poorly differentiated breast cancer	per 5 kg	1.07 (0.98-1.17)		
		86/			Incidence, breast	per 5 kg	1.04 (0.95-1.14)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					cancer hER-2 +				
		77/			Incidence, breast cancer ER+/PR-	per 5 kg	0.98 (0.88-1.09)		
		68/			Incidence, luminal b breast cancer	per 5 kg	1.03 (0.93-1.15)		
		63/			Incidence, well differentiated breast cancer	per 5 kg	1.09 (0.99-1.21)		
		59/			Incidence, breast cancer ER-	per 5 kg	1.06 (0.97-1.16)		
		52/			Incidence, breast cancer ER-/PR-	per 5 kg	1.06 (0.97-1.17)		
		38/			Incidence, triple negative breast cancer	per 5 kg	1.07 (0.97-1.17)		
Canchola, 2012 BRE80401 USA	CTS, Prospective Cohort, Age: 56-70 years, Mean age 62 years W, Postmenopausal	1 355/ 56 542 12.1 years	Cancer registry and national death Index	Self-reported weight at age 18 years and study baseline in questionnaire	Incidence, breast cancer ER+/PR+	≥40 vs ±9.9 lbs	1.24 (1.06-1.47)	Age at baseline, age at first child birth, age at menarche, alcohol, breast biopsies, family history of breast cancer, height, HRT use, parity,	Included in the analysis of hormone receptor defined breast cancer only

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								weight at 18 yrs	
						per 10 lbs	1.03 (1.01-1.05)		
		282/			Incidence, breast cancer ER+/PR-	≥40 vs ±9.9 lbs	0.91 (0.64-1.30)		
						per 10 lbs	1.00 (0.95-1.04)		
		279/			Incidence, breast cancer ER-/PR-	≥40 vs ±9.9 lbs	1.53 (1.02-2.29)		
						per 10 lbs	1.00 (0.96-1.04)		
White, 2012 BRE80396 Hawai, California	MEC, Prospective Cohort, Age: 45-75 years, Postmenopausal	2 872/ 82 971 9 years	Cancer registry and national death Index	Self-reported weight at age 21 years and study baseline, compared with the driving license	Incidence, breast cancer	≥22.7 vs 3.65-9.09 kg	1.50 (1.32-1.69)	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, energy, family history of breast cancer, height, HRT use, number of childbirths, physical activity, smoking status, type of menopause	
						per 5 kg	1.07 (1.05-1.08)		
						≥22.7 vs 3.65-9.09 kg	1.39 (1.18-1.64)	BMI	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		893/			Japanese	per 5 kg	1.16 (1.12-1.21)		
		790/			White	per 5 kg	1.06 (1.03-1.09)		
		523/			African American	per 5 kg	1.05 (1.02-1.08)		
		420/			Latina	per 5 kg	1.03 (0.99-1.07)		
		246/			Native Hawaiian	per 5 kg	1.07 (1.03-1.12)		
Kawai, 2010b BRE80316 Japan	MCS, Prospective Cohort, Age: 40-64 years, M/W, Postmenopausal	108/ 10 106 129 891 person-years	Cancer registry	Self-reported weight at age 20 years and study baseline	Incidence, breast cancer	≥ +12 vs ±1.9kg	1.55 (0.70-3.45)	Age, age at menarche, age at menopause, alcohol Intake, educational level, family history of breast cancer, HRT use, parity, smoking, walking	
Ahn, 2007 BRE80139 USA	NIH-AARP, Prospective Cohort, Age: 50- years, Mean age 63	99 039 4 years 948/	Cancer registry	Self-reported weight at age 18 years and study baseline in questionnaire,	Incidence, breast cancer, MHT nonusers	≥50 vs -1.9 to 1.9 kg	2.15 (1.35-3.42) Ptrend:<0.001	Age, age at menarche, age at menopause, age at first live birth, parity, smoking,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	years W, Postmenopausal	1162/		Weight change from age 18 years to current age	Current MHT users	≥50 vs -1.9 to 1.9 kg	0.83 (0.43-1.62) Ptrend:0.32	education leve, race, family history of breast cancer, fat intake, alcohol, consumption, oophorectomy, physical activity, height, weight at age 18 years	
		202/			MHT nonusers ER+PR+	≥30 vs -2.0 to 9.9 kg	2.69 (1.74-4.17) Ptrend<0.001		
		44/			MHT nonusers ER+PR-	≥30 vs -2.0 to 9.9 kg	1.28 (0.47-3.48) Ptrend:0.95		
		53/			MHT nonusers ER-PR-	≥30 vs -2.0 to 9.9 kg	0.61 (0.21-1.82) Ptrend:0.06		
		189/			MHT nonusers Unknown ER/PR status	≥30 vs -2.0 to 9.9 kg	1.91 (1.21-3.02) Ptrend<0.001		
		948/		Weight change in the early reproductive years (age 18-35 years)	MHT nonusers	≥30 vs -1.9 to 1.9 kg	1.89 (1.11-3.22) Ptrend:0.06		
		1162/			Current MHT users	≥30 vs -1.9 to 1.9 kg	1.12 (0.52-2.41) Ptrend:0.53		
		948/			MHT nonusers	≥30 vs -1.9 to 1.9 kg	1.65 (0.99-2.91)	As above but with weight change from 35-50 years and 50 years-current age	
		948/		Weight change in the late reproductive	MHT nonusers	≥30 vs -1.9 to 1.9 kg	2.29 (1.51-3.46) Ptrend:<0.001	As above but with weight at age 35 years	
		1162/			Current MHT	≥30 vs -1.9 to	1.08 (0.59-2.01)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
				years (age 35-50 years)	users	1.9 kg	Ptrend: 0.49		
		948/			MHT nonusers	≥30 vs -1.9 to 1.9 kg	2.23 (1.46-3.41)	As above but with weight change from age 18-35 years and 50 years to current age	
		948/		Weight change in the perimenopausal and postmenopausal years (age 50 years to the current age)	MHT nonusers	≥30 vs -1.9 to 1.9 kg	1.89 (1.20-2.97) Ptrend:<0.001	As above but with weight at age 50 years	
		1162/			Current MHT users	≥30 vs -1.9 to 1.9 kg	0.99 (0.49-2.01) Ptrend: 0.66		
		948/			MHT nonusers	≥30 vs -1.9 to 1.9 kg	1.94 (1.23-3.06)	As above but with weight change from age 18-35 years and 35-50 years	
Palmer, 2007 BRE80122 USA	BWHS, Prospective Cohort, Age: 21-69 years	443/ 59 000 10 years	Death certificate / patient records / self-report	Self-reported weight at age 18 years and at last follow-up	Incidence, breast cancer, postmenopausal	≥25 vs ≤9 kg	1.19 (0.88-1.61)	Age, age at first child birth, age at menarche, age at menopause, educational level, family history of cancer, parity, physical activity	
						≥25 vs ≤9 kg	1.09 (0.81-1.48)	BMI	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		160/			Postmenopausal and HRT nonusers	≥25 vs ≤9 kg	1.40 (0.84-2.32)		
						≥25 vs ≤9 kg	1.42 (0.86-2.34)		
		82/			Incidence, breast cancer ER+/PR+, postmenopausal	≥25 vs ≤14 kg	1.29 (0.73-2.28)		
		52/			Incidence, breast cancer ER-/PR-, postmenopausal	≥25 vs ≤14 kg	1.03 (0.52-2.05)		
		36/			Incidence, breast cancer ER+/PR- or ER-/PR+, postmenopausal	≥25 vs ≤14 kg	0.31 (0.13-0.77)		
Eliassen, 2006 BRE80114 USA	NHS, Prospective Cohort, Age: 30-55 years, Postmenopausal	4 393/ 121 700 26 years 4 089/	Medical records	Self-reported weight at 18 years and current wt (simple update) Weight change since age 18 years	Incidence, Invasive breast cancer, postmenopausal	≥25 vs +/-2 kg	1.45 (1.27-1.66) Ptrend: <0.001	Age, time in 2-year periods, age at first child, age at menarche, age at menopause, alcohol, benign breast disease, family history, height, PMH use, parity, weight at 18 years	Superseded by Zhang X, 2015, results by MHT use was included in the subgroup analyses

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		1 304/			PMH never users	≥25 vs +/-2 kg	1.98 (1.55-2.53) Ptrend<0.001		
		2 496/			PMH ever users	≥25 vs +/-2 kg	1.20 (1.01-1.43) Ptrend:0.05		
		2 038/		Weight change since menopause	Postmenopausal	≥10 vs +/-2 kg	1.18 (1.03-1.35) Ptrend:0.02	As above and weight at menopause	
		745/			PMH never users	≥10 vs +/-2 kg	1.19 (0.94-1.50) Ptrend:0.002		
		1 191/			PMH ever users	≥10 vs +/-2 kg	1.15 (0.96-1.38) Ptrend:0.22		
		2 173/		Weight change from age 18 years to menopause	Postmenopausal	per 5 kg	1.04 (1.01-1.06)	As above and weight gain at menopause	
		809/			PMH never users	per 5 kg	1.12 (1.08-1.16)		
		1 264/			PMH ever users	per 5 kg	0.97 (0.94-1.01)		
		2 173/		Weight change since menopause	Postmenopausal	per 5 kg	1.06 (1.02-1.09)		
		809/			PMH never users	per 5 kg	1.07 (1.01-1.13)		
		1 264/			PMH ever users	per 5 kg	1.04 (0.99-1.09)		
Feigelson, 2006 BRE80117 USA	CPS II, Prospective Cohort,	877/ 97 786	Cancer registries and patients records	Self-reported, weight gain from age 18	Incidence, localized breast cancer,	≥61 vs 5-20 lbs	1.68 (1.36-2.08)	Age , age at first child, age at menarche, age at	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Age: 50-74 years, Postmenopausal			years to 1992				menopause, alcohol, breast diseases , educational level, ethnicity, family history, height, mammography, oc use, other factors , parity/pregnancies, physical activity	
		865/			Incidence, ductal carcinomas,	≥61 vs 5-20 lbs	1.89 (1.53-2.34)		
		621/			Incidence, localized breast cancer, mammographic screening	≥61 vs 5-20 lbs	1.64 (1.27-2.11)		
		549/			Incidence, unknown ER/PR status,	≥61 vs 5-20 lbs	1.91 (1.47-2.48)		
		445/			Incidence, breast cancer ER+/PR+,	≥61 vs 5-20 lbs	2.42 (1.82-3.23)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		387/			Incidence, grade 2 breast cancer,	≥61 vs 5-20 lbs	1.67 (1.22-2.29)		
		328/			Incidence, grade 3 breast cancer,	≥61 vs 5-20 lbs	2.84 (1.99-4.06)		
		296/			Incidence, regional and distant breast cancer,	≥61 vs 5-20 lbs	3.15 (2.21-4.48)		
		208/			Incidence, lobular and mixed lobular/ductal carcinomas,	≥61 vs 5-20 lbs	1.54 (1.01-2.33)		
		184/			Incidence, grade 1 breast cancer,	≥61 vs 5-20 lbs	2.17 (1.37-3.44)		
		183/			Incidence, regional and distant breast cancer, mammographic screening	≥61 vs 5-20 lbs	3.92 (2.49-6.17)		
		127/			Incidence, non ductal, lobular, or mixed breast carcinomas ,	≥61 vs 5-20 lbs	4.67 (2.72-8.01)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		108/			Incidence, breast cancer ER+/PR- or ER-/PR+,	≥61 vs 5-20 lbs	1.32 (0.70-2.49)		
		98/			Incidence, breast cancer ER-/PR-,	≥61 vs 5-20 lbs	1.78 (0.98-3.23)		
Li, 2006 BRE80166 China	SWHS, Prospective Cohort, Age: 40-70 years, Mean age: 52 years W	213/ 73 410 5.66 years	Medical records	Self-reported weight at age 20 years; height and weight measured by trained interviewers at study baseline	Incidence, breast cancer, postmenopausal	≥13.6 vs ≤6 kg	1.80 (1.31-2.48)	Age, age at first child birth, age at menopause, breastfeeding, educational level, energy Intake, family history, family history of cancer	
						≥13.6 vs ≤6 kg	1.61 (1.09-2.37)	BMI	
Lahmann, 2005a BRE23014 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 25-70 years, W	626/ 98 352 5.8 years	Partially histological - over 80%	Self-reported weight at age 20 years, measurements obtained at the time of enrolment (1992-2000)	Incidence, Invasive breast cancer, postmenopausal and other	> 20 kg vs +/- 2 kg kg	1.52 (1.08-2.13)	Age at first child, age at menarche, age-underlying cox models, alcohol, body weight, educational level, height, leisure time physical activity, smoking habits	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		456/			Postmenopausal and other	> 20 kg vs +/- 2 kg kg	0.95 (0.65-1.38)		
Feigelson, 2004 BRE02721 USA	CPS II, Prospective Cohort, Age: 50-74 years, W, Postmenopausal	1 182/ 62 756 9 years	Medical records + self-reported +death certificate	Self-reported weight at age 18 years and in questionnaire administered in 1992	Incidence, breast cancer, HRT - no	≥71 vs ±5lb	2.13 (1.50-3.01)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI at baseline, educational level, ethnicity, family history, height, mammography, oc use, parity/pregnancies, physical activity	
						≥71 vs ±5lb	2.08 (1.59-2.73)		
		752/			HRT - yes	≥71 vs ±5lb	1.13 (0.72-1.76)		
						≥71 vs ±5lb	1.11 (0.75-1.64)		
Radimer, 2004 BRE16401 USA	FHS, Prospective Cohort, Age: 28-62 years,	165/ 2 873 48 years 143/	All histology	Self-reported weight at age 25 years; physician administered measurements at	Incidence, late onset breast cancer,	≥25.1 vs +/-2 kg	1.20 (0.50-2.70) Ptrend:0.048	Age , age at first child, alcohol, HRT use, parity, smoking habits, height, BMI at	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	W	102/		study baseline	No HRT use	≥25.1 vs +/-2 kg	0.80 (0.30-2.30) Ptrend:0.478	start of age period	
		44/		Weight gain from age 25 years	Any HRT use	≥25.1 vs +/-2 kg	2.60 (0.70-9.00) Ptrend:0.071		
		65/		Weight gain between age 25-44 years (premenopausal)	Late onset breast cancer	≥15.1 vs +/-2 kg	0.80 (0.40-1.60) Ptrend: 0.620		
		107/		Weight gain between age 45-55 years (perimenopausal	Late onset breast cancer	≥5.1 vs +/-1 kg	1.0 (0.60-1.80) Ptrend:0.921		
		66/		Weight gain from age 56 years (postmenopausal	Late onset breast cancer	≥5.1 vs +/-2 kg	1.10 (0.60-1.90) Ptrend:0.562		
Breslow, 2001 BRE01123 USA	NHEFS, Prospective Cohort, Age: 24-75 years, W	94/ 6 160 9.2 years	Medical records + self-reported	Self-reported weight at age 25 years; measured by skilled personnel in 1982-1984	Incidence, breast cancer, postmenopausal	≥20 vs ±4.9 kg	1.74 (0.91-3.30)	Age , BMI, ethnicity, height, Income, physical activity , socio-economic status	
van den Brandt, 1997 BRE12717	NLCS, Case Cohort, Age: 55-69	500/ 4.3 years	All histology	Self-reported weight at age 20 years and study	Incidence, Invasive breast cancer,	≥25 vs 0-4.9 kg	1.57 (0.99-2.47)	Age , age at first child, age at menarche,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Netherlands	years, W, Postmenopausal			basline	postmenopausal			alcohol, height, parity/pregnancies	
					BMI<21 kg/m^2 at age 20	≥20 vs <5 kg	1.23 (0.70-2.17) Ptrend:0.36		
					BMI≥21 kg/m^2 at age 20	≥20 vs <5 kg	1.36 (0.83-2.23) Ptrend: 0.06		
Folsom, 1990 BRE02836 USA	IWHS, Nested Case Control, Age: 55-69 years, W, Postmenopausal	225/ 1804 controls 2 years	All histology	Self-reported weight at age 18 years and study basline; reliability and accuracy of measurements are good	Incidence, breast cancer, postmenopausal	≥17.31 vs ≤8.19 kg	1.60 (1.13-2.27)	Age	

Table 564 Weight change and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Rosner, 2015 BRE80548 USA	NHS, Prospective Cohort, W	3 009/ 77 232 1 445 578 person-years	Self-report verified by medical record	Self-reported since 1980, weight change over past 4 years	Incidence, breast cancer, postmenopause	per 25 lb	1.08 (1.00-1.16)	Unknown/NA	Publication on short-term weight change
						≥15 vs 0-5 lb	1.10 (0.97-1.25)		
		1 518/			Incidence, breast cancer ER+/PR+, postmenopause	≥15 vs 0-5 lb	1.06 (0.88-1.27)		
						per 25 lb	1.05 (0.94-1.16)		
		1 475/			Incidence, breast cancer, postmenopausal non PMH users	per 25 lb	1.07 (0.97-1.19)		
						≥15 vs 0-5 lb	1.04 (0.87-1.25)		
		1 068/			Postmenopausal PMH users	per 25 lb	1.10 (0.95-1.28)		
						≥15 vs 0-5 lb	1.16 (0.94-1.43)		
		419/			Incidence, breast cancer ER-/PR-, postmenopause	≥15 vs 0-5 lb	1.01 (0.70-1.46)		
						≥15 vs 0-5 lb	0.91 (0.63-1.30)		
						per 25 lb	0.99 (0.80-1.23)		
						per 25 lb	1.25 (1.01-1.54)		
Emaus, 2014 BRE80540 Europe	EPIC-PANACEA, Prospective	2 714/ 205 723 1 396 538	Active follow up and cancer registry	Most study centres measured the	Incidence, Invasive breast cancer,	0.84-4.98 vs ≤0.36 kg/year	1.12 (1.01-1.24)	Age, age at first child birth, age at menarche,	Excluded, study on weight chante during

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Cohort, Age: 25-70 years, Mean age: 51.9 years W	person-years		initial weight and used self-reported data from the second weight assessment; weight change between age 40-50 years	BMI<=25, age >50y			alcohol consumption, alcohol drinking, BMI at baseline, educational level, energy Intake, HRT use, physical activity, smoking, study center, time between measurements, use of oral contraception	middle adulthood
		2 624/			Incidence, breast cancer ER+, age at diagnosis >50yrs	0.84-4.98 vs ≤0.36 kg/year	1.08 (0.97-1.20)		
		2 592/			Incidence, Invasive breast cancer, postmenopausal at 1st assess, 2nd assess, diagnosis	0.84-4.98 vs ≤0.36 kg/year	1.07 (0.96-1.20)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		2 372/			Incidence, breast cancer, HRT never, >50y	0.84-4.98 vs ≤0.36 kg/year	1.06 (0.95-1.18)		
		1 720/			Incidence, breast cancer PR+, age at diagnosis >50yrs	0.84-4.98 vs ≤0.36 kg/year	1.07 (0.94-1.22)		
		1 659/			Incidence, breast cancer ER+ & PR+, age at diagnosis >50yrs	0.84-4.98 vs ≤0.36 kg/year	1.08 (0.95-1.24)		
		1 652/			Incidence, breast cancer, HRT ever, >50y	0.84-4.98 vs ≤0.36 kg/year	1.13 (0.98-1.29)		
		1 647/			Incidence, Invasive breast cancer, BMI>25, age >50y	0.84-4.98 vs ≤0.36 kg/year	1.03 (0.90-1.19)		
		943/			Incidence, breast cancer PR-, age at diagnosis >50yrs	0.84-4.98 vs ≤0.36 kg/year	1.06 (0.89-1.27)		
		515/			Incidence, breast cancer ER-, age at diagnosis >50yrs	0.84-4.98 vs ≤0.36 kg/year	1.06 (0.84-1.35)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		404/			Incidence, breast cancer ER- & PR-, age at diagnosis >50yrs	0.84-4.98 vs ≤0.36 kg/year	1.17 (0.90-1.53)		
		394/			Incidence, Invasive breast cancer, premenopausal at 1st assess, >50y at 2nd assess, >50y at diagnosis	0.84-4.98 vs ≤0.36 kg/year	1.08 (0.82-1.42)		
		393/			Premenopausal at 1st assess, <= 50 years at 2nd assess, > 50 years at diagnosis	0.84-4.98 vs ≤0.36 kg/year	1.27 (0.97-1.65)		
Han, 2014 BRE80525 USA	ARIC, Prospective Cohort, Age: 45-64 years, W, Postmenopausal	372/ 7 569 20 years	Cancer registry and hospital records	Weight at 25y self-reported measured baseline weight and height	Incidence, postmenopausal breast cancer	per 5 %	1.05 (1.02-1.07)	Age, age at menarche, age at menopause, alcohol, BMI at age 25 years, cigarette smoking status, education years, height, physical	Excluded, measured percentage weight change

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								activity, race, smoking status	
						per 5 %	1.04 (1.02-1.06)		
		36/			Mortality, postmenopausal breast cancer	per 5 %	1.08 (1.01-1.15)		
						per 5 %	1.08 (1.01-1.14)		
Hartz, 2013 BRE80483 USA	Women's Health Initiative, Prospective Cohort, Age: 55-70 years, Mean age: 63.1 years W	147 202 8 years	Self reported/death certificate/ medical records	Self-reported weight at different periods, change from minimal weight	Incidence, breast cancer, observation study	per 1 sd	1.05 (P>0.01)	Age, race, study	Excluded, measured per 1 SD increment
Manders, 2011 BRE80314 Netherlands	HEBON, Historical Cohort, W, Subjects with BRCA1/2 mutation	63/ 719 10 years	Cancer registry	Self-reported weight change during adulthood	Incidence, breast cancer, postmenopausal	≥5gain vs <5 gain kg	1.56 (0.85-2.87)	HRT use, parity, physical activity, type of menopause	Excluded, two exposure categories only
Wilson, 2011 BRE80380 USA	NHS, Nested Case Control, W,	205/ 1415 controls	Medical record	Self reported weight during pregnancy	Incidence, breast cancer, >=50y at diagnosis	≥40 vs 20-29 lbs	0.65 (0.28-1.49)	Age, family history of breast cancer, smoking	Publication on weight change during pregnancy

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	mothers and daughters								
Krebs, 2006 BRE80106 USA	SOF, Prospective Cohort, Age: 65- years, Mean age: 74 years Postmenopausal	350/ 9 704 11.3 years	Self report verified by medical record	Self reported weight and height at age 25 years, current anthropometics were measured at 2nd health exam	Incidence, Invasive breast cancer, postmenopausal	≥29.8 vs ≤5.1 %	1.64 (1.15-2.34)	Age , age at menarche, age at menopause, anthropometry, benign breast disease, educational level, family history, HRT use, parity/pregnancies, physical activity , smoking habits	Excluded, percentage weight change
					Age >=70 years	≥29.8 vs ≤5.1 %	1.94 (1.28-2.94)		
Harvie, 2005 BRE22559 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	1 987/ 33 660 15 years	Partially histological - over 80%	Self-reported current height and weight at baseline as well as weight at age 18, 30, 40, and 50 years	Incidence, breast cancer, postmenopausal	no change/loss+loss vs gain+gain	0.46 (0.34-0.64)	Age , age at first child, age at menarche, age at menopause, alcohol, BMI, educational level, HRT use, oc use, parity/pregnanci	Publication on weight change during different periods

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								es, smoking habits	
		1 981/			Postmenopausal	no change/loss+loss vs gain+gain	0.35 (0.21-0.59)		
Lahmann, 2004c BRE18516	EPIC, Prospective Cohort, Age: 39-80 years, Postmenopausal	732/ 56 470 4.6 years	Partially histological - over 80%	Self-reported weight at age 20 years, measurements performed by trained personnel at study baseline	Incidence, breast cancer, HRT - no	≥20.1 vs ±2 kg	1.52 (1.02-2.27)	Age , age at first child, age at menarche, alcohol, educational level, HRT use, leisure time physical activity, parity/pregnancies, recruitment center, smoking habits	Superseded by Lahmann, 2005a, BRE23014
Sweeney, 2004 BRE80599 USA	IWHS, Prospective Cohort, Mean age: 61 years, W, Postmenopausal	1 291/ 36 658 16 years	Seer registry	Self-reported current weight and height, weight at age 18 years	Incidence, breast cancer, 65-74 years	gain, >45 vs lose or gain ≤13 lb	1.78 (1.52-2.08)	Age at baseline, age at first child birth, age at menarche, age at menopause, educational level, family history of breast cancer, height,	Analysis in publication was split by age at follow-up

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								parity	
		559/			Aged 75-84	gain, >45 vs lose or gain ≤13 lb	1.79 (1.40-2.30)		
		424/			55 - 64 years	gain, >45 vs lose or gain ≤13 lb	1.47 (1.13-1.91)		
Lahmann, 2003 BRE20119 Sweden	MDCS, Prospective Cohort, Age: 50-73 years, Mean age 60 years W, Postmenopausal	191/ 12 159 5.7 years	Cancer registry + death certificate	Self-reported weight at age 20 years, measured at study baseline	Incidence, Invasive & In situ breast cancer,	≥21.1 vs ≤4.9 kg	1.75 (1.11-2.77)	Age , age at first child, age at menarche, alcohol, body weight, height, marital status, oc use, occupation, parity/pregnancies, smoking habits	Study superseded by Lahmann, 2005a
Manjer, 2001a BRE80623 Sweden	MPP, Prospective Cohort, Mean age: 49.9 years, W, Ex-smokers	50/ 2 082 13.3 years	Cancer registry	Self-reported weight gain (>10 kg) since age 30 years, weight and height measured at study baseline	Incidence, Invasive & In situ breast cancer, peri/postmenopa use	yes vs no	1.10 (0.63-1.92)	Age, HRT use, oc use	Excluded, two exposure categories only
French, 1997 BRE02957 USA	IWHS, Prospective Cohort, Age: 55-69	660/ 33 834 7 years	Partially histological - over 80%	Weigh variability during adulthood (age	Incidence, breast cancer, postmenopausal	>10% ++ large gain vs < 5% +/- no change %	1.29 (1.02-1.63)	Age , alcohol, BMI, BMI, educational level, HRT use,	Supserseded by Folsom, 1990

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	years, W, Postmenopausal			18-62 years), self report				marital status, physical activity , smoking habits, whr	
		658/			Postmenopausal	≥1 vs ≥-1	0.88 (0.70-1.12)	Body weight	
Huang, 1997 BRE04117 USA	NHS, Prospective Cohort, Age: 35-55 years, W, Registered nurses	1 517/ 95 256 16 years	Medical records + self-reported +death certificate	Self-reported weight at age 18 years and each follow-up interval	Incidence, Invasive breast cancer, postmenopausal	≥25 vs ±2 kg	1.41 (1.12-1.78)	Age , age at first child, age at menarche, age at menopause, family history, height, HRT use, parity/pregnancies	Supserseded by Zhang, 2015
					HRT - no	≥25 vs ±2 kg	2.00	BMI	
					HRT - yes	gain 20.0 vs no HRT-loss or gain 2.0 kg	1.70	Parous/nulliparous	
					HRT - former	gain 20.0 vs no HRT-loss or gain 2.0	1.30		
Barnes-Josiah, 1995 BRE00566 USA	IWHS, Prospective Cohort, Age: 55-69	623/ 37 105 6 years	Partially histological - over 80%	Self-reported weight at age 18 years and study baseline	Incidence, breast cancer, postmenopausal	Low BMI at age 18 and high weight gain to enrollment vs	1.92 (1.45-2.53)	Age , age at first child, age at menarche, age at menopause,	Superseded by Folsom, 1990

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	years, W, Postmenopausal					high BMI at age 18 and low weight gain to enrollment		alcohol, educational level, family history, HRT use, oc use, parity/pregnancies, smoking habits	
London, 1989 BRE80626 USA	NHS, Prospective Cohort, Age: 30-55 years, W	384/ 115 534 743 716 person-years	Self report verified by medical record	Self-reported weight at age 18 years and most recent follow-up	Incidence, Invasive breast cancer, postmenopausal	>20 vs ±3 kg	1.4 (1.0-2.0)	Age, Quetelet's index at age 18 years, parity, age at birth of first child, family history of breast cancer, age at menarche, smoking, history of benign breast disease, number of years since menopause	Supserseded by Zhang X, 2015

Figure 585 RR estimates of postmenopausal breast cancer by levels of weight gain

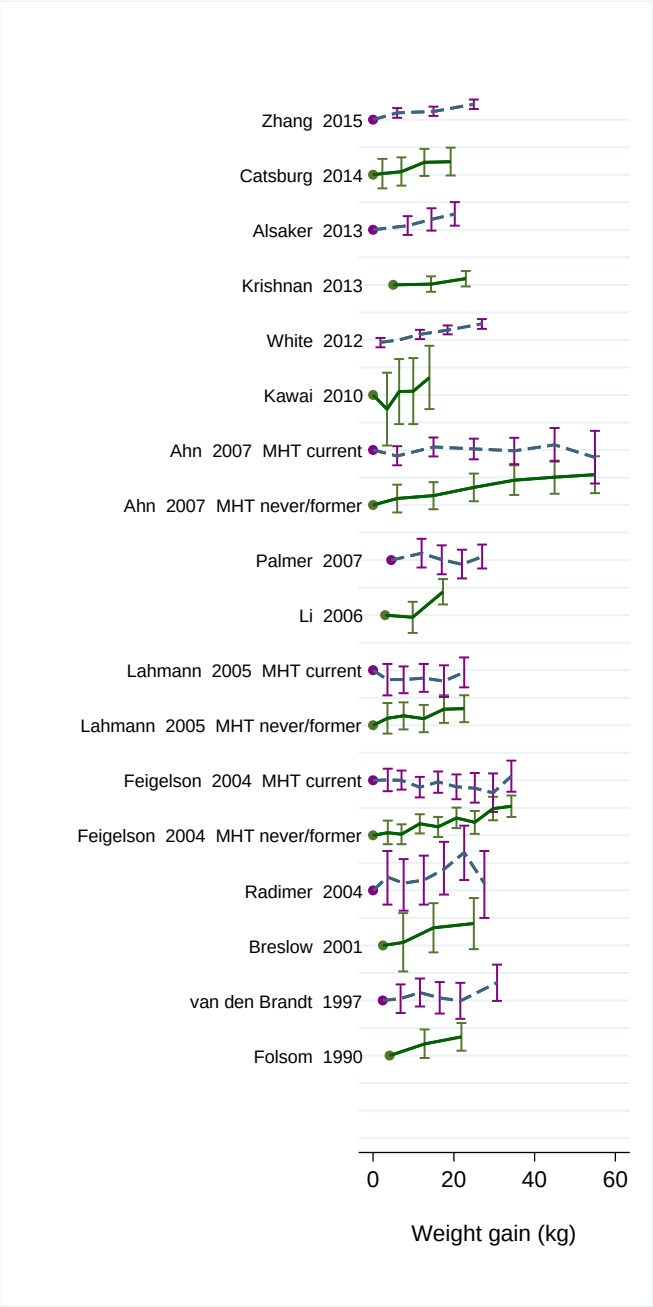


Figure 586 RR (95% CI) of postmenopausal breast cancer for the highest weight gain compared with reference category

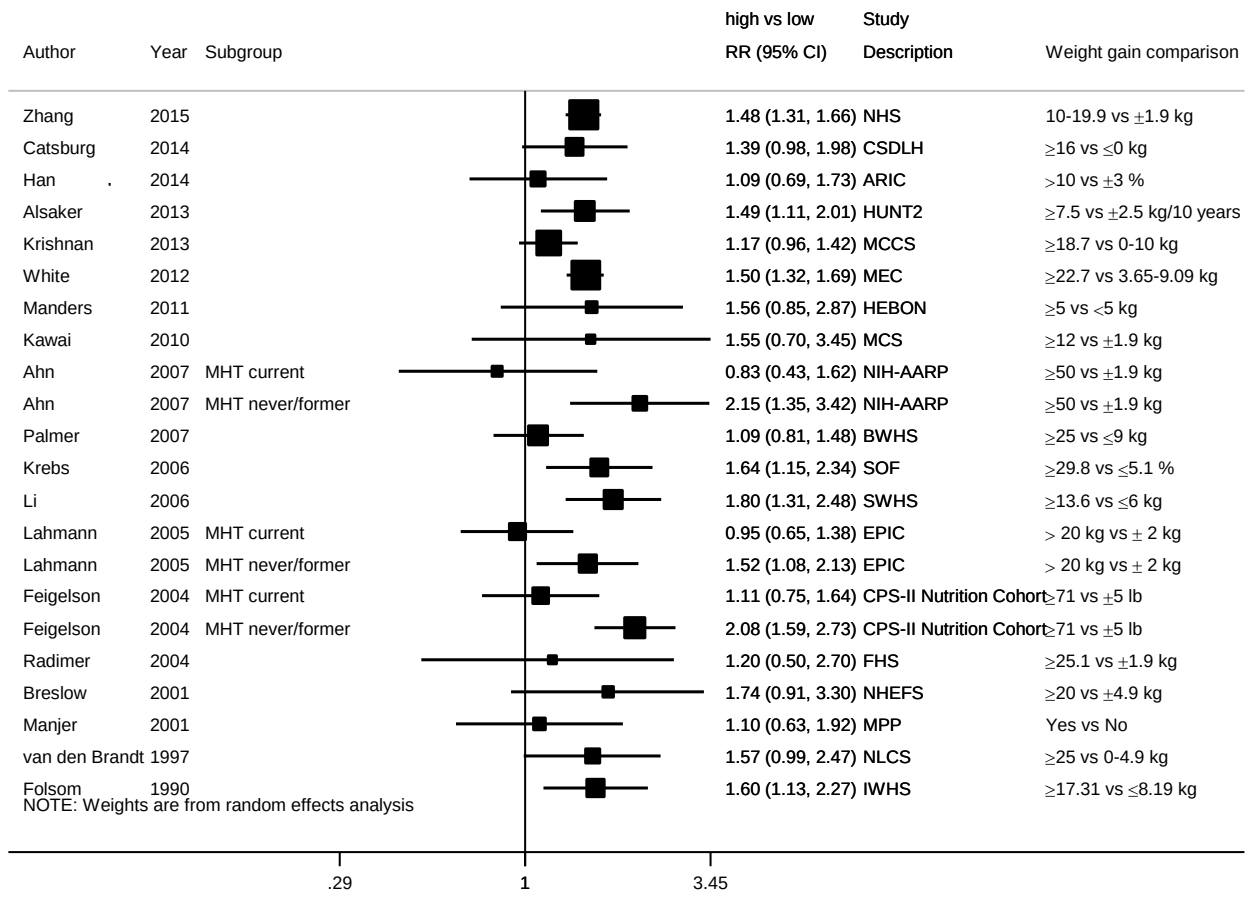


Figure 587 Relative risk of postmenopausal breast cancer for 5 kg increase of weight gain

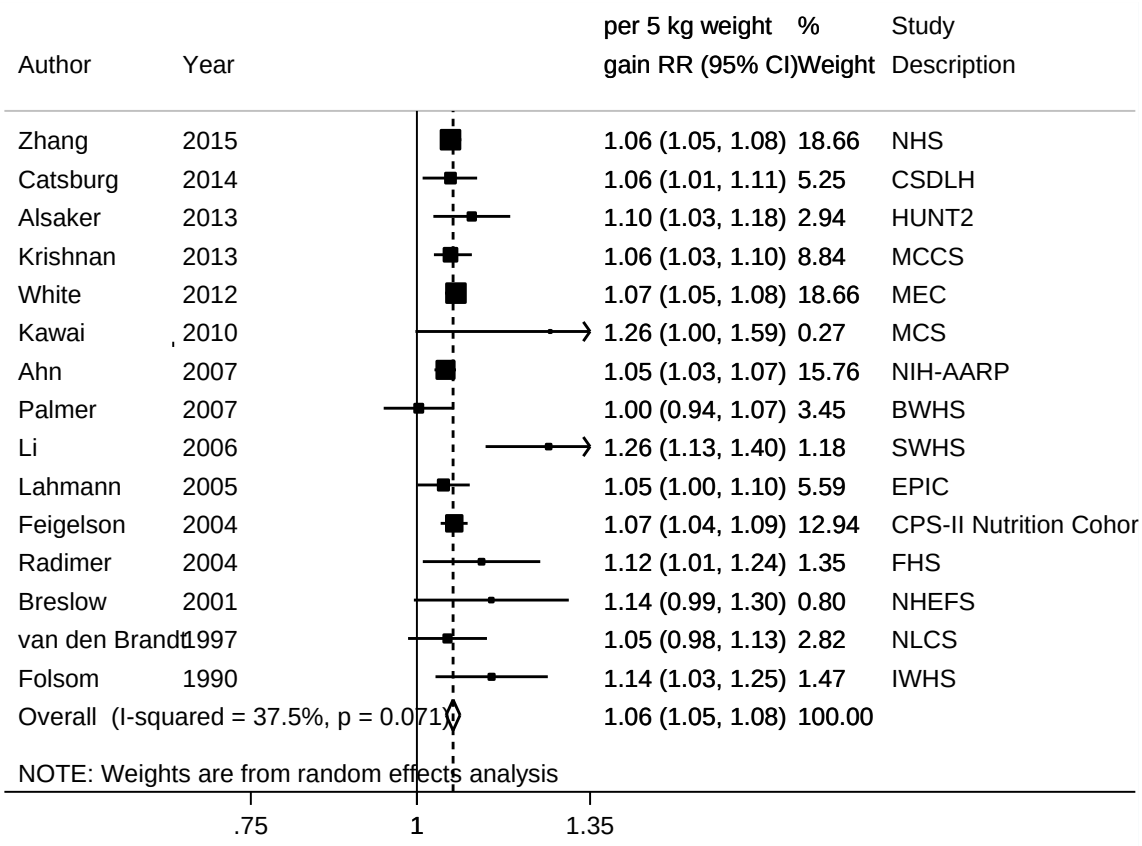


Figure 588 Funnel plot of studies included in the dose response meta-analysis of weight gain and postmenopausal breast cancer

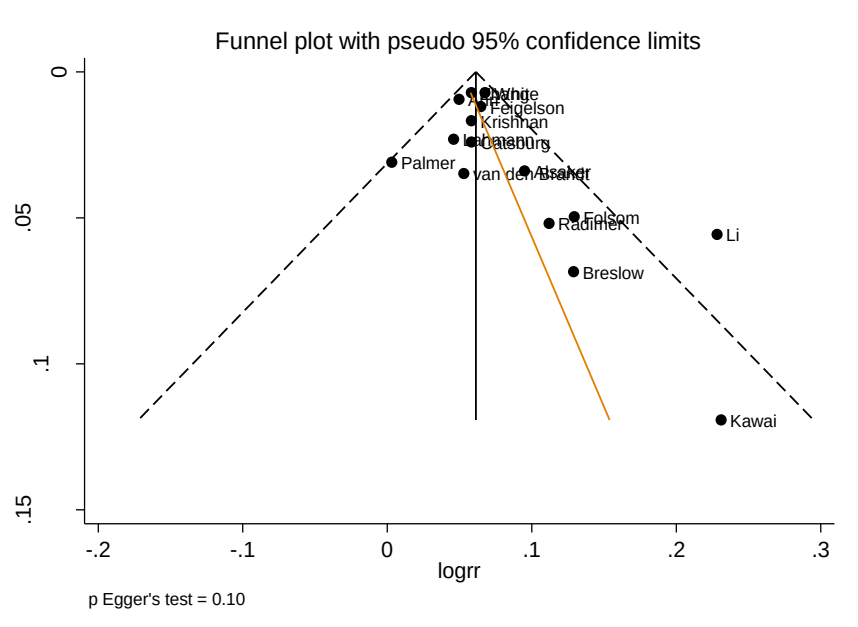


Figure 589 Relative risk of postmenopausal breast cancer for 5 kg increase of weight gain, by geographic location

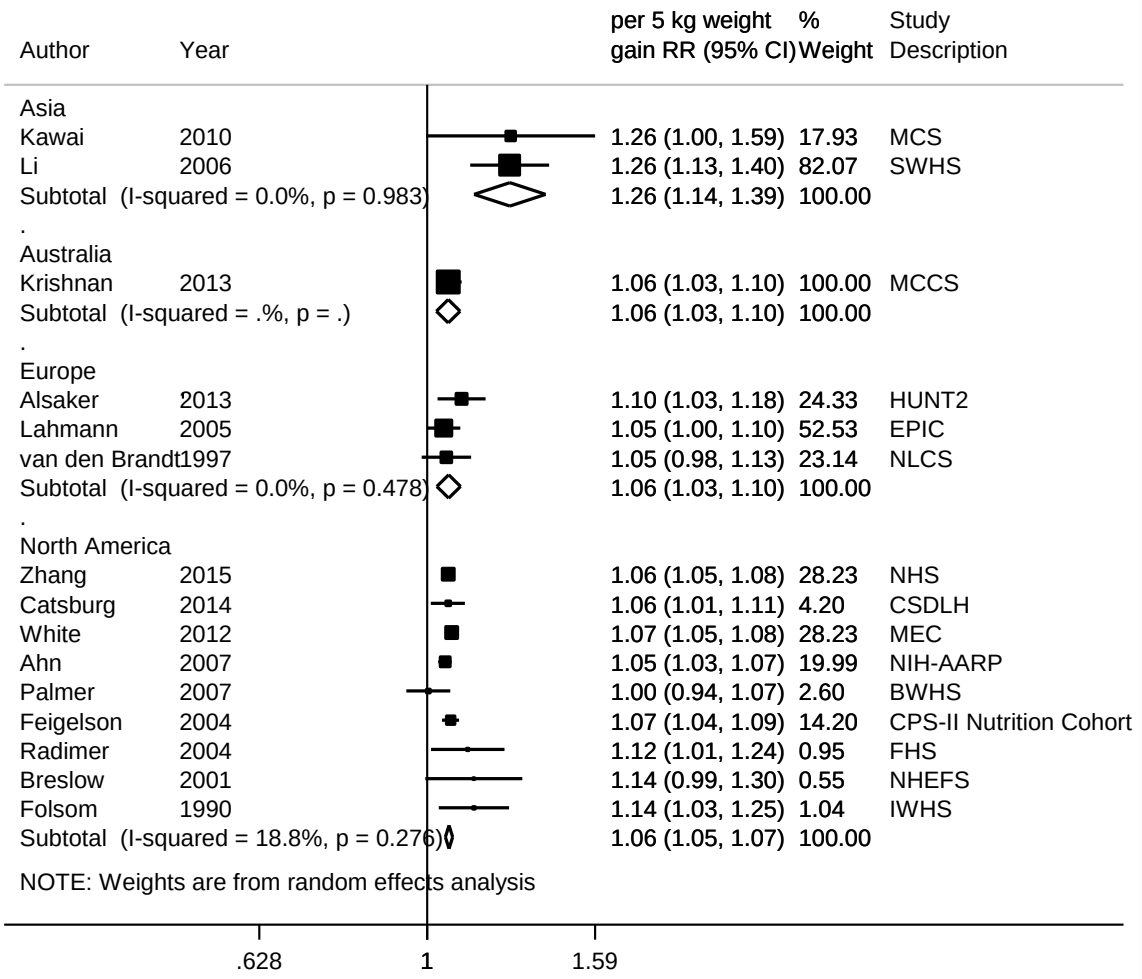


Figure 590 Relative risk of postmenopausal breast cancer for 5 kg increase of weight gain, by weight change measurement methods

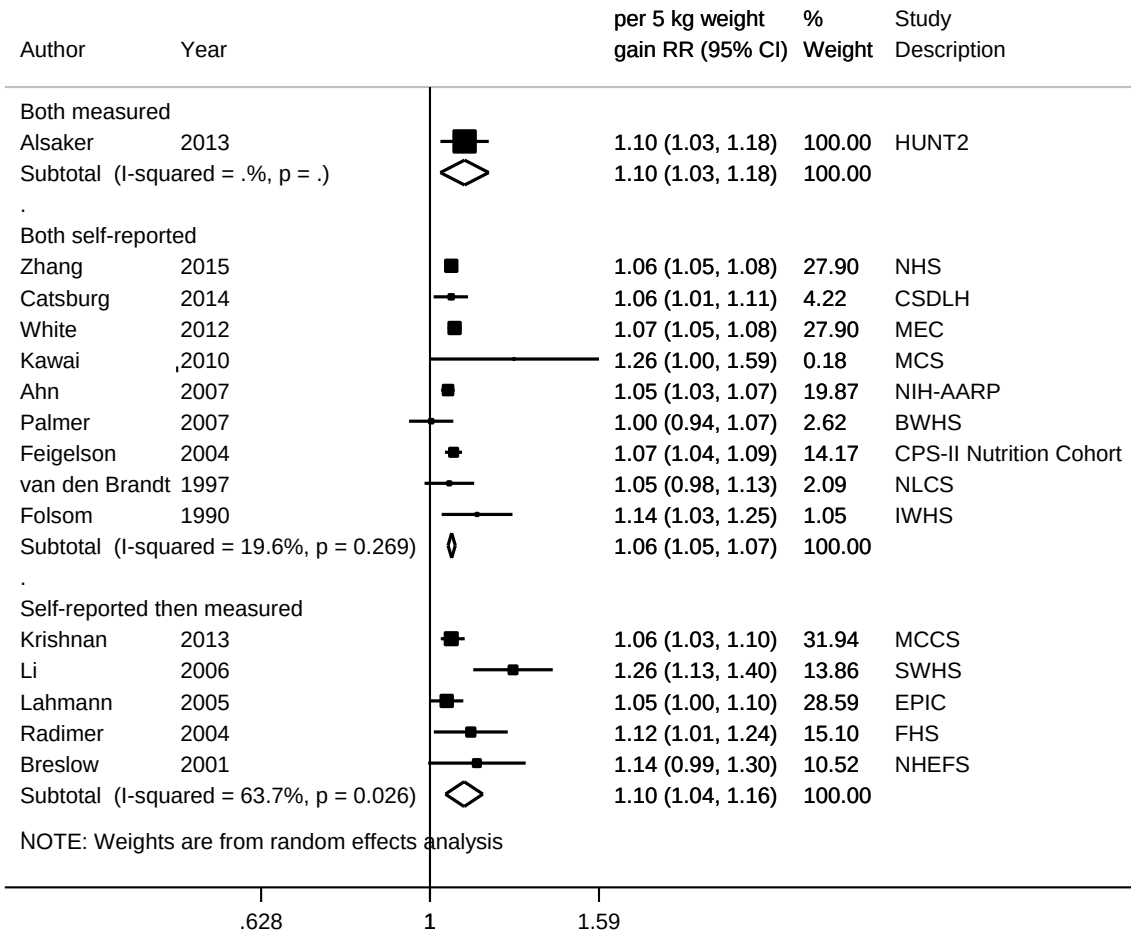
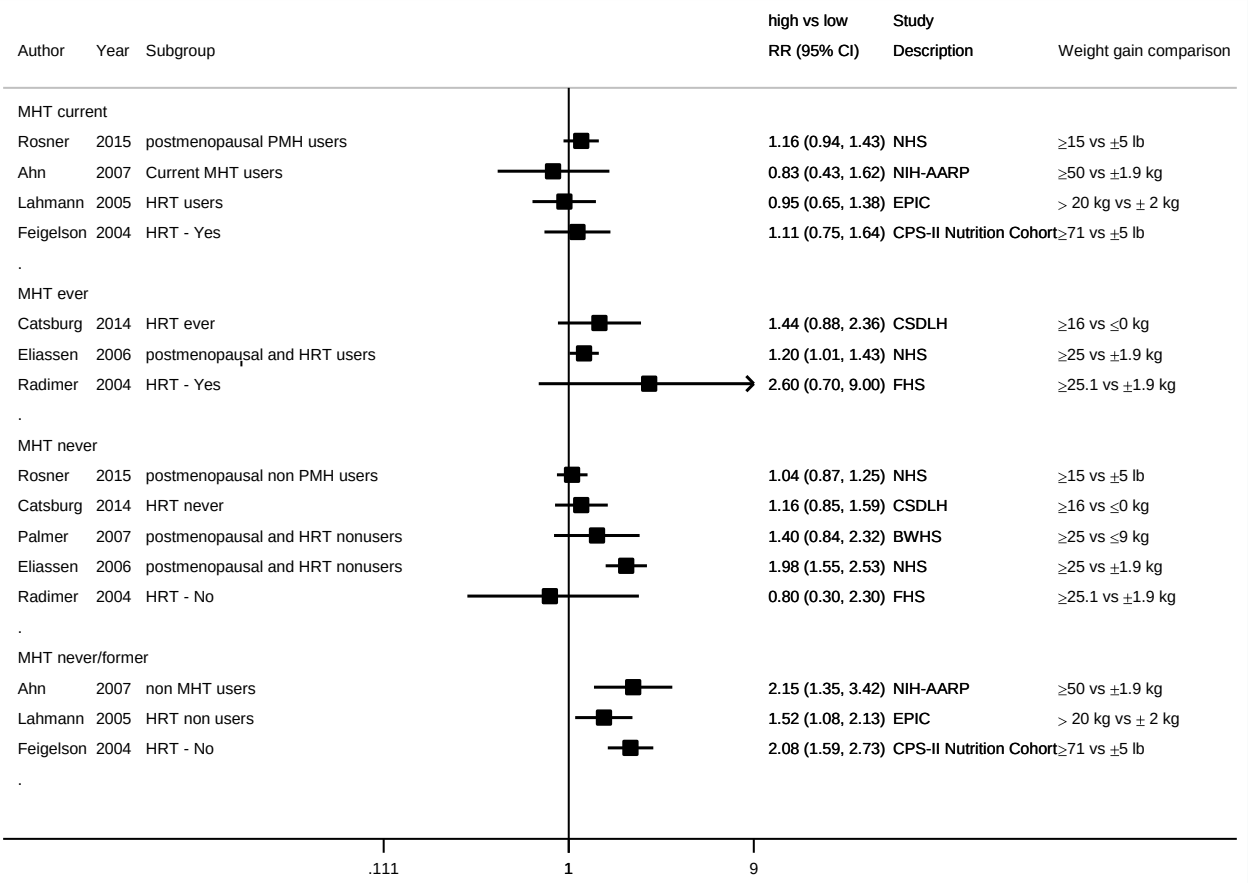


Figure 591 RR (95% CI) of postmenopausal breast cancer for the highest weight gain compared with reference category, by MHT use



Note: Rosner, 2015 was on short-term weight change during adulthood only was not included in the meta-analysis of adult weight change.

Figure 592 Relative risk of postmenopausal breast cancer for 5 kg increase of weight gain, by MHT use

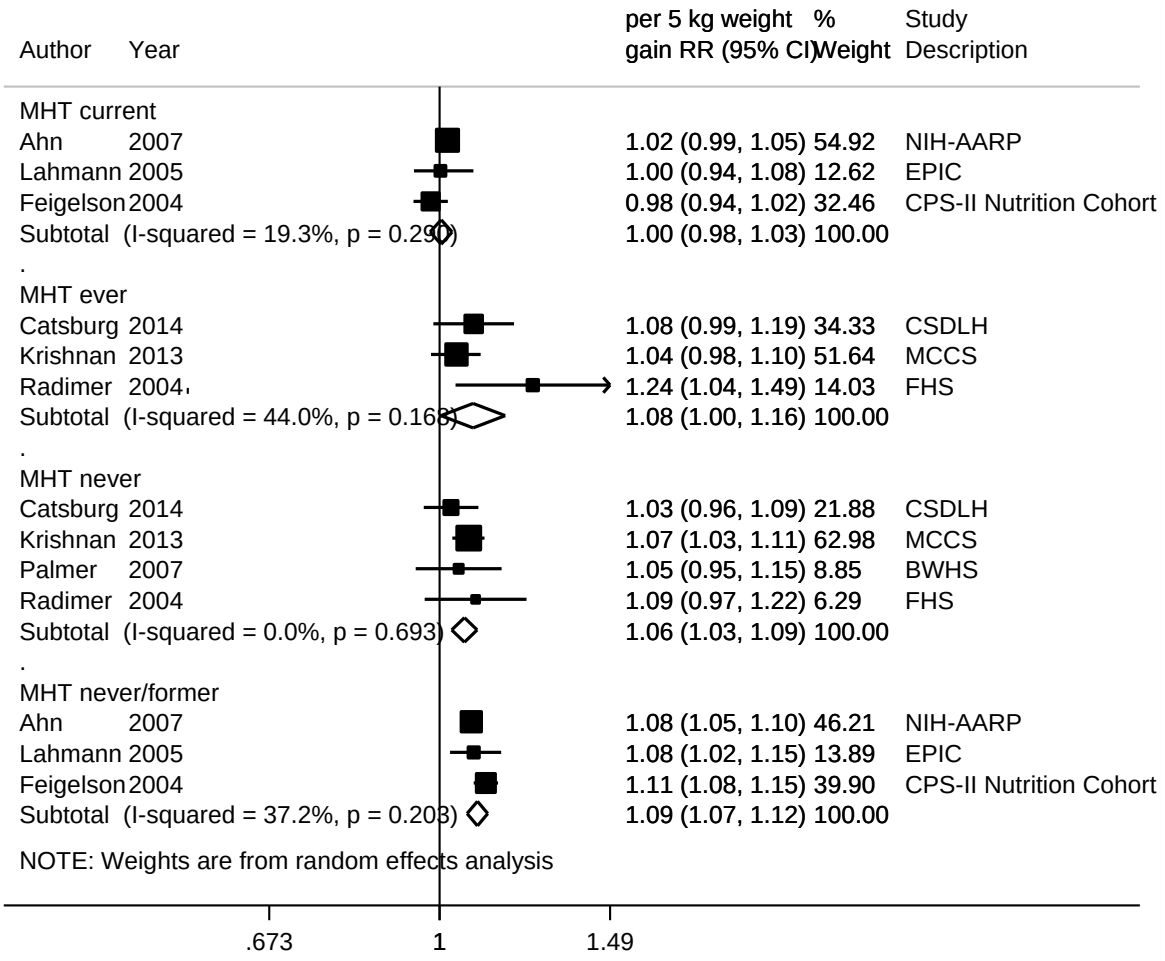
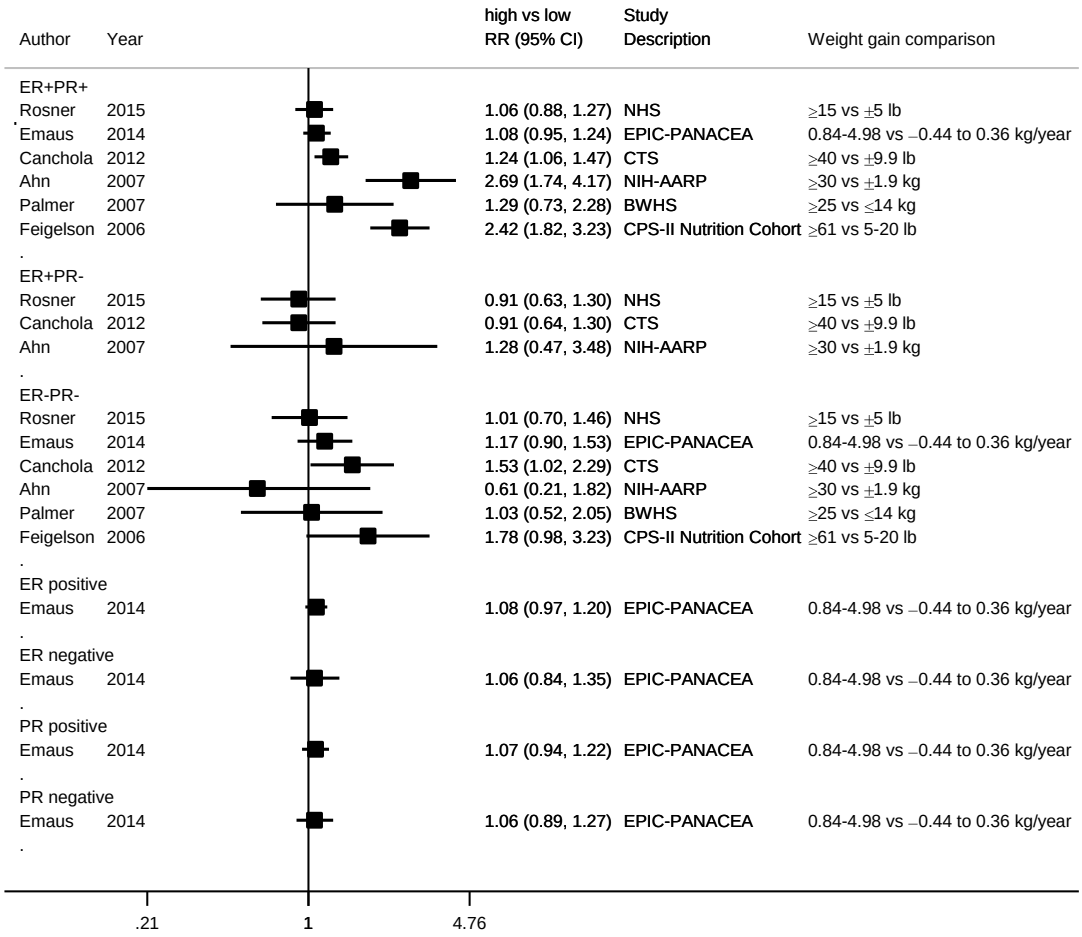


Figure 593 RR (95% CI) of hormone receptor defined postmenopausal breast cancer for the highest weight gain compared with reference category



Note: Ahn, 2007 consisted of MHT non-users only; Rosner, 2015 was on short-term weight change during adulthood only was not included in the meta-analysis of adult weight change.

Figure 594 Relative risk of joint hormone receptor defined postmenopausal breast cancer for 5 kg increase of weight gain

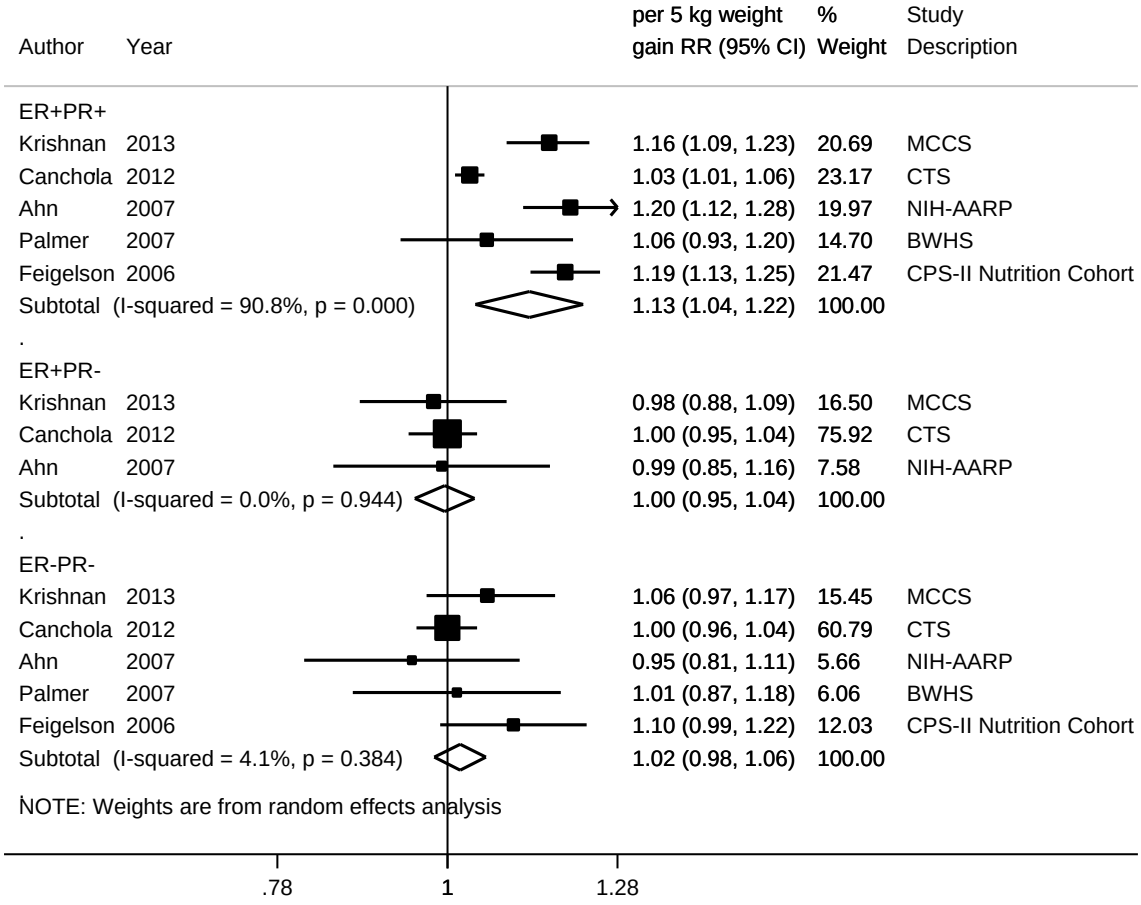


Figure 595 Non-linear dose-response meta-analysis of weight gain and postmenopausal breast cancer

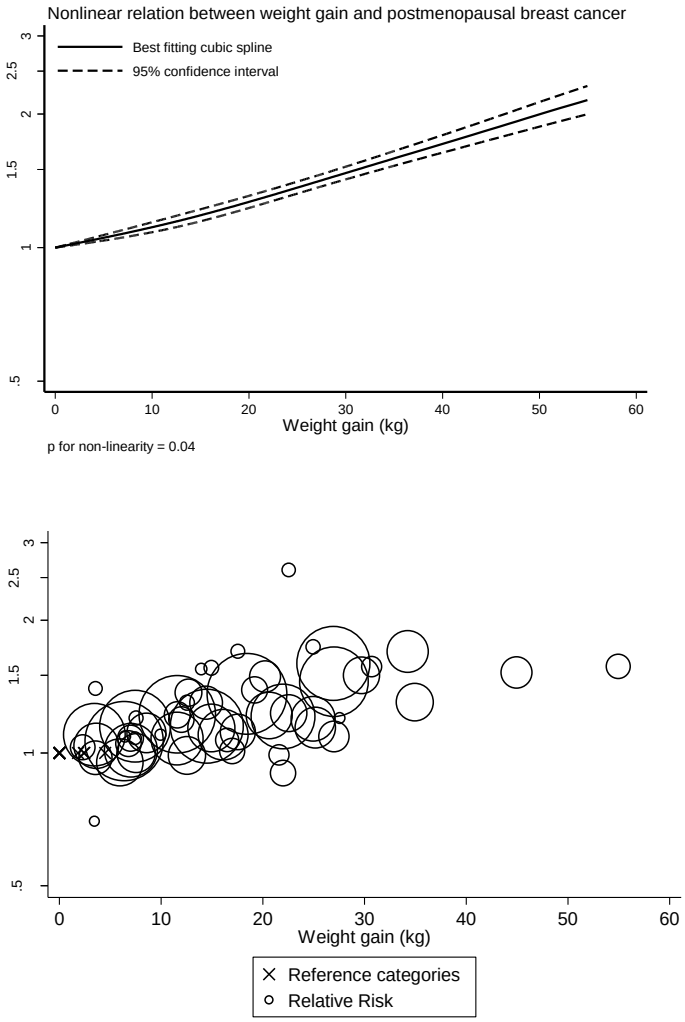


Table 565 Relative risk of postmenopausal breast cancer and weight gain estimated using non-linear models

Weight gain (kg)	RR (95%CI)
0	1.00
4.5	1.05 1.03-1.06
12.0	1.14 (1.11-1.17)
19.0	1.25 (1.21-1.29)
25.0	1.37 (1.33-1.41)
30.0	1.49 (1.44-1.54)

8.1.6 BMI change

Cohort studies

Overall summary

Ten publications from 10 studies were identified. No pooled analysis or meta-analysis was identified.

Dose-response meta-analysis was conducted to examine the association of gain in BMI during adulthood with risk of postmenopausal breast cancer.

Table 566 Summary of results of the dose-response meta-analysis in the CUP SLR

	Breast cancer (any)	Premenopausal breast cancer	Postmenopausal breast cancer
Increment unit used	-	-	5 kg/m^2
Studies (n)	-	-	5
Cases	-	-	2 575
RR (95%CI)	-	-	1.17 (1.11-1.24)
Heterogeneity (I^2, p-value)	-	-	0%, 0.74
P value Egger test	-	-	0.34

Breast cancer (any)

Three studies were identified. Meta-analysis was not conducted due to low number of studies. One study from Austria (Rapp, 2008) observed a non-significant inverse association between highest short-term gain in BMI during middle adulthood and breast cancer risk. One American study (Ballard-Barbash, 1990) reported a significant positive association for the highest versus the lowest gain in BMI during adulthood. One Dutch study (Taghizadeh, 2015) reported that breast cancer mortality was positively associated with high long-term annual gain and inversely associated with high short-term annual gain when compared with no BMI change during adulthood.

Premenopausal breast cancer

Three studies were identified. Meta-analysis was not conducted due to low number of studies. One Japanese study (Suzuki, 2011b) reported a non-significant inverse association with premenopausal breast cancer risk for ≥5 kg/m^2 gain in BMI from age 20 years versus stable BMI (±2.5 kg/m^2). One Swedish and Norwegian study (Weiderpass, 2004) reported a significant inverse association for the highest versus the lowest gain in BMI from age 18 years. The association became non-significant when current BMI was adjusted. A non-significant inverse association with premenopausal breast cancer was also observed in the Finnish study (Hilakivi-Clarke, 2005) that reported change of BMI during adult life.

Postmenopausal breast cancer

Summary

Main results:

Five studies (2 575 cases) were identified and all could be included in the dose-response meta-analysis of BMI gain during adulthood and postmenopausal breast cancer. The studies – MCCS (Krishnan, 2013) and NLCS (van den Brandt, 1997) were included in the meta-analysis of weight gain (kg) and postmenopausal breast cancer (see section 8.1.6 weight gain). Other studies (Suzuki, 2011b; Torio, 2010; Morimoto, 2002) only assessed body weight change in BMI (kg/m^2).

A significant positive association was observed for postmenopausal breast cancer risk. No heterogeneity between studies was observed. There was no evidence of significant publication or small study bias, although full inspection was not possible due to low number of study.

Subgroup analysis was not conducted due to low number of studies in the strata. There was one Australian study, one Japanese study, one study form the Netherlands, and two American studies. Initial BMI was adjusted in MCCS (Krishnan, 2013) and JPHC (Suzuki, 2011b). Current BMI was not adjusted in the studies.

One study (Morimoto, 2002) further reported results on gain in BMI since age 50 years and observed a positive association with a significant dose-response trend among MHT never users, but not among MHT current/former users, where a non-significant inverse association was reported.

Sensitivity analyses:

The summary RR did not change materially when studies were omitted in turn in influence analysis

Non-linear dose-response meta-analysis:

Non-linear dose-response meta-analysis was not conducted due to insufficient data.

Study quality:

All studies used self-reported body measurements to assessed change of BMI, except MCCS (Krishnan, 2013) which used self-reported earlier BMI and measured current BMI. Only Suzuki, 2011b performed a validation study on earlier BMI reported by the participants. No studies updated BMI change over time. Change of BMI was measured from age 18 – 21 years in the studies. All studies included invasive breast cancer only. Follow-up was short (< 5 years) in two studies (Morimoto, 2002; van den Brandt, 1997).

Apart from CLUE II (Torio, 2010), all other studies were adjusted for age, alcohol intake, and reproductive factors. NLCS (van den Brandt, 1997) was not further adjusted for MHT use, although postmenopausal hormone use could be low in this study.

The positive association remained significant when each study was omitted in turn.

Table 567 BMI change and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	5 (5 publications)
Studies included in forest plot of highest compared with lowest exposure	5
Studies included in linear dose-response meta-analysis	5
Studies included in non-linear dose-response meta-analysis	Not enough studies

Note: Include cohort, and case-cohort designs.

Table 568 BMI change and postmenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2008 SLR and CUP SLR

	2005/2008 SLR*	**CUP SLR**
Gain in BMI **Increment unit used**	-	5 kg/m^2
Studies (n)	-	5
Cases	-	2 575
RR (95%CI)	-	1.17 (1.11-1.24)
Heterogeneity (I^2, p-value)	-	0%, 0.74
P value Egger test	-	0.34

*No meta-analysis in the past reports.

Table 569 BMI change and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Krishnan, 2013 BRE80482 Australia	MCCS, Prospective Cohort, Age: 39-76 years, W, Postmenopausal	631/ 14 441 16.5 years	Cancer registry / database / pathology reports	Self-reported weight at age 18-21 years, weight and height measured by trained nurse at study baseline	Incidence, breast cancer	≥7.4 vs 0-3.9 kg/m^2	1.20 (0.99-1.46)	Age at menarche, age-underlying cox models, alcohol, breastfeeding, country of birth, educational level, energy intake, HRT use, OC use, parity, physical activity, smoking
		668/				per 5 kg/m^2	1.17 (1.08-1.27)	
		631/				≥7.4 vs 0-3.9 kg/m^2	1.20 (0.98-1.46)	As above + BMI at age 18 to 21 years
		668/				per 5 kg/m^2	1.16 (1.07-1.27)	Included in the meta-analysis
		261/			ER+	per 5 kg/m^2	1.28 (1.12-1.46)	Age at menarche, age-underlying cox models, alcohol, breastfeeding, country of birth, educational level, energy intake, HRT use, OC use, parity, physical activity, smoking, BMI at age 18 to 21 years
		59/			ER-	per 5 kg/m^2	1.18 (0.94-1.48)	
		175/			PR+	per 5 kg/m^2	1.43 (1.23-1.66)	
		129/			PR-	per 5 kg/m^2	1.05 (0.87-1.26)	
		168/			ER+PR+	per 5 kg/m^2	1.45 (1.24-1.69)	
		77/			ER+PR-	per 5 kg/m^2	0.94 (0.72-1.22)	
		52/			ER-PR-	per 5 kg/m^2	1.20 (0.94-1.53)	
Suzuki, 2011b BRE80318	JPHC, Prospective Cohort,	232/ 41 594	Hospital records + cancer	Self-reported weight at age 20	Incidence, breast cancer,	≥5 vs ≥-2.5 to >2.5 kg/m^2	1.79 (1.02-3.16) Ptrend:0.0048	Age, area, age at menarche, age at first birth, parity, use

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Japan	Age: 40-69 years	14 years	registry	years, and weight and height at baseline and 5- and 10-year follow-up surveys, BMI change from age 20 years to recent age	postmenopausal	per 5 kg/m^2	1.32 (1.09-1.60)	of exogenous female hormones, smoking status, leisure-time physical activity, alcohol intake, green-yellow vegetables, meat and meat products, isoflavones, age at menopause BMI at age 20 years
		167/			Exogenous hormone never users	≥5 vs ≥-2.5 to >4.9 kg/m^2	1.40 (0.92-2.11)	
						per 5 kg/m^2	1.42 (1.14-1.77)	
		65/			Exogenous hormone never users	≥5 vs ≥-2.5 to >4.9 kg/m^2	1.07 (0.54-2.13)	
						per 5 kg/m^2	1.08 (0.73-1.61)	
		45/			ER+PR+	per 5 kg/m^2	2.24 (1.50-3.34)	
		23/			ER+PR-	per 5 kg/m^2	0.63 (0.31-1.27)	
		36/			ER-PR-	per 5 kg/m^2	0.67 (0.38-1.17)	
		126/			Unkonwn ER/PR status	per 5 kg/m^2	1.41 (1.09-1.84)	
Torio, 2010 BRE80277	CLUE II, Prospective Cohort,	172/ 5 642	Cancer registry	Self-reported weight at age 21	Incidence, breast cancer, complete	per 1 kg/m^2	1.04 (1.00-1.07)	Age, age at first child birth, breastfeeding, educational

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
USA	Age: 63.00years, W, Postmenopausal	16 years		years and study baseline	data available			level, HRT use, parity, social class
Morimoto, 2002 BRE20457	Women's Health Initiative - Observational study, Prospective Cohort, Age: 50-79 years, Postmenopausal	85 917 34.8 months 311/ 32,547	Medical records + Self-reported	Self-reported weight at age 18 and 50 years, and at study baseline	Incidence, breast cancer, HRT never users	≥9.71 vs ≤0 kg/m^2	1.92 (1.07-3.43) Ptrend: <0.001	Age , age at first child, age at menarche, age at menopause, alcohol, educational level, energy intake , ethnicity, family history, leisure time physical activity, parity/pregnancies, smoking habits
		692/ 53,370		BMI change since age 18 years	Incidence, breast cancer, HRT current/former users	≥9.71 vs ≤0 kg/m^2	1.36 (0.94-1.97) Ptrend: 0.27	
		314/ 32,547		BMI change since age 50 years	Incidence, breast cancer, HRT never users	>4.0 vs ≤0 kg/m^2	1.45 (0.98-2.15) Ptrend: 0.02	
		699/ 53,370			Incidence, breast cancer, HRT current/former users	>4.0 vs ≤0 kg/m^2	0.90 (0.68-1.17) Ptrend: 0.36	
van den Brandt, 1997 BRE12717 Netherlands	NLCS, Case Cohort, Age: 55-69 years, W, Postmenopausal	500/ 4.3 years		Self-reported height and weight at age 20 years and study baseline	Incidence, invasive breast cancer, postmenopausal	≥10 vs 0-1.9 kg/m^2/20 yr	1.42 (0.83-2.43)	Age , age at first child, age at menarche, alcohol, parity/pregnancies

Figure 596 RR estimates of postmenopausal breast cancer by levels of BMI gain

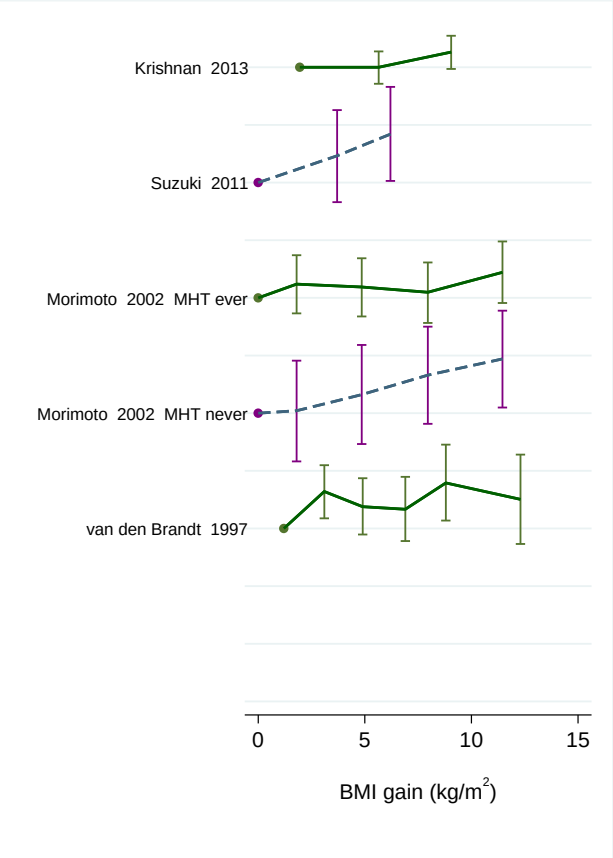


Figure 597 RR (95% CI) of postmenopausal breast cancer for the highest BMI gain compared with reference category

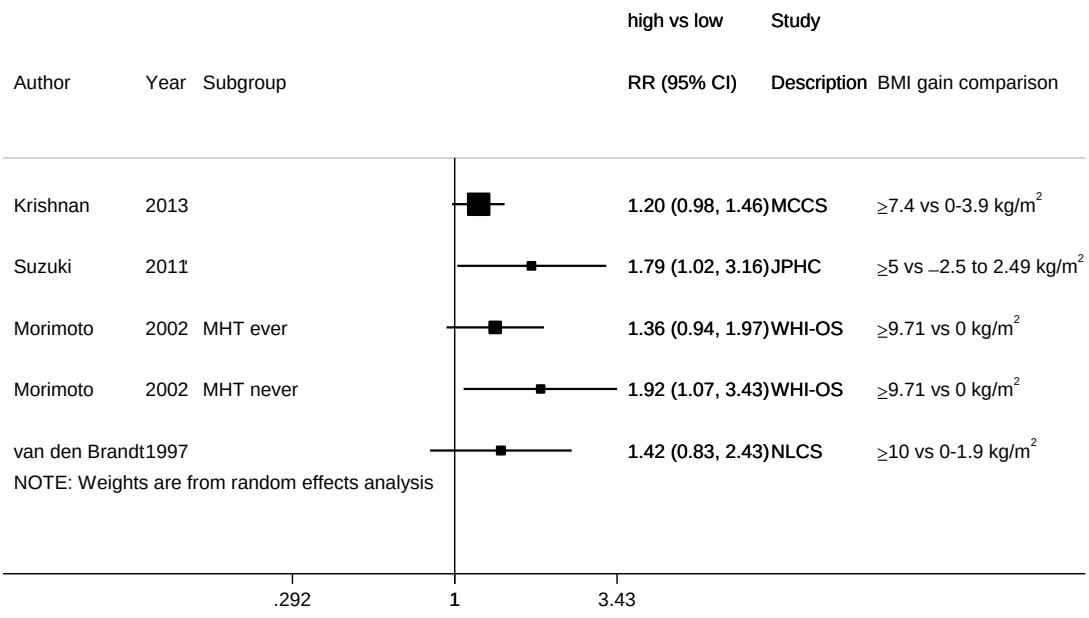


Figure 598 Relative risk of postmenopausal breast cancer for 5 kg/m^2 increase of BMI gain

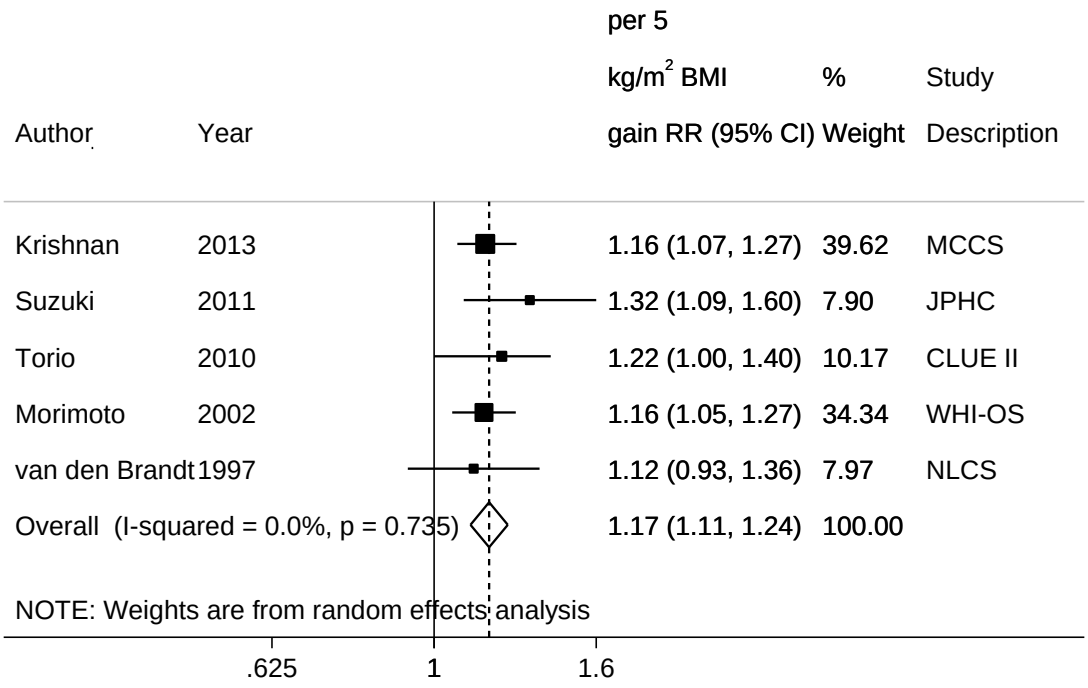
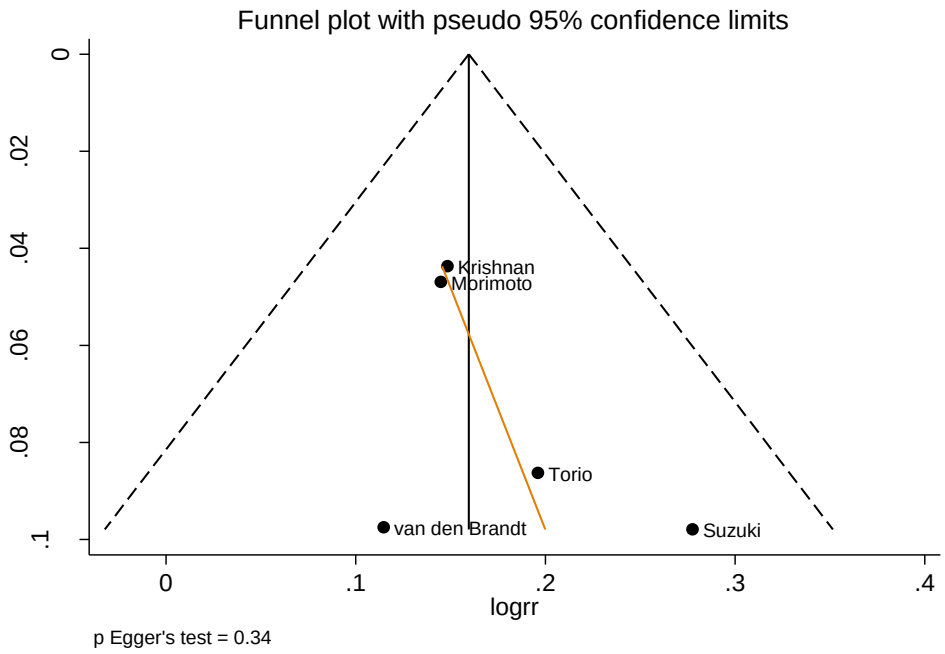


Figure 599 Funnel plot of studies included in the dose response meta-analysis of BMI gain and postmenopausal breast cancer



8.2.1 Waist Circumference

Cohort studies

Overall summary

Forty-three publications from 31 studies that examined waist circumference during adulthood were identified. This included one pooled study (Harding, 2015, ANZDCC, 10 cohorts). Dose-response meta-analyses were conducted to examine the associations of waist circumference with risk of premenopausal and postmenopausal breast cancer.

Notes on method:

Meta-analyses by menopausal status were performed using results from the models indicated as best-adjusted models, i.e. models that were maximally adjusted but without further adjustment of BMI. Further meta-analyses were conducted including only the results additionally adjusted for BMI.

Table 570 Summary of results of the dose-response meta-analysis in the CUP SLR

	Breast cancer (any)	**Premenopausal breast cancer**	**Postmenopausal breast cancer**
Increment unit used	-	Per 10 cm	Per 10 cm
Studies not adjusted for BMI			
Studies (n)	-	6	11
Cases	-	2 423	14 033
RR (95%CI)	-	0.99 (0.95-1.04)	1.11 (1.09-1.13)
Heterogeneity (I^2, p-value)	-	0%, 0.90	0%, 0.59
P value Egger test	-	0.17	0.90
Studies adjusted for BMI			
Studies (n)	-	3	5
Cases	-	1 291	12 022
RR (95%CI)	-	1.14 (1.04-1.26)	1.06 (1.01-1.12)
Heterogeneity (I^2, p-value)	-	0%, 0.85	72%, <0.01
P value Egger test	-	-	0.22

Breast cancer (any)

Five studies (five publications) were identified. Dose-response meta-analysis was not conducted due to insufficient data.

Positive associations were reported in three studies that were not adjusted for current BMI (Catsburg, 2014b; van Kruijsdijk, 2013; Bosco, 2012) and inverse associations were observed in two studies that were adjusted for BMI (Parekh, 2013; Wu, 2006). None of the results were statistically significant.

Table 571 Waist circumference and breast cancer risk. Main characteristics of studies identified.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Catsburg, 2014b BRE80529 Canada	CSDLH, Case Cohort, W	1 078/ 4 417 15 years	Cancer registry	Self-reported	Incidence, Invasive breast cancer	≥92.8 vs ≤72.9 cm	1.06 (0.84-1.34) Ptrend:0.12	Age at first child birth, age at menarche, alcohol Intake, family history of breast cancer, HRT use, menopausal status, number of childbirths, OC use, physical activity
Parekh, 2013 BRE80492 USA	FHS-Offspring Cohort, Prospective Cohort, Age: 20- years, W	164/ 2 353 37 years	Death certificate and medical records	Measured by trained personnel	Incidence, breast cancer	≥34.7 vs ≤31.4 inch	0.68 (0.38-1.23)	Age, BMI, alcohol, smoking status
van Kruijsdijk, 2013 BRE80475 Netherlands	SMART study, Prospective Cohort, Age: 18-80 years, W, Manifest vascular disease patients	17/ 1 589 5.5 years	Cancer registry	Height and weight measured, vat was estimated by ultrasonography	Incidence, breast cancer	per 12.8 cm	1.14 (0.67-1.96)	Age, alcohol consumption, pack years of smoking, smoking status
Bosco, 2012 BRE80602 USA	BWHS, Prospective Cohort, Age: 21-69 years, W,	1 228/ 49 172 10.5 years	Self report verified by medical record	Self-reported in questionnaire	Incidence, breast cancer	≥88 vs ≤87.9 cm	1.08 (0.95-1.22)	Age, BMI at age 18 years, cholesterol, diabetes, educational level, hypertension, vigorous activity

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Wu, 2006 BRE24628 China	Taiwan 1990, Prospective Cohort, Age: 47 years, W, Community-based cancer-screening Program	104/ 11 899 10.3 years	Partially histological - over 80%	Measured by well-trained assistants using standardized techniques.	Incidence, breast cancer,	≥83.1 vs ≤70.9 cm	0.70 (0.20-2.50)	BMI, age at first child, age at menarche,

Premenopausal breast cancer

Summary

Main results:

Six out of seven studies (nine publications) identified could be included in the dose-response meta-analysis. Three of the studies further reported results adjusted for BMI.

Waist circumference was not significantly associated with premenopausal breast cancer risk (summary RR per 10 cm=0.99, 95% CI=0.95-1.04) (I^2=0%, P=0.90). For studies with BMI adjusted results, on average a significant positive association was observed (summary RR=1.14, 95% CI=1.04-1.26) (I^2=0%, P=0.85). When the study (Harris, 2011b) that contributed 56% weight in the analysis was excluded, the association became borderline significant (summary RR=1.15, 95 % CI=1.00-1.32).

The component study (two publications) (Tehard, 2006; Fagherazzi, 2012a) of a multi-centre study that was already included in the analysis was excluded.

There was no evidence of significant publication or small studies bias (P for Egger's test=0.17). The asymmetry in the funnel plot could be driven by a smaller study (Kaaks, 1998, DOM-project) that reported a stronger association than the average.

Two studies reported results on hormone receptor-defined breast cancer subtypes. For the highest compared with the lowest waist circumference, inverse associations with ER-positive or ER+/PR+ breast cancer and positive associations with ER-negative or ER-/PR- breast cancer were reported (Fagherazzi, 2012a; Harris, 2011b). Waist circumference became positively associated with ER-positive breast cancer when BMI was accounted for in Harris, 2011b.

Sensitivity analyses:

Summary RR remained non-significant when studies were omitted in turn in influence analysis. For studies that were further adjusted for BMI, the association became borderline significant when Harris, 2011b was excluded (summary RR per 10 cm=1.15, 95 % CI=1.00-1.32). Subgroup analysis was not conducted due to low number of studies in the strata.

Non-linear dose-response meta-analysis:

There was evidence of non-linear relationship between waist circumference and premenopausal breast cancer risk (P for non-linearity<0.01). The curve shows an initial increase in risk with an increase of waist circumference that dropped after 80 cm.

Study quality:

Studies were either from North America or Europe. BWHS (Palmer, 2007) was of black women only and the DOM-project (Kaaks, 1998) was a mammography screening cohort. All but one study used waist circumference measurement reported by the participants and EPIC (Lahmann, 2004a) measured the participants for the data. The DOM-project (Kaaks, 1998) observed a stronger association than the average but summary RR did not change materially in influence analysis. Case ascertainment was through cancer registries or confirmed through medical records. Most studies were adjusted for age, alcohol intake, and reproductive factors.

Palmer, 2007 and Kaaks, 1998 were not adjusted for alcohol intake. Not all studies reported results with and without BMI adjustment.

Table 572 Waist circumference premenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	7 (9 publications)
Studies included in forest plot of highest compared with lowest exposure	6 (6 publications) BMI not adjusted studies 3 (3 publications) BMI adjusted studies
Studies included in linear dose-response meta-analysis	6 (6 publications) BMI not adjusted studies 3 (3 publications) BMI adjusted studies
Studies included in non-linear dose-response meta-analysis	6 (6 publications) BMI not adjusted studies

Table 573 Waist circumference premenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2008 SLR and CUP SLR

	2008 SLR		**CUP**	
Studies	**BMI not adjusted**	**BMI adjusted**	**BMI not adjusted**	**BMI adjusted**
Increment unit used	**Per 8 cm**	**Per 8 cm**	**Per 10 cm**	**Per 10 cm**
Studies (n)	4	2	6	3
Cases	998	671	2 423	1 291
RR (95%CI)	0.97 (0.90-1.05)	1.12 (1.00-1.25)	0.99 (0.95-1.04)	1.14 (1.04-1.26)
Heterogeneity (I^2, p-value)	40%, 0.17	0%, 0.58	0%, 0.90	0%, 0.85
P value Egger test	-	-	0.17	-

Table 574 Waist circumference and premenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Amadou, 2013	5 studies overall (3 cohorts*, 2 case-control studies)	1 848	Canada, Taiwan, USA, European countries	Incidence, premenopausal breast cancer	Per 10 cm	No statistically significant association (P=0.196)	0%, 0.88

*All cohort studies identified were included in the present review.

Table 575 Waist circumference and premenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Catsburg, 2014b BRE80529 Canada	CSDLH, Case Cohort, W, alumnae	548/ 4 417 15 years	Cancer registry	Self-reported	Incidence, Invasive breast cancer, premenopausal	≥92.8 vs ≤72.9 cm	0.84 (0.59-1.21) Ptrend:0.51	Age at first child birth, age at menarche, alcohol Intake, family history of breast cancer, HRT use, menopausal status, number of childbirths, OC use, physical activity
Harris, 2011b BRE80317 USA	NHS II, Prospective Cohort, Age: 25-42 years, W, Premenopausal	620/ 45 799 426 164 person-years	Self report verified by medical record	Self-reported waist and hip	Incidence, premenopausal breast cancer	≥34.25 vs ≤26.99 in	0.86 (0.65-1.14) Ptrend:0.25	Age, age at first child birth, age at menarche, alcohol consumption, benign breast disease, family history of breast cancer, height, oral contraceptive use, parity, physical activity
						≥34.25 vs ≤26.99 in	1.27 (0.88-1.84) Ptrend:0.17	BMI
		415/			Incidence, breast cancer ER+	≥34.25 vs ≤26.99 in	0.82 (0.58-1.17) Ptrend:0.16	
						≥34.25 vs ≤26.99 in	1.32 (0.83-2.11) Ptrend:0.25	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
						≥34.25 vs ≤26.99 in	2.09 (1.04-4.19) Ptrend:0.09	
						≥34.25 vs ≤26.99 in	2.75 (1.15-6.54) Ptrend:0.09	
Palmer, 2007 BRE80122 USA	BWHS, Prospective Cohort, Age: 21-69 years	437/ 59 000 10 years	Death certificate / patient records / self report	Self-reported, validated	Incidence, breast cancer, premenopausal	≥37 vs ≤27 inch	1.04 (0.73-1.48)	Age, age at first child birth, age at menarche, BMI at 18 years, educational level, family history of breast cancer, parity, physical activity
Lahmann, 2004a BRE15804 Europe	EPIC, Prospective Cohort, Age: 18-80 years, W	474/ 176 886 4.7 years	Partially histological - over 80%	Measurements performed by trained personnel	Incidence, breast cancer, premenopausal	≥89.3 vs ≤70.9 cm	1.07 (0.77-1.48) Ptrend:0.631	Age , age at first child, age at menarche, alcohol, educational level, OC use, parity/pregnancies, recruitment center, smoking habits
						≥89.3 vs ≤70.9 cm	1.81 (1.11-2.97) Ptrend:0.161	BMI
						per 1 cm	1.01 (0.99-1.03)	
Huang, 1999 BRE04118 USA	NHS, Prospective Cohort, Age: 30-55	197/ 47 382	Hospital discharge records	Self-measured - validated method	Incidence, breast cancer, premenopausal	36-55 vs 15-27.9 inch	0.90 (0.52-1.55) Ptrend:0.78	Age , age at first child, age at menarche, benign breast disease, family

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	years, W, Registered nurses							history, height, parity/pregnancies, physical activity
						36-55 vs 15-27.9 inch	1.74 (0.74-4.07) Ptrend:0.15	BMI
Kaaks, 1998 BRE04522 Netherlands	DOM-project Utrecht, Prospective Cohort, Age: 39-73 years, W	147/ 11 480 7.1 years	Partially histological - over 80%		Incidence, breast cancer, premenopausal	≥83.51 vs ≤71 cm	0.92 (0.57-1.50) Ptrend:0.45	Age , age at first child, age at menarche, menopausal status, parity/pregnancies

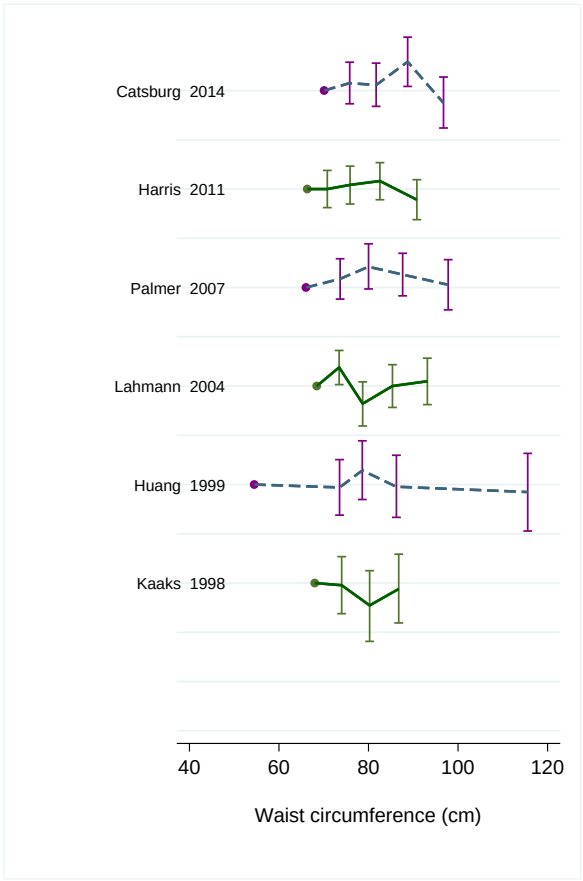
Table 576 Waist circumference and premenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Bosco, 2012 BRE80602 USA	BWHS, Prospective Cohort, Age: 21-69 years	514/ 49 172 10.5 years	Self-report verified by medical record	Self-reported In questionnaire defined abdominal obesity as a waist circumference of 88 cm or greater	Incidence, breast cancer, premenopause	≥88 vs ≤87.9 cm	0.97 (0.78-1.19)	Age, BMI at age 18 years, cholesterol, diabetes, educational level, hypertension, vigorous activity	Superseded by Palmer, 2007, two categories only
Fagherazzi, 2012a BRE80539 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W	223/ 63 726 582 144 person-years	Self-report verified by medical record and pathology report	Self-reported	Incidence, breast cancer ER+/PR+, premenopausal	≥77 vs ≤70.9 cm	0.67 (0.46-0.96) Ptrend:0.04	Age at first child birth, age at menarche, age at menopause, alcohol Intake, breastfeeding, educational level, family history of breast cancer, height, history of benign breast disease, mammography, non-alcohol energy, oc use, parous/nulliparous, smoking	Superseded by Lahmann, 2004a, by HR type only

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								status, total physical activity, use of HRT, year of birth	
		54/			Incidence, breast cancer ER-/PR-, premenopausal	≥77 vs ≤70.9 cm	1.52 (0.75-3.07) Ptrend:0.25		
						≥77 vs ≤70.9 cm	0.81 (0.42-1.54) Ptrend:0.51		
		24/			Incidence, breast cancer ER-/PR+, premenopausal	≥77 vs ≤70.9 cm	0.74 (0.25-2.15) Ptrend:0.61		
Tehard, 2006 BRE80103 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years	217/ 69 116 3.6 years	Patient records/direct contact/health Insurance records	Self-reported In questionnaire	Incidence, breast cancer, premenopausal	≥79 vs ≤68.9 cm	0.58 (0.38-0.88) Ptrend:<=0.05	Age at first child, age at menarche, age-underlying cox models, alcohol, benign breast disease, educational level, family history, marital status, parity/pregnancies, physical activity	Superseded by Lahmann, 2004a
						≥79 vs ≤68.9 cm	0.66 (0.38-1.15) Ptrend:>0.05	BMI	

Figure 600 RR estimates of premenopausal breast cancer by levels of waist circumference

BMI not adjusted studies



BMI adjusted studies

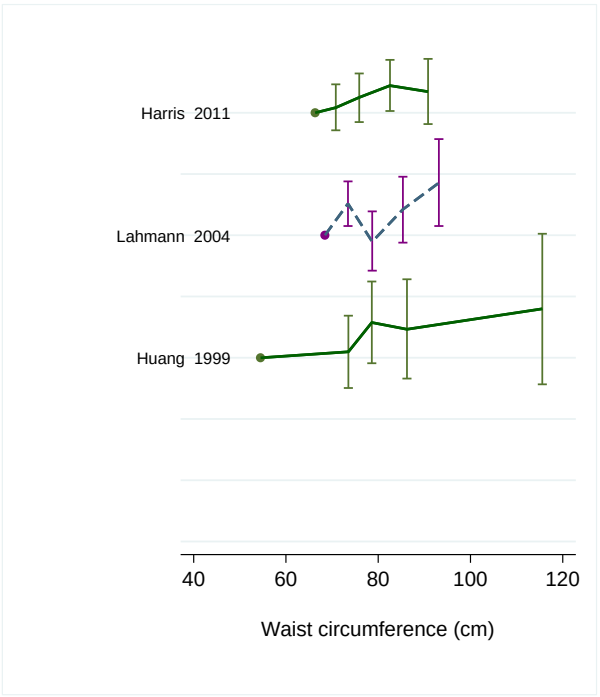


Figure 601 RR (95% CI) of premenopausal breast cancer for the highest compared with the lowest waist circumference

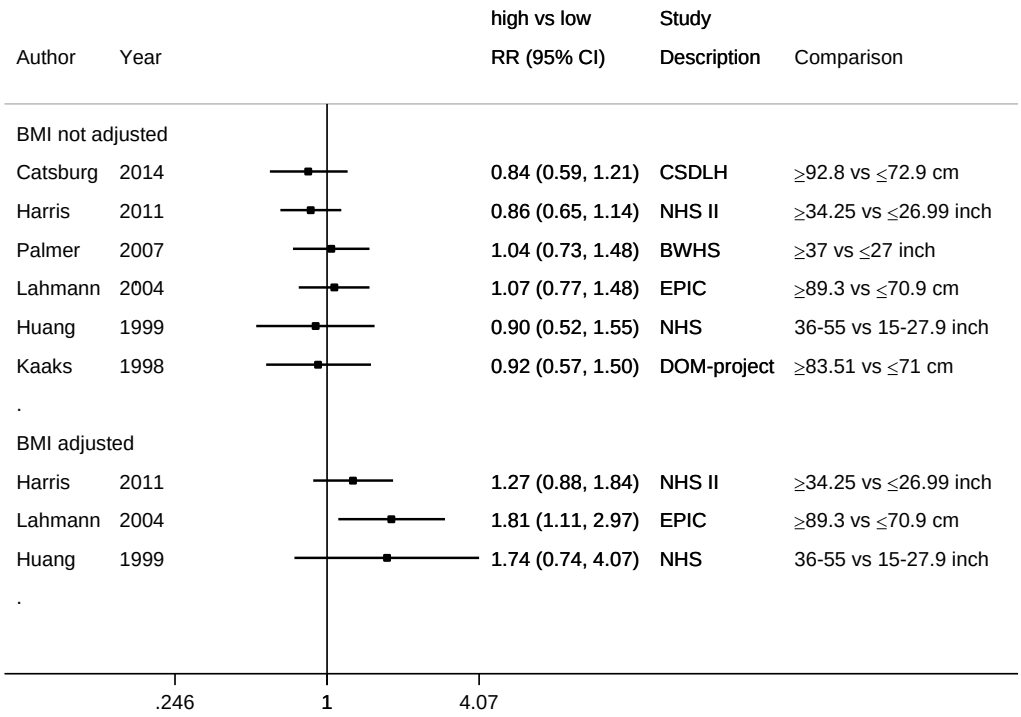


Figure 602 Relative risk of premenopausal breast cancer for 10 cm of waist circumference

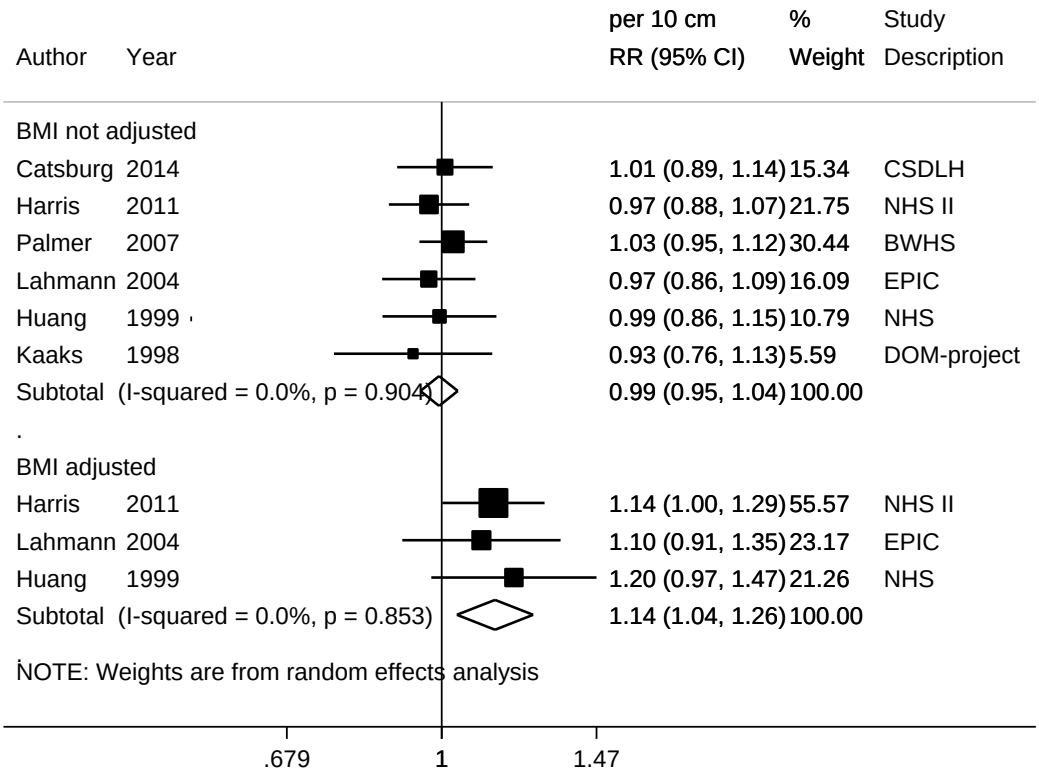


Figure 603 Funnel plot of studies included in the dose response meta-analysis of waist circumference and premenopausal breast cancer

BMI not adjusted studies

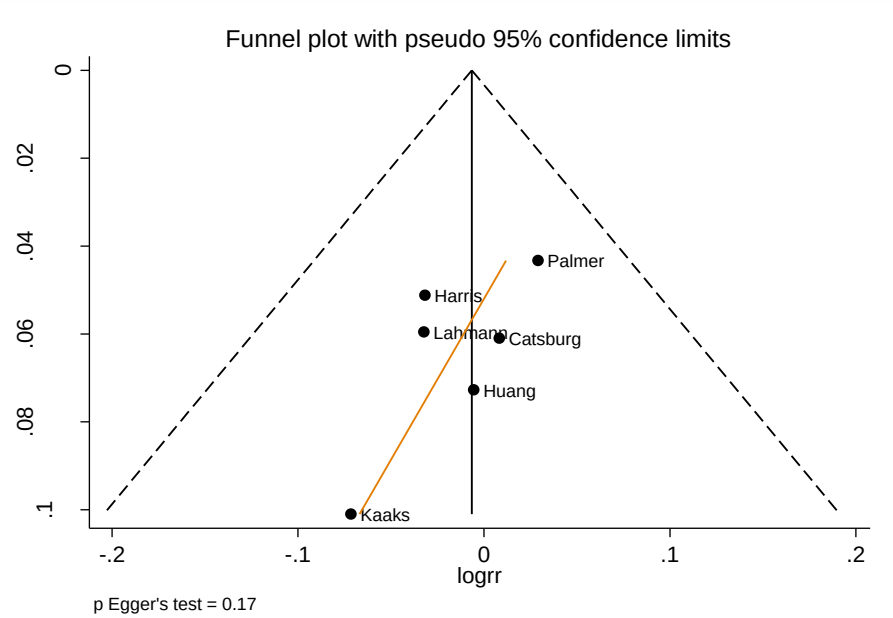
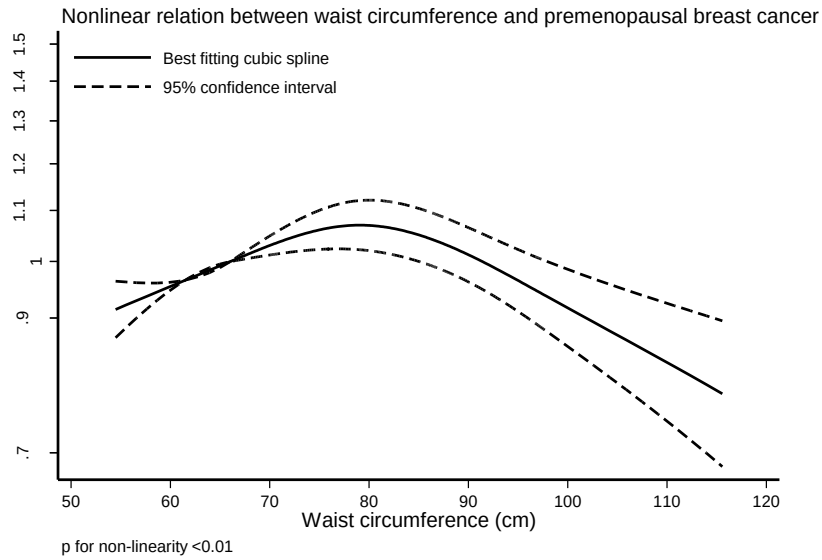


Figure 604 Non-linear dose-response meta-analysis of waist circumference and premenopausal breast cancer

BMI not adjusted studies



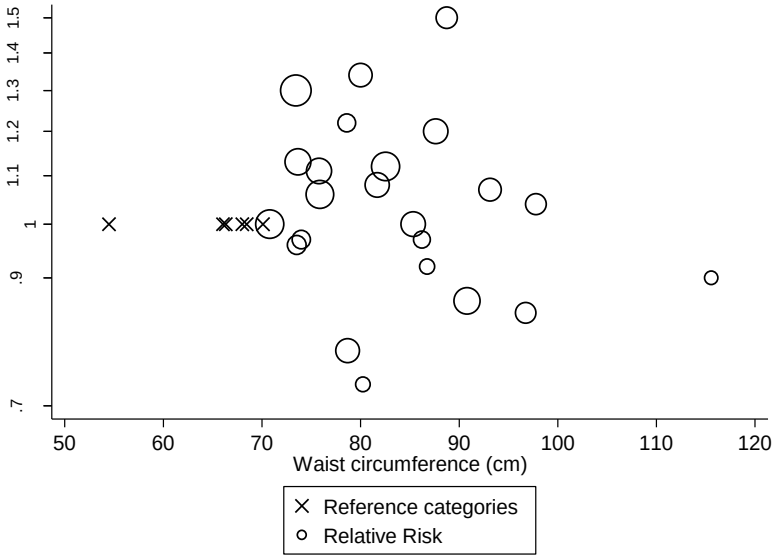


Table 577 Relative risk of premenopausal breast cancer and waist circumference estimated using non-linear models

Waist circumference (cm)	RR (95%CI)
66.0	1.00
73.5	1.05 (1.02-1.09)
82.6	1.06 (1.01-1.12)
93.2	0.98 (0.93-1.04)

Postmenopausal breast cancer

Main results:

Eleven out of 27 studies (39 publications) identified could be included in the dose-response meta-analysis. Five of the studies further reported results adjusted for BMI.

Waist circumference was significantly positively associated with postmenopausal breast cancer risk. Summary RRs were 1.11 (95% CI=1.09-1.13) in studies not adjusted for BMI and 1.06 (95% CI=1.01-1.12) in studies adjusted for BMI. No heterogeneity (I^2=0%, P=0.59) and high heterogeneity (I^2=72%, P<0.01) were observed between the studies, respectively.

Sixteen studies (eight publications) were excluded from the meta-analysis. Study populations in four excluded studies (Mellemkjaer, 2006; Tehard, 2006; Lahmann, 2003; Morimoto, 2002, WHI-OS) overlapped with studies that were already included in the analysis. One study (Fourkala, 2014, UKCTOCS) used skirt size as a proxy measure of abdominal obesity and

was excluded. One study (Agnoli, 2010, ORDET) and another pooled study (Harding, 2015, ANZDCC, nine non-overlapping studies) did not have sufficient data to be included in the analysis. Agnoli, 2010 reported a non-significant positive association for the highest versus the lowest comparison (RR=1.23 95% CI=0.83-1.81) and Hardling, 2015 observed a significant increased risk for each 1 SD increase of waist circumference (RR=1.06 95% CI=1.01-1.12). One study (Canchola, 2012, CTS) only reported results by postmenopausal breast cancer subtypes.

There was no evidence of significant publication or small studies bias (P for Egger's test=0.90).

Significant positive associations were observed in two of the four studies reported results on ER-positive breast cancer (Reeves, 2012; Phipps, 2011), and in both studies on ER+PR+ breast cancer (Canchola, 2012; Fagherazzi, 2012a). Non-significant inverse or positive associations were reported with ER-negative (Gaudet, 2014; Sellers, 2002) or other joint hormone-receptor subtypes (ER+PR-; ER-PR+; ER-PR-) (Canchola, 2012; Fagherazzi, 2012a).

Sensitivity analyses:

Influence analysis showed summary RRs of similar magnitude when studies without BMI adjustment were omitted in turn. Significant positive associations were observed in the subgroup analyses by geographic location, anthropometric measurement method, and confounder adjustment.

For studies with BMI adjusted results, summary RR became non-significant when Lahmann, 2004a was omitted (RR= 1.06, 95% CI= 0.99-1.12) and borderline significant when Kabat, 2015b and Huang 1999 was omitted (RR=1.04, 95% CI=1.00-1.08; RR=1.06, 95% CI=1.00-1.13, respectively). When Kabat, 2015b was excluded, heterogeneity dropped from 72% (P<0.01) to 9% (P=0.35).

Non-linear dose-response meta-analysis:

Although the test for non-linearity was significant (P for non-linearity=0.02), the curve shows an almost linear increase in risk of postmenopausal breast cancer with the increase of waist circumference.

Study quality:

Most were North America studies, one of which was in black women only (Palmer, 2007). There were two European studies (Rinaldi, 2006; Kaaks, 1998) and one Australian study (MacInnis, 2004). DOM-project (Kaaks, 1998) was a mammography screening cohort. SOF (Krebs, 2006) was of older women (mean age 75 years). CPS-II Nutrition Cohort (Gaudet, 2014) included only women not currently taking menopausal hormones in the analysis. Most studies used waist circumference reported by the participants. Case ascertainment was through cancer registries or confirmed through medical records. About half of the studies were simultaneously adjusted for age, alcohol intake, reproductive factors, and MHT use. Summary RR did not change materially when studies were omitted in turn in influence analysis.

Table 578 Waist circumference and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	27[1] (39 publications)
Studies included in forest plot of highest compared with lowest exposure	11 (11 publications) BMI not adjusted studies 5 (5 publications) BMI adjusted studies
Studies included in linear dose-response meta-analysis	11 (11 publications) BMI not adjusted studies 5 (5 publications) BMI adjusted studies
Studies included in non-linear dose-response meta-analysis	10 (10 publications) BMI not adjusted studies

[1]Included one pooled study (Harding, 2015, ANZDCC, 10 studies)

Table 579 Waist circumference and postmenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2008 SLR and CUP SLR

	2008 SLR		**CUP**	
Studies	**BMI not adjusted**	**BMI adjusted**	**BMI not adjusted**	**BMI adjusted**
Increment unit used	**Per 8 cm**	**Per 8 cm**	**Per 10 cm**	**Per 10 cm**
Studies (n)	7	3	11	5
Cases	2 856	4 119	14 033	12 022
RR (95%CI)	1.07 (1.04-1.10)	1.04 (1.00-1.06)	1.11 (1.09-1.13)	1.06 (1.01-1.12)
Heterogeneity (I^2, p-value)	6%, 0.38	17%, 0.30	0%, 0.59	72%, <0.01
P value Egger test	-	-	0.90	0.22
Stratified analysis in the CUP				
Studies not adjusted for BMI				
Increment unit used	**Per 10 cm**	**Per 10 cm**	**Per 10 cm**	

Geographic location	**Europe**	**North America**	**Australia**	
Studies (n)	2	8	1	
Cases	689	12 987	357	
RR (95%CI)	1.13 (1.03-1.24)	1.11 (1.09-1.13)	1.13 (1.03-1.24)	
Heterogeneity (I^2, p-value)	0%, 0.53	10%, 0.36	-	
Adjustment for age, alcohol intake, reproductive factors, and MHT use	**Adjusted**	**Not adjusted**		
Studies (n)	6	5		
Cases	11 558	2 475		
RR (95%CI)	1.11 (1.09-1.13)	1.12 (1.06-1.18)		
Heterogeneity (I^2, p-value)	0%, 0.93	38%, 0.17		
Anthropometric assessment method	**Measured**	**Self-reported**	**Self-reported or measured**	
Studies (n)	3	7	1	
Cases	7 746	5 674	613	
RR (95%CI)	1.11 (1.09-1.14)	1.11 (1.08-1.14)	1.12 (1.02-1.23)	
Heterogeneity (I^2, p-value)	0%, 0.82	25%, 0.24	-	

Table 580 Waist circumference and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Kabat, 2015b BRE80526 USA	Womens Health Initiative (WHI), Prospective Cohort, Age: 50-79 years, W, Postmenopausal	7 039/ 143 901 12.7 years	Self-report verified by medical record and pathology report	Measured by trained staff at baseline	Incidence, breast cancer	Q 5 vs Q 1	1.40 (1.29-1.52) Ptrend:<0.0001	Age, alcohol, smoking, MET-hours/week, age at menarche, age at first birth, parity, hormone therapy, family history of breast cancer, history of breast biopsy, education, ethnicity, treatment allocation	Midpoints of exposure category estimated from the mean value in study population
						Q 5 vs Q 1	1.42 (1.31-1.53) Ptrend:<0.0001	BMI	
					Ever used HRT	Q 5 vs Q 1	1.17 (0.99-1.38) Ptrend:0.07	Age, alcohol, smoking, MET-hours/week, age at menarche, age at first birth, parity, family history of breast cancer, history of breast biopsy, education, ethnicity,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								treatment allocation	
					Never used HRT	Q 5 vs Q 1	1.30 (1.05-1.61) Ptrend:0.07		
					Never used HRT	Q 2 vs Q 1	1.67 (1.46-1.90)	BMI	
Catsburg, 2014b BRE80529 Canada	CSDLH, Case Cohort, W, alumnae	530/ 4 417 15 years	Cancer registry	Self-reported	Incidence, Invasive breast cancer, postmenopausal	≥92.8 vs ≤72.9 cm	1.30 (0.92-1.82) Ptrend:0.09	Age at first child birth, age at menarche, alcohol Intake, family history of breast cancer, HRT use, menopausal status, number of childbirths, OC use, physical activity	
Gaudet, 2014 BRE80533 USA	CPS II, Prospective Cohort, W, Postmenopausal	1 088/ 28 965 11.58 years	Self report verified by medical records or by linkage with state cancer registries	Self-reported	Incidence, Invasive breast cancer, HRT - no	97-139 vs 39-74 cm	1.36 (1.12-1.65)	Age, age at first child birth, age at menopause, alcohol Intake, benign breast disease, diabetes, educational level, exercise, family history of breast cancer,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								height, mammography, oral contraceptive use, parity, postmenopausal hormone use, race, smoking	
						per 10 cm	1.13 (1.08-1.19)		
						97-139 vs 39-74 cm	0.85 (0.65-1.12)	BMI	
						per 10 cm	1.00 (0.92-1.08)		
Ahn, 2007 BRE80139 USA	NIH-AARP, Prospective Cohort, Age: 50- years, W, Postmenopausal	830/ 99 039 4 years	Cancer registry	Self-reported	Incidence, breast cancer, current MHT users	≥104 vs ≤75 cm	1.07 (0.80-1.43) Ptrend:0.71	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, educational level, family history of cancer, fat Intake, height, oophorectomy/hysterectomy, parity, physical activity, race, smoking habits	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		618/			Non MHT users	≥104 vs ≤75 cm	1.55 (1.16-2.06) Ptrend:<0.001		
Palmer, 2007 BRE80122 USA	BWHS, Prospective Cohort, Age: 21-69 years	393/ 59 000 10 years	Death certificate / patient records / self-report	Self-reported, validated	Incidence, breast cancer, postmenopausal	≥37 vs ≤27 inch	1.05 (0.73-1.51)	Age, , age at first child birth, age at menarche, age at menopause, educational level, family history of cancer, parity, physical activity, BMI at 18 years	
		142/			Postmenopausal and HRT nonusers	≥37 vs ≤27 inch	1.07 (0.57-2.01)		
Krebs, 2006 BRE80106 USA	SOF, Prospective Cohort, Mean age: 75 years, Postmenopausal	350/ 9 704 11.3 years	Self-report verified by medical record	Current anthropometrics were measured at 2nd health exam	Incidence, Invasive breast cancer, postmenopausal	≥91.3 vs ≤75.7 cm	1.40 (0.98-1.98) Ptrend:0.03	Age , age at menarche, age at menopause, anthropometry, benign breast disease, educational level, family history, HRT use, parity/pregnancies, physical	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								activity , smoking habits	
Rinaldi, 2006 BRE80101 The Netherlands, UK, Germany, Spain, Italy, Greece, France	EPIC, Nested Case Control, W, Postmenopausal	613/ 1139 controls	Population cancer registries and other procedures	Measured and self-report	Incidence, Invasive & In situ breast cancer, postmenopausal	per 10 cm	1.12 (1.02-1.24)	Age at first child, parity/pregnancies	Dose-response results only
Lahmann, 2004a BRE15804 Europe	EPIC, Prospective Cohort, Age: 18-80 years, W	494/ 176 886 4.7 years	Partially histological - over 80%	Measurements performed by trained personnel	Incidence, breast cancer, HRT current users	≥89.3 vs ≤70.9 cm	0.68 (0.41-1.12)	Age , BMI, age at first child, age at menarche, alcohol, educational level, parity/pregnancies, recruitment center, smoking habits	
						per 1 cm	1.00 (0.97-1.03)		
		911/			Never/former used HRT	≥89.3 vs ≤70.9 cm	1.21 (0.87-1.67) Ptrend:0.192		
						per 1 cm	1.01 (1.00-1.02)		
MacInnis, 2004 BRE80159 Australia	MCCS, Prospective Cohort, Age: 27-75	357/ 13 598 9.1 years	Medical records	Direct anthropometric measurements	Incidence, Invasive breast cancer, postmenopausal	≥87 vs ≤70.9 cm	1.50 (1.10-2.10)	Age, birthplace, educational level, HRT use, physical activity	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	years, W, Postmenopausal					per 10 cm	1.13 (1.03-1.24)		
		97/			Incidence, breast cancer ER+, >=15 years postmenopausal	per 10 cm	1.24 (1.06-1.46)		
		29/			Incidence, breast cancer ER-, >=15 years postmenopausal	per 10 cm	0.79 (0.58-1.07)		
		84/			Incidence, breast cancer PR+, >=15 years postmenopausal	per 10 cm	1.18 (0.99-1.40)		
		42/			Incidence, breast cancer PR-, >=15 years postmenopausal	per 10 cm	1.05 (0.82-1.33)		
Sellers, 2002 BRE20892 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	1 368/ 37 105 13 years	Partially histological - over 80%	Waist and hip circumferences measured by a friend of the participant after reading a detailed protocol	Incidence, postmenopausal breast cancer, No family history of breast cancer	≥39.1 vs ≤29.75 inch	1.14 (0.88-1.48) Ptrend:0.61	BMI, BMI at 18 years, age at first child, age at menarche, age at menopause, alcohol, educational level, family history, HRT use, OC use,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								parity/pregnancies, physical activity, smoking habits, height	
		282/			Yes family history of breast cancer	≥39.1 vs ≤29.75 inch	1.12 (0.72-1.75) Ptrend: 0.75		
		1 043/			Incidence, breast cancer ER+	≥39.1 vs ≤29.75 inch	1.05 (0.77-1.44)		
		232/			Incidence, breast cancer ER-	≥39.1 vs ≤29.75 inch	1.03 (0.50-2.09)		
		993/			Incidence, breast cancer PR+	≥39.1 vs ≤29.75 inch	1.10 (0.78-1.57)		
		362/			Incidence, breast cancer PR-	≥39.1 vs ≤29.75 inch	0.98 (0.56-1.72)		
Folsom, 2000 BRE80610 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	1 299/ 31 702 10 years	Active follow up, cancer registry, death certificate and national death Index	Tape measure sent to participants Instructing them to have a friend take the measurements	Incidence, breast cancer	≥96 vs ≤74.3	1.70 (1.40-2.10)	Age, age at first child, alcohol Intake, educational level, energy, fish Intake, fruits and vegetables Intake, keys score, pack years of	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								smoking, physical activity, red meat Intake, smoking status, vitamin use, whole grains, oestrogen use	
Huang, 1999 BRE04118 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	840/ 47 382	Hospital discharge records	Self-measured, validated	Incidence, breast cancer, postmenopausal	36-55 vs 15-27.9 inch	1.34 (1.05-1.72) Ptrend:0.007	Age , age at first child, age at menarche, benign breast disease, family history, height, parity/pregnancies, physical activity	
						36-55 vs 15-27.9 inch	1.26 (0.88-1.81) Ptrend:0.15	BMI	
Kaaks, 1998 BRE04522 Netherlands	DOM-project Utrecht, Prospective Cohort, Age: 39-73 years, W	76/ 11 480 7.1 years	Partially histological - over 80%	Measured by trained medical assistants	Incidence, breast cancer, postmenopausal	≥83.51 vs ≤71 cm	1.99 (0.81-4.86) Ptrend:0.17	Age , age at first child, age at menarche, menopausal status, parity/pregnancies	

Table 581 Waist circumference and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Harding, 2015 Australia and New Zealand	ANZDCC, Pooled study of 11 cohorts*, W	1 323/ 38 724 Mean age: 54.3 years 16 years of follow-up	Cancer database and National death index	Measured	Incidence, breast cancer, diagnosed ≥ 50 years	Per 1 SD	1.06 (1.01-1.12)	Age as the timescale in model, adjusted for smoking status, education, study cohort	Excluded, exposure values not available
		901/			Never smokers	Per 1 SD	1.08 (1.02-1.16)		
		422/			Ever smokers	Per 1 SD	1.02 (0.93-1.13)		
*Current analysis used data from 10 cohorts - Australian National Blood Pressure Trial; Australian Longitudinal Study of Aging; Australian Diabetes Obesity and Lifestyle Study; Crossroads Undiagnosed Study; Fremantle Diabetes Study; Geelong Osteoporosis Study; Melbourne Collaborative Cohort Study; North West Adelaide Health Study; Perth Risk Factor Prevalence Cohort Study 1989; Perth Risk Factor Prevalence Cohort Study 1994									
Heo, 2015 BRE80581 USA	Women's Health Initiative, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	6 798/ 144 701 12 years	Self-report verified by medical record and pathology report	Measured	Incidence, breast cancer	≥87 vs ≤86.9 cm	1.17 (1.12-1.23)	Age, age at first child birth, age at menopause, alcohol, breast biopsies, educational level, ethnicity, family history of breast cancer In first degree relatives, height, hormone use, pack years of smoking, parity,	Superseded

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								randomisation	
						per 1 score	1.11 (1.08-1.14)		
					HRT ever	≥93 vs ≤92.9 cm	1.16 (1.07-1.25)		
						per 1 score	1.09 (1.05-1.13)		
					HRT never	≥82 vs ≤81.9 cm	1.30 (1.19-1.41)		
						per 1 score	1.14 (1.10-1.18)		
						per 1 score	1.14 (1.10-1.19)		
Zhang X, 2015 BRE80578 USA	NHS, Prospective Cohort, Age: 30-55 years, W	857/ 103 577 26 years	Self report verified by medical record	Self-reported In questoinnaire	Incidence, breast cancer AR+, postmenopause	36-55 vs 15-27.9 inch	1.34 (1.00-1.80)	Age at menarche, age at menopause, alcohol Intake, BMI, family history of breast cancer, height, history of benign breast disease, parity and age at first birth, physical activity, postmenopausal hormone use	Superseded
		257/			Incidence, breast cancer AR-, postmenopause	36-55 vs 15-27.9 inch	2.13 (1.22-3.73)		
Fourkala, 2014	UKCTOCS,	1 018/	Nhs records	Self-reported	Incidence, breast	per 1 unit	1.05 (1.01-1.09)	Age at	Excluded,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
BRE80562 UK	Prospective Cohort, Age: 50- years, W	92 834 3.19 years		height and weight, and skirt size 3-4 years after recruitment	cancer			menarche, age at menopause, alcohol consumption, cancer diagnosis, deprivation category, educational level, family history of cancer, health status, HRT use, hysterectomy, Infertility, oral contraceptive use, parity, smoking, sterilisation, trouser/skirt size	exposure was a proxy measure of abdominal obesity
Gaudet, 2013 BRE80493 USA	CPS II, Nested Case Control, Age: 50-74 years, W, Postmenopausal	279/ 277 controls	Self-report verified by medical record	Self-report waist circumference (in 1997), weight (in 1997) and height (in 1982)	Incidence, breast cancer, HRT - no	≥89 vs ≤79.9 cm	1.56 (1.02-2.37) Ptrend:0.02	Age, age at first child birth, age at menarche, age at menopause, alcohol, educational level, family history of breast cancer, history of breast cyst,	Superseded

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								mammography, parity, smoking	
						per 10 cm	1.17 (1.02-1.34)		
						≥89 vs ≤79.9 cm	1.31 (0.84-2.05) Ptrend:0.13	C- peptide	
						per 10 cm	1.12 (0.97-1.29)		
Rohan, 2013 BRE80478 USA	Women's Health Initiative, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	502/ 10 960 12.9 years	Self report verified by medical record and pathology report	waist, hip circumference were measured by trained staff using standardized protocols	Incidence, Invasive breast cancer	Q 5 vs Q 1	1.97 (1.46-2.65) Ptrend:<0.0001	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, breast biopsies, educational level, energy Intake, ethnicity, family history of breast cancer, HRT use, oc use, pack-years smoking, parity, physical activity, randomisation	Superseded
Bosco, 2012 BRE80602 USA	BWHS, Prospective Cohort, Age: 21-69	542/ 49 172 10.5 years	Self report verified by medical record	Self-reported In questionnaire defined	Incidence, breast cancer, postmenopause	≥88 vs ≤87.9 cm	1.09 (0.91-1.31)	Age, BMI at age 18 years, cholesterol, diabetes,	Superseded

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	years			abdominal obesity as a waist circumference of 88 cm or greater				educational level, hypertension, vigorous activity	
Canchola, 2012 BRE80401 USA	CTS, Prospective Cohort, Age: 56-70 years, W, Postmenopausal	829/ 56 542 12.1 years	Cancer registry and national death Index	Self-measure waist and hip circumferences.	Incidence, breast cancer ER+/PR+	≥36 vs <30 inch	1.33 (1.09-1.62) Ptrend:0.02	Age at baseline, age at first child birth, age at menarche, alcohol, breast biopsies, family history of breast cancer, height, HRT use, parity	Excluded, results by breast cancer subtypes only, not enough studies to analyse
						per 1 inch	1.02 (1.00-1.03)		
		181/			Incidence, breast cancer ER+/PR-	≥36 vs <30 inch	1.02 (0.67-1.57) Ptrend:0.90		
						per 1 inch	0.99 (0.96-1.02)		
		156/			Incidence, breast cancer ER-/PR-	≥36 vs <30 inch	1.10 (0.70-1.73) Ptrend:0.69		
						per 1 inch	1.01 (0.98-1.04)		
Fagherazzi, 2012a BRE80539 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years,	944/ 63 726 582 144 person-years	Self-report verified by medical record and pathology report	Self-reported	Incidence, breast cancer ER+/PR+, postmenopausal	≥77 vs ≤70.9 cm	1.21 (1.02-1.44) Ptrend:0.03	Age at first child birth, age at menarche, age at menopause, alcohol Intake, breastfeeding,	Results by breast cancer subtypes only, other publication of the same study was

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	W							educational level, family history of breast cancer, height, history of benign breast disease, mammography, non-alcohol energy, oc use, parous/nulliparous, smoking status, total physical activity, use of HRT, year of birth	included in the analysis
		302/			Incidence, breast cancer ER+/PR-, postmenopausal	≥77 vs ≤70.9 cm	1.03 (0.77-1.36) Ptrend:0.86		
		243/			Incidence, breast cancer ER-/PR-, postmenopausal	≥77 vs ≤70.9 cm	0.81 (0.59-1.12) Ptrend:0.20		
		52/			Incidence, breast cancer ER-/PR+, postmenopausal	≥77 vs ≤70.9 cm	0.60 (0.28-1.28) Ptrend:0.14		
Hartz, 2012 BRE80400	Women's Health Initiative,	6 052/ 141 652		Measured	Incidence, breast cancer	per 1 sd units	1.10	Age, alcohol, educational	Superseded

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
USA	Prospective Cohort, Age: 50-79 years, W, Postmenopausal	8 years						level, Income, physical activity, race, region, smoking, treatment allocation	
Reeves, 2012 BRE80601 USA	SOF, Prospective Cohort, Age: 65- years, W, Postmenopausal	551/ 8 956 14.4 years	Self-reported/death certificate/ medical records	Measured	Incidence, Invasive & In situ breast cancer	≥88 vs ≤87.9 cm	1.18 (0.97-1.44)	Age, diabetes, family history of breast cancer, HRT use, hypertension	Superseded
		475/			Incidence, Invasive breast cancer	≥88 vs ≤87.9 cm	1.18 (0.95-1.48)		
		385/			Incidence, breast cancer ER+	≥88 vs ≤87.9 cm	1.30 (1.03-1.66)		
		303/			Incidence, breast cancer PR+	≥88 vs ≤87.9 cm	1.51 (1.16-1.97)		
Phipps, 2011 BRE80343 USA	Women's Health Initiative, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	2 607/ 155 723 7.9 years	Mail or telephone questionnaires verified by trained physician adjudicators	Measured at baseline	Incidence, breast cancer ER+	≥95 vs ≤76 cm	1.34 (1.09-1.64) Ptrend:0.01	Age, BMI, educational level, family history of breast cancer, Income, mammography, mammography, race, recreational activity	Results by breast cancer subtypes only, other publication of the same study was included in the analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		307/			Incidence, triple negative breast cancer	≥95 vs ≤76 cm	0.66 (0.37-1.20) Ptrend:0.23		
		1 125/			Incidence, breast cancer ER+, HRT never	≥95 vs ≤76 cm	1.46 (1.06-2.00) Ptrend:0.02		
		155/			Incidence, triple negative breast cancer, HRT never	≥95 vs ≤76 cm	1.07 (0.47-2.45) Ptrend:0.63		
Agnoli, 2010 BRE80228 Varese Province	ORDET, Nested Case Control, Age: 35-69 years, W, Postmenopausal	163/ 629 controls 13.5 years	Cancer registry	Measured by trained nurse	Incidence, breast cancer, postmenopausal	86 vs ≥85 cm	1.11 (0.76-1.61)	Age, date of enrollment, laboratory batch	Excluded, two exposure categories only
						86 vs ≥85 cm	1.23 (0.83-1.81)	Age at first child birth, age at menarche, alcohol Intake, breastfeeding, educational level, family history of cancer, HRT use, menopausal age, ocp use, parity/pregnancies, smoking habits	
Kabat, 2010	Women's Health	450/	Pathology and	Waist and hip	Incidence,	≥100.7 vs ≤76.2	0.90 (0.39-2.09)	Age, age at first	Results in in situ

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
BRE80312 USA	Initiative, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	58 8 years	medical record	circumferences measured at baseline	ductal In situ breast cancer	cm	Ptrend:0.50	child birth, age at menarche, age at menopause, BMI, breast biopsies, educational level, ethnicity, family history of breast cancer, HRT use, mammogram In the past 2 years, oral contraceptive history, randomisation, smoking, waist circumference	breast cancer, not analyse
Borgquist, 2009 BRE80214 Sweden	MDCS, Prospective Cohort, Age: 61 years, W, Peri/postmenopausal, not currently using HRT	231/ 9 685 10.3 years	Cancer registry	Measured	Incidence, breast cancer	≥0.85 vs ≤0.7 m	1.93 (1.29-2.89) Ptrend:<0.01	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, educational level, marital status, occupation, oophorectomy/hysterectomy,	Superseded by Rinaldi, 2006

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								oral contraceptive use, parity, smoking habits	
		162/			Ductal carcinomas	≥0.85 vs ≤0.7 m	2.02 (1.25-3.27) Ptrend:<0.01		
		45/			Lobular carcinoma	≥0.85 vs ≤0.7 m	3.29 (1.20-9.03) Ptrend:0.06		
		175			HER2 (0-1+)	≥0.85 vs ≤0.7 m	1.92 (1.22-3.02) Ptrend:0.02		
		24/			HER2 (2+3+)	≥0.85 vs ≤0.7 m	2.41 (0.65-9.02) Ptrend:0.24		
		26/			ERα+≤10%	≥0.85 vs ≤0.7 m	2.00 (0.60-6.64) Ptrend:0.19		
		194/			ERα+>10%	≥0.85 vs ≤0.7 m	1.88 (1.21-2.90) Ptrend:0.02		
		93/			ERβ≤10%	≥0.85 vs ≤0.7 m	2.89 (1.49-5.61) Ptrend:0.002		
		83/			ERβ>10%	≥0.85 vs ≤0.7 m	1.14 (0.63-2.06) Ptrend:0.70		
		108/			PR≤10%	≥0.85 vs ≤0.7 m	1.80 (1.01-3.21) Ptrend:0.14		
		100/			PR>10%	≥0.85 vs ≤0.7 m	2.12 (1.14-3.94) Ptrend:0.02		
Kabat, 2009b	Women's Health	162/	Self report,	Measured	Incidence,	88.0 vs ≥78.9	0.78 (0.46-1.31)	Age, age at first	Superseded

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
BRE80249 USA	Initiative, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	4 888 8 years	medical record and pathology report reviewed by centrally trained physician		Invasive & In situ breast cancer	cm	Ptrend:0.34	child birth, age at menarche, age at menopause, alcohol consumption, benign breast disease, blood glucose levels, BMI, calcium Intake, cholesterol, educational level, energy Intake, ethnicity, family history of cancer, HRT use, ocp use, physical activity, plasma lipids (cholesterol plus triglycerides), randomized treatment assignment, smoking habits, systolic blood pressure	
		128/			Incidence, Invasive breast	88.0 vs ≥78.9 cm	0.73 (0.41-1.32) Ptrend:0.30		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					cancer				
Mellemkjaer, 2006 BRE80039 Denmark	DCH, Prospective Cohort, Age: 50-65 years, Postmenopausal	416/ 23 788 6.1 years	Cancer registry	Recorded by trained technician	Incidence, breast cancer, HRT ever	≥89 vs 74-80.9 cm	0.94 (0.71-1.24)	Age, age at first child birth, alcohol consumption, benign breast disease, duration of HRT use, educational level, HRT use, parity	Superseded by Rinaldi, 2006
						per 5 cm	0.98 (0.93-1.03)		
		217/			HRT never	≥89 vs 74-80.9 cm	0.97 (0.66-1.41)		
						per 5 cm	1.01 (0.95-1.06)		
Tehard, 2006 BRE80103 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years	1 072/ 69 116 3.6 years	Patient records/direct contact/health Insurance records	Self-reported In questionnaire	Incidence, breast cancer, postmenopausal	≥81 vs ≤69.9 cm	1.21 (0.95-1.54) Ptrend:<=0.05	Age at first child, age at menarche, age-underlying cox models, alcohol, benign breast disease, educational level, family history, marital status, parity/pregnancies, physical	Superseded by Rinaldi 2006 and Lahmann, 2004a

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								activity	
						≥81 vs ≤69.9 cm	1.01 (0.73-1.39) Ptrend:>0.05	BMI	
Wirfält, 2005 BRE11111 Sweden	MDCS, Nested Case Control, Age: 50- years, Postmenopausal	237/ 673 controls	Cancer registry	Measured	Incidence, breast cancer,	(mean exposure)			Superseded
Mattisson, 2004a BRE17807 Sweden	MDCS, Prospective Cohort, Age: 50- years, W, Postmenopausal	342/ 11 726 7.6 years	Partially histological - over 80%		Incidence, breast cancer, postmenopausal	(mean exposure)			Superseded
Wirfalt, 2004 BRE17083 Sweden	MDCS, Nested Case Control, Age: 50- years, W, Postmenopausal	12 803 8 years	Partially histological - over 80%		Incidence, breast cancer, postmenopausal	(mean exposure)			Superseded
Lahmann, 2003 BRE20119 Sweden	MDCS, Prospective Cohort, Age: 50-73 years, W, Postmenopausal	236/ 12 159 5.7 years	Cancer registry + death certificate		Incidence, Invasive & In situ breast cancer,	≥86.1 vs ≤69.9 cm	1.14 (0.62-2.12) Ptrend:0.881	Age , age at first child, age at menarche, alcohol, height, marital status, oc use, occupation, parity/pregnancies, smoking	Superseded by Rinaldi, 2006

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								habits	
Morimoto, 2002 BRE20457	Women's Health Initiative - Observational study, Prospective Cohort, Age: 50-79 years, Postmenopausal	708/ 85 917 34.8 months	Medical records + self-reported	Measurements performed by clinical staff	Incidence, breast cancer, HRT - yes	≥95.1 vs ≤73 cm	0.89 (0.68-1.18) Ptrend:0.71	Age , age at first child, age at menarche, age at menopause, alcohol, educational level, energy Intake , ethnicity, family history, leisure time physical activity, parity/pregnancies, smoking habits	Superseded by Kabat, 2015b
		319/			HRT - no	≥95.1 vs ≤73 cm	1.99 (1.30-3.02) Ptrend:0.001		
Wirfalt, 2002 BRE13504 Sweden	MDCS, Nested Case Control, Age: 50- years, W, Postmenopausal	237/ 673 controls 8 years	Partially histological - over 80%		Incidence, breast cancer, postmenopausal	(mean exposure)			Superseded
den Tonkelaar, 1995 BRE02224 Netherlands	DOM-project Utrecht, Prospective Cohort,	38/ 9 491 4 years	Not specified	Measurements performed by trained personnel	Incidence, breast cancer, postmenopausal	≥83.9 vs ≤75.99 cm	2.86 (1.12-7.32) Ptrend:0.08	Age	Superseded

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Age: 40-73 years, W, Screening Program								
Folsom, 1990 BRE02836 USA	IWHS, Nested Case Control, Age: 55-69 years, W, Postmenopausal	227/ 1812 controls 2 years	All histology	Self-measured	Incidence, breast cancer, postmenopausal	≥36.61 vs ≤31.4 inch	1.05 (0.73-1.49) Ptrend:0.83	Age	Superseded

Figure 605 RR estimates of postmenopausal breast cancer by levels of waist circumference

BMI not adjusted studies

BMI adjusted studies

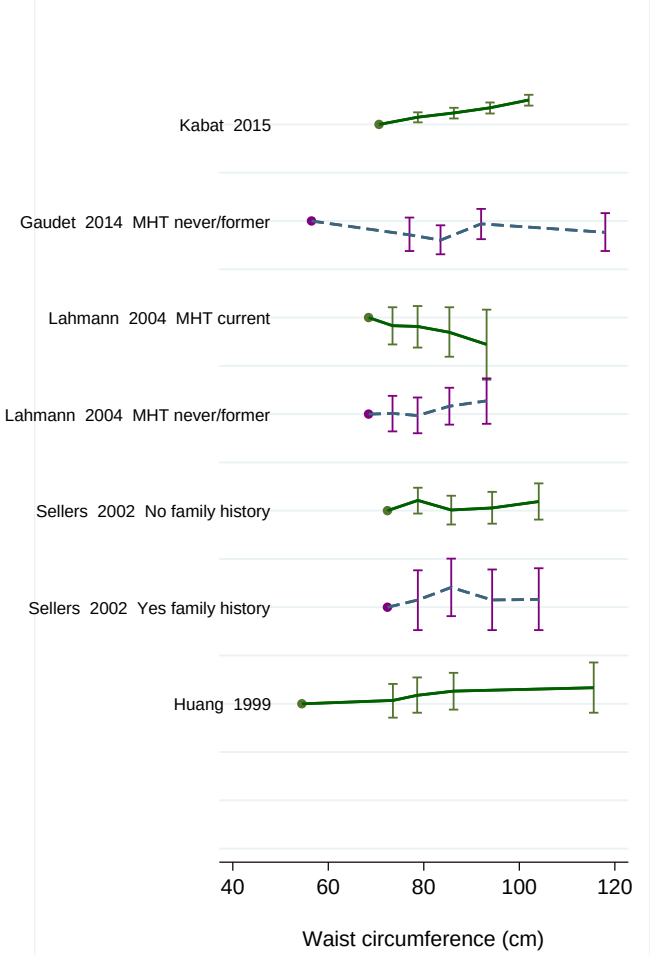


Figure 606 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest waist circumference

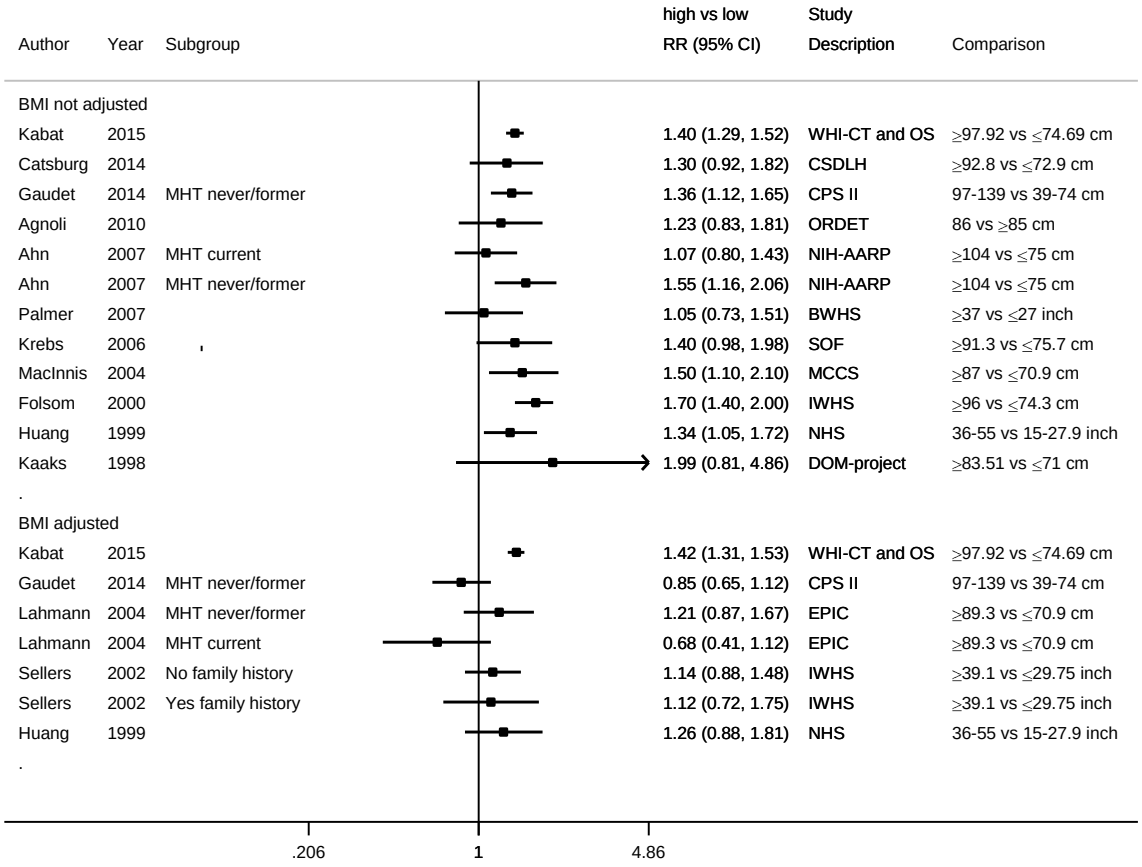


Figure 607 Relative risk of postmenopausal breast cancer for 10 cm of waist circumference

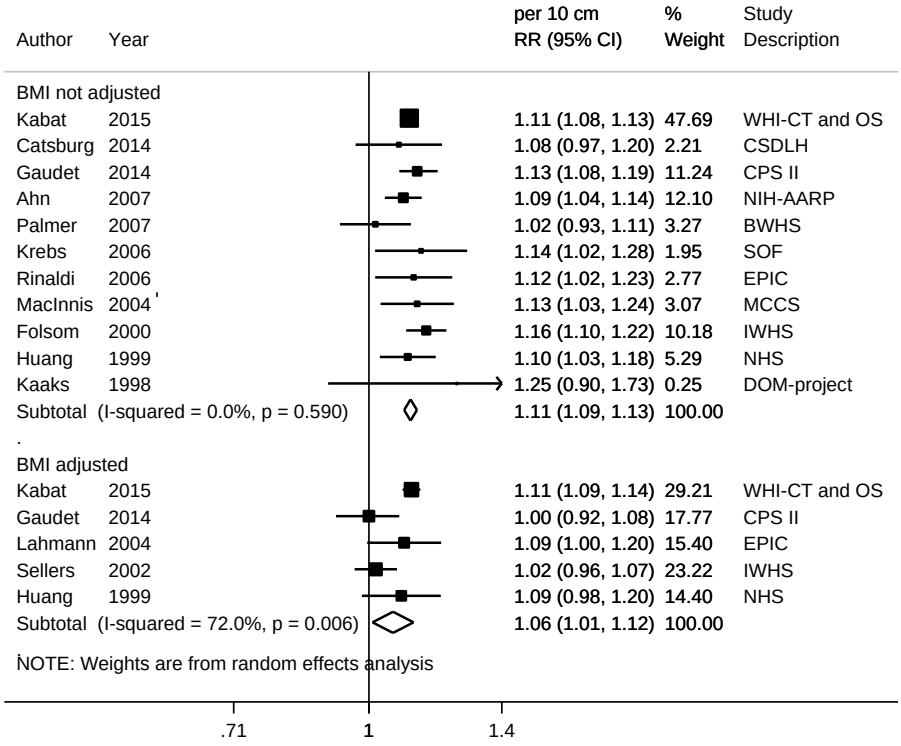
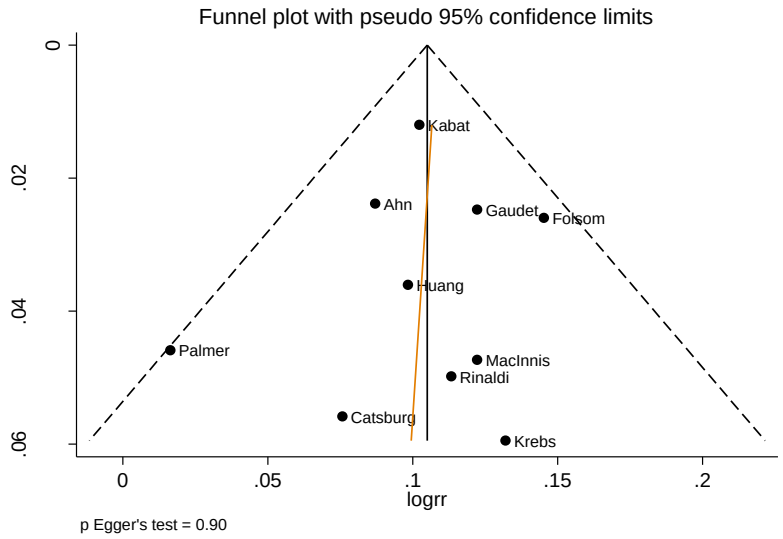


Figure 608 Funnel plot of studies included in the dose response meta-analysis of waist circumference and postmenopausal breast cancer

BMI not adjusted studies



Note: The small study (Kaaks, 1998) that observed a positive association (RR per 10 cm=1.25, 95% CI=0.90-1.73) was excluded from the funnel plot to facilitate presentation. Funnel plot of studies with BMI adjusted results was not produced because of low number of studies.

Figure 609 Relative risk of postmenopausal breast cancer for 10 cm waist circumference, by geographic location

BMI not adjusted studies

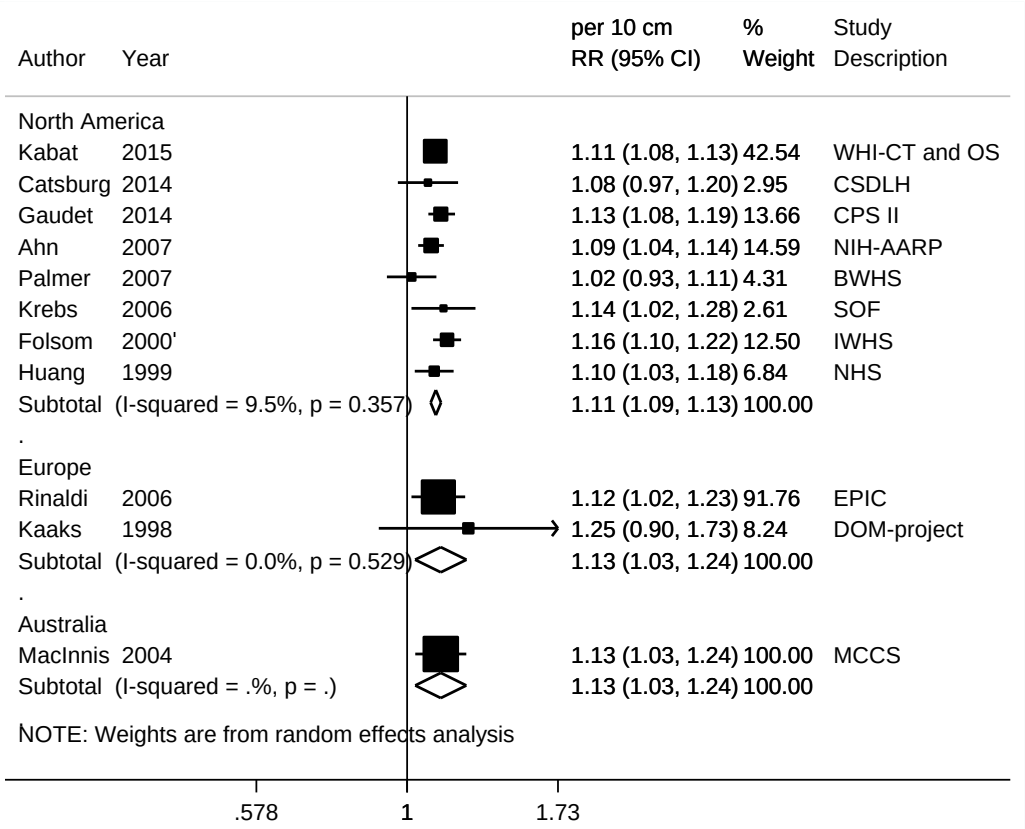


Figure 610 Relative risk of postmenopausal breast cancer for 10 cm waist circumference, by exposure assessment method

BMI not adjusted studies

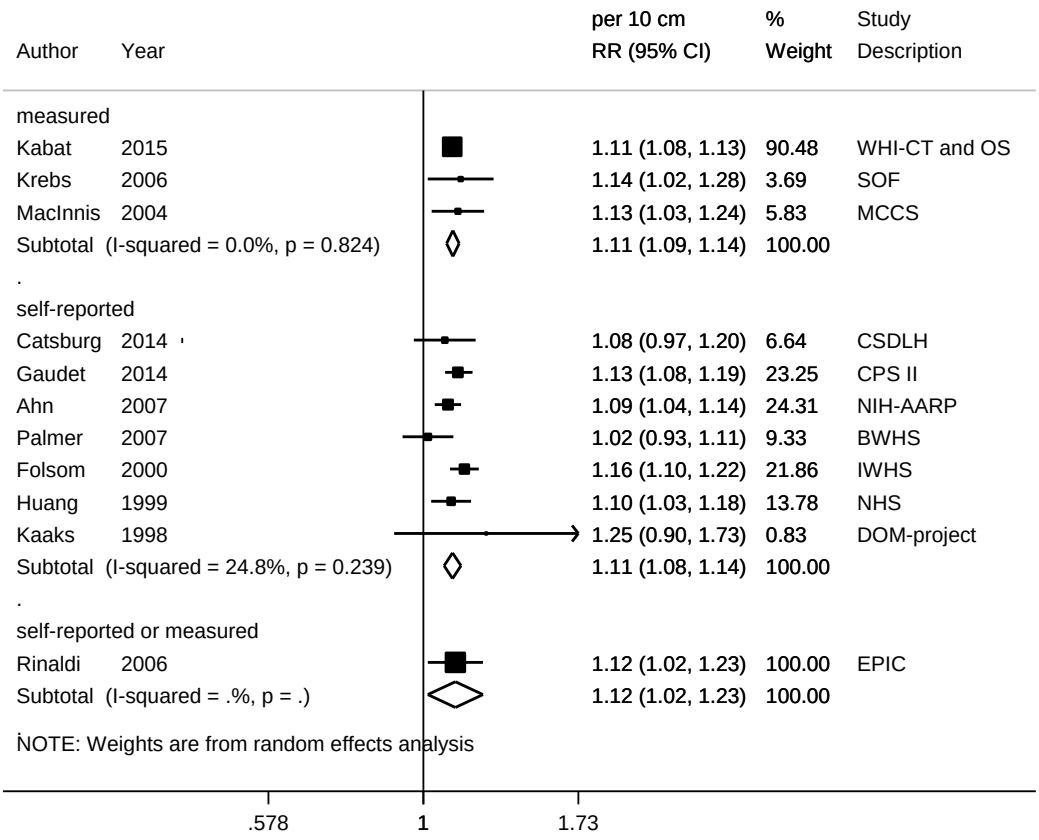
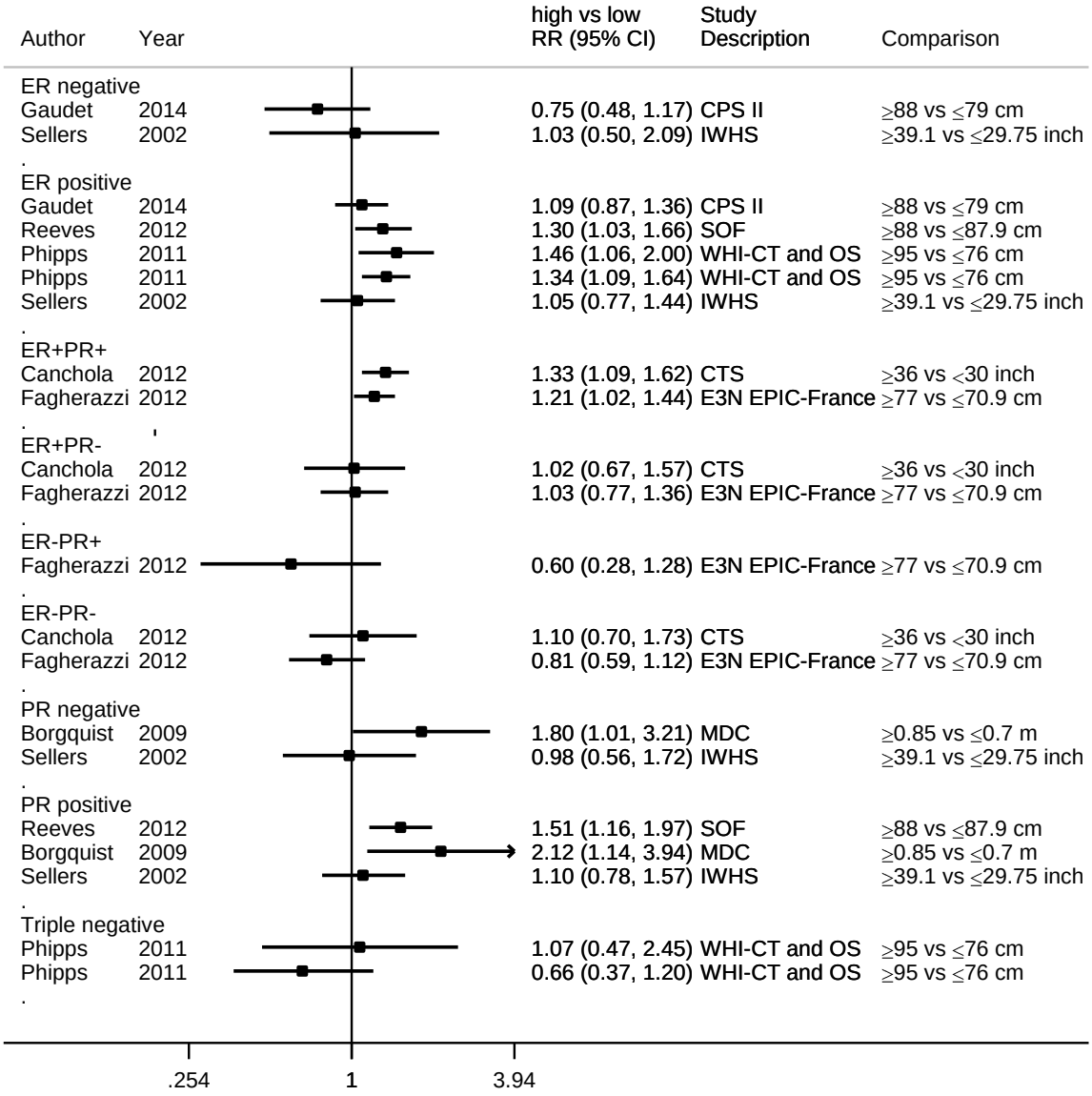


Figure 611 RR (95% CI) of postmenopausal hormone receptor-defined breast cancer for the highest compared with the lowest waist circumference



Note: Dose-response meta-analysis of hormone receptor-defined breast cancer in postmenopausal women was not conducted due to limited number of studies. The highest versus lowest forest plot was produced to facilitate results interpretation.

Phipps, 2011 reported results overall (RR=1.34, 95% CI=1.09-1.64 for ER-positive breast cancer; RR=0.66, 95% CI=0.37-1.20 for triple-negative breast cancer) and in HT non-users (RR=1.46, 95% CI=1.06-2.00; RR=1.07, 95% CI= 0.47-2.45, respectively).

Figure 612 Non-linear dose-response meta-analysis of waist circumference and postmenopausal breast cancer

BMI not adjusted studies

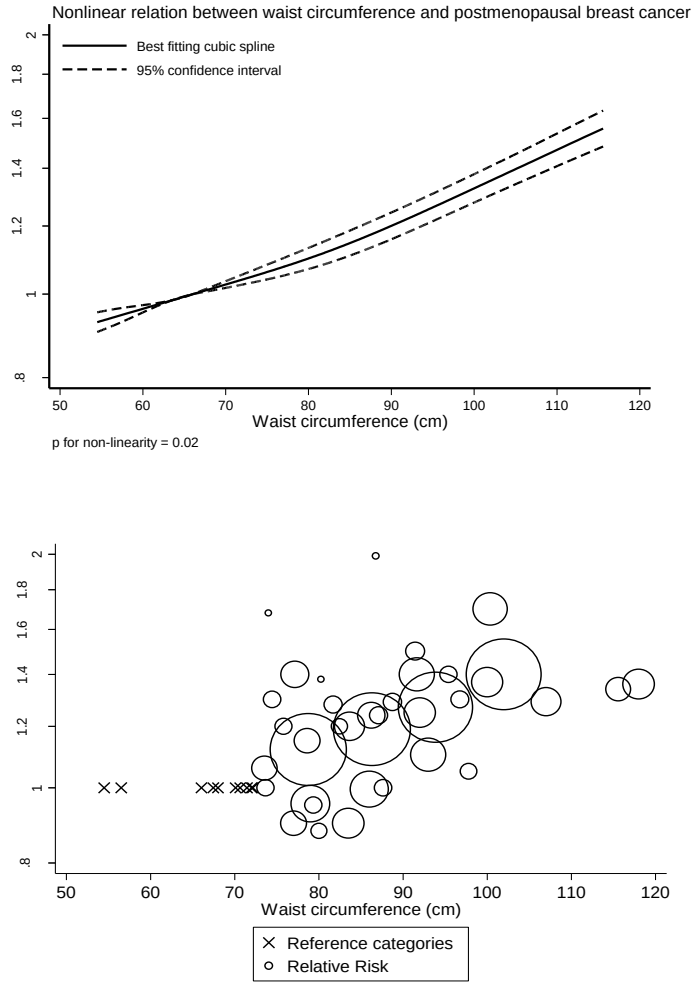


Table 582 Relative risk of postmenopausal breast cancer and waist circumference estimated using non-linear models

Waist circumference (cm)	RR (95%CI)
66.0	1.00
75.8	1.07 (1.04-1.09)
86.0	1.16 (1.12-1.20)
95.4	1.27 (1.22-1.31)
102.0	1.35 (1.30-1.41)

8.2.3 Waist to hip ratio

Cohort studies

Overall summary

Thirty-nine publications from 31 studies that examined waist to hip ratio during adulthood were identified. This included two pooled studies (Bandera, 2015, AMBER Consortium, four studies; Harding, 2015, ANZDCC, 10 studies).

Dose-response meta-analyses were conducted to examine the associations of waist to hip ratio with risk of premenopausal and postmenopausal breast cancer.

Notes on method:

Meta-analyses by menopausal status were performed using results from the models indicated as best-adjusted models, i.e. models that were maximally adjusted but without further adjustment of BMI. Further meta-analyses were conducted including only the results additionally adjusted for BMI.

Table 583 Summary of results of the dose-response meta-analysis in the CUP SLR

	Breast cancer (any)	**Premenopausal breast cancer**	**Postmenopausal breast cancer**
Increment unit used	-	Per 0.1 unit	Per 0.1 unit
Not adjusted for BMI			
Studies (n)	-	11[1]	18[1]
Cases	-	3 465	15 643
RR (95%CI)	-	1.06 (0.98-1.16)	1.10 (1.05-1.16)
Heterogeneity (I^2, p-value)	-	27%, 0.20	60%, <0.01
P value Egger test	-	0.40	0.42
Adjusted for BMI			
Studies (n)	-	9[1]	10[1]
Cases	-	2 772	5 700
RR (95%CI)	-	1.15 (1.01-1.31)	1.06 (0.99-1.15)
Heterogeneity (I^2, p-value)	-	56%, 0.03	41%, 0.12
P value Egger test	-	0.17	0.65

[1]Included the AMBER Consortium (Bandera, 2015) that pooled data on premenopausal women from one cohort and two case-control studies and data on postmenopausal women from two cohorts and two case-control studies.

Breast cancer (any)

Three studies (three publications) were identified. Dose-response meta-analysis was not conducted due to insufficient data.

A non-significant inverse association was reported in one study (Catsburg, 2014b) that was not adjusted for BMI. Two other studies with BMI adjusted results reported a non-significant inverse association (Wu, 2006) and a significant positive association (Wen, 2009).

Table 584 Waist to hip ratio and breast cancer risk. Main characteristics of studies identified.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Catsburg, 2014b BRE80529 Canada	CSDLH, Case Cohort, W	1 075/ 4 417 15 years	Cancer registry	Self-reported	Incidence, Invasive breast cancer	≥0.89 vs ≤0.75	0.95 (0.75-1.20) Ptrend:0.41	Age at first child birth, age at menarche, alcohol Intake, family history of breast cancer, HRT use, menopausal status, number of childbirths, OC use, physical activity
Wen, 2009 BRE80209 China	SWHS, Prospective Cohort, Age: 40-70 years, W	616/ 73 328 7.35 years	Cancer registry		Incidence, Invasive & In situ breast cancer	>0.81 vs ≤0.81	1.20 (1.02-1.41)	Age, BMI, age at first child birth, age at menarche, age at menopause, alcohol Intake, benign breast disease, educational level, energy Intake, family history of cancer, HRT use, physical activity, smoking status
Wu, 2006 BRE24628 China	Taiwan 1990, Prospective Cohort, Age: 47 years, W, Screening Program	104/ 11 899 10.3 years	Partially histological - over 80%	Measured by assistants using standardized techniques	Incidence, breast cancer,	≥0.86 vs ≤0.76	0.60 (0.30-1.20) Ptrend:0.3065	Age , BMI

Premenopausal breast cancer

Summary

Main results:

Eleven out of 12 studies (12 publications) identified could be included in the dose-response meta-analysis. Nine of these studies further reported results adjusted for BMI.

Waist to hip ratio was non-significantly positively associated with premenopausal breast cancer risk (summary RR per 0.1 unit=1.06, 95% CI=0.98-1.16; I^2=27%, P=0.20). When studies with BMI adjusted results were pooled, a significant positive association was observed (summary RR=1.15, 95% CI=1.01-1.31), with high heterogeneity between studies (I^2=56%, P=0.03).

The component study (two publications) (Tehard, 2006; Fagherazzi, 2012a) of a multi-centre study that was already included in the analysis was excluded.

There was no evidence of significant publication or small studies bias from studies that were not adjusted or adjusted for BMI (P for Egger's test=0.40; 0.17, respectively). Visual inspection of the funnel plots shows asymmetry that was driven by smaller studies (Li, 2006; Muti, 2000; Sonnerschein, 1999) with a stronger association than the average.

Two studies and one pooled study reported results on hormone receptor-defined breast cancer subtypes. For the highest compared with the lowest waist to hip ratio, positive associations though not always significant were observed with ER-positive and ER-negative breast cancer (Bandera, 2015; Harris, 2011b). Inverse associations with ER+PR+, ER+PR-, and ER-PR- breast cancer, and positive association with ER-PR+ breast cancer were reported in Fagherazzi, 2012a.

Sensitivity analyses:

A significant positive association was observed in influence analysis when Catsburg, 2014b was omitted from the studies with BMI unadjusted results (summary RR per 0.1 unit=1.09, 95% CI=1.02-1.17). For studies with BMI adjusted results, influence analysis showed mostly non-significant or borderline significant positive associations, except for Lahmann, 2004a, when excluded, a significant positive association remained (summary RR=1.17, 95% CI=1.08-1.27). The summary RRs were 1.06 (95% CI=0.95-1.18) and 1.18 (95% CI=0.99-1.42) when the pooled study of African American women (two cohorts and two case-control studies) was omitted from the BMI unadjusted and adjusted studies, respectively.

Studies not accounted for major confounders (age, alcohol intake, and reproductive factors) on average showed significant positive associations (summary RR for BMI unadjusted studies=1.15, 95% CI=1.02-1.29; RR for BMI adjusted studies=1.28, 95% CI=1.04-1.59). No significant associations were observed in studies with confounder adjustment (RR=0.99, 95% CI=0.90-1.09; RR=1.07, 95% CI=0.88-1.28, respectively) (graph not shown).

Significant positive associations of BMI adjusted waist circumference were only observed in the subgroup analyses of North American studies (summary RR=1.16, 95% CI=1.07-1.26)

and studies that used waist circumference measurement reported by the participants (RR=1.14, 95% CI=1.05-1.24).

Non-linear dose-response meta-analysis:

There was no evidence of significant non-linear relationship (P for non-linearity=0.28 and 0.87 for BMI unadjusted and adjusted studies, respectively) (graphs not shown).

Study quality:

Studies were mostly from North America or Europe. There was only one Chinese study (Li, 2006) and a pooled study of African American women (Bandera, 2015). Participants were recruited from a breast screening clinic in NYUWHS (Sonnenschein, 1999) and DOM-project was a mammography screening study (Kaaks, 1998). Sonnenschein, 1999 observed a stronger positive association than the other studies.

About half of the studies used waist and hip measurements reported by the participants and another half measured the participants for the data. North American studies and studies that used self-reported waist and hip measurements found significant positive associations on average. This was observed in studies with BMI adjusted results but not BMI unadjusted results. Case ascertainment was through cancer registries or confirmed through medical records. Studies not adjusted for age, alcohol intake, and reproductive factors observed stronger associations on average. Not all studies reported results with and without BMI adjustment.

Table 585 Waist to hip ratio premenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	12[1] (12 publications)
Studies included in forest plot of highest compared with lowest exposure	11 (9 publications) BMI not adjusted studies 9 (7 publications) BMI adjusted studies
Studies included in linear dose-response meta-analysis	11 (9 publications) BMI not adjusted studies 9 (7 publications) BMI adjusted studies
Studies included in non-linear dose-response meta-analysis	9 (7 publications) BMI not adjusted studies

[1]Included the AMBER Consortium (Bandera, 2015) that pooled data from one cohort and two case-control studies in the analysis of premenopausal women.

Table 586 Waist to hip ratio premenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2008 SLR and CUP SLR

	2008 SLR		CUP	
Studies	**BMI not adjusted**	**BMI adjusted**	**BMI not adjusted**	**BMI adjusted**
Increment unit used	**Per 0.1 unit**	**Per 0.1 unit**	**Per 0.1 unit**	**Per 0.1 unit**
Studies (n)	6	4	11[1]	9[1]
Cases	1 169	844	3 465	2 772
RR (95%CI)	1.07 (0.90-1.26)	1.24 (0.91-1.67)	1.06 (0.98-1.16)	1.15 (1.01-1.31)
Heterogeneity (I^2, p-value)	59%, 0.03	76%, <0.01	27%, 0.20	56%, 0.03
P value Egger test	-	-	0.40	0.17
Stratified analysis in the CUP				
Studies	**BMI not adjusted**	**BMI not adjusted**	**BMI adjusted**	**BMI adjusted**
Increment unit used	**Per 0.1 unit**	**Per 0.1 unit**	**Per 0.1 unit**	**Per 0.1 unit**
Geographic location[2]	**Europe**	**North America**	**Europe**	**North America**
Studies (n)	3	7	2	6
Cases	691	2 553	544	2 007
RR (95%CI)	1.04 (0.85-1.26)	1.06 (0.95-1.19)	1.21 (0.61-2.43)	1.16 (1.07-1.26)
Heterogeneity (I^2, p-value)	21%, 0.28	46%, 0.12	80%, 0.03	0%, 0.44
Adjustment for age, alcohol intake, reproductive factors	**Adjusted**	**Not adjusted**	**Adjusted**	**Not adjusted**
Studies (n)	4	7	3	6
Cases	1 837	1 628	1 291	1 481
RR (95%CI)	0.99 (0.90-1.09)	1.15 (1.02-1.29)	1.07 (0.88-1.28)	1.28 (1.04-1.59)
Heterogeneity (I^2, p-value)	0%, 0.44	9%, 0.35	68%, 0.05	39%, 0.18

Anthropometric assessment method	**Measured**	**Self-reported**	**Measured**	**Self-reported**
Studies (n)	4	7	4	5
Cases	874	2 591	874	1 898
RR (95%CI)	1.22 (0.95-1.57)	1.05 (0.97-1.13)	1.27 (0.88-1.82)	1.14 (1.05-1.24)
Heterogeneity (I^2, p-value)	50%, 0.11	8%, 0.36	74%, 0.01	0%, 0.87

[1]Included the AMBER Consortium (Bandera, 2015) that pooled data from one cohort and two case-control studies in the analysis of premenopausal women. [2]Also one Chinese study (Li, 2006, 221 cases), BMI unadjusted and adjusted RRs for 0.1 unit waist hip ratio were 1.28 (95% CI=0.84-1.97) and 1.23 (95% CI=0.77-1.96), respectively

Table 587 Waist to hip ratio and premenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Amadou, 2013	12 studies overall (3 cohorts*, 9 case-control studies)	7 954	Africa, Canada, China, Taiwan, USA, European countries	Incidence, premenopausal breast cancer	Per 0.1	1.08 (1.01-1.16)	76%, <0.001
					Asian (4 studies)	1.19 (1.15-1.24)	45%, 0.14
					African (3 studies)	1.06 (1.01-1.12)	71%, 0.03
					Caucasian (6 studies)	1.05 (1.01-1.08)	44%, 0.11

*All cohort studies identified were included in the present review.

Table 588 Waist to hip ratio and premenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Bandera, 2015 USA	AMBER Consortium, Pooled study, 1 cohort and 2 case-control studies (BWHS; CBCS; WCHS) W African American	1081 cases 3648 controls	Record linkage to cancer registries, identified through hospitals, self-reported and verified with medical records and cancer registry data	Self-reported and measured	Incidence, premenopausal breast cancer	>0.88 vs ≤0.74	1.21 (0.96-1.53) Ptrend:0.07	Age, education, study, time period, geographical region, family history of breast cancer, age at menarche, parity, breastfeeding, age at first birth, hormone therapy use, OC use
					Premenopausal breast cancer		1.26 (0.99-1.60) Ptrend:0.04	BMI
		643 cases 3648 controls			ER+ breast cancer	>0.88 vs ≤0.74	1.28 (0.96-1.69) Ptrend:0.05	Age, education, study, time period, geographical region, family history of breast cancer, age at menarche, parity, breastfeeding, age at first birth, hormone therapy use, OC use
					ER+ breast cancer	>0.88 vs ≤0.74	1.35 (1.01-1.80) Ptrend:0.02	BMI

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		438 cases 3648 controls			ER- breast cancer	>0.88 vs ≤0.74	1.12 (0.81-1.56) Ptrend:0.51	Age, education, study, time period, geographical region, family history of breast cancer, age at menarche, parity, breastfeeding, age at first birth, hormone therapy use, OC use
					ER- breast cancer	>0.88 vs ≤0.74	1.14 (0.81-1.59) Ptrend:0.47	BMI
		222 cases 3648 controls			Triple-negative breast cancer	>0.88 vs ≤0.74	1.44 (0.89-2.33) Ptrend:0.18	Age, education, study, time period, geographical region, family history of breast cancer, age at menarche, parity, breastfeeding, age at first birth, hormone therapy use, OC use
					Triple-negative breast cancer	>0.88 vs ≤0.74	1.40 (0.85-2.31) Ptrend:0.24	BMI
Catsburg, 2014b BRE80529 Canada	CSDLH, Case Cohort, W	546/ 4 417 15 years	Cancer registry	Self-reported	Incidence, Invasive breast cancer, premenopausal	≥0.89 vs ≤0.75	0.74 (0.49-1.11) Ptrend:0.39	Age at first child birth, age at menarche, alcohol Intake, family history of breast cancer, HRT use,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								menopausal status, number of childbirths, OC use, physical activity
Harris, 2011b BRE80317 USA	NHS II, Prospective Cohort, Age: 25-42 years, W, Premenopausal	620/ 45 799 426 164 person-years	Self-report verified by medical record	Self-reported waist and hip	Incidence, premenopausal breast cancer	≥0.84 vs ≤0.73	1.00 (0.78-1.28) Ptrend:0.66	Age, age at first child birth, age at menarche, alcohol consumption, benign breast disease, family history of breast cancer, height, oral contraceptive use, parity, physical activity
						≥0.84 vs ≤0.73	1.14 (0.88-1.48) Ptrend:0.13	BMI
		393/			Incidence, breast cancer ER+	≥0.84 vs ≤0.73	0.91 (0.66-1.24) Ptrend:0.67	
						≥0.84 vs ≤0.73	1.07 (0.77-1.48) Ptrend:0.53	
		131/			Incidence, breast cancer ER-	≥0.84 vs ≤0.73	1.88 (1.09-3.27) Ptrend:0.009	
						≥0.84 vs ≤0.73	1.95 (1.10-3.46) Ptrend:0.01	
Li, 2006 BRE80166 China	SWHS, Prospective Cohort,	221/ 73 410 5.66 years	Medical records	Measured by trained Interviewers	Incidence, breast cancer, premenopausal	≥0.84 vs ≤0.79	1.22 (0.87-1.73) Ptrend:0.25	Age, age at first child birth, breastfeeding, educational level,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Age: 40-70 years, W							energy Intake, family history, family history of cancer
						≥0.84 vs ≤0.79	1.18 (0.81-1.72) Ptrend:0.39	BMI
Lahmann, 2004a BRE15804 Europe	EPIC, Prospective Cohort, Age: 18-80 years, W	474/ 176 886 4.7 years	Partially histological - over 80%	Measurements performed by trained personnel	Incidence, breast cancer, premenopausal	≥0.85 vs ≤0.74	0.92 (0.66-1.27) Ptrend:0.731	Age , age at first child, age at menarche, alcohol, educational level, OC use, parity/pregnancies, recruitment center, smoking habits
						≥0.85 vs ≤0.74	1.05 (0.74-1.50) Ptrend:0.657	BMI
						per 0.01 unit	0.99 (0.98-1.01)	
Muti, 2000 BRE80180 Italy	ORDET, Nested Case Control, Age: 35-69 years, W	70/ 277 controls 5.5 years	Cancer registry	Measured by nurses based on a standard protocol	Incidence, Invasive breast cancer, premenopausal	≥0.8 vs ≤0.75	1.70 (0.90-3.30) Ptrend:0.11	Age, recruitment center, time of recruitment
						≥0.8 vs ≤0.75	2.20 (1.00-4.80) Ptrend:0.03	BMI
Huang, 1999 BRE04118 USA	NHS, Prospective Cohort, Age: 30-55 years, W,	197/ 47 382	Hospital discharge records	Self-measured - validated	Incidence, breast cancer, premenopausal	≥0.84 vs ≤0.72	1.18 (0.74-1.88) Ptrend:0.43	Age , age at first child, age at menarche, benign breast disease, family history, height, parity/pregnancies,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Registered nurses							physical activity
						≥0.84 vs ≤0.72	1.43 (0.86-2.37) Ptrend:0.13	BMI
Sonnenschein, 1999 BRE11604 USA	NYUWHS, Prospective Cohort, Age: 35-65 years, W	109/ 8 416 6.6 years	All histology	Measured	Incidence, breast cancer, premenopausal	≥0.78 vs ≤0.7	1.72 (0.96-3.08)	Age , age at first child, age at menarche, breast biopsies, family history
						≥0.78 vs ≤0.7	1.86 (1.01-3.45)	BMI
Kaaks, 1998 BRE04522 Netherlands	DOM-project Utrecht, Prospective Cohort, Age: 39-73 years, W	147/ 11 480 7.1 years	Partially histological - over 80%	Self-reported	Incidence, breast cancer, premenopausal	≥0.8 vs ≤0.73	0.96 (0.60-1.54) Ptrend:0.97	Age , age at first child, age at menarche, menopausal status, parity/ pregnancies

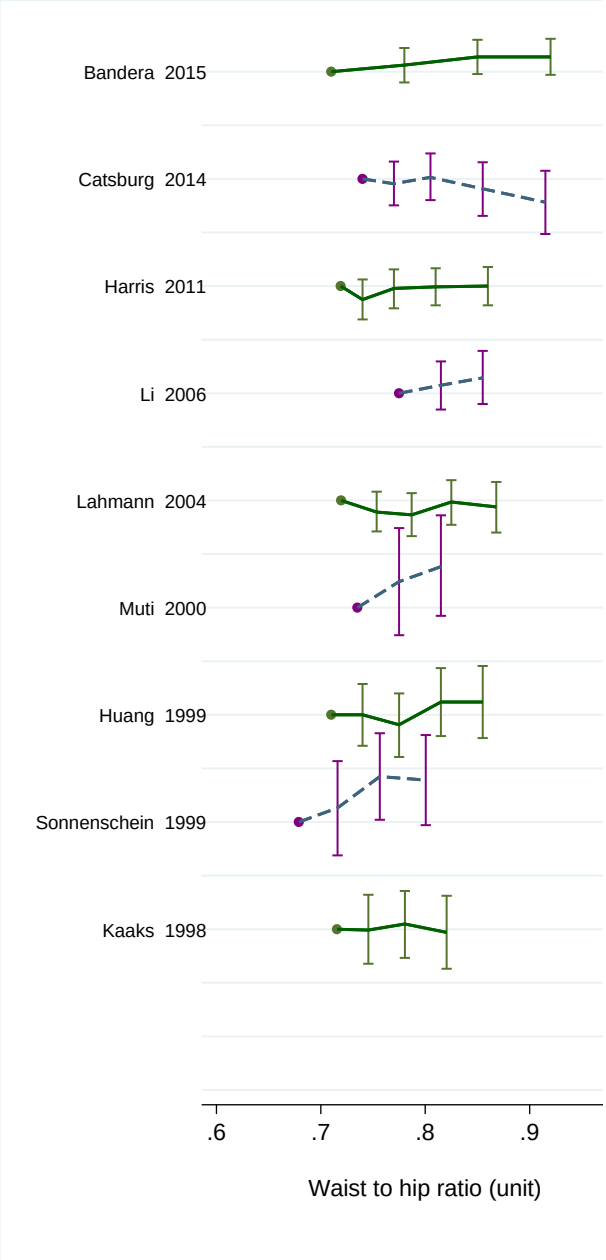
Table 589 Waist to hip ratio and premenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Fagherazzi, 2012a BRE80539 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W	223/ 63 726 582 144 person-years	Self report verified by medical record and pathology report	Self-reported	Incidence, breast cancer ER+/PR+, premenopausal	≥0.8 vs ≤0.74	0.66 (0.46-0.95) Ptrend:0.02	Age at first child birth, age at menarche, age at menopause, alcohol Intake, breastfeeding, educational level, family history of breast cancer, height, history of benign breast disease, mammography, non-alcohol energy, oc use, parous/nulliparous, smoking status, total physical activity, use of HRT, year of birth	Superseded by Lahmann, 2004a
		54/			Incidence, breast cancer ER-/PR-, premenopausal	≥0.8 vs ≤0.74	0.84 (0.44-1.62) Ptrend:0.64		
						≥0.8 vs ≤0.74	0.64 (0.33-1.27) Ptrend:0.80		
		24/			Incidence, breast	≥0.8 vs ≤0.74	1.63 (0.55-4.84)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					cancer ER-/PR+, premenopausal		Ptrend:0.38		
Palmer, 2007 BRE80122 USA	BWHS, Prospective Cohort, Age: 21-69 years	429/ 59 000 10 years	Death certificate / patient records / self report	Self-reported, validated	Incidence, breast cancer, premenopausal	≥0.87 vs ≤0.7	1.16 (0.85-1.59)	Age, age at first child birth, age at menarche, educational level, family history of breast cancer, parity, physical activity	Superseded by Bandera, 2015
						≥0.87 vs ≤0.7	1.19 (0.87-1.64)	BMI	
Tehard, 2006 BRE80103 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years	217/ 69 116 3.6 years	Patient records/direct contact/health Insurance records	Self-reported in questionnaire	Incidence, breast cancer, premenopausal	≥0.82 vs ≤0.73	0.60 (0.39-0.91) Ptrend:>0.05	Age at first child, age at menarche, age-underlying cox models, alcohol, benign breast disease, educational level, family history, marital status, parity/pregnancies, physical activity	Superseded by Lahmann, 2004a
						≥0.82 vs ≤0.73	0.68 (0.43-1.06) Ptrend:>0.05	BMI	

Figure 613 RR estimates of premenopausal breast cancer by levels of waist to hip ratio

BMI not adjusted studies



BMI adjusted studies

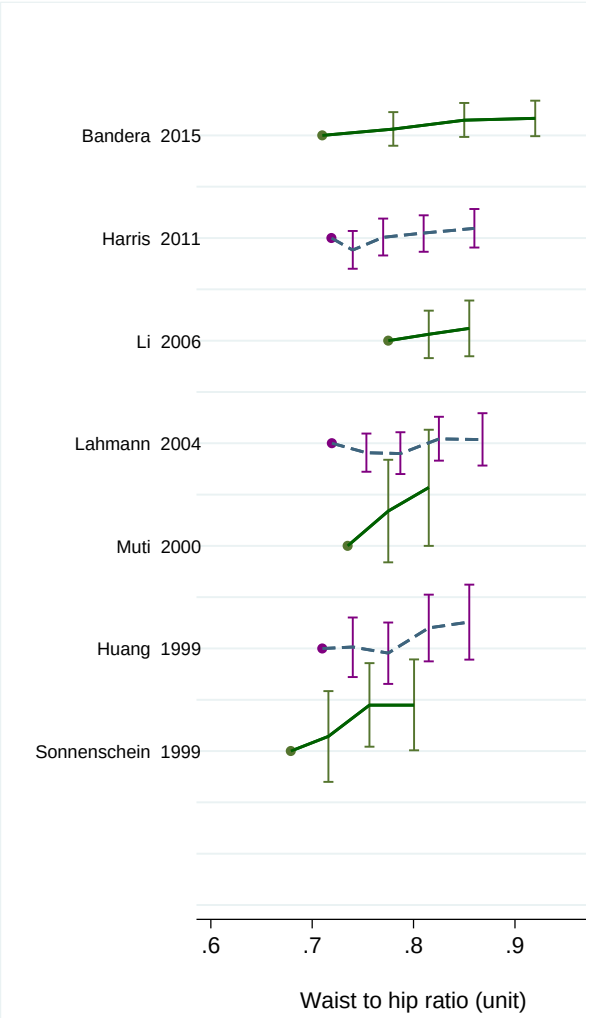


Figure 614 RR (95% CI) of premenopausal breast cancer for the highest compared with the lowest waist to hip ratio

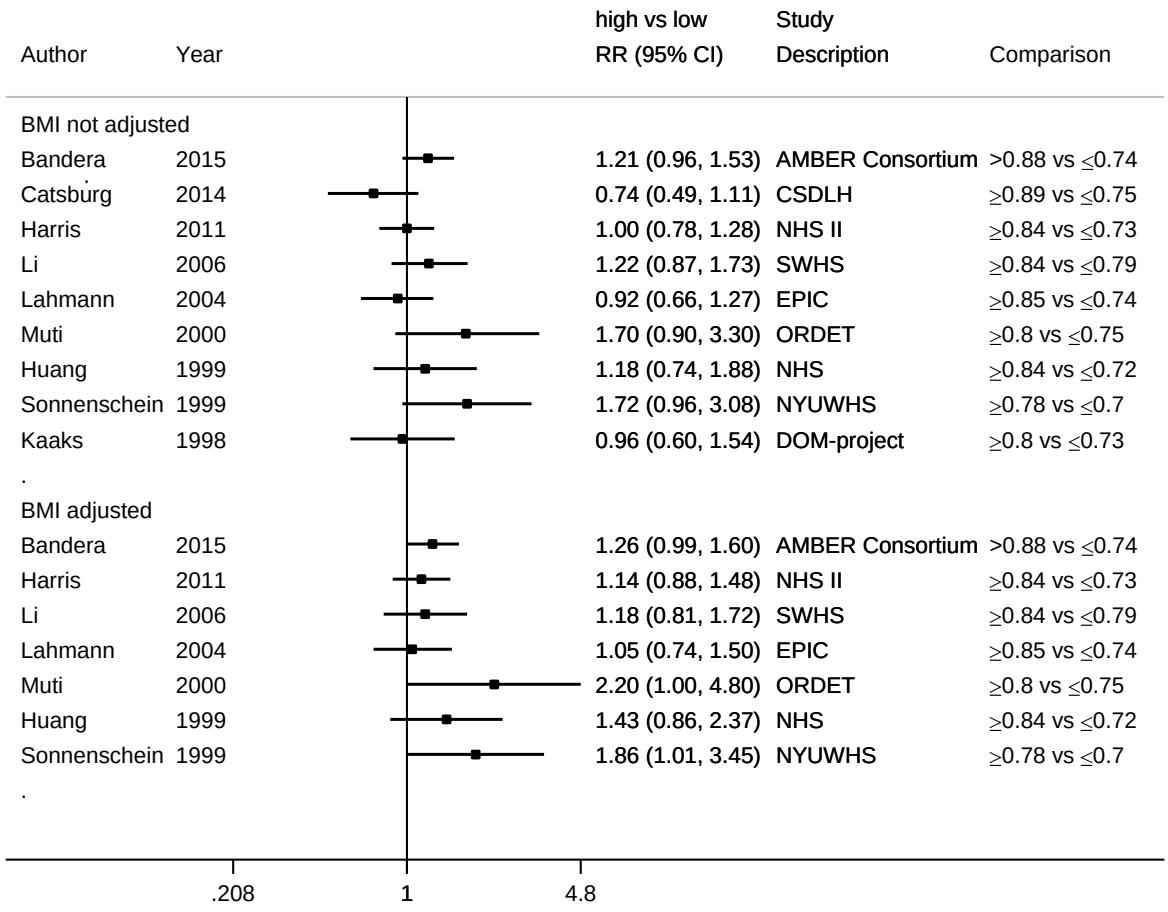


Figure 615 Relative risk of premenopausal breast cancer for 0.1 unit of waist to hip ratio

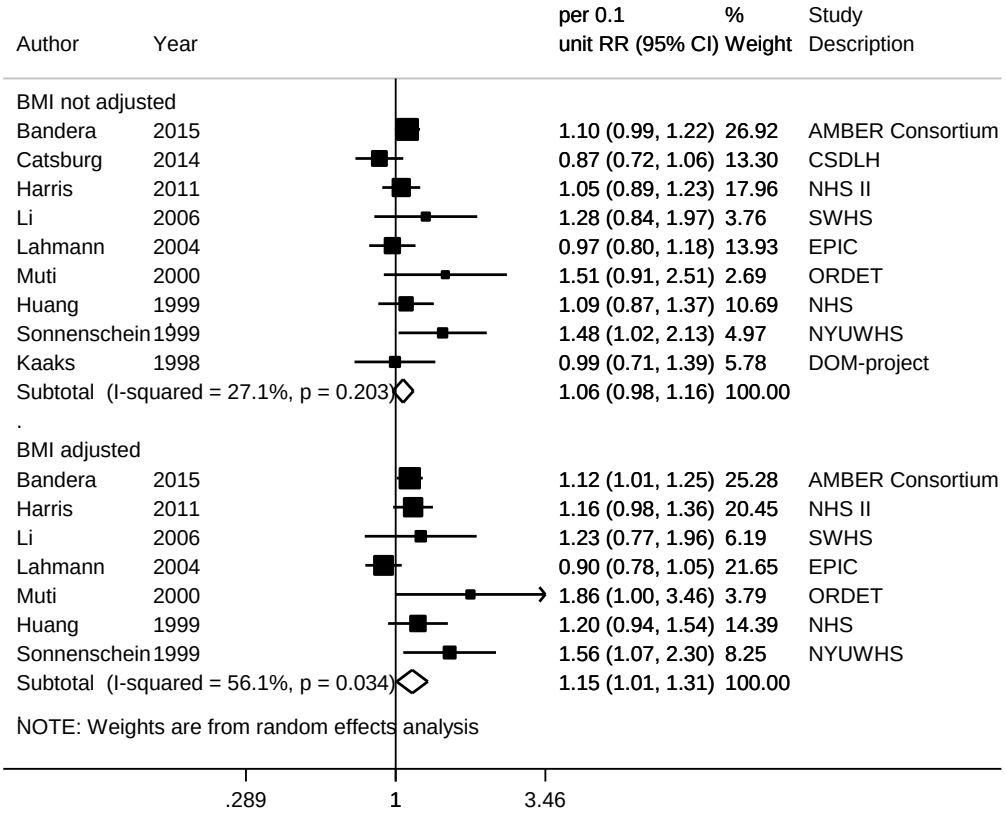
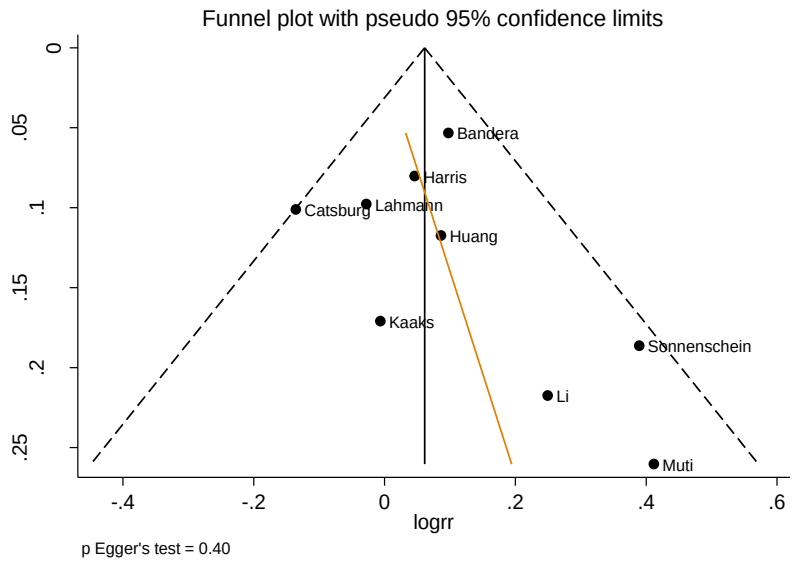


Figure 616 Funnel plot of studies included in the dose response meta-analysis of waist to hip ratio and premenopausal breast cancer

BMI not adjusted studies



BMI adjusted studies

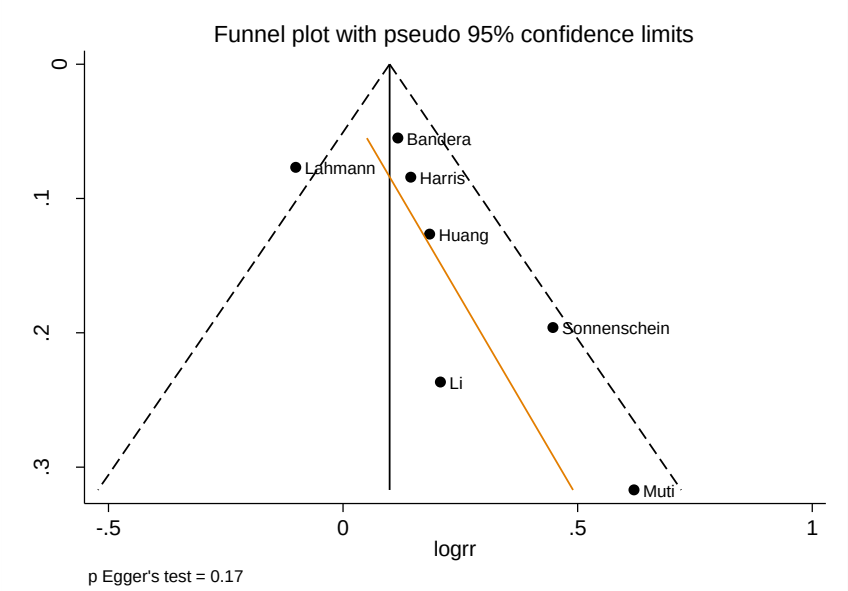
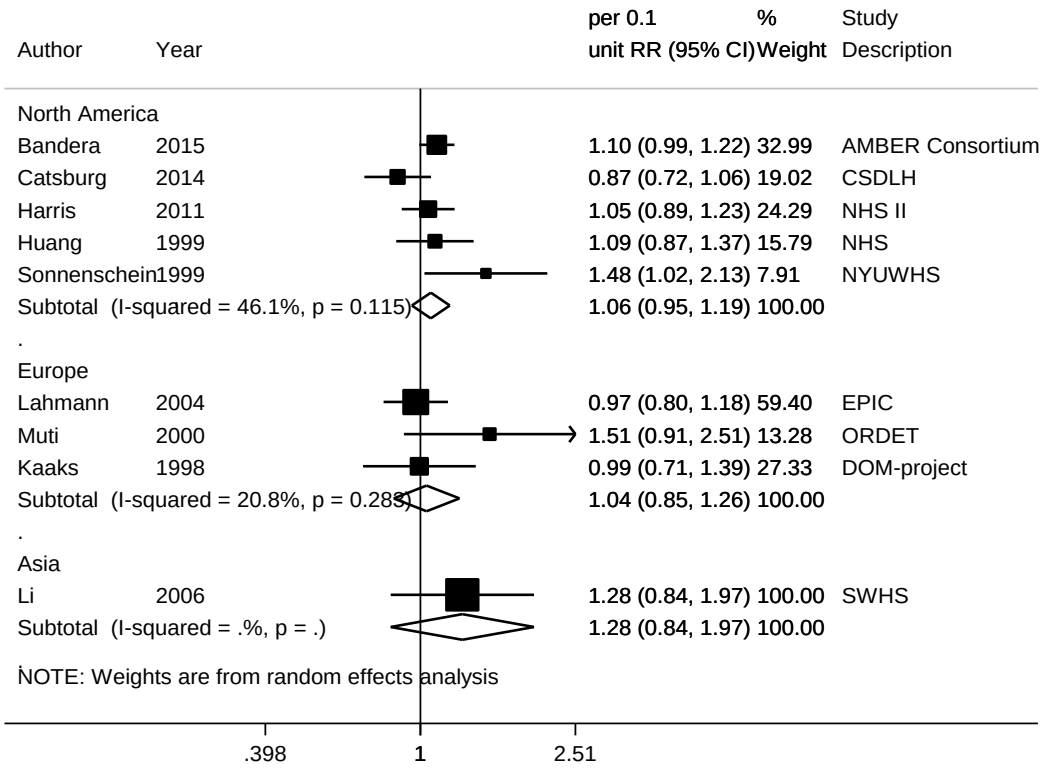


Figure 617 Relative risk of premenopausal breast cancer for 0.1 unit of waist to hip ratio, by geographic location

BMI not adjusted studies



BMI adjusted studies

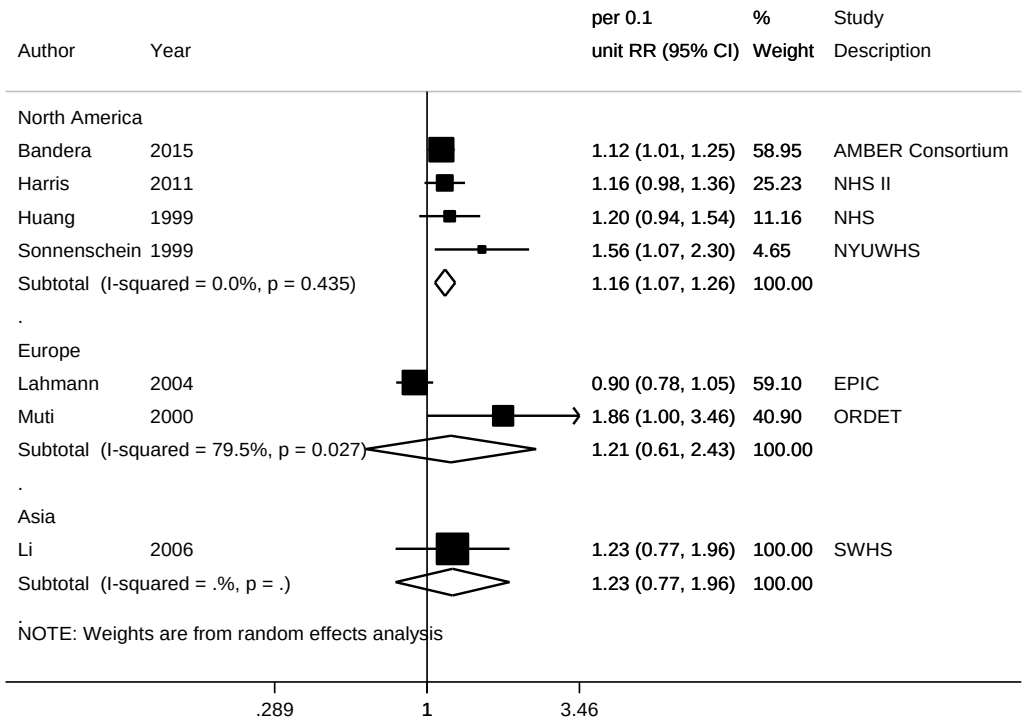
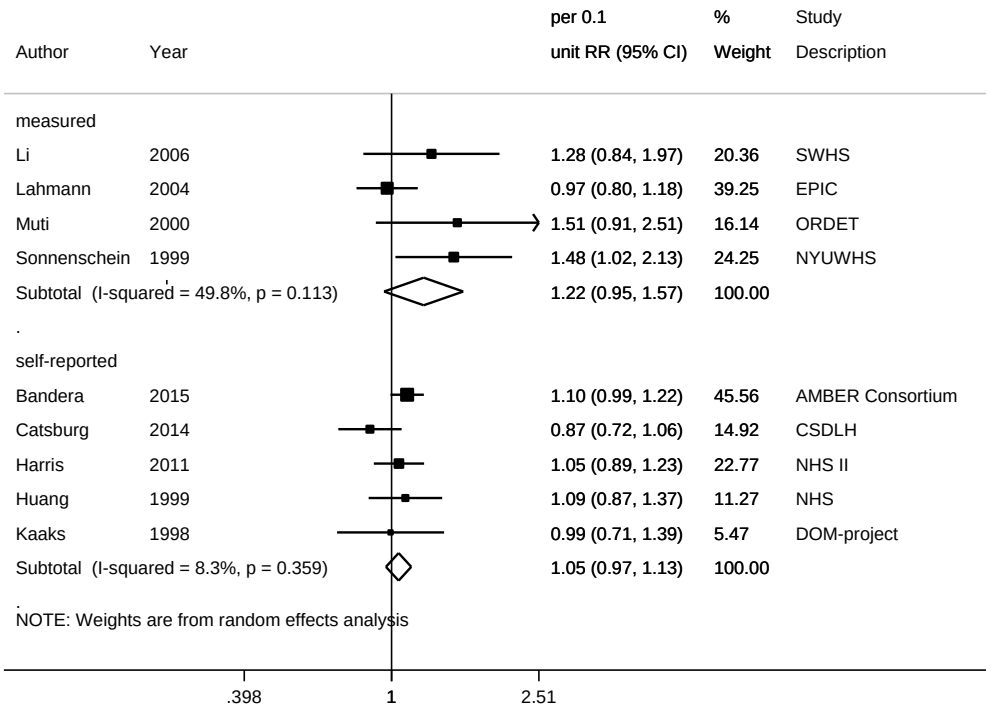
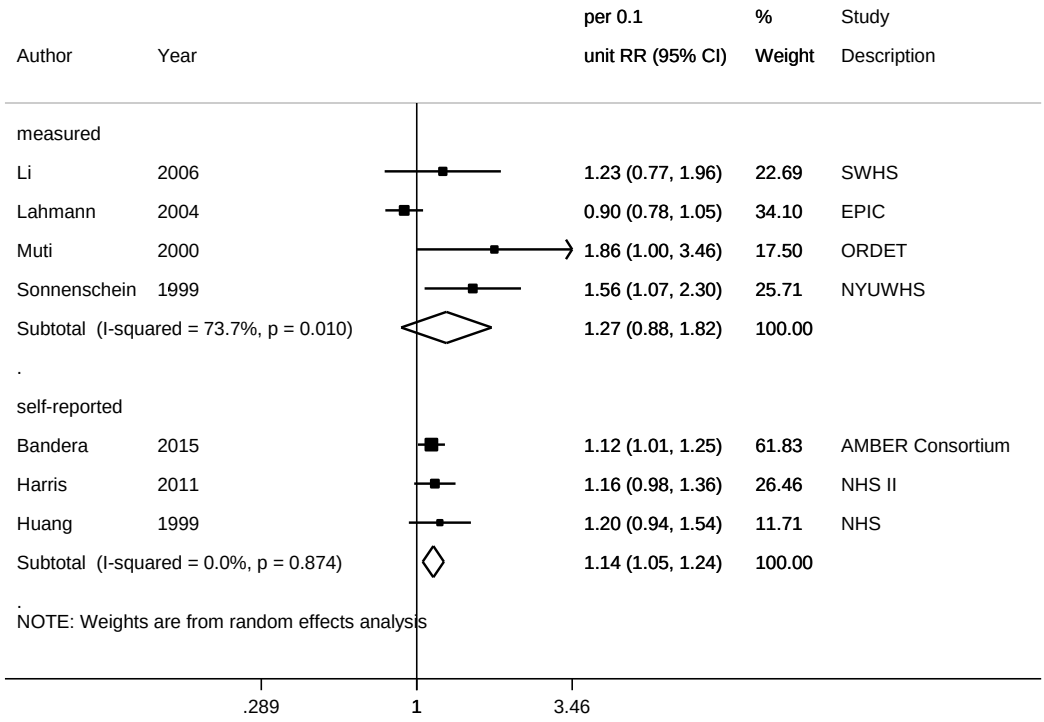


Figure 618 Relative risk of premenopausal breast cancer for 0.1 unit of waist to hip ratio, by exposure assessment method

BMI not adjusted studies



BMI adjusted studies



Postmenopausal breast cancer

Summary

Main results:

Nineteen out of 29 studies (36 publications) on waist to hip ratio identified could be included in the dose-response meta-analyses, of which 18 studies with BMI unadjusted results and nine of these studies and one additional study with BMI adjusted results.

Waist to hip ratio was significantly positively associated with postmenopausal breast cancer risk (summary RR per 0.1 unit=1.10, 95% CI=1.05-1.16, I^2=60%, P<0.01). When studies with BMI adjusted results were pooled, the positive association was not significant (summary RR=1.06, 95% CI=0.99-1.15, I^2=41%, P=0.12).

Ten studies were excluded from the meta-analysis. One study (Morimoto, 2002) overlapped with another study that was already included in the analysis and was excluded. Another pooled study (Harding, 2015, ANZDCC, 9 non-overlapping studies) did not have sufficient data to be included in the analysis. No significant association was reported (RR per one SD increase in WHR=1.01, 95% CI=0.95-1.07).

There was no evidence of significant publication or small studies bias from studies that were not adjusted or adjusted for BMI (P for Egger's test=0.42; 0.65, respectively). Visual inspection of the funnel plots shows asymmetry that was driven by smaller studies with a stronger association than the average (Li, 2006, Lahmann, 2003, Sonnerschein, 1999, and Kaaks, 1998; Li, 2006, respectively).

Non-signficant positive associaitons with ER-positive breast cancer (Bandera, 2015; Phipps, 2011; Sellers, 2002) or ER+PR+ breast cancer (Fagherazzi, 2012a; Potter, 1995) were reported. One study observed a non-signficant positive association (Bandera, 2015) and one, inverse association (Sellers, 2002) with ER-negative breast cancer. Two studies observed non-signficant inverse associaiton with ER-PR- breast cancer (Fagherazzi, 2012a; Potter, 1995).

Sensitivity analyses:

Summary RR remained unchanged materially when studies with BMI unadjusted results were omitted in turn in influence analysis. For studies with BMI adjusted results, the summary RR became significant when Lahmann, 2004a was omitted (summary RR per 0.1 unit=1.09, 95% CI=1.03-1.15) and heterogeneity between studies dropped from 41% (P=0.12) to 9% (P=0.36). When the pooled study of two cohorts and two case-control studies of African American women (Bandera, 2015) was omitted, summary RRs remained similar.

Subgroup analyses showed significant positive associations in studies from North America, used waist and hip measurements reported by the participants, and without simultaneously adjustment for age, alcohol intake, reproductive factors, and MHT use. Non-significant positive associations were mostly observed in other subgroups.

Non-linear dose-response meta-analysis:

There was evidence of significant non-linear relationship (P for non-linearity<0.01). The curve shows an increase in risk of postmenopausal breast cancer with the increase of waist to hip ratio which became slightly steeper after 0.80 units.

Study quality:

Studies were mostly from North America or Europe. There was one Chinese study (Li, 2006), one Australian study (MacInnis, 2004), and a pooled study of African American women (Bandera, 2015). Participants were recruited from a breast screening clinic in NYUWHS (Sonnenschein, 1999) and DOM-project (Kaaks, 1998) was a mammography screening study. SOF (Krebs, 2006) was of older women (mean age 75 years). Kaaks, 1998 and Li, 2006 observed a stronger positive association than the other studies but did not influence the summary RR.

Case ascertainment was through cancer registries or confirmed through medical records. About half of the studies used waist and hip measurements reported by the participants and another half measured the participants for the data. North America studies, studies that used waist and hip measurements reported by the participants, and those without simultaneously adjustment for age, alcohol intake, reproductive factors, and MHT use observed stronger associations on average.

Table 590 Waist to hip ratio and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	29[1] (36 publications)
Studies included in forest plot of highest compared with lowest exposure	18 BMI not adjusted studies 10 BMI adjusted studies
Studies included in linear dose-response meta-analysis	18 BMI not adjusted studies 10 BMI adjusted studies
Studies included in non-linear dose-response meta-analysis	16 BMI not adjusted studies

[1]Included two pooled studies (Bandera, 2015, AMBER Consortium, two cohorts and two case-control studies; Harding, 2015, ANZDCC, 10 cohorts)

Table 591 Waist to hip ratio and postmenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2008 SLR and CUP SLR

	2008 SLR		**CUP**	
Studies	**BMI not adjusted**	**BMI adjusted**	**BMI not adjusted**	**BMI adjusted**
Increment unit used	**Per 0.1 unit**	**Per 0.1 unit**	**Per 0.1 unit**	**Per 0.1 unit**
Studies (n)	11	5	18[1]	10[1]
Cases	4 648	3 857	15 643	5 700
RR (95%CI)	1.09 (1.00-1.19)	1.03 (0.95-1.12)	1.10 (1.05-1.16)	1.06 (0.99-1.15)
Heterogeneity (I^2, p-value)	63%, <0.01	30%, 0.22	60%, <0.01	41%, 0.12
P value Egger test	-	-	0.42	0.65
Stratified analysis in the CUP				
Studies	**BMI not adjusted**	**BMI not adjusted**	**BMI adjusted**	**BMI adjusted**
Increment unit used	**Per 0.1 unit**	**Per 0.1 unit**	**Per 0.1 unit**	**Per 0.1 unit**
Geographic location[2]	**Europe**	**North America**	**Europe**	**North America**
Studies (n)	5	11	2	7

Cases	2 080	12 995	1 469	4 020
RR (95%CI)	1.05 (0.87-1.28)	1.11 (1.08-1.14)	0.93 (0.82-1.06)	1.08 (1.02-1.15)
Heterogeneity (I^2, p-value)	69%, 0.01	0%, 0.57	0%, 0.51	11%, 0.34
Adjustment for age, alcohol intake, reproductive factors, and MHT use	**Adjusted**	**Not adjusted**	**Adjusted**	**Not adjusted**
Studies (n)	6	12	3	7
Cases	10 685	4 958	3 895	1 805
RR (95%CI)	1.06 (0.99-1.14)	1.15 (1.07-1.23)	1.03 (0.93-1.15)	1.13 (1.03-1.23)
Heterogeneity (I^2, p-value)	72%, <0.01	36%, 0.13	64%, 0.06	0%, 0.52
Anthropometric assessment method	**Measured**	**Self-reported**	**Measured**	**Self-reported**
Studies (n)	8	10	4	6
Cases	9 040	6 603	1 830	3 870
RR (95%CI)	1.09 (0.98-1.21)	1.12 (1.06-1.19)	1.02 (0.85-1.23)	1.09 (1.02-1.17)
Heterogeneity (I^2, p-value)	69%, <0.01	43%, 0.10	31%, 0.23	36%, 0.21

[1]Included the AMBER Consortium (Bandera, 2015) that pooled data from two cohorts and two case-control studies. [2]Also one Chinese study (Li, 2006, 211 cases), BMI unadjusted and adjusted RRs for 0.1 unit waist hip ratio were 1.87 (95% CI=1.19-2.96) and 1.55 (95% CI=0.95-2.52), respectively and one Australia study (MacInnis, 2004, 357 cases) BMI unadjusted RR=1.10 (95% CI=0.94-1.29).

Table 592 Waist to hip ratio and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Bandera, 2015 USA	AMBER Consortium, Pooled study, 2 cohorts and 2 case-control studies (BWHS; MEC; CBCS; WCHS) W African American	1380 cases 4621 controls	Record linkage to cancer registries, identified through hospitals, self-reported and verified with medical records and cancer registry data	Self-reported and measured	Incidence, postmenopausal breast cancer	>0.88 vs ≤0.74	1.26 (1.02-1.56) Ptrend:0.01	Age, education, study, time period, geographical region, family history of breast cancer, age at menarche, parity, breastfeeding, age at first birth, hormone therapy use, OC use, age at menopause	
					Postmenopausal breast cancer		1.26 (1.02-1.56) Ptrend:0.01	BMI	
		930 cases 4621 controls			ER+ breast cancer	>0.88 vs ≤0.74	1.26 (0.98-1.61) Ptrend:0.04	Age, education, study, time period, geographical region, family history of breast cancer, age at menarche, parity, breastfeeding, age at first birth,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								hormone therapy use, OC use, age at menopause	
					ER+ breast cancer	>0.88 vs ≤0.74	1.24 (0.97-1.60) Ptrend:0.05	BMI	
		450 cases 4621 controls			ER- breast cancer	>0.88 vs ≤0.74	1.27 (0.91-1.77) Ptrend:0.09	Age, education, study, time period, geographical region, family history of breast cancer, age at menarche, parity, breastfeeding, age at first birth, hormone therapy use, OC use, age at menopause	
					ER- breast cancer	>0.88 vs ≤0.74	1.31 (0.93-1.83) Ptrend:0.06	BMI	
		214 cases 4621 controls			Triple-negative breast cancer	>0.88 vs ≤0.74	1.55 (0.91-2.64) Ptrend:0.12	Age, education, study, time period, geographical region, family history of breast cancer, age at	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								menarche, parity, breastfeeding, age at first birth, hormone therapy use, OC use, age at menopause	
					Triple-negative breast cancer	>0.88 vs ≤0.74	1.60 (0.94-2.73) Ptrend:0.09	BMI	
Kabat, 2015b BRE80526 USA	Womens Health Initiative (WHI), Prospective Cohort, Age: 50-79 years, W, Postmenopausal	7 039/ 143 901 12.7 years	Self report verified by medical record and pathology report	Measured by trained staff at baseline.	Incidence, breast cancer	Q 5 vs Q 1	1.17 (1.09-1.27) Ptrend:<0.0001	Age, alcohol, aspirin use, diabetes, educational level, ethnicity, family history of colon cancer, HRT use, MET-hours per week, smoking, treatment allocation	Estimated midpoints of exposure categories using mean waist hip ratio in study population
Catsburg, 2014b BRE80529 Canada	CSDLH, Case Cohort, W, alumnae	529/ 4 417 15 years	Cancer registry	Self-reported	Incidence, Invasive breast cancer, postmenopausal	≥0.89 vs ≤0.75	1.08 (0.78-1.49) Ptrend:0.79	Age at first child birth, age at menarche, alcohol Intake, family history of breast cancer, HRT use, menopausal	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								status, number of childbirths, OC use, physical activity	
Ahn, 2007 BRE80139 USA	NIH-AARP, Prospective Cohort, Age: 50- years, W, Postmenopausal	790/ 99 039 4 years	Cancer registry	Self-reported In questionnaire	Incidence, breast cancer, current MHT users	≥0.95 vs ≤0.7	1.00 (0.66-1.51) Ptrend:0.18	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, educational level, family history of cancer, fat Intake, height, oophorectomy/hysterectomy, parity, physical activity, race, smoking habits	
		618/			Non-MHT users	≥0.95 vs ≤0.7	1.88 (1.10-3.23) Ptrend:<0.001		
Krebs, 2006 BRE80106 USA	SOF, Prospective Cohort, Age: 65- years, Postmenopausal	350/ 9 704 11.3 years	Self report verified by medical record	Current anthropometrics were measured at 2nd health exam	Incidence, Invasive breast cancer, postmenopausal	≥0.89 vs ≤0.78	1.37 (0.98-1.92) Ptrend:0.12	Age , age at menarche, age at menopause, anthropometry, benign breast disease, educational	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								level, family history, HRT use, parity/pregnancies, physical activity , smoking habits	
Li, 2006 BRE80166 China	SWHS, Prospective Cohort, Age: 40-70 years, W	211/ 73 410 5.66 years	Medical records	Measured by trained Interviewers	Incidence, breast cancer, postmenopausal	≥0.84 vs ≤0.79	1.64 (1.12-2.39) Ptrend:0.0077	Age, age at first child birth, age at menopause, breastfeeding, educational level, energy Intake, family history, family history of cancer	
						≥0.84 vs ≤0.79	1.41 (0.95-2.11) Ptrend:0.078	BMI	
Mellemkjaer, 2006 BRE80039 Denmark	DCH, Prospective Cohort, Age: 50-65 years, Postmenopausal	416/ 23 788 6.1 years	Cancer registry	Recorded by trained technician	Incidence, breast cancer, HRT ever	≥0.85 vs 0.79-0.84	0.89 (0.68-1.17)	Age, age at first child birth, alcohol consumption, benign breast disease, duration of HRT use, educational level, HRT use, parity	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
						per 0.05	0.92 (0.86-0.99)		
		217/			HRT never	≥0.85 vs 0.79-0.84	1.08 (0.75-1.55)		
						per 0.05	0.95 (0.86-1.04)		
Tehard, 2006 BRE80103 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years	1 071/ 69 116 3.6 years	Patient records/direct contact/health Insurance records	Self-reported In questionnaire	Incidence, breast cancer, postmenopausal	≥0.82 vs ≤0.74	1.03 (0.83-1.28) Ptrend:>0.05	Age at first child, age at menarche, age-underlying cox models, alcohol, benign breast disease, educational level, family history, marital status, parity/pregnancies, physical activity	(Lahmann, 2004a did not report BMI unadjusted results)
						≥0.82 vs ≤0.74	0.95 (0.75-1.21) Ptrend:>0.05	BMI	Superseded by Lahmann, 2004a
Lahmann, 2004a BRE15804 Europe	EPIC, Prospective Cohort, Age: 18-80 years, W	494/ 176 886 4.7 years	Partially histological - over 80%	Measurements performed by trained personnel	Incidence, breast cancer, current HRT users	≥0.85 vs ≤0.74	0.85 (0.60-1.20) Ptrend:0.25	Age , age at first child, age at menarche, alcohol, BMI, educational level, parity/pregnancies, recruitment	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								center, smoking habits	
						per 0.01 unit	1.00 (0.97-1.03)		
		911/			Never/former HRT users	≥0.85 vs ≤0.74	0.94 (0.74-1.21) Ptrend:0.740		
						per 0.01 unit	0.99 (0.98-1.01)		
MacInnis, 2004 BRE80159 Australia	MCCS, Prospective Cohort, Age: 27-75 years, W, Postmenopausal	357/ 13 598 9.1 years	Medical records	Direct anthropometric measurements	Incidence, Invasive breast cancer, postmenopausal	≥0.83 vs ≤0.73	1.20 (0.80-1.60)	Age, birthplace, educational level, HRT use, physical activity	
						per 0.1 unit	1.10 (0.94-1.29)		
		97/			Incidence, breast cancer ER+, >=15 years postmenopausal	per 0.1 unit	1.19 (0.88-1.61)		
		29/			Incidence, breast cancer ER-, >=15 years postmenopausal	per 0.1 unit	0.69 (0.41-1.16)		
		84/			Incidence, breast cancer PR+, >=15 years postmenopausal	per 0.1 unit	1.13 (0.82-1.57)		
		42/			Incidence, breast cancer PR-, >=15 years	per 0.1 unit	0.93 (0.58-1.49)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					postmenopausal				
Lahmann, 2003 BRE20119 Sweden	MDCS, Prospective Cohort, Age: 50-73 years, W, Postmenopausal	236/ 12 159 5.7 years	Cancer registry + death certificate		Incidence, Invasive & In situ breast cancer,	≥0.84 vs ≤0.75	1.23 (0.79-1.92) Ptrend:0.252	Age , age at first child, age at menarche, alcohol, height, marital status, OC use, occupation, parity/pregnancies, smoking habits	
Sellers, 2002 BRE20892 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	282/ 37 105 13 years	Partially histological - over 80%	Measured waist and hip circumferences by a friend of the participant after reading a detailed protocol.	Incidence, breast cancer, family history breast cancer - yes and postmenopausal	≥0.91 vs ≤0.76	1.55 (1.04-2.32) Ptrend:0.06	Age at first child, age at menarche, age at menopause, alcohol, BMI, body weight, educational level, family history, HRT use, OC use, parity/pregnancies, physical activity , smoking habits, whr	
		1 368/			Family history breast cancer - no and	≥0.91 vs ≤0.76	1.02 (0.85-1.23) Ptrend:0.87		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					postmenopausal				
		1 043/			Incidence, breast cancer ER+, postmenopausal	≥0.91 vs ≤0.76	1.01 (0.82-1.26)		
		232/			Incidence, breast cancer ER-, postmenopausal	≥0.91 vs ≤0.76	0.81 (0.50-1.31)		
		993/			Incidence, breast cancer PR+, postmenopausal	≥0.91 vs ≤0.76	1.05 (0.83-1.34)		
		362/			Incidence, breast cancer PR-, postmenopausal	≥0.91 vs ≤0.76	0.88 (0.60-1.30)		
Folsom, 2000 BRE80610 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	1 299/ 31 702 10 years	Active follow up, cancer registry, death certificate and national death Index	Tape measure sent to participants Instructing them to have a friend take the measurements	Incidence, breast cancer	≥0.9 vs ≤0.76	1.30 (1.10-1.50) Ptrend:0.002	Age at first child, alcohol Intake, educational level, energy, fish Intake, fruits and vegetables Intake, keys score, pack years of smoking, physical activity, red meat Intake,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								smoking status, vitamin use, whole grains, oestrogen use	
Muti, 2000 BRE80180 Italy	ORDET, Nested Case Control, Age: 35-69 years, W	64/ 253 controls 5.5 years	Cancer registry	Measured by nurses based on a standard protocol	Incidence, Invasive breast cancer, postmenopausal	≥0.84 vs ≤0.79	0.90 (0.50-1.70) Ptrend:0.7	Age, recruitment center, time of recruitment	
						≥0.84 vs ≤0.79	1.10 (0.60-2.20) Ptrend:0.9	BMI, age at first child birth, age at menarche, age at menopause, parity, study center	
Huang, 1999 BRE04118 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	840/ 47 382	Hospital discharge records	Self-measured - validated	Incidence, breast cancer, postmenopausal	≥0.84 vs ≤0.72	1.28 (1.02-1.61) Ptrend:0.005	Age , age at first child, age at menarche, benign breast disease, family history, height, parity/pregnancies, physical activity	
						≥0.84 vs ≤0.72	1.22 (0.96-1.55) Ptrend:0.03	BMI	
Sonnenschein, 1999 BRE11604 USA	NYUWHS, Prospective Cohort, Age: 35-65	150/ 8 416 6.6 years	All histology	Measured	Incidence, breast cancer, postmenopausal	≥0.78 vs ≤0.7	1.28 (0.78-2.08)	Age , age at first child, age at menarche, breast biopsies, family	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	years, W							history	
						≥0.78 vs ≤0.7	0.94 (0.56-1.57)	BMI	
Kaaks, 1998 BRE04522 Netherlands	DOM-project Utrecht, Prospective Cohort, Age: 39-73 years, W	76/ 11 480 7.1 years	Partially histological - over 80%		Incidence, breast cancer, postmenopausal	≥0.8 vs ≤0.73	2.63 (1.09-6.35) Ptrend:0.007	Age , age at first child, age at menarche, menopausal status, parity/pregnancies	

Table 593 Waist to hip ratio and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Harding, 2015 Australia and New Zealand	ANZDCC, Pooled study of 11 cohorts*, W	1 323/ 38 724 Mean age: 54.3 years 16 years of follow-up	Cancer database and National death index	Measured	Incidence, breast cancer, diagnosed ≥ 50 years	Per 1 SD	1.01 (0.95-1.07)	Age as the timescale in model, adjusted for smoking status, education, study cohort	Excluded, exposure values not available
		901/			Never smokers	Per 1 SD	1.01 (0.95-1.08)		
		422/			Ever smokers	Per 1 SD	0.98 (0.89-1.09)		
*Current analysis used data from 10 cohorts - Australian National Blood Pressure Trial; Australian Longitudinal Study of Aging; Australian Diabetes Obesity and Lifestyle Study;									

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Crossroads Undiagnosed Study; Fremantle Diabetes Study; Geelong Osteoporosis Study; Melbourne Collaborative Cohort Study; North West Adelaide Health Study; Perth Risk Factor Prevalence Cohort Study 1989; Perth Risk Factor Prevalence Cohort Study 1994									
Heo, 2015 BRE80581 USA	Women's Health Initiative, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	6 798/ 144 701 12 years	Self-report verified by medical record and pathology report	Measured	Incidence, breast cancer	≥0.79 vs ≤0.78	1.09 (1.03-1.15)	Age, age at first child birth, age at menopause, alcohol, breast biopsies, educational level, ethnicity, family history of breast cancer In first degree relatives, height, hormone use, pack years of smoking, parity, randomisation	Superseded
						per 1 score	1.06 (1.03-1.08)		
Zhang X, 2015 BRE80578 USA	NHS, Prospective Cohort, Age: 30-55 years, W	857/ 103 577 26 years	Self-report verified by medical record	Self-reported In questionnaire	Incidence, breast cancer AR+, postmenopausal	≥0.84 vs ≤0.72	1.20 (0.96-1.49)	Age at menarche, age at menopause, alcohol Intake, BMI, family history of breast cancer, height, history of benign breast disease, parity and age at first birth, physical activity, postmenopausal hormone use	Results by breast cancer subtypes only, not analysed

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		257/			Incidence, breast cancer AR-, postmenopausal	≥0.84 vs ≤0.72	1.08 (0.70-1.67)		
Poynter, 2013 BRE80453 USA	IWHS, Prospective Cohort, Age: 55-71 years, Postmenopausal	1 586/ 37 459 22 years	Health registers	A measuring tape was sent for a friend to measure the woman's waist and hip circumference	Incidence, postmenopausal breast cancer, age <75y	0.89-2.84 vs 0.34-0.78	1.18 (1.01-1.38) Ptrend:0.02	Age at baseline, age at first child birth, age at menarche, age at menopause, alcohol, BMI, number of childbirths, physical activity, smoking	Superseded
		1 065/			Postmenopausal breast cancer. age >=75y	0.89-2.84 vs 0.34-0.78	1.05 (0.87-1.28) Ptrend:0.63		
Rohan, 2013 BRE80478 USA	Women's Health Initiative, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	502/ 10 960 12.9 years	Self report verified by medical record and pathology report	Waist, hip circumference were measured at baseline by trained staff using standardized protocols	Incidence, Invasive breast cancer	Q 5 vs Q 1	1.91 (1.41-2.58) Ptrend:0.0001	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, breast biopsies, educational level, energy Intake, ethnicity, family history of breast cancer, HRT use, oc use, pack-years smoking, parity, physical activity, randomisation	Superseded

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Fagherazzi, 2012a BRE80539 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years, W	944/ 63 726 582 144 person-years	Self-report verified by medical record and pathology report	Self-reported	Incidence, breast cancer ER+/PR+, postmenopausal	≥0.8 vs ≤0.74	1.02 (0.86-1.21) Ptrend:0.80	Age at first child birth, age at menarche, age at menopause, alcohol Intake, breastfeeding, educational level, family history of breast cancer, height, history of benign breast disease, mammography, non-alcohol energy, oc use, parous/nulliparous, smoking status, total physical activity, use of HRT, year of birth	Superseded
		302/			Incidence, breast cancer ER+/PR-, postmenopausal	≥0.8 vs ≤0.74	0.95 (0.73-1.25) Ptrend:0.99		
		243/			Incidence, breast cancer ER-/PR-, postmenopausal	≥0.8 vs ≤0.74	0.86 (0.62-1.19) Ptrend:0.42		
		52/			Incidence, breast cancer ER-/PR+, postmenopausal	≥0.8 vs ≤0.74	0.56 (0.28-1.14) Ptrend:0.12		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Hartz, 2012 BRE80400 USA	Women's Health Initiative, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	6 052/ 141 652 8 years		Measured	Incidence, breast cancer	per 1 sd units	1.05	Age, alcohol, educational level, Income, physical activity, race, region, smoking, treatment allocation	Superseded
Phipps, 2011 BRE80343 USA	Women's Health Initiative, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	2 606/ 155 723 7.9 years	Mail or telephone questionnaires verified by trained physician adjudicators	Measured at baseline	Incidence, breast cancer ER+	≥0.86 vs ≤0.76	1.06 (0.93-1.21) Ptrend:0.21	Age, BMI, educational level, family history of breast cancer, Income, mammography, mammography, race, recreational activity	Superseded
						≥0.86 vs ≤0.76	0.99 (0.66-1.49) Ptrend:0.82		
Palmer, 2007 BRE80122 USA	BWHS, Prospective Cohort, Age: 21-69 years	382/ 59 000 10 years	Death certificate / patient records / self report	Self-reported, validated	Incidence, breast cancer, postmenopausal	≥0.87 vs ≤0.7	0.99 (0.72-1.37)	Age, age at first child birth, age at menarche, age at menopause, BMI, educational level, family history of cancer, parity, physical activity	Superseded
		136/			Postmenopausal	≥0.87 vs ≤0.7	1.15 (0.69-1.94)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					and HRT nonusers				
Rinaldi, 2006 BRE80101 The Netherlands, UK, Germany, Spain, Italy, Greece, France	EPIC, Nested Case Control, W, Postmenopausal	613/ 1139 controls	Population cancer registries and other procedures	Measured and self-report	Incidence, Invasive & In situ breast cancer, postmenopausal	Q 5 vs Q 1		Age at first child, parity/pregnancies	Superseded
Sweeney, 2004 BRE80599 USA	IWHS, Prospective Cohort, Age: 61 years, W, Postmenopausal	425/ 36 658 16 years	Seer registry	Hip and waist circumferences measured, usually by a friend, using a paper tape measure provided with the questionnaire	Incidence, postmenopausal breast cancer, 55 - 64 years	≥0.89 vs ≤0.77 kg/m^2	1.38 (1.06-1.80) Ptrend:0.01	Age at baseline, age at first child birth, age at menarche, age at menopause, educational level, family history of breast cancer, height, parity	Superseded
		1 291/			65-74 years	≥0.89 vs ≤0.77 kg/m^2	1.34 (1.15-1.56) Ptrend:0.0004		
		558/			75-84 years	≥0.89 vs ≤0.77 kg/m^2	1.49 (1.16-1.90) Ptrend:0.002		
Wirfalt, 2004 BRE17083 Sweden	MDCS, Nested Case Control, Age: 50- years, W, Postmenopausal	12 803 8 years	Partially histological - over 80%		Incidence, breast cancer, postmenopausal	(mean exposure)			Superseded

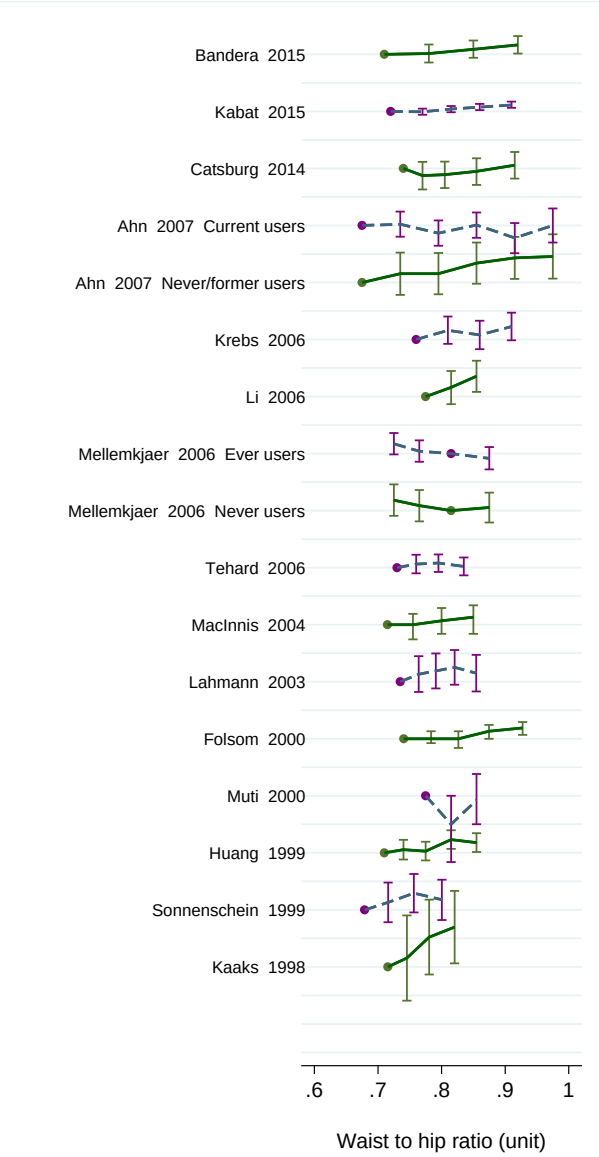
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Morimoto, 2002 BRE20457	Women's Health Initiative - Observational study, Prospective Cohort, Age: 50-79 years, Postmenopausal	708/ 85 917 34.8 months	Medical records + self-reported	Measurements performed by clinical staff	Incidence, breast cancer, HRT - yes	≥0.86 vs ≤0.74	0.95 (0.72-1.25) Ptrend:1	Age , age at first child, age at menarche, age at menopause, alcohol, educational level, energy Intake , ethnicity, family history, leisure time physical activity, parity/pregnancies, smoking habits	Superseded by Kabat, 2015b
		319/			HRT - no	≥0.86 vs ≤0.74	1.33 (0.88-2.01) Ptrend:0.1		
den Tonkelaar, 1995 BRE02224 Netherlands	DOM-project Utrecht, Prospective Cohort, Age: 40-73 years, W, Screening Program	38/ 9 491 4 years	Not specified	Measurements performed by trained personnel	Incidence, breast cancer, postmenopausal	≥0.8 vs ≤0.76	1.89 (0.80-4.48) Ptrend:0.11	Age	Superseded
Potter, 1995 BRE80164 USA	IWHS, Prospective Cohort, Age: 55-69 years, W,	412/ 37 105 7 years	National cancer registers	Waist and hip measured by a friend with tape provided	Incidence, breast cancer ER+/PR+, postmenopausal	≥0.9 vs ≤0.89	1.37 (1.11-1.69)	Age	Superseded
		99/			Incidence, breast cancer ER+/PR-,	≥0.9 vs ≤0.89	0.89 (0.55-1.44)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Postmenopausal				postmenopausal				
		17/			Incidence, breast cancer ER-/PR+, postmenopausal	≥0.9 vs ≤0.89	1.85 (0.68-5.03)		
		78/			Incidence, breast cancer ER-/PR-, postmenopausal	≥0.9 vs ≤0.89	0.79 (0.45-1.39)		
		328/			Incidence, breast cancer unknown ER/PR status, postmenopausal	≥0.9 vs ≤0.89	1.19 (0.93-1.52)		
Sellers, 1994 BRE80624 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	461/ 36 603 5 years	Seer registry	Waist and hip circumference measured by others	Incidence, postmenopausal breast cancer, no family history of bc, no diabetes	≥0.87 vs ≤0.86	1.19 (0.99-1.44)		Superseded
Sellers, 1993 BRE18025 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	87/ 37 105 5 years	Partially histological - over 80%	Measured waist and hip circumferences by a friend of the paritcipant after reading a detailed protocol.	Incidence, breast cancer, family history breast cancer - yes	≥0.91 vs ≤0.91	1.78 (1.09-2.84)	Age	Superseded
		485/			Family history breast cancer - no	≥0.91 vs ≤0.91	1.12 (0.92-1.39)		
Gapstur, 1992	IWHS,	489/	Partially	Self-	Incidence, breast	≥0.91 vs ≤0.76	1.50 (1.13-2.00)	Age	Superseded

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
BRE03101 USA	Prospective Cohort, Age: 55-69 years, W, Postmenopausal	37 105 4 years	histological - over 80%	measurement of the waist, hips	cancer, postmenopausal		Ptrend:0.005		
Folsom, 1990 BRE02836 USA	IWHS, Nested Case Control, Age: 55-69 years, W, Postmenopausal	224/ 1806 controls 2 years	All histology	Self-measured	Incidence, breast cancer, postmenopausal	≥0.87 vs ≤0.79	1.39 (0.99-1.96) Ptrend:0.06	Age	Superseded

Figure 619 RR estimates of postmenopausal breast cancer by levels of waist to hip ratio

BMI not adjusted studies



BMI adjusted studies

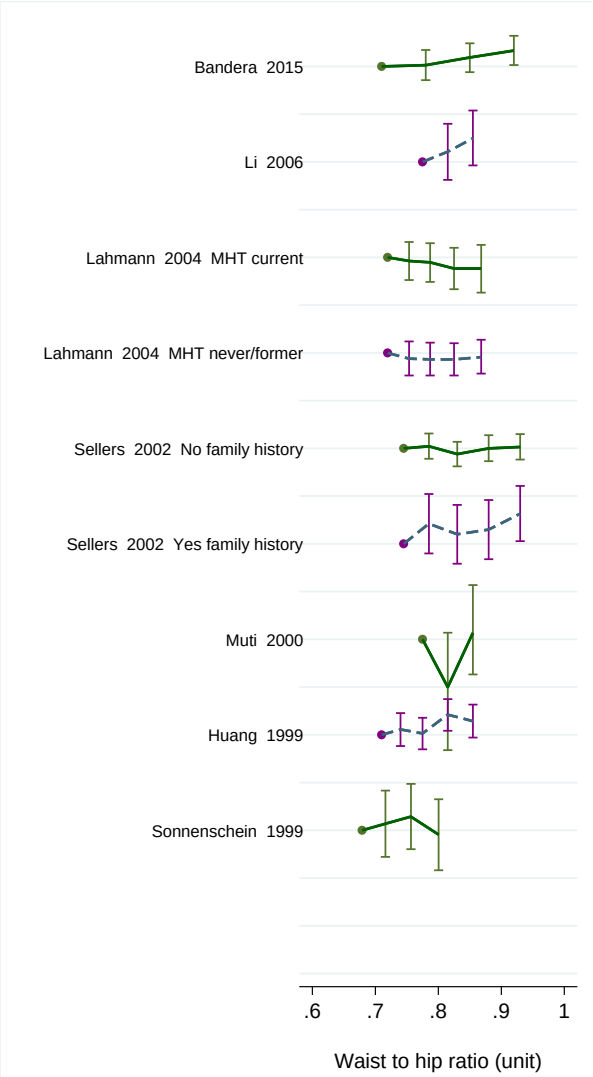


Figure 620 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest waist to hip ratio

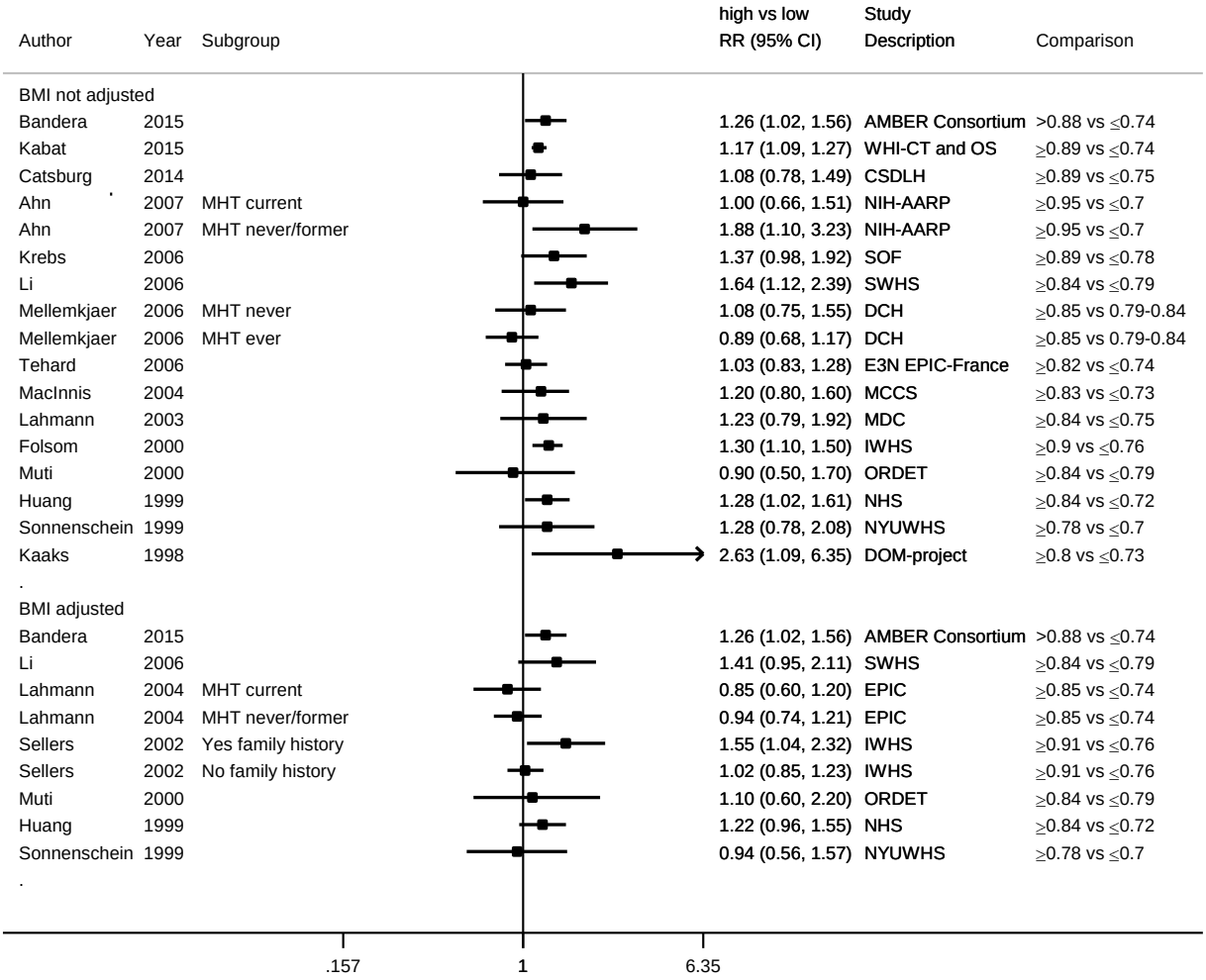


Figure 621 Relative risk of postmenopausal breast cancer for 0.1 unit waist to hip ratio

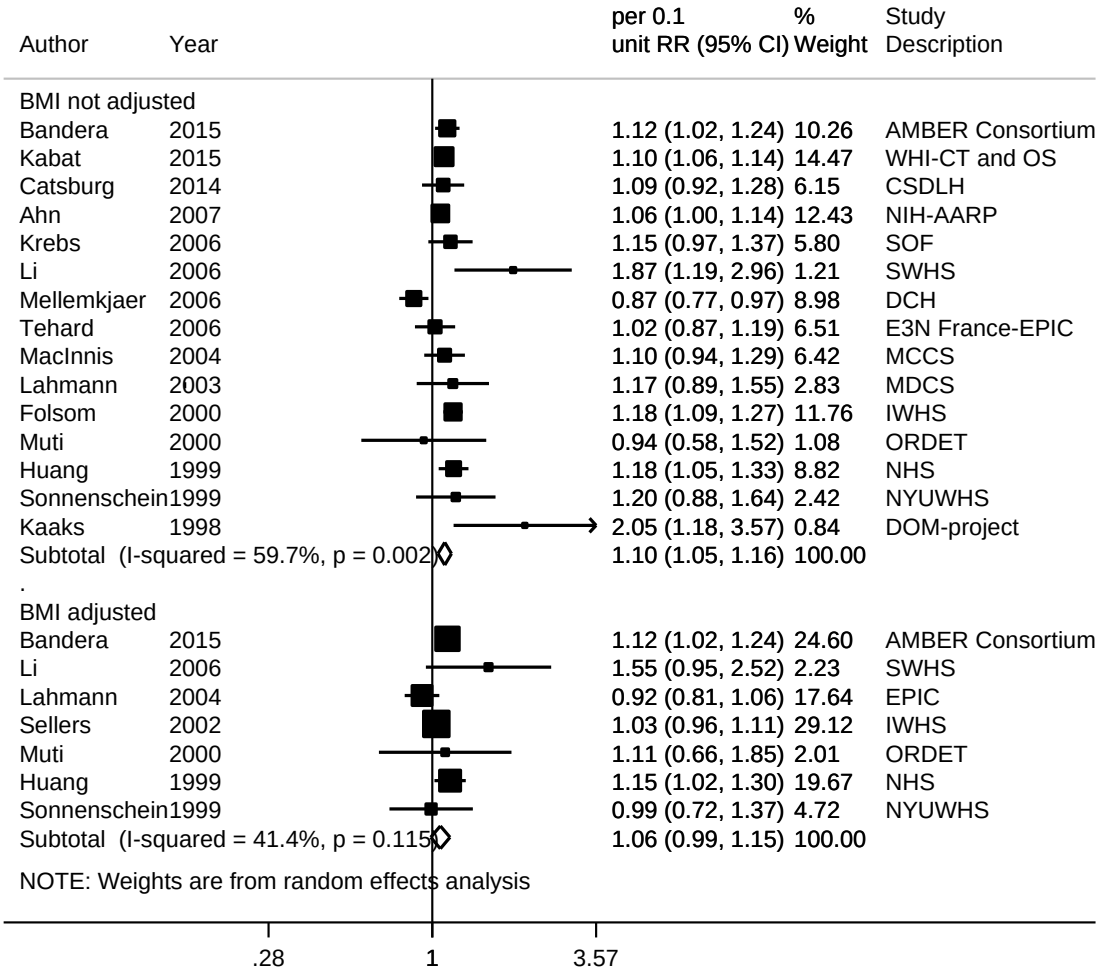
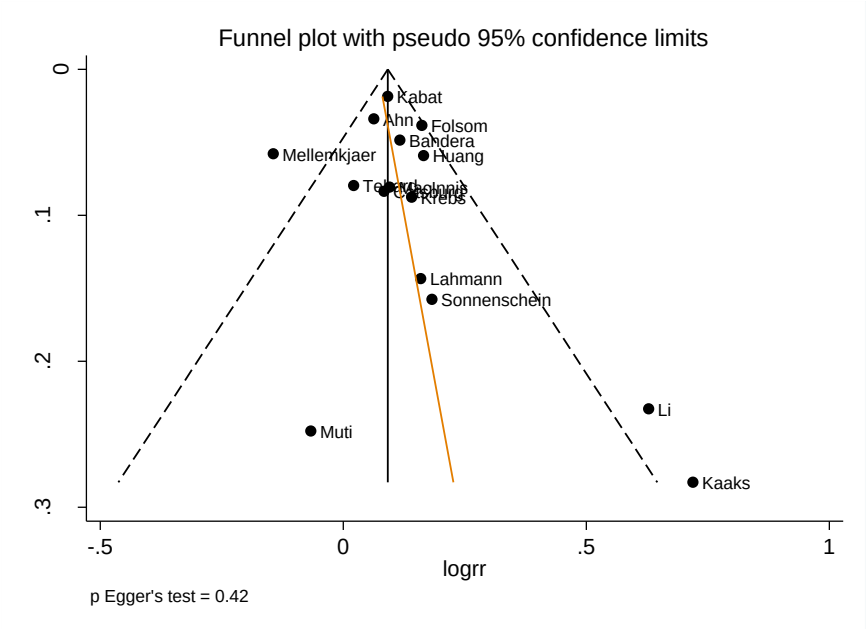


Figure 622 Funnel plot of studies included in the dose response meta-analysis of waist to hip ratio and postmenopausal breast cancer

BMI not adjusted studies



BMI adjusted studies

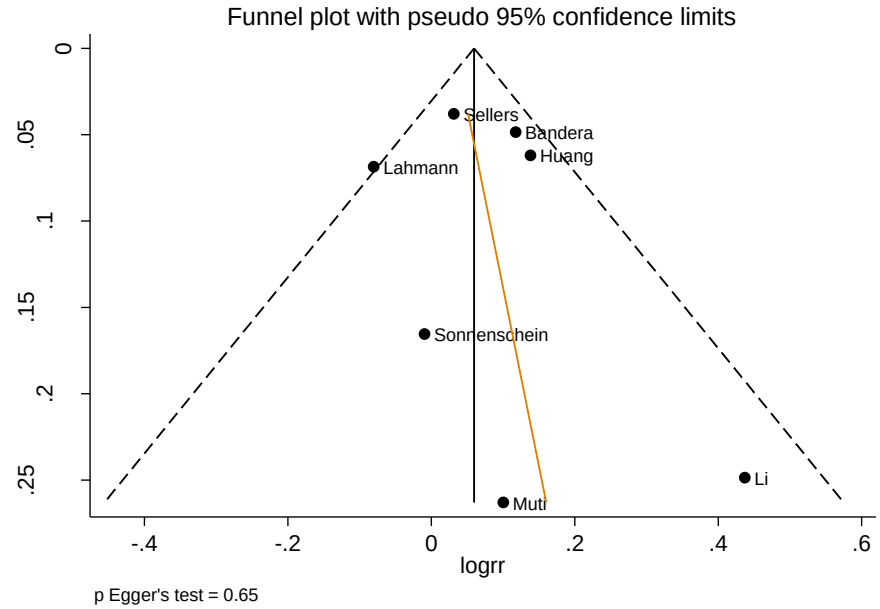
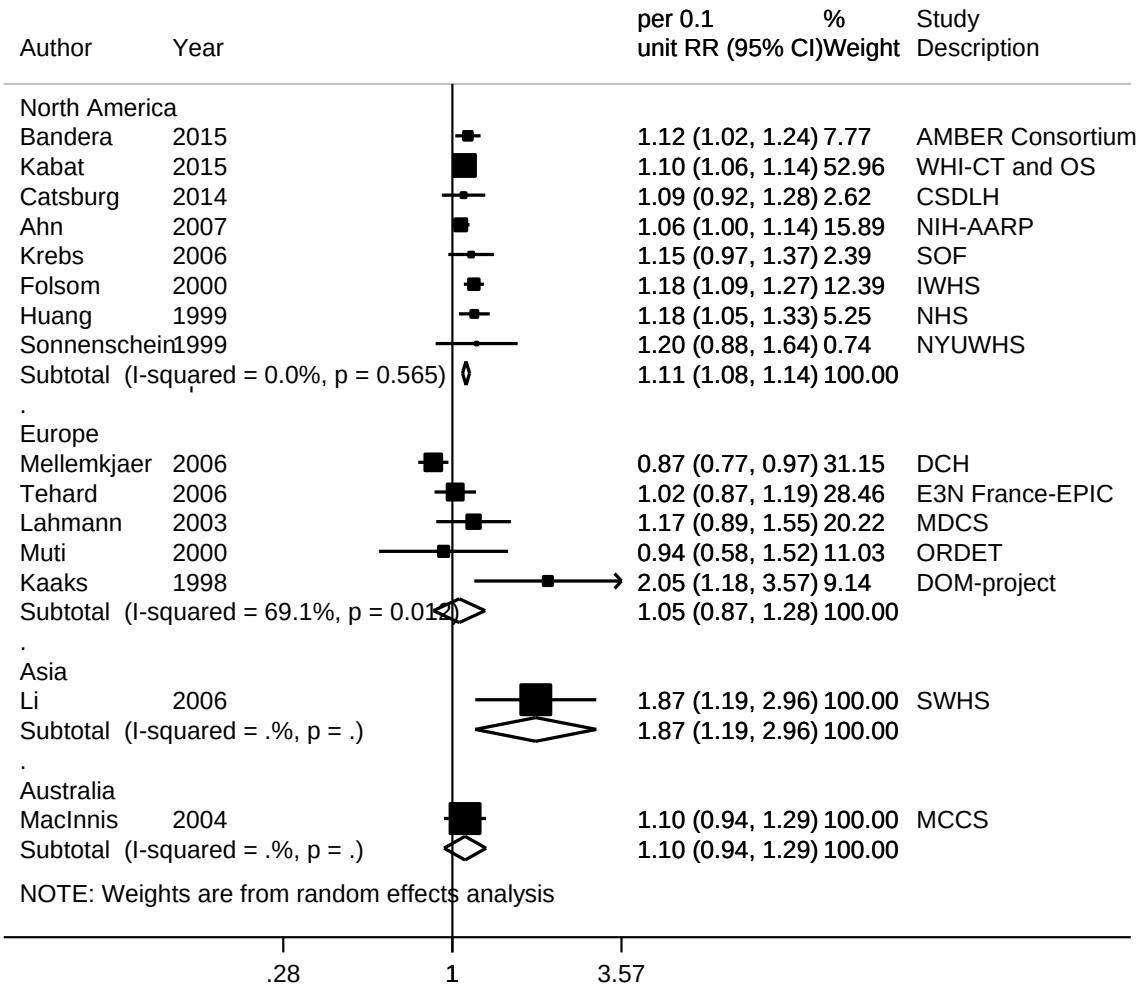


Figure 623 Relative risk of postmenopausal breast cancer for 0.1 unit waist to hip ratio, by geographic location

BMI not adjusted studies



BMI adjusted studies

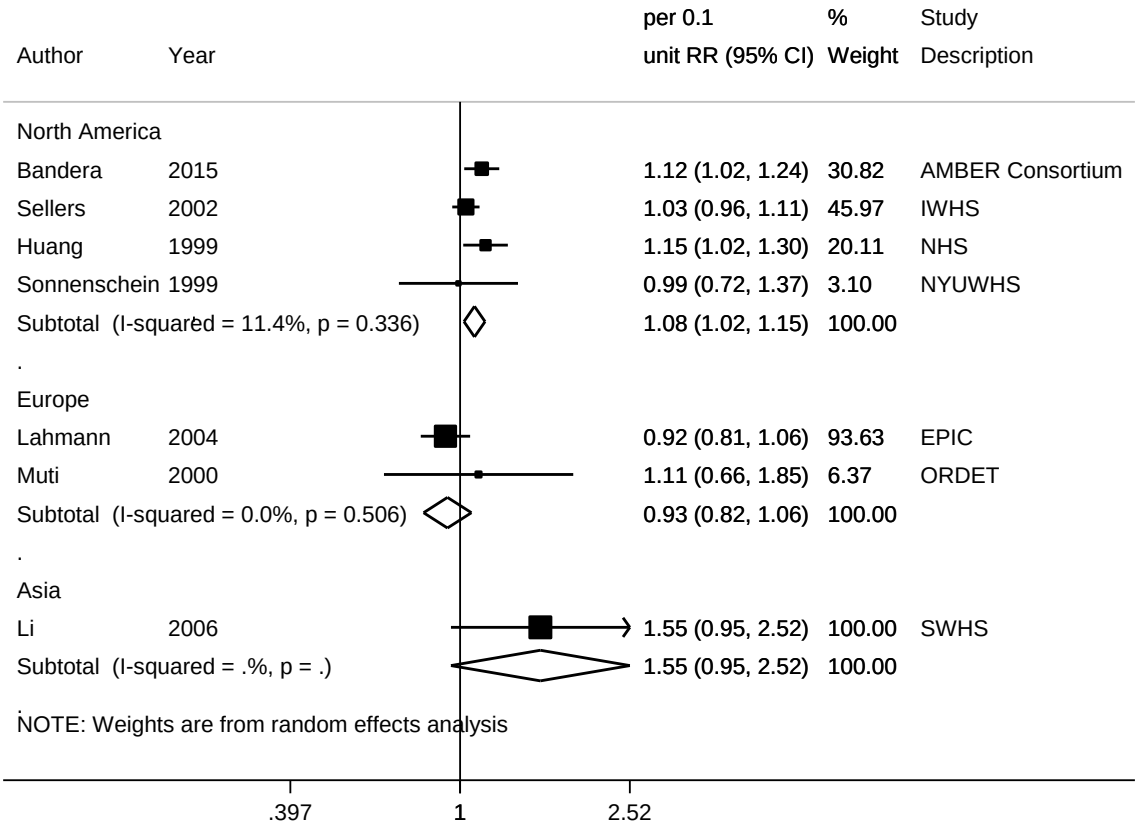
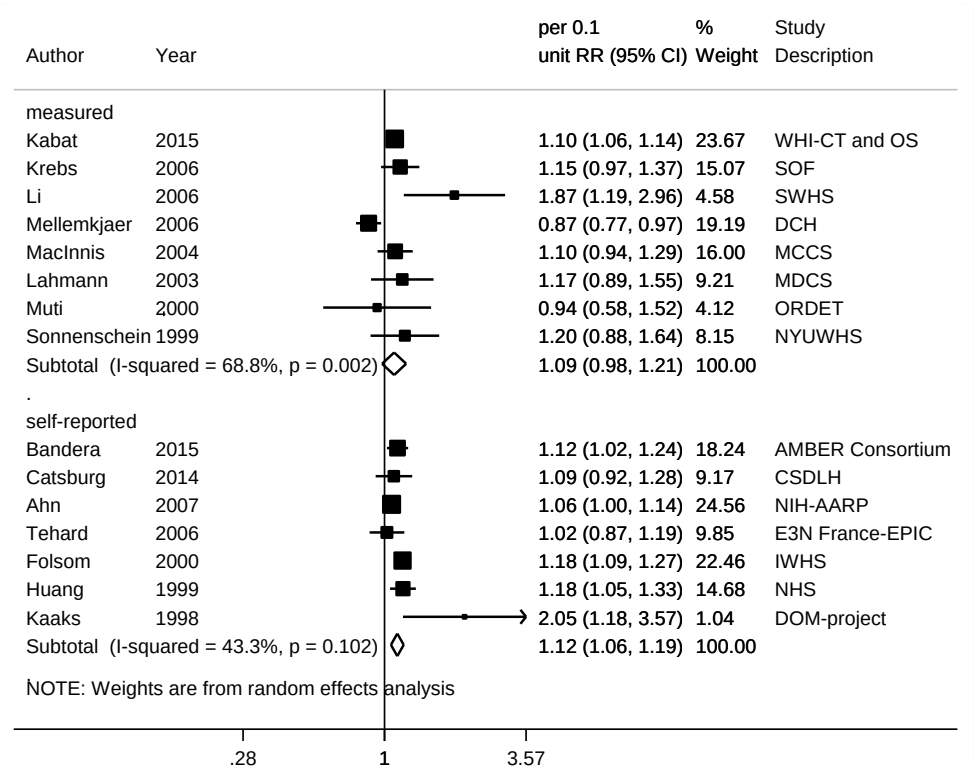


Figure 624 Relative risk of postmenopausal breast cancer for 0.1 unit waist to hip ratio, by exposure assessment method

BMI not adjusted studies



BMI adjusted studies

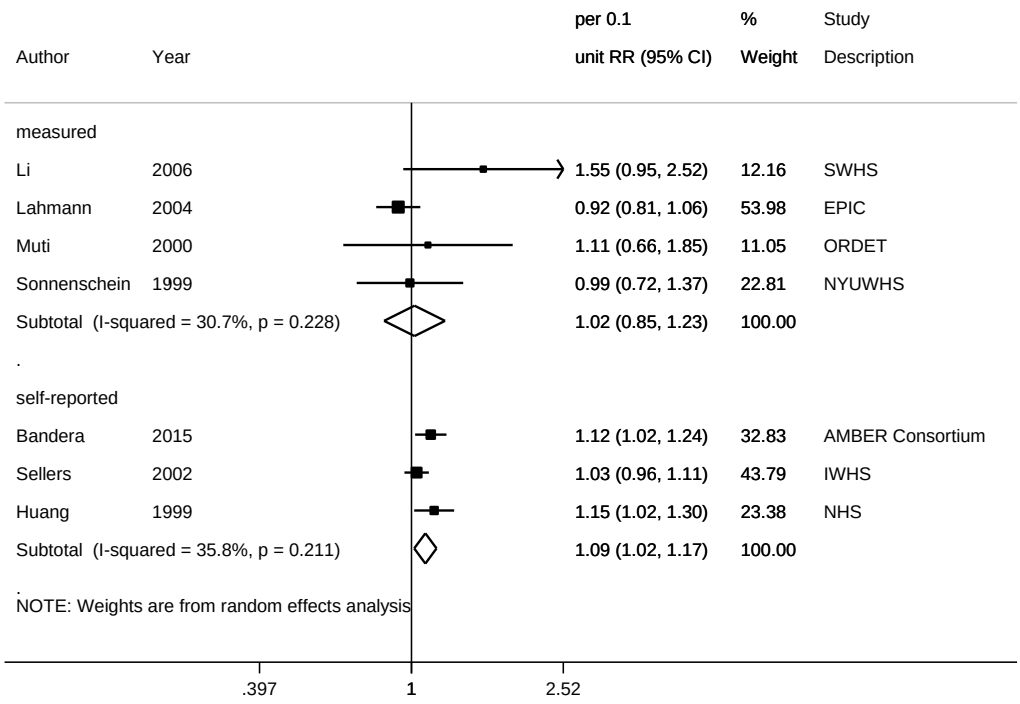
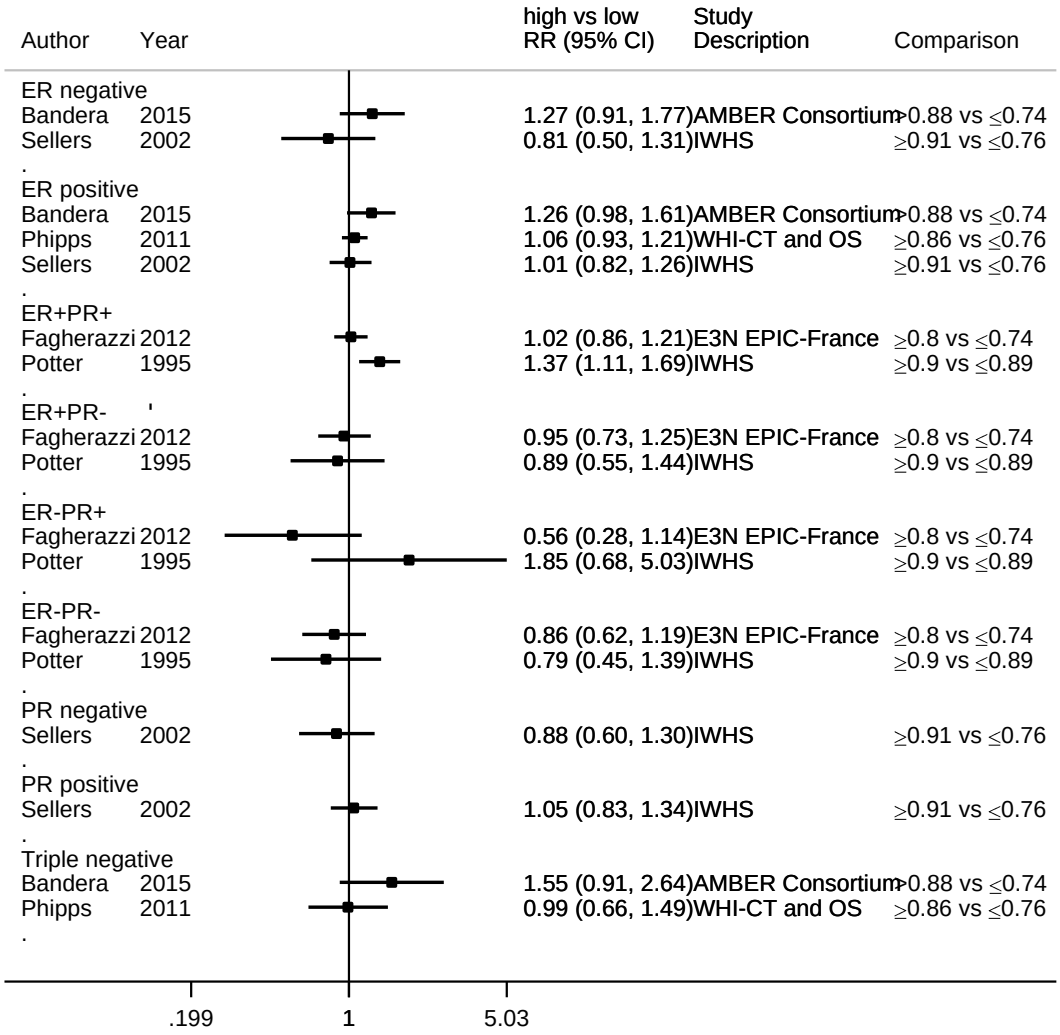


Figure 625 RR (95% CI) of postmenopausal hormone receptor-defined breast cancer for the highest compared with the lowest waist to hip ratio



Note: Dose-response meta-analysis of hormone receptor-defined breast cancer in postmenopausal women was not conducted due to limited number of studies. The highest versus lowest forest plot was produced to facilitate results interpretation

Figure 626 Non-linear dose-response meta-analysis of waist to hip ratio and postmenopausal breast cancer

BMI not adjusted studies

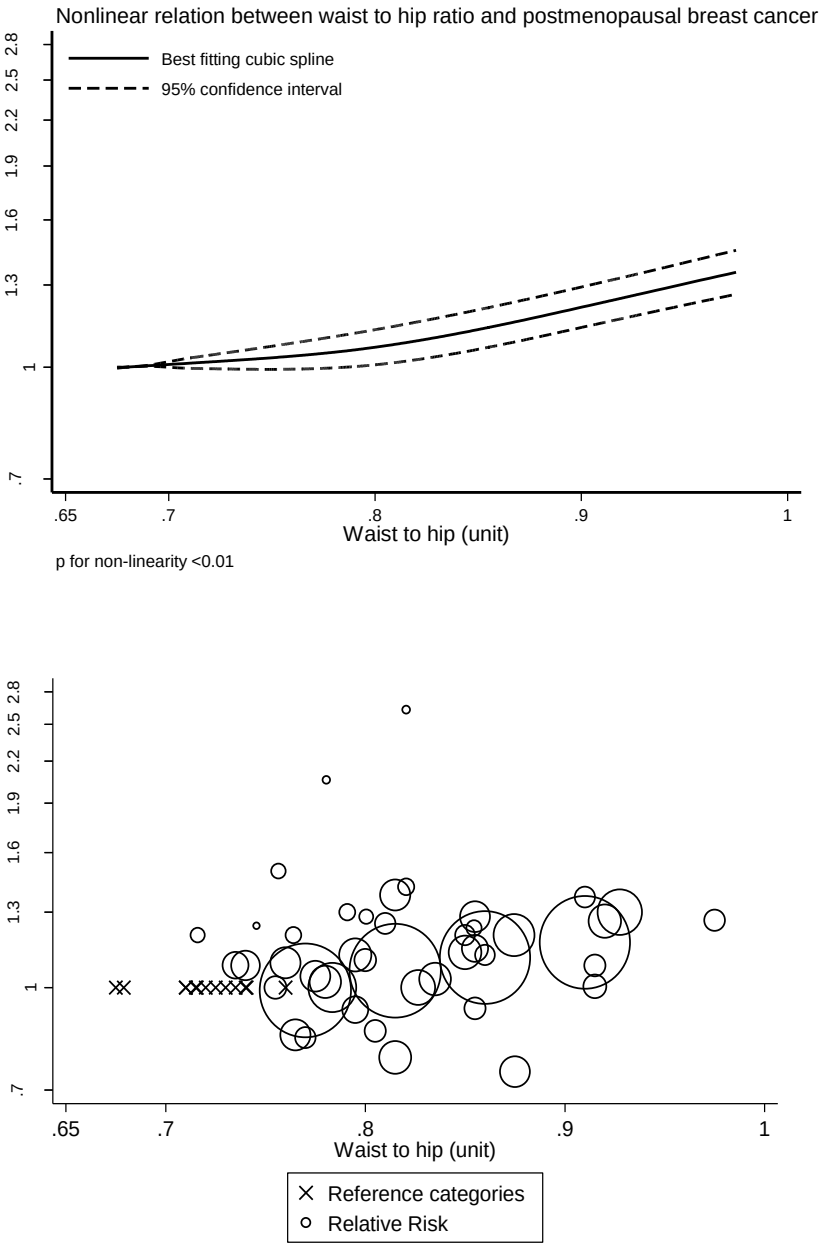


Table 594 Relative risk of postmenopausal breast cancer and waist to hip ratio estimated using non-linear models

Waist to hip ratio (unit)	RR (95%CI)
0.68	1.00
0.75	1.03 (0.99-1.06)
0.80	1.07 (1.01-1.13)
0.85	1.13 (1.06-1.20)
0.91	1.23 (1.15-1.31)

8.3.1 Height (and proxy measure)

Cohort studies

Overall summary

Eighty-eight publications from 108 studies that examined adult height were identified. This included two pooled studies on breast cancer risk (Wiren, 2014, Me-Can, six cohorts; van den Brandt, 2000, The Pooling Project, seven cohorts) and two pooled studies on breast cancer mortality (Wiren, 2014, Me-Can, six cohorts; Batty, 2010, APCSC, 36 cohorts). Only one published meta-analysis was identified during the CUP (Amadou, 2013, height and premenopausal breast cancer).

Dose-response meta-analyses were conducted to examine the associations of height with risk of breast cancer and of premenopausal and postmenopausal breast cancer.

Table 595 Summary of results of the dose-response meta-analysis in the CUP SLR

	Breast cancer (any)	**Premenopausal breast cancer**	**Postmenopausal breast cancer**
Height Increment unit used	Per 5 cm	Per 5 cm	Per 5 cm
Studies (n)	34[1]	26[1]	20[1]
Cases	75 196	6 479	24 975
RR (95%CI)	1.09 (1.07-1.11)	1.06 (1.02-1.11)	1.09 (1.07-1.11)
Heterogeneity (I^2, p-value)	59%, <0.001	46%, 0.02	33%, 0.08
P value Egger test	0.58	0.11	0.02

[1]Included two pooled studies (Wiren, 2014, Me-Can, six cohorts; van den Brandt, 2000, The Pooling Project, seven cohorts)

Breast cancer (any)

Summary

Main results:

Seventy-two out of 84 studies (42 publications) identified could be included in the dose-response meta-analyses. There were 34 studies (19 publications) on breast cancer risk and 44 studies (4 publications) on breast cancer mortality.

Height was significantly positively associated with breast cancer risk (summary RR per 5 cm=1.09 (95% CI=1.07-1.11). There was evidence of high heterogeneity between studies (I^2=59%, P <0.001).

For breast cancer mortality, a borderline significant positive association was observed (summary RR=1.07, 95% CI=1.00-1.14, I^2=33%, p=0.21).

There was no significant evidence of publication bias or small study bias (P for Egger's test=0.58).

Twelve studies and 20 publications were excluded from the meta-analyses. Study populations in four excluded studies (three publications) (Fagherazzi, 2012b; Harlid, 2012, MDC, MSP; Vatten, 1992) overlapped with studies that were already included in the analysis.

Seven studies (six publications) did not have sufficient data to be included in the analysis. Lundqvist, 2007 and Jonsson, 2003 reported significant positive associations (RR for highest vs lowest =1.6, 95% CI=1.4-1.8 in Lundqvist, 2007, cohort analysis; RR per 1 SD=1.26, 95% CI=1.09-1.45 in Lundqvist, 2007, case-control analysis; RR for highest vs lowest=1.5, 95% CI=1.1-2.0 in Jonsson, 2003). Hoyer, 1992 reported a non-significant inverse association (RR=0.8, 95% CI=0.3-2.3). Three studies (Kilkkinen, 2004; Drake, 2001; Overvad, 1991) reported on average similar height between the cases and the non-cases.

One study (Schairer, 2013) on specific breast cancer subtypes reported non-significant positive associations with inflammatory breast cancer, non-inflammatory breast cancer, and non-inflammatory locally advanced breast cancer.

Sensitivity analyses:

Summary RR did not change materially when studies were omitted in turn in influence analysis.

When analysed by geographic location, positive associations that were significant in European studies (summary RR per 5 cm=1.09, 95% CI=1.08-1.10) and North American studies (RR=1.08, 95% CI=1.02-1.14), and non-significant in Asian studies (RR=1.07, 95% CI=0.94-1.22) were observed. Heterogeneity was high between the Asian studies (I^2=77%, P=0.01), intermediate between the North American studies (I^2=44%, P=0.11), and between the European studies (I^2=21%, P=0.23).

Significant positive associations were observed in the subgroup analyses by anthropometric measurement method and confounding factors adjustment.

Study quality:

One Japanese study included Atomic bomb survivors (Key, 1999) and one Taiwanese study involved cancer screening (Wu, 2006). No significant positive associations were observed in these two studies (Wu, 2006; Key, 1999). Cerhan, 2004 included family members of the breast cancer cases (sisters and daughters, granddaughters and nieces, and married-ins) in the study and observed no significant positive association overall. The significant positive association observed in the meta-analysis remained when studies were omitted in turn in influence analysis.

About half of the studies included in the analyses measured the participants for their height and another half used measurements reported by the participants. One study (Tryggvadottir, 2002) used data from records. One study (Ritte, 2013b) used self-reported or measured data. Case ascertainment was through cancer registries or confirmed through medical records.

More than half of the studies did not simultaneously adjust for age, alcohol intake, and reproductive factors. On average studies adjusted or not adjusted for these factors observed similar results.

Table 596 Height and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	84 (42 publications)[1]
Studies included in forest plot of highest compared with lowest exposure	27 (17 publications) breast cancer risk
Studies included in linear dose-response meta-analysis[2]	34 (19 publications) breast cancer risk 44 (4 publications) breast cancer mortality
Studies included in non-linear dose-response meta-analysis	

Note: Include cohort, case-cohort, and nested case-control designs

[1]Included three pooled studies (Wiren, 2014, Me-Can, six studies; Batty, 2010, APCSC, 36 studies; van den Brandt, 2000, The Pooling Project, seven studies)

[2]In total, 72 studies (22 publications) were included.

Table 597 Height and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP SLR

	2005 SLR[1]	**CUP**
Increment unit used	**Per 5 cm**	**Per 5 cm**
Studies (n)	19	34
Cases	5 294	75 196
RR (95%CI)	1.09 (1.07-1.12)	1.09 (1.07-1.11)

Heterogeneity (I^2, p-value)	7%		59%, <0.001
P value Egger test	0.08		0.58
Stratified analysis in the CUP			
Geographic locations	**Asia**	**Europe**	**North America**
Studies (n)	3	18	6
Cases	2 633	57 984	10 194
RR (95%CI)	1.07 (0.94-1.22)	1.09 (1.08-1.10)	1.08 (1.02-1.14)
Heterogeneity (I^2, p-value)	77%, 0.01	21%, 0.23	44%, 0.11
Anthropometric measurement methods[2]	**Measured**		**Self-reported**
Studies (n)	18		14
Cases	10 705		54 091
RR (95%CI)	1.11 (1.07-1.15)		1.07 (1.04-1.10)
Heterogeneity (I^2, p-value)	38%, 0.08		63%, <0.01
Adjustment for age, alcohol intake, reproductive factors	**Adjusted**		**Not adjusted**
Studies (n)	14		20
Cases	64 672		10 524
RR (95%CI)	1.08 (1.06-1.10)		1.10 (1.08-1.13)
Heterogeneity (I^2, p-value)	77%, <0.001		11%, 0.33
Other analysis in the CUP			
Breast cancer mortality			
Studies (n)	44		
Cases	1 579		
RR (95%CI)	1.07 (1.00-1.14)		
Heterogeneity (I^2, p-value)	33%, 0.21		

[1]Meta-analysis was not conducted in the 2008 SLR.

[2]Also one study (Tryggvadottir, 2002) used height from records (RR per 5 cm=1.09, 95% CI=1.03-1.16, 1 120 cases) and one study (Ritte, 2013b) used self-reported or measured height (RR=1.09, 95% CI=1.07-1.10, 9 280 cases).

Table 598 Height and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Kabat, 2014 BRE80524 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W, Retired	9 169/ 192 514 10.5 years	Cancer registry and national death Index	Self-reported	Incidence, breast cancer	per 10 cm	1.09 (1.06-1.13)	Age, age at first child birth, age at menarche, alcohol, BMI, educational level, family history of cancer, HRT use, menopausal status, parity, physical activity, race, screening, smoking	
Wiren, 2014 Austria, Sweden, Norway	Me-can (Metabolic syndrome and cancer project), Pooled study of 6 cohorts (NCS; CONOR; 40-y; VIP; MPP; VMP&PP), Mean age: 43.1 years W	6 161/ 297 156 12.7 years	Record linkage to cancer registries	Measured	Incidence, breast cancer	per 5 cm	1.11 (1.08-1.13)	Age at health examination, date of birth, stratified for subcohort within the model	
		1 014/			Mortality, breast	per 5 cm	1.10 (1.04-1.16)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					cancer				
Ritte, 2013b BRE80431 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 25-70 years, W	9 280/ 306 600 3 297 579 person-years	Cancer registry, record linkage, health Insurance rec, pathology and active follow up	Self-reported or measured	Incidence, breast cancer	≥165 vs ≤159 cm	1.24 (1.17-1.31) Ptrend:<0.001	Age, age at first child birth, age at menopause, alcohol, breastfeeding, educational level, HRT use, leg length, menopausal status, oral contraceptive history, parity, physical activity, sitting height, smoking, study center, time since menopause, waist circumference	
						per 1 SD units	1.12 (1.10-1.14)		
		3 519/			Incidence, breast cancer ER+/PR+	≥165 vs ≤159 cm	1.26 (1.15-1.38) Ptrend:<0.001		
						per 1 SD units	1.12 (1.07-1.17)		
		986/			Incidence, breast cancer ER-/PR-	per 1 SD units	1.07 (1.00-1.15)		
						≥165 vs ≤159	1.08 (0.91-1.28)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
						cm	Ptrend:0.37		
		2 054/			Incidence, breast cancer PR-	≥165 vs ≤159 cm	1.19 (1.06-1.34) Ptrend:0.003		
						per 1 SD units	1.11 (1.06-1.17)		
		372/			Incidence, breast cancer PR+	≥165 vs ≤159 cm	1.27 (1.16-1.38) Ptrend:<0.001		
		3 728/				per 1 SD units	1.12 (1.08-1.16)		
		1 351/			Incidence, breast cancer ER-	≥165 vs ≤159 cm	1.10 (0.95-1.27) Ptrend:0.18		
		1 352/				per 1 SD units	1.07 (1.01-1.14)		
		3 514/			Incidence, breast cancer ER+	≥165 vs ≤159 cm	1.28 (1.20-1.38) Ptrend:<0.001		
		5 613/				per 1 SD units	1.13 (1.10-1.17)		
		3 514/			Incidence, breast cancer unknown ER/PR status	≥165 vs ≤159 cm	1.23 (1.12-1.34) Ptrend:<0.001		
						per 1 SD units	1.11 (1.07-1.15)		
		200/			Incidence, breast cancer ER-/PR+	≥165 vs ≤159 cm	1.37 (0.94-1.99) Ptrend:0.10		
						per 1 SD units	1.11 (0.95-1.30)		
		1 061/			Incidence, breast cancer ER+/PR-	≥165 vs ≤159 cm	1.32 (1.12-1.56) Ptrend:0.001		
						per 1 SD units	1.15 (1.07-1.23)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Green, 2011 BRE80381 UK	MWS, Prospective Cohort, Age: 56 years, W	39 299/ 1 297 124 9.4 years	Cancer registry	Measured	Incidence, breast cancer	per 10 cm	1.17 (1.14-1.20)	Age, age at first child birth, age at menarche, alcohol, BMI, parity, region, smoking, socio-economic status, strenuous exercise	
		18 533/			Never smoker	per 10 cm	1.18 (1.14-1.22)		
		7 647/			Current smoker	per 10 cm	1.13 (1.07-1.19)		
Batty, 2010 Asia Pacific	Asia Pacific Cohort Studies Collaboration (APCSC), Pooled study of 36 cohorts*, W, Mean age: 48 years	318/ 178 243 1 208 485 person-years		Measured	Mortality, breast cancer	per 6 cm	1.11 (0.99-1.24)	Age, study, year of birth, stratified by region	
*ALSA; ANHF; Busselton; Fletcher Challenge; Melbourne; Newcastle; Perth; Aito Town; Akabane; Anzhen; Beijing Aging; CISCH; Civil Service Workers; CVDFACTS; East Beijing; EGAT; Fangshan; Guangzhou Occupational; Hisayama; Hong Kong; Huashan; Kinmen; KMIC; Konan; Miyama; Ohasama; Saitama; Seven Cities Cohorts; Shibata; Shigaraki Town; Singapore Heart; Singapore NHS; Six Cohorts; Tanno/Soubetsu; Tianjin; Yunnan									
Sung, 2009 BRE80271 Korea	KNHIC, Prospective Cohort, Age: 40-64 years,	/ 339 575 8.72 years	Cancer registry and death records	Measured In light clothing by registered nurses	Incidence, breast cancer, complete data available	per 5 cm	1.18 (1.11-1.25)	Age, age at first child birth, age at menarche, alcohol consumption,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	W							area of residence, BMI, breastfeeding, HRT use, Income, menopausal status, occupation, OC use, physical activity, smoking status	
						≥158.1 vs ≤151 cm	1.60 (1.34-1.90)		
Fujino, 2007 BRE80442 Japan	JACC, Prospective Cohort, W	100/		Obtained from survey, no further details were provided.	Mortality, breast cancer	≥154 vs ≤148.9 cm	1.24 (0.72-2.12)	Age, study area	
Wu, 2006 BRE24628 China	Taiwan 1990, Prospective Cohort, Age: 47 years, W, Screening Program	104/ 11 899 10.3 years	Partially histological - over 80%	Measured	Incidence, breast cancer	≥160 vs ≤150 cm	1.00 (0.60-1.80) Ptrend:0.7963	Age , waist-hip ratio	
Cerhan, 2004 BRE01495 USA	Minesota, 1944, Prospective Cohort, W	79/ 4 633 5 years	Partially histological - over 80%	Self reported by telephone Interview and mailed	Incidence, breast cancer, granddaughters and nieces	≥1.66 vs ≤1.59 m	1.27 (0.74-2.18) Ptrend:0.37	Age , birth cohort (reproductive	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
				questionnaire				factors and alcohol intake did not change RR materially and were not included in the final model)	
		33/			Sisters and daughters	≥1.66 vs ≤1.59 m	1.41 (0.59-3.34) Ptrend:0.43		
		61/			Married-ins	≥1.66 vs ≤1.59 m	0.63 (0.31-1.28) Ptrend:0.23		
De Stavola, 2004 BRE02123 UK	MRC-NSHD, Prospective Cohort, W	50/ 2 187 29 years	Partially histological - over 80%	Self reported or measures performed by trained personnel	Incidence, breast cancer	per 1 SD units	1.28 (0.96-1.69)	Age as time axis in model	
Tryggvadottir, 2002 BRE12507 Iceland	Iceland, 1979, Nested Case Control, Age: 20-81 years, W	3 572 17 years	Partially histological - over 80%	From records	Incidence, breast cancer	per 5 cm	1.09 (1.03-1.16)	Age at first child, age at menarche, body weight, breastfeeding, OC use, parity/pregnancies, parous/nulliparous	
Nilsen, 2001 BRE16210	NNTHS, Prospective	63/ 25 204	Partially histological -	Measured	Incidence, breast cancer,	≥167 vs ≤161.9 cm	0.50 (0.20-1.10)	Age	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Norway	Cohort, Age: 20-61 years, W	11 years	over 80%		1925-1929 birth cohort				
		37/			1930-1934 birth cohort	≥167 vs ≤161.9 cm	0.90 (0.40-2.30)		
		28/			1935-1940 birth cohort	≥167 vs ≤161.9 cm	1.30 (0.50-3.10)		
		43/			1940-1945 birth cohort	≥167 vs ≤161.9 cm	2.50 (1.20-5.50)		
		43/			≥1946 birth cohort	≥167 vs ≤161.9 cm	1.00 (0.50-2.30)		
Palmer, 2001 BRE20603 USA	BWHS, Nested Case Control, Age: 21-69 years, W	210 cases 1041 controls 2 years	Medical records + self-reported	Self-administered questionnaire	Incidence, Invasive & In situ breast cancer	≥70 vs ≤61.9 inch	3.00 (1.30-6.50)	Age , age at menarche, BMI, educational level, mammography	
Davey Smith G, 2000 BRE80516 Scotland	The Renfrew/Paisley General Population Study, Prospective Cohort, Age: 45-64 years, W	147/ 8 354 20 years		Measured	Mortality, breast cancer	per 10 cm	1.13 (0.86-1.48)	Age	
van den Brandt,	The Pooling	4 385/	Follow-up	Self-reported	Incidence, breast	≥1.75 vs <1.60	1.22 (0.90-1.65)	Age at	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
2000 North America and Europe	Project, Pooled study of 7 cohorts, W (AHS; CNBSS; IWHS; NLCS; NYSC; NHS(a); NHS(b); SMC)	337 819	questionnaires and inspection of medical records and/or tumour registry linkage		cancer	m		menarche, parity, age at birth of first child, postmenopausal hormone use, oral contraceptive use, history of benign breast disease, maternal history of breast cancer, history of breast cancer in a sister, smoking status, education, fat intake, fibre intake, energy intake, alcohol intake, menopausal status at diagnosis	
						per 5 cm	1.07 (1.02- 1.11)		
					Never smokers	per 5 cm	1.05 (1.00-1.11)		
					Ever smokers	per 5 cm	1.07 (0.99- 1.16)		
Key, 1999 BRE04758 Japan	LSS, 1969, Prospective Cohort, W	427/ 34 759 24 years	Partially histological - over 80%	Mail survey questionnaire	Incidence, breast cancer	≥156 vs ≤149 cm	1.05 (0.80-1.39) Ptrend:0.861	Age , calendar year, other factors , other factors , place of residence	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Galanis, 1998 BRE03058 hawaii	Hawaii State Department of Health, 1975, Prospective Cohort, Age: 43 years, W	378/ 17 628 14.9 years	Partially histological - over 80%	Self reported questionnaire	Incidence, breast cancer	≥160.1 vs ≤154.9 cm	1.40 (1.10-1.90) Ptrend:0.02	Age , alcohol, educational level, ethnicity	
Hoyer, 1998 BRE15433 Denmark	CCHS, Nested Case Control, Age: 20- years, W	239/ 475 controls 17 years	Partially histological - over 80%	Physical examinations	Incidence, breast cancer	≥1.65 vs ≤1.56 m	1.65 (1.03-2.65) Ptrend:0.05	Matched by age, date of exam and vital status at diagnosis	
Tulinius, 1997 BRE12565 Iceland	Reykjavik Study, 1968, Prospective Cohort, Age: 45-59 years, W	/ 11 580 27 years	Partially histological - over 80%	Measured	Incidence, breast cancer	per 1 cm	1.03 (1.01-1.05)	Age	
Schatzkin, 1989 BRE18013 USA	FHS, Prospective Cohort, Age: 31-64 years, W	143/ 2 636 26 years	All histology	Measured	Incidence, breast cancer	≥64.8 vs ≤60.4 in	1.00 (0.50-1.70)	Age , alcohol, BMI, educational level, menopausal status, parity/pregnancies, smoking habits	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Swanson, 1988 BRE11981 USA	NHANES I, Prospective Cohort, Age: 25-74 years, W	121/ 7 149 10 years	Medical records + death certificate	Trained technicians with standardised techniques	Incidence, breast cancer	169 vs 153 cm	1.90 (1.10-3.20) Ptrend:0.03	Age , age at first child, alcohol, educational level, menopausal status	
Tornberg, 1988 BRE12418 Sweden	Swedish cohort, 1963, Prospective Cohort, Age: 17-74 years, W	/ 46 570 20 years	Partially histological - over 80%	Measured	Incidence, breast cancer	per 5 cm	1.10 (1.05-1.16)	Age , place of residence	

Table 599 Height and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Boggs, 2015 BRE80582 USA	BWHS, Prospective Cohort, Age: 30-69 years, W	896/ 55 093 10 years	Cancer registry, national death Index, self-report, pathology reports	Self-reported	Incidence, Invasive breast cancer	≥165.1 vs ≤165 cm	1.15 (1.01-1.32)	Age, age at first child birth, age at menarche, benign breast disease, BMI at age 18 years, estrogen plus progesterone use, family history, oophorectomy/hysterectomy, oral contraceptive use	Publication superseded by Palmer, 2001
Yang, 2014 BRE80521 UK	MWS, Prospective Cohort, Age: 50-64 years, W	14 542/ 453 023 9.2 years	Cancer registry	Self-reported	Incidence, breast cancer	≥170 vs ≤154 cm	1.18 (1.13-1.23)	Age, age at first child birth, age at menarche, alcohol, birthweight, BMI, breastfeeding, exercise, HRT use, maternal and paternal height, parity, region, ses, smoking, smoking habbits, year of birth	Publication superseded by Green, 2011
Schairer, 2013 BRE80568 USA	BCSC, Nested Case Control,	7 600/ 93 654	Seer registry/hospital records/patholog	Self-reported height and weight In the	Incidence, non-inflammatory breast cancer	≥67 vs ≤62 inch	1.11 (0.92-1.33)	Age at first child birth, BMI, breast biopsies,	Results by breast cancer subtype, not

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	W		y	questionnaire completed closest In time before or on the date of diagnosis				educational level, family history of breast cancer In first degree relatives, mammographic density, parous/nulliparous, race/ethnicity	analysed
		1 151/			Incidence, non-inflammatory locally advanced breast cancer	≥67 vs ≤62 inch	1.17 (0.75-1.83)		
		617/			Incidence, Inflammatory breast cancer	≥67 vs ≤62 inch	1.67 (0.66-4.25)		
		243/			Incidence, Inflammatory breast cancer ER+	≥67 vs ≤62 inch	1.81 (0.72-4.54)		
		600/			Incidence, LABC ER+	≥67 vs ≤62 inch	1.09 (0.68-1.73)		
		4 784/			Incidence, non-inflammatory breast cancer ER+	≥67 vs ≤62 inch	1.15 (0.96-1.38)		
		218/			Incidence,	≥67 vs ≤62 inch	1.52 (0.50-4.65)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					Inflammatory breast cancer ER-				
		220/			Incidence, LABC ER-	≥67 vs ≤62 inch	1.49 (0.83-2.68)		
		1 124/			Incidence, non-inflammatory breast cancer ER-	≥67 vs ≤62 inch	0.94 (0.70-1.27)		
Fagherazzi, 2012b BRE80412 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years	2 065/ 50 704 6 years	Pathology	Self-reported	Incidence, breast cancer	≥165 vs ≤158 cm	1.15 (1.01-1.31) Ptrend:0.008	Age at first child birth, age at menarche, age at menarche, age at menopause, benign breast disease, birth length, birthweight, breastfeeding, educational level, family history of breast cancer, HRT use, mammography, menopausal status, oral contraceptive use, parity, physical activity,	Study superseded by Ritte, 2013b

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								progesterone	
		1 600/			Incidence, breast cancer ER+	≥165 vs ≤158 cm	1.28 (1.11-1.48) Ptrend:<0.001		
		374/			Incidence, breast cancer ER-	≥165 vs ≤158 cm	0.75 (0.56-1.00) Ptrend:0.098		
Harlid, 2012 BRE80422 Sweden	NSHDC (VIP and MSP), Prospective Cohort, Age: 27-95 years, W	1 279/ 3 994	Cancer registry	Weight and height reported In a questionnaire	Incidence, breast cancer	≥166 vs ≤162	1.21 (1.01-1.44)	Age	Excluded, study (VIP) overlapped with Wiren, 2014 (One publication, three studies)
Harlid, 2012 BRE80421 Sweden	MDCS, Prospective Cohort, Age: 45-84 years, W	666/ 17 035 16 years	Cancer registry	Measured height and weight	Incidence, breast cancer	≥166 vs ≤162 cm	0.93 (0.73-1.18)	Age	Study superseded by Ritte, 2013b (One publication, three studies)
Lundqvist, 2007 BRE80002 Sweden, Finland	Sweden,Finland Co-twin study,1975, Prospective Cohort, Age: 44 years, W	1 644/ 36 490 25.2 years	Cancer registry	Measured	Incidence, breast cancer	per 1 standard deviation	1.17 (1.12-1.24)	Age, country of birth, diabetes, educational level, parity, physical activity, smoking habits	Excluded, insufficient data (One publication, two studies)

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
						q 4 vs q 1	1.60 (1.40-1.80)	Age , parity/pregnancies , physical activity	
Lundqvist, 2007 BRE80003 Sweden, Finland	Sweden,Finland Co-twin study,1975, Nested Case Control, Age: 44 years, W	1 181/ 1181 controls		Measured	Incidence, breast cancer	per 1 standard deviation	1.26 (1.09-1.45)	Diabetes, educational level, parity/pregnancies , physical activity , smoking habits	Excluded, insufficient data (One publication, two studies)
		402/ 402 controls			Monozygotic twins	q 4 vs q 1	1.90 (0.70-5.10)		
		764/ 764 controls			Dizygotic twins	q 4 vs q 1	1.90 (1.30-2.80)		
		1 181/ 1181 controls				q 4 vs q 1	1.80 (1.30-2.70)		
Colditz, 2004 BRE01783 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	1 281/ 66 145 19 years	All histology	Self-reported	Incidence, breast cancer ER+/PR+, HRT - no	per 35 year*in	0.99 (0.89-1.12)	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, duration of HRT use, family history, menopausal status, other menstrual	Publication superseded by van den Brandt, 2000

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								characteristics	
					HRT - yes	per 35 year*in	1.04 (1.01-1.07)		
		318/			Incidence, breast cancer ER+/PR-, HRT - yes	per 35 year*in	1.00 (0.95-1.06)		
					HRT - no	per 35 year*in	1.02 (0.83-1.25)		
		417/			Incidence, breast cancer ER-/PR-, HRT - yes	per 35 year*in	1.02 (0.98-1.07)		
					HRT - no	per 35 year*in	1.03 (0.83-1.27)		
		80/			Incidence, breast cancer ER-/PR+, HRT - yes	per 35 year*in	1.11 (1.01-1.21)		
					HRT - no	per 35 year*in	0.64 (0.37-1.11)		
Kilkkinen, 2004 BRE17698 Finland	Helsinki and Oulu, 1982, Nested Case Control, Age: 25-74 years, W	15 497 15 years	Partially histological - over 80%	Measured by study nurses	Incidence, breast cancer	(mean exposure)		Age , place of residence	Excluded, mean exposure comparison only
Jonsson, 2003 BRE04482 Sweden	Swedish twin cohort, 1969, Prospective Cohort,	421/ 11 598 29 years	Partially histological - over 80%	Self-reported	Incidence, breast cancer	≥168.5 vs 159-162 cm	1.50 (1.10-2.00)	Age	Excluded, insufficient data

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Age: 44-83 years, W, Twins								
Drake, 2001 BRE02418 USA	ACLS, 1970, Prospective Cohort, Age: 21-86 years, W, Fitness centre members	4 520 25 years	Not specified		Incidence, breast cancer	(mean exposure)			Excluded, mean exposure comparison only
Manjer, 2001a BRE80623 Sweden	MPP, Prospective Cohort, Age: 49.9 years, W, Non smokers	93/ 2 082 13.3 years	Cancer registry	Measured	Incidence, Invasive & In situ breast cancer	per 1 cm	1.02 (0.99-1.06)	Age, HRT use, OC use	Publication superseded by Wiren, 2014
Colditz, 2000 BRE19251 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	58 520 14 years	Partially histological - over 80%	Questionnaire self reported, validated	Incidence, Invasive breast cancer	≥67 vs ≤61 inch	1.12 (0.97-1.28)	Age at first child, age at menarche, age at menopause, alcohol, benign breast disease, body weight, family history, height, HRT use, other menstrual characteristics	Publication superseded by van den Brandt, 2000

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Goodman, 1997 BRE03352 Japan	LSS, 1969, Prospective Cohort, W, Atomic bomb survivors	150/ 22 200 8.31 years	Partially histological - over 80%	Questionnaire self reported	Incidence, breast cancer	≥157 vs ≤148.9 cm	1.15 (0.71-1.86) Ptrend:0.82	Age , other age Indicator, other specified factor, place of residence	Publication superseded by Key, 1999
Gaard, 1994 BRE03044 Norway	NNHSS, 1974, Prospective Cohort, Age: 20-54 years, W, Screening Program	31 209 13 years	Partially histological - over 80%	Measured by trained nurses	Incidence, breast cancer	168-197 vs ≤159 cm	2.09 (1.50-2.91) Ptrend:<0.001	Age	Publication superseded by Wiren, 2014
Hoyer, 1992 BRE04086 Denmark	Glostrup Population Studies, 1982, Prospective Cohort, Age: 30-80 years, W	5 207 26 years	Partially histological - over 80%	Measurements of height and weight	Incidence, breast cancer	≥1.71 vs ≤1.6 m	0.80 (0.30-2.30) Ptrend:>0.20		Excluded, insufficient data
Vatten, 1992 BRE12828 Norway	NNHSS, 1974, Prospective Cohort, Age: 26-49 years, W, Screening	291/ 25 967 14 years	Partially histological - over 80%	Measured	Incidence, breast cancer	≥167 vs ≤158.9 cm	1.43 (1.18-1.73) Ptrend:0.001	Age , age at first child, occupation, parity/pregnancies , place of residence	Study superseded by Wiren, 2014

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Program								
Overvad, 1991 BRE17893 Guernsey	Guernsey, 1967, Case Cohort, Age: 35- years, W	5 162 11 years	All histology		Incidence, breast cancer	(mean exposure)			Excluded, mean exposure comparison only
Vatten, 1990d BRE12827 Norway	NNHSS, 1974, Prospective Cohort, Age: 35-51 years, W, Screening Program	236/ 23 831 12.5 years	Partially histological - over 80%	Measured	Incidence, breast cancer	≥167 vs ≤158.9 cm	2.03 (1.36-3.01) Ptrend:0.001	Age	Publication superseded by Wiren, 2014
Vatten, 1990b BRE12833 Norway	NNHSS, 1974, Prospective Cohort, W	14 593 12 years	Partially histological - over 80%	Measured	Incidence, breast cancer	≥163 vs ≤162.9 cm	1.50	Age	Publication superseded by Wiren, 2014
Albanes, 1988 BRE80515 USA	NHANES I, Prospective Cohort, Age: 25-74 years, W	122/ 7 413 10 years	Death certificate and medical records	Self-reported	Incidence, breast cancer	169.3 vs 153.1 cm	2.10 (2.10-3.40)	Age	Publication superseded by Swanson, 1988

Figure 627 RR estimates of breast cancer by height

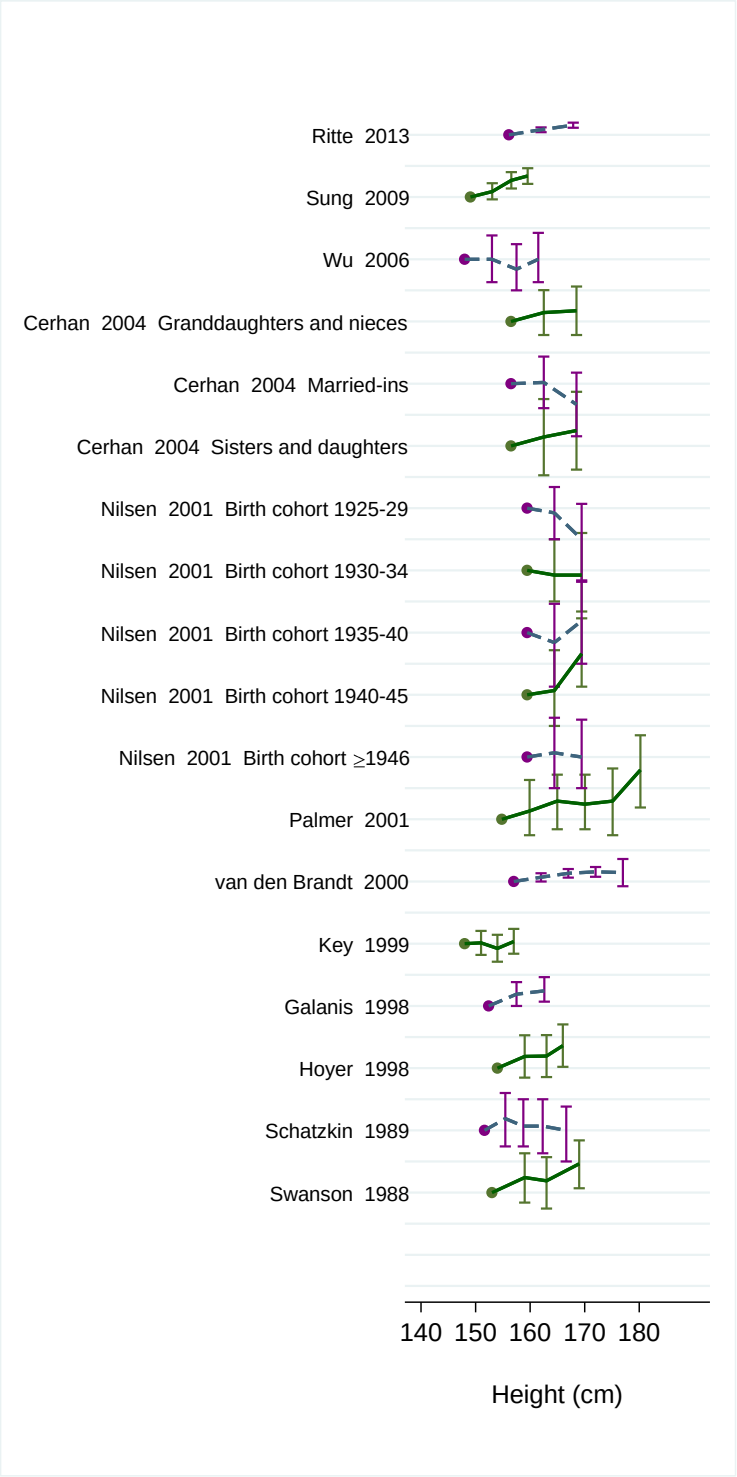


Figure 628 RR (95% CI) of breast cancer for the highest compared with the lowest level of height

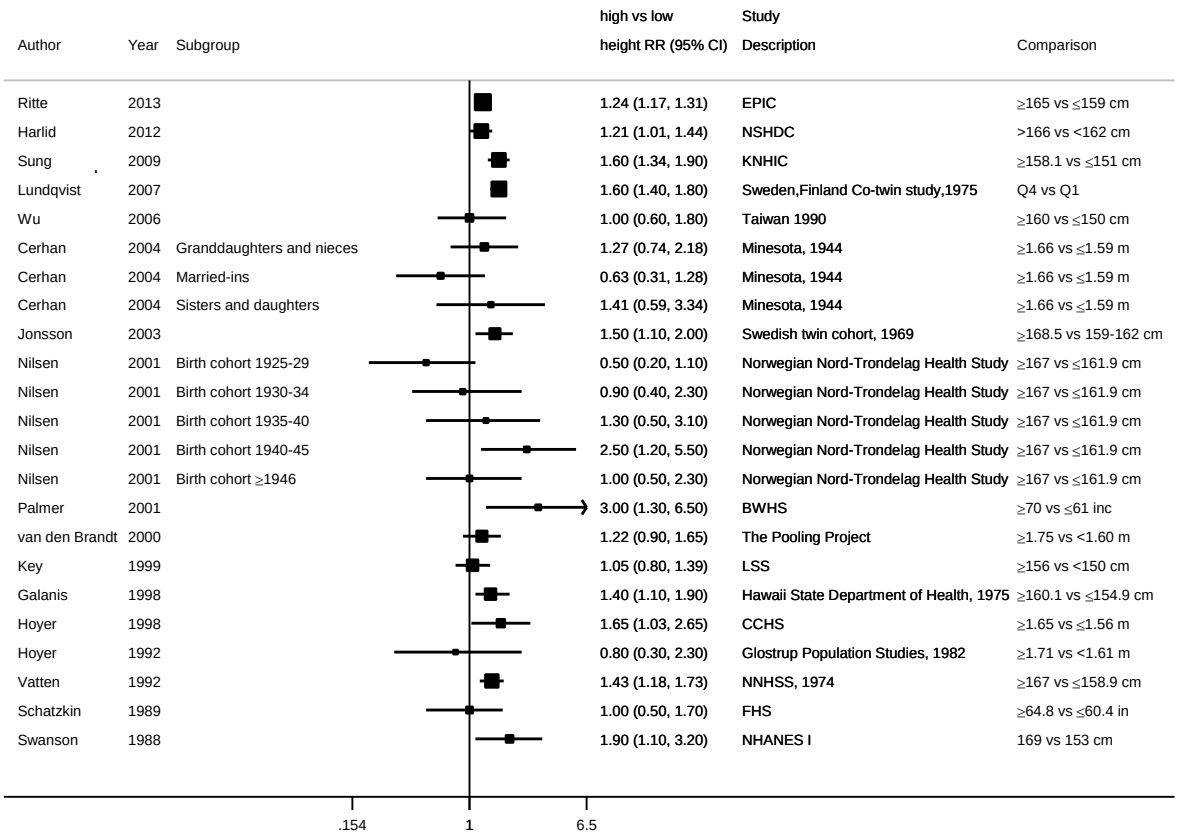


Figure 629 Relative risk of breast cancer for 5 cm increase of height

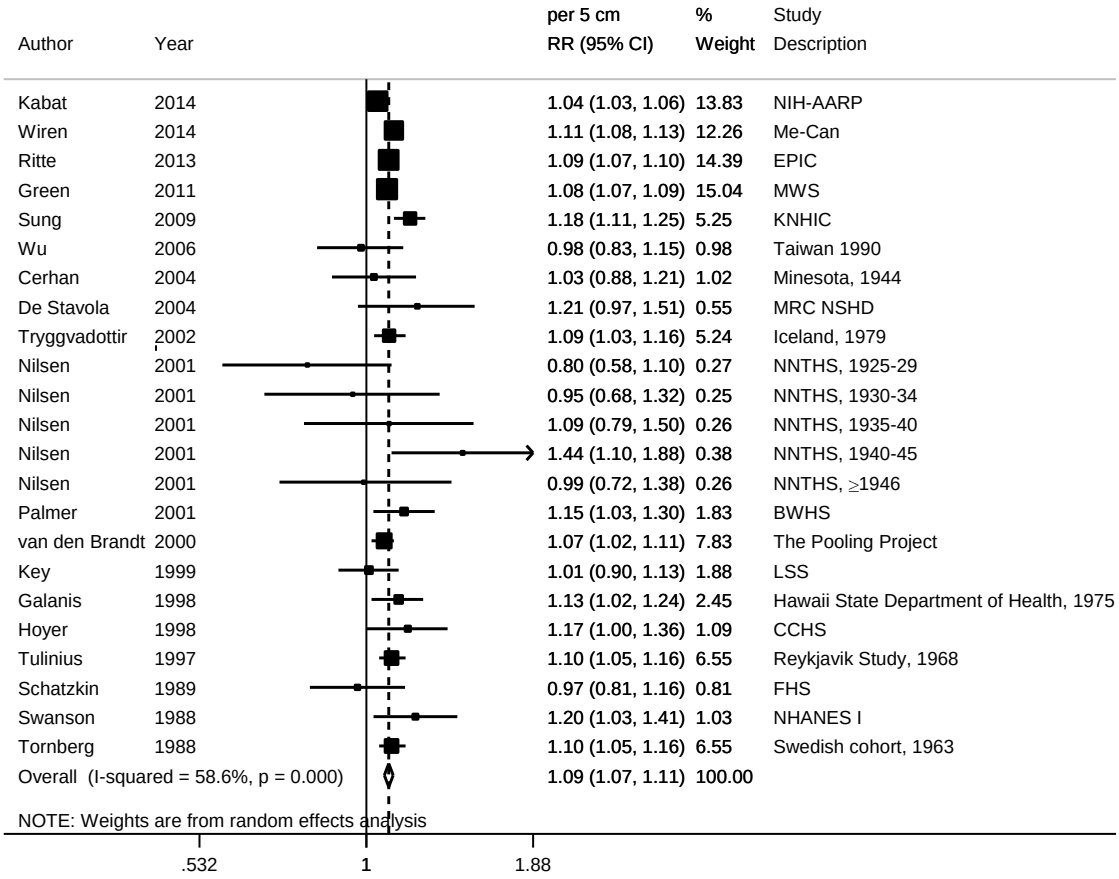


Figure 630 Funnel plot of studies included in the dose response meta-analysis of height and breast cancer

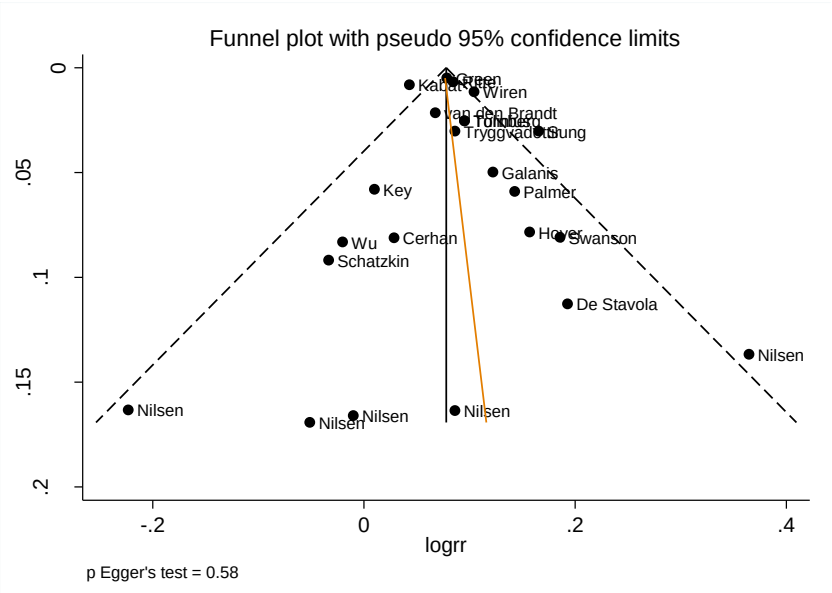


Figure 631 Relative risk of breast cancer for 5 cm increase of height, by geographic location

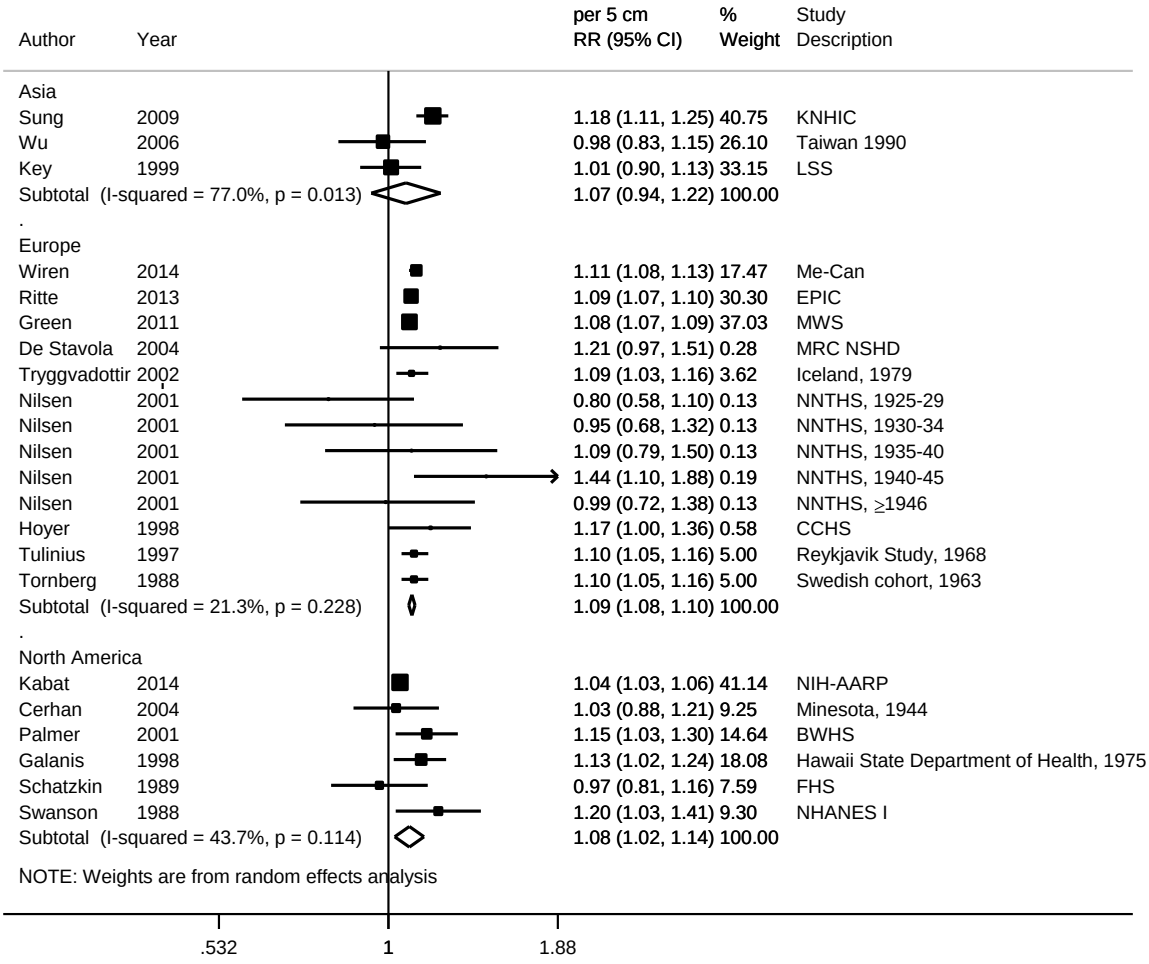


Figure 632 Relative risk of breast cancer for 5 cm increase of height, by anthropometric measurement methods

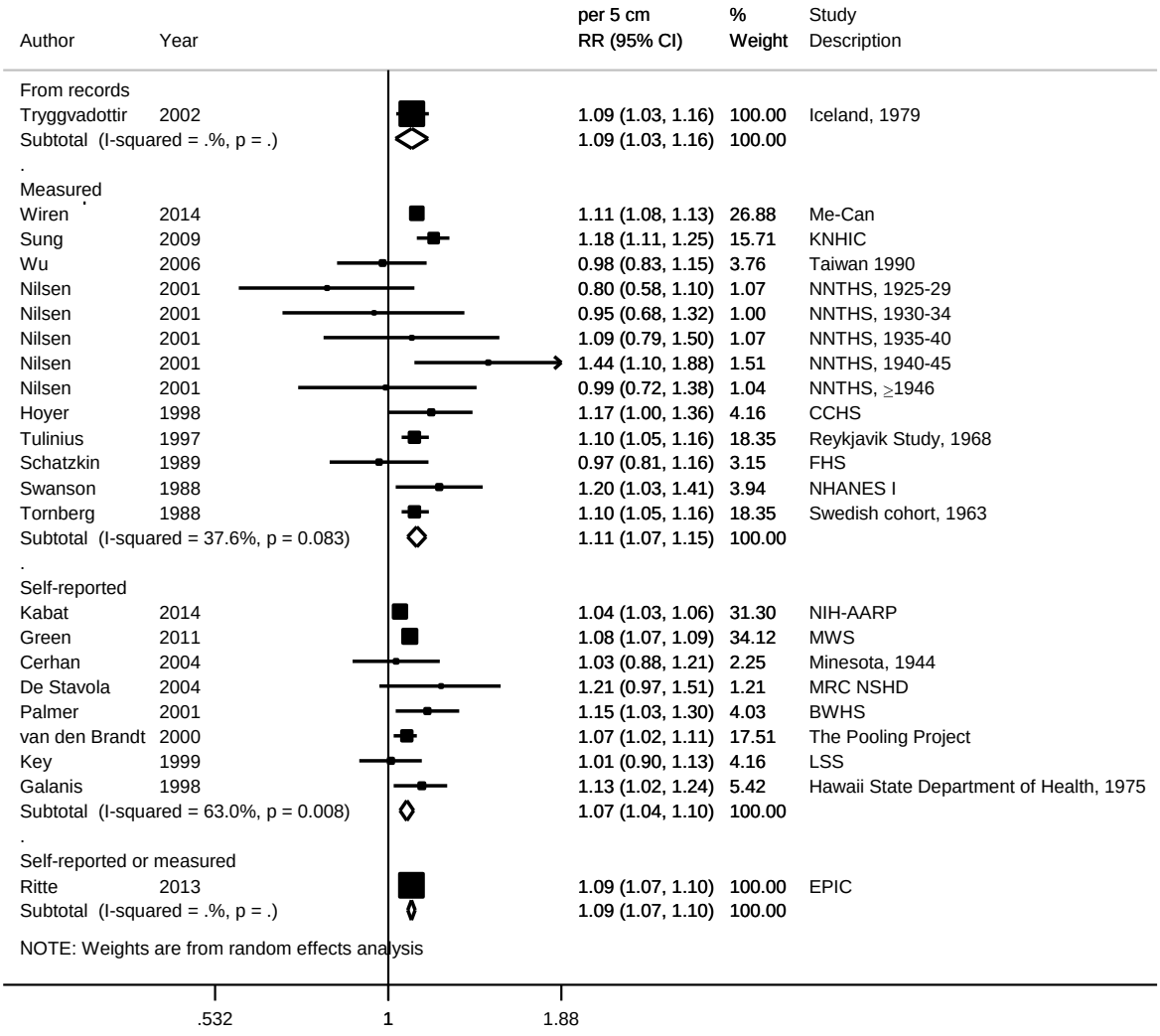
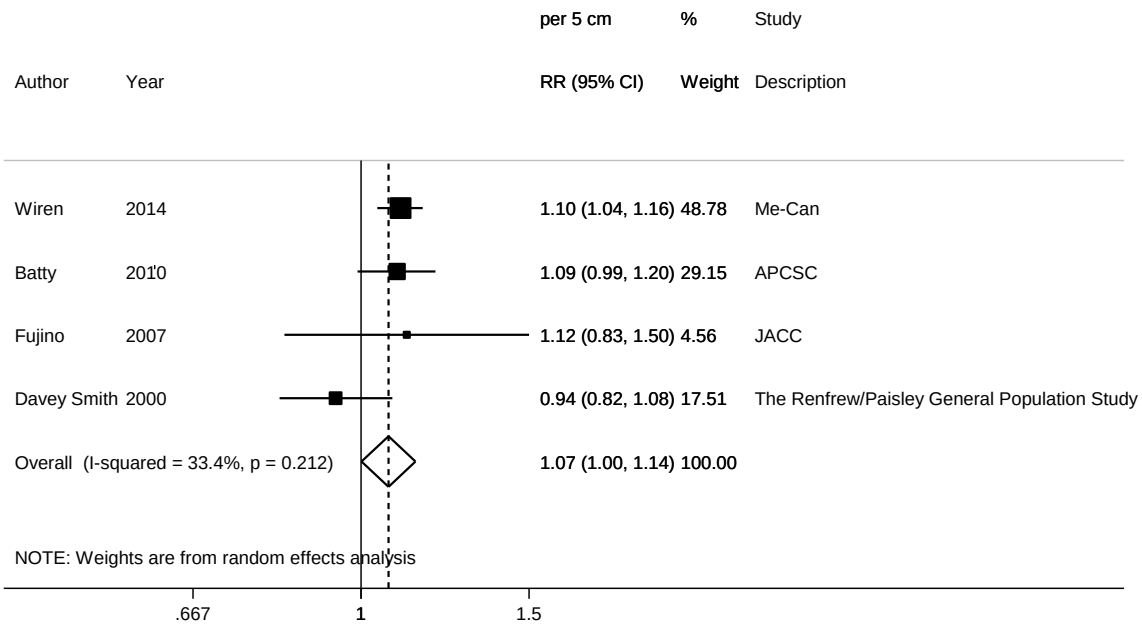


Figure 633 Relative risk of breast cancer mortality for 5 cm increase of height



Note: The highest versus the lowest forest plot was not produced as only Fujino, 2007 reported categorical results (RR for ≥154 versus ≤148.9 cm=1.24, 95% CI=0.72-2.12).

Premenopausal breast cancer

Summary

Main results:

Twenty-six out of 31 studies (33 publications) identified could be included in the dose-response meta-analysis of breast cancer risk.

Height was significantly positively associated with premenopausal breast cancer risk (summary RR per 5 cm=1.06 (95% CI=1.02-1.11). There was evidence of intermediate heterogeneity between studies (I^2=46%, P=0.02).

Only the pooled study (Wiren, 2014, Me-Can, six studies) reported results on premenopausal breast cancer mortality and observed no significant association (RR per 5 cm=1.02, 95% CI=0.94-1.11).

There was no significant evidence of publication bias or small study bias (P for Egger's test=0.11). The asymmetry in the funnel plot could be driven by the smaller studies that reported stronger associations than the average.

Five studies were excluded from the meta-analysis. Study populations in two excluded studies overlapped with studies that were already included in the analysis (Tehard, 2006; Vatten, 1992). Le Marchand, 1988 did not have sufficient data to be included in the analysis. A non-significant positive association was reported (Le Marchand, 1988). Palmer 2001 was excluded because the study included both incidence and prevalence cases. A significant

positive association was reported (Palmer, 2001). Schairer, 2013 observed non-significant positive associations with inflammatory breast cancer and non-inflammatory locally advanced breast cancer and a non-significant inverse association with non-inflammatory breast cancer.

Sensitivity analyses:

Summary RR did not change materially when studies were omitted in turn in influence analysis.

When analysed by geographic location, slightly stronger positive association among the three Asian studies (summary RR per 5 cm=1.20, 95% CI=1.04-1.37, I^2=26%, P=0.24), and positive associations that was significant among the six North American studies (RR=1.08, 95% CI=1.03-1.12, I^2=0%, P=0.50 and not the European studies (RR=1.04, 95% CI=0.99-1.09, I^2=27%, P=0.19) were observed.

Significant or borderline significant positive associations were observed in the subgroup analyses by anthropometric measurement method and confounding factors adjustment.

Study quality:

One study included BRAC1/2 mutation carriers (Manders, 2011) and one study involved mammography screening (Kaaks, 1998, DOM-project). No significant positive associations were observed in these two studies (Manders, 2011; Kaaks, 1998). The significant positive association observed in the meta-analysis remained when studies were omitted in turn in influence analysis.

About half of the studies included in the analysis measured the participants for their height and another half used measurements reported by the participants. One study (Tryggvadottir, 2002) used data from records. Case ascertainment was through cancer registries or confirmed through medical records.

Most studies did not simultaneously adjust for age, alcohol intake, and reproductive factors. Positive associations were observed in the studies adjusted or not for confounding factors. The summary RRs were significant and borderline significant, respectively.

Table 600 Height and premenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	31 (33 publications)[1]
Studies included in forest plot of highest compared with lowest exposure	20 (16 publications) breast cancer risk
Studies included in linear dose-response meta-analysis	26 (17 publications) breast cancer risk
Studies included in non-linear dose-response meta-analysis	

Note: Include cohort, and nested case-control designs

[1]Included two pooled studies (Wiren, 2014, Me-Can, six studies; van den Brandt, 2000, The Pooling Project, three studies in the premenopausal women analysis)

Table 601 Height and premenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2008 SLR and CUP SLR

	2008 SLR	**CUP**
Increment unit used	**Per 5 cm**	**Per 5 cm**
Studies (n)	12	26
Cases	3 206	6 479
RR (95%CI)	1.09 (1.05-1.12)	1.06 (1.02-1.11)
Heterogeneity (I^2, p-value)	0%, 0.45	46%, 0.02
P value Egger test	-	0.11

Stratified analysis in the CUP			
Geographic locations	**Asia**	**Europe**	**North America**
Studies (n)	3	17	6
Cases	422	4 028	1 306
RR (95%CI)	1.20 (1.04-1.37)	1.04 (0.99-1.09)	1.08 (1.03-1.12)
Heterogeneity (I^2, p-value)	26%, 0.24	27%, 0.19	0%, 0.50

Anthropometric measurement methods[1]	**Measured**	**Self-reported**
Studies (n)	14	11
Cases	3 127	3 255
RR (95%CI)	1.08 (1.01-1.16)	1.06 (1.02-1.12)
Heterogeneity (I^2, p-value)	57%, 0.02	23%, 0.25

Adjustment for age, alcohol intake, reproductive factors	**Adjusted**	**Not adjusted**
Studies (n)	8	18
Cases	2 594	3 885
RR (95%CI)	1.07 (1.03-1.12)	1.06 (1.00-1.13)
Heterogeneity (I^2, p-value)	15%, 0.32	44%, 0.05

[1]Also one study (Tryggvadottir, 2002) used height from records (RR per 5 cm=0.99, 95% CI=0.79-1.22, 97 cases).

Table 602 Height and premenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Amadou, 2013	14 studies overall (5 cohorts*, 9 case-control studies)	8 738	Canada, China, France, Germany, Japan, Nigeria, Norway/Sweden, Thailand, UK, USA,	Incidence, premenopausal breast cancer	Per 10 cm Overall Asian African Caucasian	 1.03 (1.02-1.05) 1.02 (1.00-1.03) 1.12 (1.07-1.18) 1.03 (1.02-1.05)		 32%, <0.09 26%, 0.24 0%, <0.89 0%, <0.84

*All cohort studies identified were included in the present review. The case-control study, Hirose, 2001, was included as a cohort study in the meta-analysis of Amadou, 2013

Table 603 Height and premenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Wiren, 2014 Austria, Sweden, Norway	Me-can (Metabolic syndrome and cancer project), Pooled study of 6 cohorts Mean age: 43.1 years W (NCS; CONOR; 40-y; VIP; MPP; VMP&PP)	1 855/ 12.7 years	Record linkage to cancer registries	Measured	Incidence, breast cancer, premenopausal, <50 years	per 5 cm	0.98 (0.94-1.02)	Age at health examination, date of birth, stratified for subcohort within the model
		432/			Mortality, breast cancer, premenopausal, <50 years	per 5 cm	1.02 (0.94-1.11)	
Manders, 2011 BRE80314 Netherlands	HEBON, Historical Cohort, W, Subjects with BRCA1/2 mutation	155/ 719 10 years	Cancer registry	Self-reported	Incidence, breast cancer, premenopausal	≥1.73 vs 1.65-1.68 m	0.89 (0.46-1.71)	Physical activity, stratified by gene mutation, birth cohort (reproductive factors and alcohol intake did not change RR materially and were not included in final model)
Oberg, 2009 BRE80261	Swedish Twin Cohort,	212/ 11 923	Cancer registry	Self-reported	Incidence, breast cancer, age at	≥168 vs ≤159 cm	1.86 (1.14-3.03)	Age as time axis of mode, stratified by

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Sweden	Historical Cohort, Age: 15-47 years, W	33 years			diagnosis <=50yrs			birth cohort
Iwasaki, 2007b BRE20027 Japan	JPHC I and II, Prospective Cohort, Age: 40-69 years, W	201/ 53 857 9.9 years	Cancer registry	Self-reported	Incidence, breast cancer, premenopausal	≥160 vs ≤147 cm	1.48 (0.79-2.74) Ptrend:0.08	Age , age at first child, parity/pregnancies
		62/			Incidence, breast cancer ER+, premenopausal	per 1 cm	1.03 (0.99-1.07)	Area
		41/			Incidence, breast cancer ER-, premenopausal	per 1 cm	1.03 (0.97-1.09)	
		53/			Incidence, breast cancer PR+, premenopausal	per 1 cm	1.03 (0.98-1.07)	
		42/			Incidence, breast cancer PR-, premenopausal	per 1 cm	1.04 (0.99-1.09)	
Baer, 2006 BRE80118 USA	NHS II, Prospective Cohort, Age: 25-42 years, W, Premenopausal	1 041/ 116 671 12 years	Self-report verified by medical record	Self-reported	Incidence, Invasive breast cancer, premenopausal	≥1.75 vs ≤1.59 meters	1.57 (1.23-2.01) Ptrend:<0.0001	Age at first child, age at menarche, age-underlying Cox proportional hazards models, alcohol, anthropometry, benign breast disease, BMI,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								body weight, design , duration of OC use, family history, height, OC use, parity/pregnancies
						per 5cm	1.11 (1.06-1.17)	
Li, 2006 BRE80166 China	SWHS, Prospective Cohort, Age: 40-70 years, W	221/ 73 410 5.66 years	Medical records	Measured by trained Interviewers	Incidence, breast cancer, premenopausal	≥160.1 vs ≤155 cm	1.65 (1.11-2.44) Ptrend:0.0062	Age, age at first child birth, breastfeeding, educational level, energy Intake, family history, family history of cancer
Lahmann, 2004a BRE15804 Europe	EPIC, Prospective Cohort, Age: 18-80 years, W	474/ 176 886 4.7 years	Partially histological - over 80%	Measurements performed by trained personnel	Incidence, breast cancer, premenopausal	per 1 cm	1.01 (1.00-1.03)	Age , age at first child, age at menarche, alcohol, educational level, OC use, parity/pregnancies, recruitment center, smoking habits
						≥167.7 vs ≤155.9 cm	1.33 (0.96-1.84) Ptrend:0.134	
Weiderpass, 2004 BRE18151 Sweden, Norway	WLHS, Sweden and Norway, Prospective Cohort, Age: 30-49 years, W,	728/ 99 717 8 years	Partially histological - over 80%	Self reported In a questionnaire	Incidence, breast cancer, premenopausal	≥175 vs 165-169 cm	0.90 (0.67-1.21) Ptrend:0.02	Age, age at first child, age at menarche, duration of breastfeeding, family history of breast cancer, OC use, parity, place of residence

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Premenopausal					≥175 vs 165-169 cm	0.91 (0.67-1.23) Ptrend:0.03	Baseline BMI
Tryggvadottir, 2002 BRE12507 Iceland	Iceland, 1979, Nested Case Control, Age: 20-81 years, W	97/ 970 controls 17 years	Partially histological - over 80%	From records	Incidence, breast cancer, premenopausal	per 5 cm	0.99 (0.79-1.22)	Age at first child, age at menarche, body weight, breastfeeding, OC use, parity/pregnancies, parous/nulliparous
van den Brandt, 2000 North America and Europe	The Pooling Project, Pooled study of 7 cohorts, W (AHS; CNBSS; IWHS; NLCS; NYSC; NHS(a); NHS(b); SMC)	723/	Follow-up questionnaires and inspection of medical records and/or tumour registry linkage	Self-reported	Incidence, breast cancer	≥1.75 vs <1.60 m	1.42 (0.95-2.12)	Age at menarche, parity, age at birth of first child, postmenopausal hormone use, oral contraceptive use, history of benign breast disease, maternal history of breast cancer, history of breast cancer in a sister, smoking status, education, fat intake, fibre intake, energy intake, alcohol intake
						per 5 cm	1.02 (0.96- 1.10)	
	CNBSS	122/				per 5 cm	0.98 (0.75-1.28)	
	NHS(a)	383/				per 5 cm	1.05 (0.97-1.15)	
	NHS(b)	130/				per 5 cm	0.97 (0.83-1.12)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	SMC	68/				per 5 cm	0.98 (0.78-1.23)	
Sonnenschein, 1999 BRE11604 USA	NYUWHS, Prospective Cohort, Age: 35-65 years, W	109/ 8 416 6.6 years	All histology	Self-reported	Incidence, breast cancer, premenopausal	≥170.1 vs ≤160.9 cm	0.96 (0.55-1.66)	Age , age at first child, age at menarche, breast biopsies, family history
Galanis, 1998 BRE03058 hawaii	Hawaii State Department of Health, 1975, Prospective Cohort, Age: 43 years, W	86/ 17 628 14.9 years	Partially histological - over 80%	Self-reported in questionnaire	Incidence, breast cancer, premenopausal	≥160.1 vs ≤154.9 cm	1.10 (0.60-1.90) Ptrend:0.9	Age , alcohol, educational level, ethnicity
Kaaks, 1998 BRE04522 Netherlands	DOM-project Utrecht, Prospective Cohort, Age: 39-73 years, W	147/ 11 480 7.1 years	Partially histological – over 80%	Measured	Incidence, breast cancer, premenopausal	≥169.1 vs ≤160.8 cm	1.28 (0.78-2.11) Ptrend:0.25	Age , age at first child, age at menarche, menopausal status, parity/pregnancies
Tulinius, 1997 BRE12565 Iceland	Reykjavik Study, 1968, Prospective Cohort, Age: 45-59 years, W	91/ 11 580 27 years	Partially histological - over 80%	Measured	Incidence, breast cancer, premenopausal	per 1 cm	1.04 (1.00-1.08)	Age

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Freni, 1996 BRE02960 USA	NHANES I, Prospective Cohort, Age: 25-74 years, W	70/ 7 622 155 months	Medical records + death certificate	Measured	Incidence, breast cancer, premenopausal	≥167 vs ≤155.9 cm	1.60 (0.60-3.80) Ptrend:>0.10	Age , age at first child, age at menarche, educational level, family history
De Stavola, 1993 BRE02122 UK	Guernsey G2 and G3, Prospective Cohort, W	73/ 4 528 15 years	Partially histological - over 80%	Measurements performed by trained personnel	Incidence, breast cancer, premenopausal	≥166 vs ≤157.9 cm	1.30 (0.70-2.50) Ptrend:0.36	Age , body weight, family history, other age Indicator
Tornberg, 1988 BRE12418 sweden	Swedish cohort, 1963, Prospective Cohort, Age: 17-74 years, W, Screening Program	46 570 20 years	Partially histological - over 80%	Measured	Incidence, breast cancer, premenopausal	per 5 cm	1.11 (0.98-1.27)	Age , place of residence

Table 604 Height and premenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Kabat, 2013a BRE80439 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	1 908/ 88 256 16.2 years	Record linkages to cancer database and to the national mortality database	Measured	Incidence, premenopausal breast cancer	per 10 cm	1.11 (1.03-1.20)	Age at entry, age at menarche, BMI, family history of breast cancer In first degree relatives, history of benign breast disease, oral contraceptive use, pack yrs of smoking, parity, years of education	Publication superseded by van den Brandt, 2000
Ritte, 2013b BRE80431 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 25-70 years, W	306 600 3 297 579 person-years	Cancer registry, record linkage, health Insurance rec, pathology and active follow up	Self-reported or measured	Incidence, breast cancer ER+/PR+, age <= 49 years	≥165 vs ≤159 cm	1.06 (0.80-1.39)	Age, age at first child birth, age at menopause, alcohol, breastfeeding, educational level, HRT use, leg length, menopausal status, oral contraceptive history, parity, physical	Publication superseded by Lahmann, 2004a

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								activity, sitting height, smoking, study center, time since menopause, waist circumference	
Schairer, 2013 BRE80568 USA	BCSC, Nested Case Control, W	1 744/ 93 654	Seer registry/hospital records/pathology	Self-reported height and weight In the questionnaire completed closest In time before or on the date of diagnosis	Incidence, non-inflammatory breast cancer, premenopausal	≥67 vs ≤62 inch	0.94 (0.80-1.12)	Age at first child birth, BMI, breast biopsies, educational level, family history of breast cancer In first degree relatives, mammographic density, parous/nulliparous, race/ethnicity	Results by breast cancer subtype, not analysed
		255/			Incidence, non-inflammatory locally advanced breast cancer, premenopausal	≥67 vs ≤62 inch	1.14 (0.67-1.94)		
		182/			Incidence, Inflammatory breast cancer, premenopausal	≥67 vs ≤62 inch	1.55 (0.55-4.36)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Fagherazzi, 2012b BRE80412 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years	306/ 50 704 6 years	Pathology	Self-reported	Incidence, breast cancer, premenopausal	≥165 vs ≤158 cm	0.88 (0.63-1.23) Ptrend:0.576	Age at first child birth, age at menarche, age at menarche, age at menopause, benign breast disease, birth length, birthweight, breastfeeding, educational level, family history of breast cancer, HRT use, mammography, oral contraceptive use, parity, physical activity, progesterone	Publication superseded by Lahmann, 2004a
		235/			Incidence, breast cancer ER+, premenopausal	≥165 vs ≤158 cm	1.15 (0.77-1.71) Ptrend:0.372		
		71/			Incidence, breast cancer ER-, premenopausal	≥165 vs ≤158 cm	0.35 (0.18-0.70) Ptrend:0.003		
Fagherazzi,	E3N EPIC-	223/	Self report	Self-reported	Incidence, breast	≥164 vs ≤158.9	1.13 (0.81-1.58)	Age at first child	Results by

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
2012a BRE80539 France	France, Prospective Cohort, Age: 40-65 years, W	63 726 582 144 person-years	verified by medical record and pathology report		cancer ER+/PR+, premenopausal	cm	Ptrend:0.47	birth, age at menarche, age at menopause, alcohol Intake, breastfeeding, educational level, family history of breast cancer, history of benign breast disease, mammography, non-alcohol energy, OC use, parous/nulliparous, smoking status, total physical activity, use of HRT, year of birth	breast cancer subtype, not analysed (same study as Tehard, 2006)
		54/			Incidence, breast cancer ER-/PR-, premenopausal	≥164 vs ≤158.9 cm	0.59 (0.31-1.10) Ptrend:0.11		
					Incidence, breast cancer ER+/PR-, premenopausal	≥164 vs ≤158.9 cm	0.96 (0.51-1.79) Ptrend:.97		
		24/			Incidence, breast cancer ER-/PR+,	≥164 vs ≤158.9 cm	0.43 (0.18-1.07) Ptrend:0.07		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					premenopausal				
Tehard, 2006 BRE80103 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years	275/ 69 116 3.6 years	Patient records/direct contact/health Insurance records	Self-reported In questionnaire	Incidence, breast cancer, premenopausal	≥166 vs ≤158 cm	1.26 (0.80-1.98) Ptrend:>0.05	Age at first child, age at menarche, age-underlying cox models, alcohol, benign breast disease, educational level, family history, marital status, parity/pregnancies, physical activity	Publication superseded by Lahmann, 2004a
Saadatian-Elahi, 2002 BRE21486 USA	NYUWHS, Nested Case Control, Age: 34-65 years, W	91/ 91 controls 4.3 years	Partially histological - over 80%		Incidence, breast cancer, premenopausal	(mean exposure)			Excluded, mean exposure levels comparison only
Manjer, 2001b BRE17790 Sweden	MPP, Prospective Cohort, Age: 55 years, W	112/ 9 738 13.1 years	Partially histological - over 80%	Measured by trained personnel	Incidence, Invasive breast cancer, premenopausal	≥169.1 vs ≤159 cm	1.00 (0.59-1.70) Ptrend:0.89	Age	Publication superseded by Wiren, 2014
Palmer, 2001 BRE20603	BWHS, Nested Case	433/ 1712 controls	Medical records + self-reported	Self-reported In questionnaire	Incidence / prevalence,	≥70 vs ≤61.9 inch	2.10 (1.20-3.60) Ptrend:0.0003	Age , age at menarche,	Excluded, incidence and

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
USA	Control, Age: 21-69 years, W	2 years			Invasive & In situ breast cancer, premenopausal			educational level	prevalence
Berkey, 1999 BRE00743 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	806/ 65 140 16 years	Partially histological - over 80%	Self-reported In questionnaire	Incidence, breast cancer, premenopausal	≥67 vs ≤62 inch	1.11 Ptrend:,56	Age , age at menarche, age at menopause, alcohol, benign breast disease, family history, height, other anthropometric Index, other anthropometric Index, smoking habits, socio-economic status	Publication superseded by van den Brandt, 2000
Toniolo, 1994 BRE12398 USA	NYUWHS, Nested Case Control, Age: 35-65 years, W	79 cases 366 controls 7 years	Medical records	Self-reported In questionnaires	Incidence, Invasive breast cancer, premenopausal	≥168 vs ≤157.9 cm	0.65 (0.33-1.30) Ptrend:0.99		Publication superseded by Sonnenschein, 1999
Vatten, 1992 BRE12828 Norway	NNHSS, 1974, Prospective Cohort, Age: 26-49 years, W,	164/ 25 967 14 years	Partially histological - over 80%	Measured	Incidence, breast cancer, premenopausal	≥167 vs ≤158.9 cm	1.62 (1.23-2.14) Ptrend:0.001	Age , age at first child, occupation, parity/pregnancies, place of residence	Study superseded by Wiren, 2014

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Screening Program								
Vatten, 1990d BRE12827 Norway	NNHSS, 1974, Prospective Cohort, Age: 35-51 years, W, Screening Program	137/ 23 831 12.5 years	Partially histological - over 80%	Measured	Incidence, breast cancer, premenopausal	≥167 vs ≤158.9 cm	2.63 (1.48-4.68) Ptrend:0.001	Age	Publication superseded by Wiren, 2014
London, 1989 BRE80626 USA	NHS, Prospective Cohort, Age: 30-55 years, W	658/ 115 534 743 716 person-years	Self report verified by medical record	Self-reported	Incidence, Invasive breast cancer, premenopausal	reference error: no min from refernce			Publication superseded by van den Brandt, 2000
Le Marchand, 1988 BRE15836 USA	Hawaii 1942, 1960, 1972, Nested Case Control, W	101/ 444 controls	All histology	From drive licence	Incidence, breast cancer, premenopausal	q 3 vs q 1	1.41 (0.68-2.91) Ptrend:0.99	Husband occupation, other anthropometric Index	Excluded, insufficient data
Willett, 1985 BRE80625 USA	NHS, Prospective Cohort, Age: 30-55 years, W	346/ 103 688 4 years	Self-reported validated by pathology report	Self-reported	Incidence, breast cancer, premenopausal	172 vs 156 cm	1.26 Ptrend:0.186	Age	Publication superseded by van den Brandt, 2000

Figure 634 RR estimates of premenopausal breast cancer by height

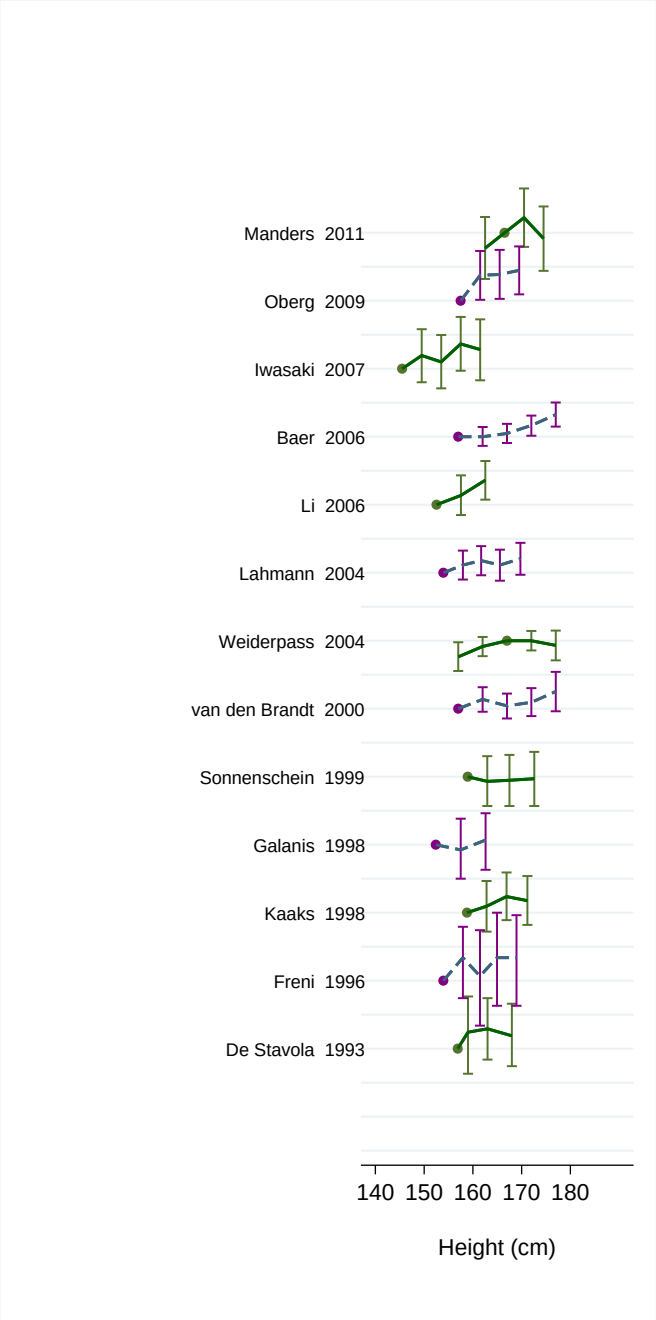


Figure 635 RR (95% CI) of premenopausal breast cancer for the highest compared with the lowest level of height

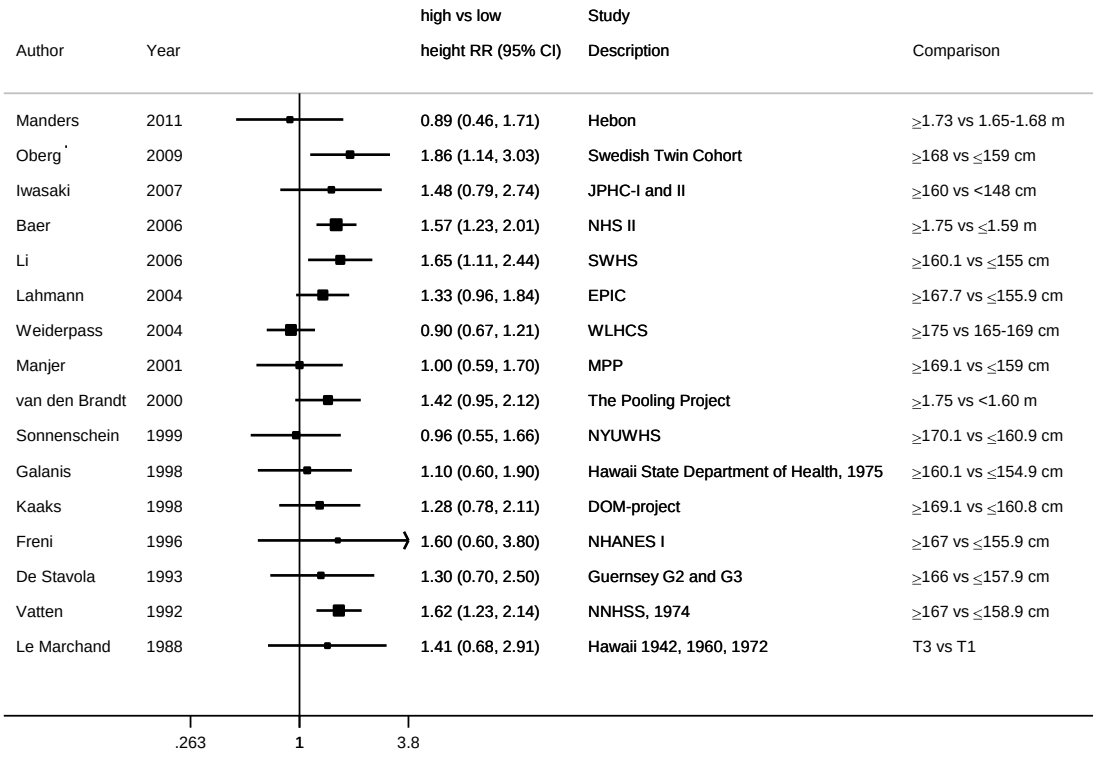


Figure 636 Relative risk of premenopausal breast cancer for 5 cm increase of height

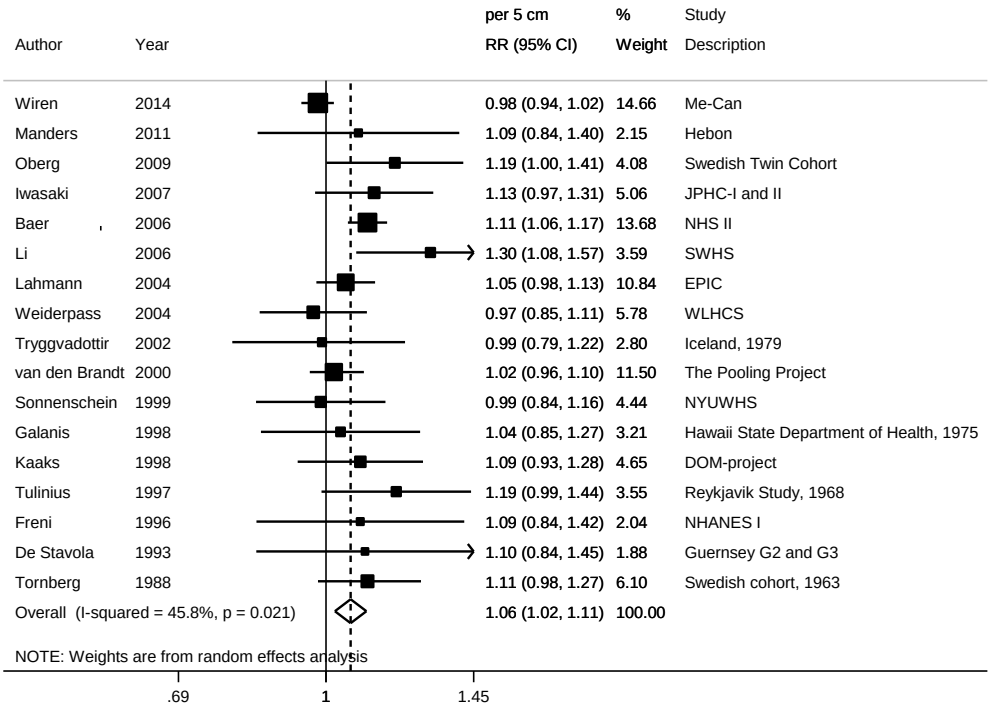


Figure 637 Funnel plot of studies included in the dose response meta-analysis of height and premenopausal breast cancer

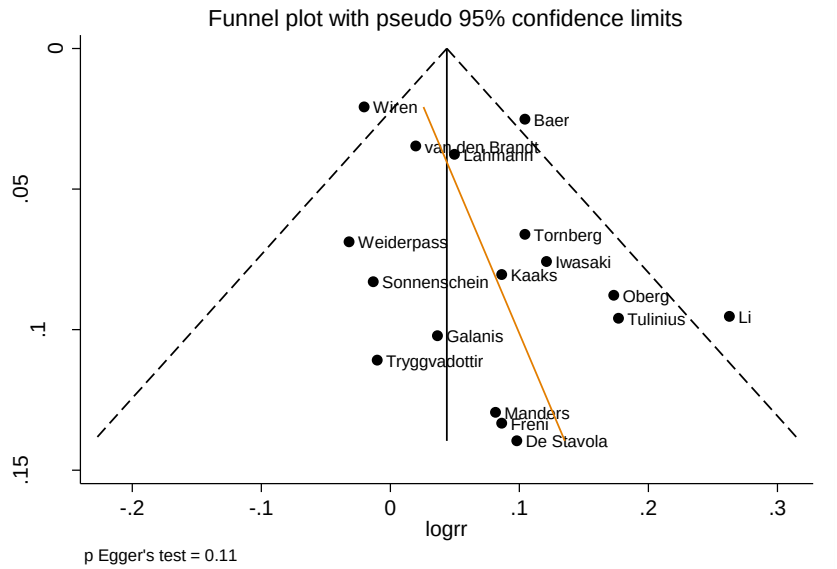


Figure 638 Relative risk of premenopausal breast cancer for 5 cm increase of height, by geographic location

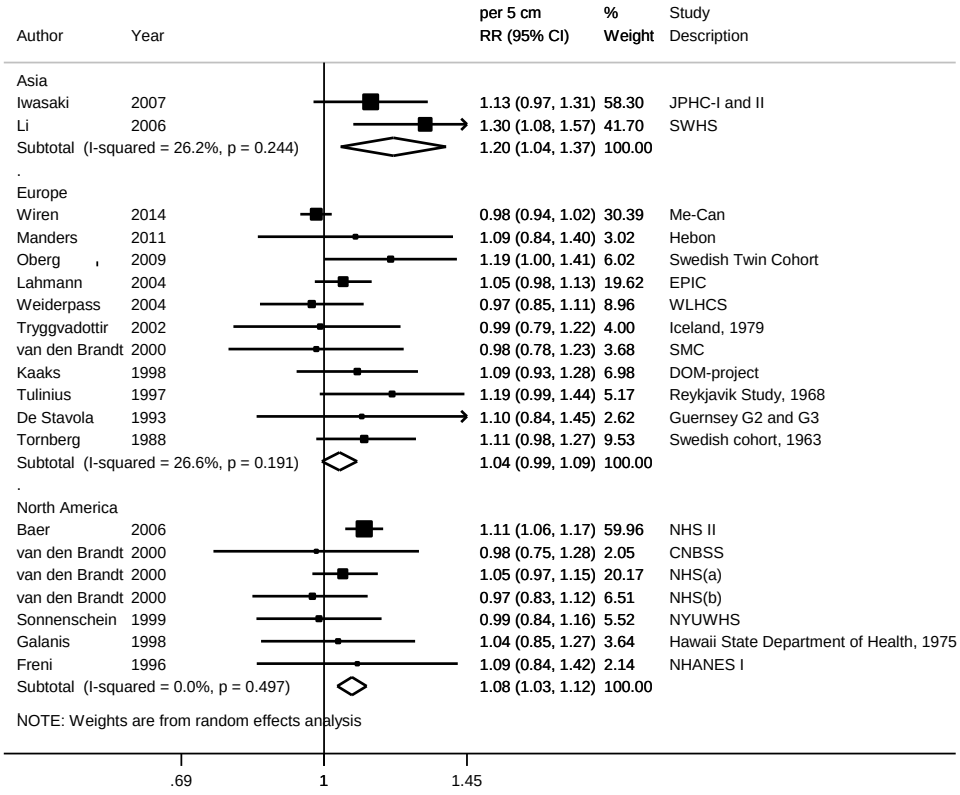
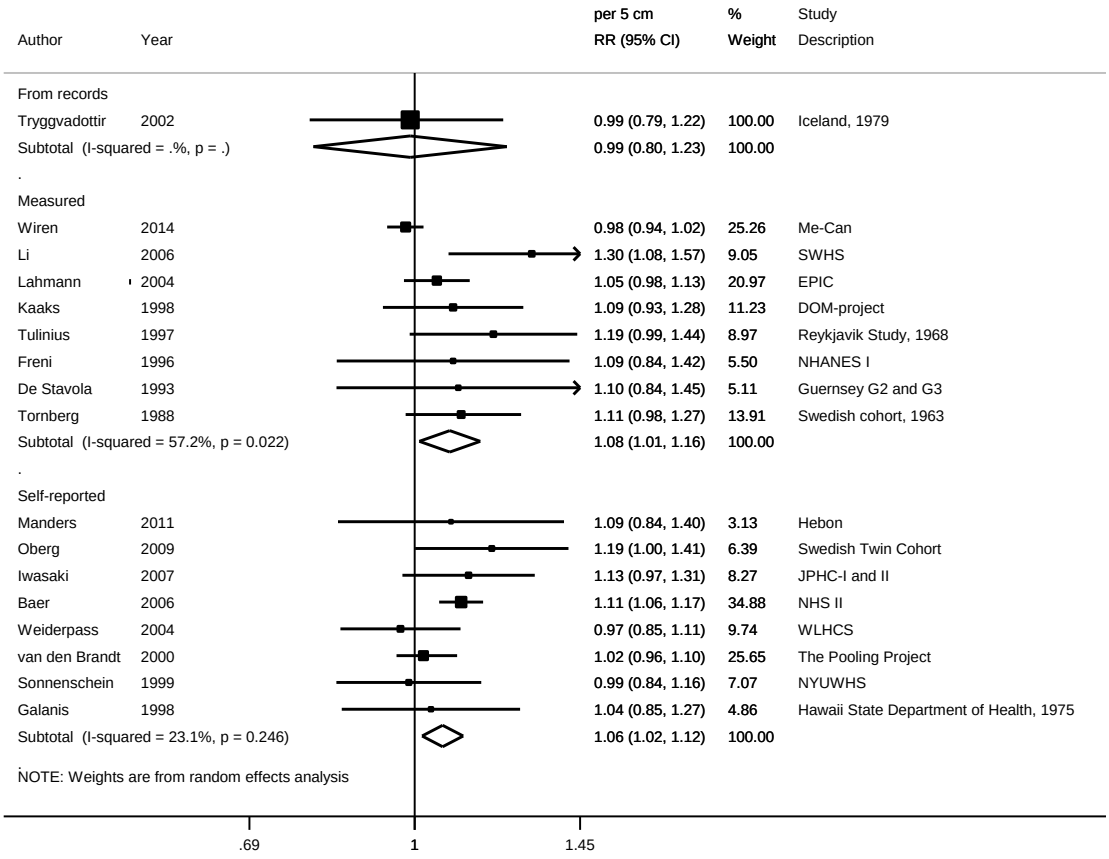


Figure 639 Relative risk of premenopausal breast cancer for 5 cm increase of height, by anthropometric measurement methods



Postmenopausal breast cancer

Summary

Main results:

Thirty-four out of 48 studies (56 publications) identified could be included in the dose-response meta-analyses. There were 33 studies (20 publications) on breast cancer risk and 7 studies (2 publications) on breast cancer mortality.

Height was significantly positively associated with postmenopausal breast cancer risk (summary RR per 5 cm=1.09 (95% CI=1.07-1.11, I^2=33%, P=0.08) and postmenopausal breast cancer mortality (RR=1.08, 95% CI=1.05-1.11, I^2=0%, P=0.72).

There was significant evidence of publication bias or small study bias (P for Egger's test=0.02). Visual inspection of the funnel plot shows that there were more studies with a positive association.

Fourteen studies and 35 publications were excluded from the meta-analyses. Study populations in seven excluded studies overlapped with studies that were already included in

the analysis (Horn, 2014b; Mellemkjaer, 2012; Harlid, 2012, VIP; Tehard, 2006; Lahmann, 2003; Morimoto, 2002; Vatten, 1990d).

Three studies did not have sufficient data to be included in the meta-analysis. Positive associations were reported in two studies, which was significant in one (Manders, 2011) and not the other (Le Marchand, 1988). Barrett-Connor, 1993 reported no significant difference in mean height between the cases and the non-cases. Palmer 2001 was excluded because the study included both incidence and prevalence cases. A non-significant positive association was reported (Palmer, 2001).

Three studies reported results only by breast cancer types. Positive associations which were only significant with ER+PR+ or ER+PR- breast cancer (Canchola, 2012) and ductal carcinoma or ductal-lobular breast cancer (Nyante, 2013) were reported. For inflammatory breast cancer, non-inflammatory breast cancer, and non-inflammatory locally advanced breast cancer, Schairer, 2013 reported non-significant positive associations.

Sensitivity analyses:

Summary RR did not change materially when studies were omitted in turn in influence analysis.

When analysed by geographic location, positive associations that were significant in European studies (summary RR per 5 cm=1.10, 95% CI=1.08-1.12) and North American studies (RR=1.06, 95% CI=1.04-1.08), and non-significant in Asian studies (RR=1.13, 95% CI=0.93-1.38) were observed. Heterogeneity was high between the Asian studies (I^2=68%, P=0.08), and low between the European studies and the North American studies (I^2=5%, P=0.40 and I^2=0%, P=0.50, respectively). There was also one Australian study (MacInnis, 2004) that observed a significant positive association (RR=1.13, 95% CI=1.03-1.23).

Significant positive associations were observed in the subgroup analyses by anthropometric measurement method and confounding factors adjustment.

Study quality:

No significant association was observed in the study that involved mammography screening (Kaaks, 1998, DOM-project).

There were more studies that measured the participants than studies that used self-reported measurements by the participants. One study (Tryggvadottir, 2002) used data from records. Case ascertainment was through cancer registries or confirmed through medical records.

More than half of the studies did not simultaneously adjust for age, alcohol intake, and reproductive factors. On average studies adjusted or not adjusted for these factors observed similar results.

Table 605 Height and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	48 (56 publications)[1]
Studies included in forest plot of highest compared with lowest exposure	29 (20 publications) on breast cancer risk 7 (2 publications) on breast cancer mortality
Studies included in linear dose-response meta-analysis[2]	33 (20 publications) on breast cancer risk 7 (2 publications) on breast cancer mortality
Studies included in non-linear dose-response meta-analysis	

Note: Include cohort, case-cohort, and nested case-control designs

[1]Included two pooled studies (Wiren, 2014, Me-Can, 6 studies; van den Brandt, 2000, The Pooling Project, seven studies)

[2]In total, 34 studies (21 publications) were included in the dose-response meta-analyses.

Table 606 Height and postmenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2008 SLR and CUP SLR

	2008 SLR	**CUP**
Increment unit used	**Per 5 cm**	**Per 5 cm**
Studies (n)	16	33
Cases	9 024	24 975
RR (95%CI)	1.10 (1.07-1.13)	1.09 (1.07-1.11)
Heterogeneity (I^2, p-value)	36%, 0.07	33%, 0.08
P value Egger test	-	0.02

Stratified analysis in the CUP			
Geographic locations[1]	**Asia**	**Europe**	**North America**
Studies (n)	3	18	11
Cases	440	11 190	9 780
RR (95%CI)	1.13 (0.93-1.38)	1.10 (1.08-1.12)	1.06 (1.04-1.08)
Heterogeneity (I^2, p-value)	68%, 0.08	5%, 0.40	0%, 0.50

Anthropometric measurement methods[2]	**Measured**	**Self-reported**
Studies (n)	18	14
Cases	15 036	9 350
RR (95%CI)	1.09 (1.07-1.11)	1.08 (1.05-1.12)

Heterogeneity (I^2, p-value)	28%, 0.17	44%, 0.10
Adjustment for age, alcohol intake, reproductive factors	**Adjusted**	**Not adjusted**
Studies (n)	13	20
Cases	15 074	9 901
RR (95%CI)	1.08 (1.06-1.10)	1.10 (1.07-1.12)
Heterogeneity (I^2, p-value)	41%, 0.13	19%, 0.24
Other analysis in the CUP		
Breast cancer mortality		
Studies (n)	7	
Cases	3 181	
RR (95%CI)	1.08 (1.05-1.11)	
Heterogeneity (I^2, p-value)	0%, 0.72	

[1]Also one Australian study (Macnnis, 2004) (RR per 5 cm=1.13 (, 95% CI=1.03-1.23, 357 cases)

[2]Also one study (Tryggvadottir, 2002) used height from records (RR per 5 cm=1.12, 95% CI=1.03-1.22, 589 cases).

Table 607 Height and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Wiren, 2014, Austria, Sweden, Norway	Me-Can, Pooled study of 6 cohorts, W (NCS; CONOR; 40-y; VIP; MPP; VHM&PP)	2 133/ 12.7 years	Record linkage to cancer registries	Measured	Incidence, breast cancer, postmenopausal, >60 years	per 5 cm	1.11 (1.07-1.15)	Age at health examination, date of birth, stratified for subcohort within the model
		329/			Mortality, breast cancer, postmenopausal, >60 years	per 5 cm	1.10 (1.00-1.21)	
Kabat, 2013b BRE80480 USA	WHI-CT and OS, Prospective Cohort, Age: 50-79 years, W	6 798/ 144 701 12 years	Self report verified by medical record and pathology report	Measured	Incidence, breast cancer	per 10 cm	1.13 (1.08-1.17)	Age, age at first child birth, age at menarche, age at menopause, breast biopsies, educational level, ethnicity, family history of breast cancer, HRT use, pack-years cigarette smoking, parity, randomisation, W/H[x]
White, 2012 BRE80396 Hawai, California	MEC, Prospective Cohort, Age: 45-75 years, Postmenopausal	3 080/ 82 971 9 years	Cancer registry and national death Index	Self-reported compared with the driving license	Incidence, breast cancer	≥1.65 vs 1.56-1.57 m	1.13 (1.00-1.29) Ptrend:0.0009	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, energy, family history of breast cancer, HRT use,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								number of childbirths, physical activity, smoking status, type of menopause
						per 0.1 m	1.14 (1.07-1.21)	
		465/			Latina	≥1.65 vs 1.56-1.57 m	1.26 (0.89-1.80) Ptrend:0.96	
						per 0.1 m	1.00 (0.87-1.16)	
		835/			White	≥1.65 vs 1.56-1.57 m	1.14 (0.91-1.43) Ptrend:0.16	
						per 0.1 m	1.09 (0.98-1.21)	
		921/			Japanese	≥1.65 vs 1.56-1.57 m	1.35 (0.88-2.07) Ptrend:0.006	
						per 0.1 m	1.21 (1.07-1.36)	
		598/			African American	≥1.65 vs 1.56-1.57 m	1.31 (0.99-1.73) Ptrend:0.006	
						per 0.1 m	1.27 (1.12-1.43)	
		261/			Native Hawaiian	≥1.65 vs 1.56-1.57 m	0.74 (0.52-1.07) Ptrend:0.70	
						per 0.1 m	1.07 (0.88-1.29)	
Opdahl, 2011 BRE80600 Norway	Norwegian Screening Programme for Tuberculosis,	1 741/ 58 191 24.1 years	Cancer registry	Measured height and weight during health examination	Incidence, breast cancer, parous women	≥170 vs 160-164 cm	1.22 (1.01-1.47) Ptrend:<0.0001	Age, age at menarche, birth cohort, county of residence, marital status, occupation,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Prospective Cohort, W, Postmenopausal							urban/rural
		432/				≥170 vs 160-164 cm	1.11 (0.77-1.61) Ptrend:0.24	
Lacey JV Jr, 2009 BRE80247 USA	PLCO, Prospective Cohort, Age: 55-74 years, W, Postmenopausal	2 078/ 70 575 4.98 years	Self reported/death certificate/ medical records	Self-reported in questionnaire	Incidence, breast cancer	≥1.7 vs ≤1.59 m	1.11 (0.97-1.27)	Age, age at first child birth, age at menarche, age at menopause, benign breast disease, calendar period, family history of cancer, height, HRT use, study center
Oberg, 2009 BRE80261 Sweden	Swedish Twin Cohort, Historical Cohort, Age: 15-47 years, W	313/ 11 923 33 years	Cancer registry	Self-reported	Incidence, breast cancer, age at diagnosis >50yrs	≥168 vs ≤159 cm	1.37 (0.98-1.93)	Age as time axis in model, stratified by birth cohort
Iwasaki, 2007b BRE20027 Japan	JPHC I and II, Prospective Cohort, Age: 40-69 years, W	229/ 53 857 9.9 years	Cancer registry	Self-reported	Incidence, breast cancer, postmenopausal	≥160 vs ≤147 cm	2.39 (1.43-3.98) Ptrend:0.003	Age , age at first child, area, parity/pregnancies (adjustment for alcohol intake did not change RR materially and not included in final model)

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		65/			Incidence, breast cancer ER+, postmenopausal	per 1 cm	1.00 (0.95-1.05)	
		41/			Incidence, breast cancer ER-, postmenopausal	per 1 cm	1.06 (1.02-1.12)	
		46/			Incidence, breast cancer PR+, postmenopausal	per 1 cm	1.02 (0.96-1.07)	
		55/			Incidence, breast cancer PR-, postmenopausal	per 1 cm	1.03 (0.98-1.08)	
Krebs, 2006 BRE80106 USA	SOF, Prospective Cohort, Age: 65- years, Postmenopausal	350/ 9 704 11.3 years	Self report verified by medical record	Measured	Incidence, Invasive breast cancer, postmenopausal	per 6 cm	1.06 (0.91-1.12)	Age
Li, 2006 BRE80166 China	SWHS, Prospective Cohort, Age: 40-70 years, W	211/ 73 410 5.66 years	Medical records	Measured by trained Interviewers	Incidence, breast cancer, postmenopausal	≥160.1 vs ≤155 cm	1.04 (0.70-1.53) Ptrend:0.89	Age, age at first child birth, age at menopause, breastfeeding, educational level, energy Intake, family history, family history of cancer
Lahmann, 2004a BRE15804	EPIC, Prospective	1 402/ 176 886	Partially histological -	Measurements performed by	Incidence, breast cancer,	per 1 cm	1.02 (1.01-1.03)	Age , age at first child, age at menarche,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Europe	Cohort, Age: 18-80 years, W	4.7 years	over 80%	trained personnel	postmenopausal			alcohol, educational level, HRT use, parity/pregnancies, recruitment center, smoking habits
						≥167.7 vs ≤155.9 cm	1.40 (1.16-1.69) Ptrend:<0.001	
MacInnis, 2004 BRE80159 Australia	MCCS, Prospective Cohort, Age: 27-75 years, W, Postmenopausal	357/ 13 598 9.1 years	Medical records	Direct anthropometric measurement	Incidence, Invasive breast cancer, postmenopausal	≥164 vs ≤154.9 cm	1.60 (1.10-2.20)	Age, birthplace, educational level, HRT use, physical activity
						per 10 cm	1.27 (1.07-1.52)	
					Never HRT users	per 10 cm	1.27 (1.03-1.58)	
					HRT former users	per 10 cm	1.20 (0.71-2.01)	
					HRT current users	per 10 cm	1.30 (0.91-1.87)	
		42/			Incidence, breast cancer PR-, >=15 years postmenopausal	per 10 cm	1.81 (1.04-3.14)	
		84/			Incidence, breast cancer PR+, >=15 years postmenopausal	per 10 cm	1.27 (0.89-1.81)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		29/			Incidence, breast cancer ER-, >=15 years postmenopausal	per 10 cm	1.41 (0.78-2.56)	
		97/			Incidence, breast cancer ER+, >=15 years postmenopausal	per 10 cm	1.43 (1.01-2.04)	
		44/			Incidence, poorly differentiated breast cancer, postmenopausal	per 10 cm	1.20 (0.74-1.95)	
		59/			Incidence, moderate differentiated breast cancer, postmenopausal	per 10 cm	1.92 (1.25-2.95)	
		36/			Incidence, well differentiated breast cancer, postmenopausal	per 10 cm	1.75 (1.10-2.78)	
Petrelli, 2002 BRE20653 USA	CPS II, Prospective Cohort, Age: 30- years, W	2 852/ 424 168 14 years	Partially histological - over 80%	Self reported in questionnaire	Mortality, breast cancer, postmenopausal	≥66 vs ≤61 inch	1.36 (1.20-1.55) Ptrend:<0.0001	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, educational level, ethnicity, family

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								history, HRT use, menopausal status, OC use, parity/pregnancies, physical activity , smoking habits
Tryggvadottir, 2002 BRE12507 Iceland	Iceland, 1979, Nested Case Control, Age: 20-81 years, W	589/ 5299 controls 17 years	Partially histological – over 80%	From records	Incidence, breast cancer	per 5 cm	1.12 (1.03-1.22)	Age at first child, age at menarche, body weight, breastfeeding, OC use, parity/pregnancies, parous/nulliparous
van den Brandt, 2000 North America and Europe	The Pooling Project, Pooled study of 7 cohorts, W (AHS; CNBSS; IWHS; NLCS; NYSC; NHS(a); NHS(b); SMC)	3 208/	Follow-up questionnaires and inspection of medical records and/or tumour registry linkage	Self-reported	Incidence, postmenopausal breast cancer	≥1.75 vs <1.60 m	1.28 (0.94-1.76) Ptrend<0.001	Age at menarche, parity, age at birth of first child, postmenopausal hormone use, oral contraceptive use, history of benign breast disease, maternal history of breast cancer, history of breast cancer in a sister, smoking status, education, fat intake, fibre intake, energy intake, alcohol intake
		3 208/			Incidence, postmenopausal	per 5 cm	1.07 (1.03-1.12)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					breast cancer			
					Incidence, postmenopausal breast cancer, HRT never users	per 5 cm	1.06 (1.00-1.13)	
					Incidence, postmenopausal breast cancer, HRT ever users	per 5 cm	1.09 (1.03-1.15)	
	AHS	87/				per 5 cm	1.10 (0.91-1.32)	
	CNBSS	242/				per 5 cm	0.99 (0.85-1.16)	
	IWHS	643/				per 5 cm	1.10 (1.03-1.17)	
	NLCS	420/				per 5 cm	1.2 (1.09-1.32)	
	NYSC	358/				per 5 cm	1.00 (0.92-1.09)	
	NHS (a)	571/				per 5 cm	1.04 (0.97-1.12)	
	NHS (b)	613/				per 5 cm	1.07 (1.00-1.15)	
	SMC	274/				per 5 cm	1.09 (0.97-1.23)	
Sonnenschein, 1999 BRE11604 USA	NYUWHS, Prospective Cohort, Age: 35-65 years, W	150/ 8 416 6.6 years	All histology	Measured	Incidence, breast cancer, postmenopausal	≥166.1 vs ≤154.9 cm	1.28 (0.75-2.18)	Age , age at first child, age at menarche, breast biopsies, family history

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Galanis, 1998 BRE03058 hawaii	Hawaii State Department of Health, 1975, Prospective Cohort, Age: 43 years, W	292/ 17 628 14.9 years	Partially histological - over 80%	Self reported in questionnaire	Incidence, breast cancer, postmenopausal	≥160.1 vs ≤154.9 cm	1.50 (1.10-2.10) Ptrend:0.008	Age , alcohol, educational level, ethnicity
Kaaks, 1998 BRE04522 Netherlands	DOM-project Utrecht, Prospective Cohort, Age: 39-73 years, W	76/ 11 480 7.1 years	Partially histological - over 80%	Measured	Incidence, breast cancer, postmenopausal	≥169.1 vs ≤160.8 cm	0.96 (0.46-1.98) Ptrend:0.53	Age , age at first child, age at menarche, menopausal status, parity/pregnancies
Tulinius, 1997 BRE12565 Iceland	Reykjavik Study, 1968, Prospective Cohort, Age: 45-59 years, W	343/ 11 580 27 years	Partially histological - over 80%	Measured	Incidence, breast cancer, postmenopausal	per 1 cm	1.02 (1.00-1.04)	Age
Freni, 1996 BRE02960 USA	NHANES I, Prospective Cohort, Age: 25-74 years, W	112/ 7 622 155 months	Medical records + death certificate	Measured	Incidence, breast cancer, postmenopausal	≥167 vs ≤155.9 cm	2.00 (1.00-3.80) Ptrend:0.04	Age , age at first child, age at menarche, educational level, family history
De Stavola,	Guernsey G2	95/	Partially	Measurements	Incidence, breast	≥166 vs ≤157.9	1.90 (1.10-3.30)	Age , body weight,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
1993 BRE02122 UK	and G3, Prospective Cohort, W	4 528 15 years	histological - over 80%	performed by trained personnel	cancer, postmenopausal	cm	Ptrend:0.02	family history, other age Indicator
Tornberg, 1988 BRE12418 sweden	Swedish cohort, 1963, Prospective Cohort, Age: 17-74 years, W, Screening Program	46 570 20 years	Partially histological - over 80%	Measured height and weight	Incidence, breast cancer, postmenopausal	per 5 cm	1.10 (1.07-1.13)	Age , place of residence

Table 608 Height and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Horn, 2014b BRE80564 Norway	NNTHS, Prospective Cohort, Age: 55 years, W, Postmenopausal	969/ 18 562 409 377 person-years	Cancer registry	Measured	Incidence, breast cancer, postmenopausal	≥170 vs ≤159 cm	1.36 (1.03-1.79) Ptrend:0.006	Age, birth cohort	Study superseded by Opdahl, 2011
						per 5 cm	1.08 (1.02-1.14)		
		734/			Incidence, breast cancer subtype	≥170 vs ≤159 cm	1.40 (1.03-1.90) Ptrend:0.03		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					classified, postmenopausal				
						per 5 cm	1.08 (1.01-1.15)		
		235/			Incidence, breast cancer unclassified subtype, postmenopausal	≥170 vs ≤159 cm	1.16 (0.60-2.25) Ptrend:0.10		
						per 5 cm	1.08 (0.96-1.21)		
		614/			Incidence, luminal breast cancer, postmenopausal	≥170 vs ≤159 cm	1.58 (1.15-2.18) Ptrend:0.01		
						per 5 cm	1.10 (1.02-1.18)		
		120/			Incidence, non-luminal breast cancer, postmenopausal	≥170 vs ≤159 cm	0.49 (0.15-1.60) Ptrend:0.89		
						per 5 cm	0.97 (0.82-1.14)		
		361/			Incidence, luminal A breast cancer, postmenopausal	≥170 vs ≤159 cm	1.59 (1.04-2.44) Ptrend:0.004		
						per 5 cm	1.14 (1.03-1.25)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		205/			Incidence, luminal B (HER2-) breast cancer, postmenopausal	≥170 vs ≤159 cm	1.62 (0.94-2.80) Ptrend:0.42		
						per 5 cm	1.07 (0.95-1.22)		
		48/			Incidence, luminal B (HER2+) breast cancer, postmenopausal	≥170 vs ≤159 cm	1.43 (0.54-3.81) Ptrend:0.55		
						per 5 cm	0.94 (0.72-1.22)		
		40/			Incidence, non-luminal (HER2+) breast cancer, postmenopausal	≥170 vs ≤159 cm	1.09 (0.24-4.90) Ptrend:0.43		
						per 5 cm	1.06 (0.80-1.41)		
		50/			Incidence, basal-like breast cancer, postmenopausal	≥170 vs ≤159 cm	0.33 (0.04-2.51) Ptrend:0.29		
						per 5 cm	0.88 (0.68-1.14)		
		30/			Incidence, five negative phenotype, postmenopausal	165-169 vs ≤159 cm	1.56 (0.60-4.02) Ptrend:0.86		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
						per 5 cm	1.01 (0.72-1.40)		
Kabat, 2013a BRE80439 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	2 316/ 88 256 16.2 years	Record linkages to cancer database and to the national mortality database	Height and weight measured at the Initial examination.	Incidence, postmenopausal breast cancer	per 10 cm	1.12 (1.05-1.20)	Age at entry, age at menarche, BMI, family history of breast cancer In first degree relatives, history of benign breast disease, hormone replacement therapy, oral contraceptive use, pack yrs of smoking, parity, years of education	Publication superseded by van den Brandy, 2000
Nyante, 2013 BRE80496 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W, Postmenopausal	5 247/ 192 076 9.6 years	Cancer registry	Self-reported	Incidence, ductal carcinomas	≥1.69 vs ≤1.57 m	1.12 (1.03-1.21) Ptrend:<0.01	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, breast biopsies, educational level, family history of breast cancer, HRT use, marital status, OC use, parity, race, type of menopause, vigorous activity	Excluded, results by breast cancer subtypes only, not analysed
		212/			Incidence, mucinous breast cancer	≥1.69 vs ≤1.57 m	1.42 (0.94-2.15) Ptrend:0.26		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		132/			Incidence, tubular breast cancer	≥1.69 vs ≤1.57 m	1.28 (0.81-2.04) Ptrend:0.32		
		822/			Incidence, lobular carcinoma	≥1.69 vs ≤1.57 m	1.19 (0.97-1.46) Ptrend:0.05		
		633/			Incidence, ductal-lobular breast cancer	≥1.69 vs ≤1.57 m	1.33 (1.06-1.67) Ptrend:0.02		
Ritte, 2013b BRE80431 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 25-70 years, W	306 600 3 297 579 person-years	Cancer registry, record linkage, health Insurance records, pathology and active follow up	Self-reported or measured	Incidence, breast cancer ER+/PR+, age 50-60	≥165 vs ≤159 cm	1.21 (1.05-1.39)	Age, age at first child birth, age at menopause, alcohol, breastfeeding, educational level, HRT use, leg length, menopausal status, oral contraceptive history, parity, physical activity, sitting height, smoking, study center, time since menopause, waist circumference	Results by breast cancer subtype, not analysed
					ER+/PR+, age >= 60 years	≥165 vs ≤159 cm	1.36 (1.20-1.55)		
Schairer, 2013 BRE80568	BCSC, Nested Case	5 856/ 93 654	Seer registry/hospital	Self-reported	Incidence, non-inflammatory	≥67 vs ≤62 inch	1.15 (0.91-1.45)	Age at first child birth, BMI, breast biopsies,	Excluded, insufficient

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
USA	Control, W		records/pathology	height and weight In the questionnaire completed closest in time before or on the date of diagnosis	breast cancer, peri/postmenopausal			educational level, family history of breast cancer In first degree relatives, mammographic density, parous/nulliparous, race/ethnicity	data
		896/			Incidence, non-inflammatory locally advanced breast cancer, peri/postmenopausal	≥67 vs ≤62 inch	1.22 (0.73-2.03)		
		435/			Incidence, Inflammatory breast cancer, peri/postmenopausal	≥67 vs ≤62 inch	1.50 (0.57-3.93)		
Canchola, 2012 BRE80401 USA	CTS, Prospective Cohort, Age: 56-70 years, W, Postmenopausal	1 371/ 56 542 12.1 years	Cancer registry and national death Index	Self-reported	Incidence, breast cancer ER+/PR+	≥67 vs <63 inch	1.35 (1.15-1.59) Ptrend:<0.01	Age at baseline, age at first child birth, age at menarche, alcohol, breast biopsies, family history of breast cancer, HRT use, parity	Excluded, results by breast cancer subtypes only, not analysed
						per 1 inch	1.03 (1.01-1.05)		
		287/			Incidence, breast	≥67 vs <63	1.55 (1.07-2.25)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					cancer ER+/PR-	inch	Ptrend:0.05		
						per 1 inch	1.06 (1.01-1.11)		
		280/			Incidence, breast cancer ER-/PR-	≥67 vs <63 inch	1.19 (0.84-1.68) Ptrend:0.29		
						per 1 inch	1.00 (0.96-1.05)		
Fagherazzi, 2012b BRE80412 France	E3N EPIC-France, Prospective Cohort, Age: 40-65 years	306/ 50 704 6 years	Pathology	Self-reported	Incidence, breast cancer, postmenopausal	≥165 vs ≤158 cm	1.22 (1.06-1.40) Ptrend:0.002	Age at first child birth, age at menarche, age at menarche, age at menopause, benign breast disease, birth length, birthweight, breastfeeding, educational level, family history of breast cancer, HRT use, mammography, oral contraceptive use, parity, physical activity, progesterone	Publication superseded by Lahmann, 2004a
		1 456/			Incidence, breast cancer ER+, postmenopausal	≥165 vs ≤158 cm	1.33 (1.13-1.57) Ptrend:<0.001		
		303/			Incidence, breast cancer ER-, postmenopausal	≥165 vs ≤158 cm	0.85 (0.61-1.19) Ptrend:0.589		
Fagherazzi, 2012a	E3N EPIC-France,	944/ 63 726	Self report verified by	Self-reported	Incidence, breast cancer ER+/PR+,	≥164 vs ≤158.9 cm	1.15 (0.98-1.35) Ptrend:0.09	Age at first child birth, age at menarche, age	Results by breast cancer

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
BRE80539 France	Prospective Cohort, Age: 40-65 years, W	582 144 person-years	medical record and pathology report		postmenopausal			at menopause, alcohol Intake, breastfeeding, educational level, family history of breast cancer, history of benign breast disease, mammography, non-alcohol energy, OC use, parous/nulliparous, smoking status, total physical activity, use of HRT, year of birth	subtypes, not analysed; Publication superseded by Lahmann, 2004a
		243/			Incidence, breast cancer ER-/PR-, postmenopausal	≥164 vs ≤158.9 cm	1.02 (0.75-1.39) Ptrend:0.86		
		302/			Incidence, breast cancer ER+/PR-, postmenopausal	≥164 vs ≤158.9 cm	1.26 (0.97-1.63) Ptrend:0.09		
		52/			Incidence, breast cancer ER-/PR+, postmenopausal	≥164 vs ≤158.9 cm	2.12 (0.96-4.68) Ptrend:0.08		
Harlid, 2012 BRE80422 Sweden	NSHDC (VIP and MSP), Prospective Cohort, Age: 27-95	873/ 3 994	Cancer registry	Self-reported In a questionnaire	Incidence, breast cancer, >50 years	≥166 vs ≤162	1.22 (0.99-1.51)	Age	Excluded, study (VSP) overlapped with Wiren, 2014

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	years, W								
Harlid, 2012 BRE80421 Sweden	MDCS, Prospective Cohort, Age: 45-84 years, W	656/ 17 035 16 years	Cancer registry	Measured	Incidence, breast cancer, >50 years	≥166 vs ≤162 cm	0.94 (0.74-1.19)	Age	Publication superseded by Lahmann, 2004a
Mellemkjær, 2012 BRE80414 Denmark	DCH, Prospective Cohort, Age: 50-64 years, W, Postmenopausal	1 209/ 23 864 11.8 years	Cancer registry	Measured	Incidence, breast cancer	per 5 cm	1.11 (1.06-1.16)	Age, age at first child birth, age at menarche, alcohol, BMI, educational level, HRT use, parity	Study superseded by Lahmann, 2004a
		742/			Incidence, breast cancer ER+	per 5 cm	1.08 (1.01-1.15)		
		169/			Incidence, breast cancer ER-	per 5 cm	1.00 (0.88-1.14)		
		710/			Incidence, ductal carcinomas	per 5 cm	1.06 (1.00-1.13)		
		129/			Incidence, lobular carcinoma	per 5 cm	1.10 (0.95-1.28)		
Manders, 2011 BRE80314 Netherlands	HEBON, Historical Cohort, W,	63/ 719 10 years	Cancer registry	Self-reported	Incidence, breast cancer, postmenopausal	1.67-12.9 vs ≤1.66 m	1.67 (1.01-2.74)	HRT use, parity, physical activity, type of menopause	Excluded, insufficient data

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Subjects with BRCA1/2 mutation								
Borgquist, 2009 BRE80214 Sweden	MDCS, Prospective Cohort, Age: 61 years, W, Postmenopausal	231/ 9 685 10.3 years	Cancer registry	Measured	Incidence, breast cancer, peri/postmenopausal	≥1.68 vs ≤1.59 m	1.33 (0.90-1.96) Ptrend:0.08	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, educational level, marital status, occupation, oophorectomy/hysterectomy, oral contraceptive use, parity, smoking habits	Publication superseded by Lahmann, 2004a (also reported results by breast cancer subtypes)
Chang, 2006 BRE80110 USA	PLCO, Prospective Cohort, Age: 55-74 years, W, participants of a RCT	764/ 38 660 4.9 years	Cancer screening programme	Self-reported In questionnaire	Incidence, breast cancer, postmenopausal	≥1.68 vs ≤1.57 meters	1.33 (1.05-1.67) Ptrend:0.012	Age at first child, age at menarche, age at menopause, benign breast disease, BMI, educational level, energy Intake , ethnicity, family history, height, HRT use, parity/pregnancies, physical activity , recruitment center	Publication superseded by Lacey, 2009
Tehard, 2006 BRE80103 France	E3N EPIC-France, Prospective	1 468/ 69 116 3.6 years	Patient records/direct contact/health	Self-reported In questionnair	Incidence, breast cancer, postmenopausal	≥165 vs ≤157.9 cm	1.06 (0.83-1.34) Ptrend:>0.05	Age at first child, age at menarche, age-underlying cox	Study superseded by Lahmann,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	Cohort, Age: 40-65 years		Insurance records	e				models, alcohol, benign breast disease, educational level, family history, marital status, parity/pregnancies, physical activity	2004a
Wirfält, 2005 BRE11111 Sweden	MDCS, Nested Case Control, Age: 50- years, Postmenopausal	237/ 673 controls	Cancer registry	Measured	Incidence, breast cancer	(mean exposure)			Publication superseded by Lahmann, 2004a
Mattisson, 2004a BRE17807 Sweden	MDCS, Prospective Cohort, Age: 50- years, W, Postmenopausal	342/ 11 726 7.6 years	Partially histological - over 80%	Measured	Incidence, breast cancer, postmenopausal	(mean exposure)			Publication superseded by Lahmann, 2004a
Sweeney, 2004 BRE80599 USA	IWHS, Prospective Cohort, Age: 61 years, W, Postmenopausal	1 297/ 36 658 16 years	Seer registry	Self-reported	Incidence, breast cancer, 65 - 74 years	≥67 vs ≤62 inch	1.41 (1.19-1.67) Ptrend:<0.0001	Age at baseline, age at first child birth, age at menarche, age at menopause, BMI, educational level, family history of breast cancer, parity	Publication superseded by van den Brandy, 2000
		428/			55 - 64 years	≥67 vs ≤62 inch	1.11 (0.82-1.49) Ptrend:.46		
		561/			Aged 75-84	≥67 vs ≤62	1.40 (1.08-1.82)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
						inch	Ptrend:0.005		
Wirfalt, 2004 BRE17083 Sweden	MDCS, Nested Case Control, Age: 50- years, W, Postmenopausal	12 803 8 years	Partially histological - over 80%	Measured	Incidence, breast cancer, postmenopausal	(mean exposure)			Publication superseded by Lahmann, 2004a
Lahmann, 2003 BRE20119 Sweden	MDCS, Prospective Cohort, Age: 50-73 years, W, Postmenopausal	236/ 12 159 5.7 years	Cancer registry + death certificate	Measured	Incidence, Invasive & In situ breast cancer	≥169.1 vs ≤158.9 cm	1.41 (0.92-2.17) Ptrend:0.009	Age , age at first child, age at menarche, alcohol, body weight, height, marital status, OC use, occupation, parity/pregnancies, smoking habits	Study superseded by Lahmann, 2004a
Morimoto, 2002 BRE20457	Women's Health Initiative - Observational study, Prospective Cohort, Age: 50-79 years, Postmenopausal	1 024/ 85 917 34.8 months	Medical records + self-reported	Measurements performed by clinical staff	Incidence, breast cancer, postmenopausal	≥167.1 vs ≤156.4 cm	1.27 (1.00-1.62) Ptrend:0.09	Age , age at first child, age at menarche, age at menopause, alcohol, educational level, energy Intake , ethnicity, family history, leisure time physical activity, parity/pregnancies, smoking habits	Study superseded by Kabat, 2013b
Saadatian-Elahi, 2002 BRE21486 USA	NYUWHS, Nested Case Control, Age: 34-65	106/ 106 controls 4.3 years	Partially histological - over 80%		Incidence, breast cancer, postmenopausal	(mean exposure)			Publication superseded by Sonnenschein, 1999

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	years, W								
Sellers, 2002 BRE20892 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	1 368/ 37 105 13 years	Partially histological - over 80%	Self-reported	Incidence, breast cancer, family history of breast cancer - no and postmenopausal	≥66.1 vs ≤62 inch	1.02 (0.85-1.22) Ptrend:0.55	Age at first child, age at menarche, age at menopause, alcohol, BMI, body weight, educational level, family history, HRT use, OC use, parity/pregnancies, physical activity , smoking habits, whr	Publication superseded by van den Brandy, 2000
		282/			Family history of breast cancer - yes and postmenopausal	≥66.1 vs ≤62 inch	1.18 (0.82-1.69) Ptrend:0.46		
		1 043/			Incidence, breast cancer ER+, postmenopausal	≥66.1 vs ≤62 inch	1.13 (0.92-1.39)		
		232/			Incidence, breast cancer ER-, postmenopausal	≥66.1 vs ≤62 inch	1.33 (0.84-2.11)		
		993/			Incidence, breast cancer PR+, postmenopausal	≥66.1 vs ≤62 inch	1.09 (0.87-1.37)		
		362/			Incidence, breast cancer PR-,	≥66.1 vs ≤62 inch	1.45 (1.01-2.08)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
					postmenopausal				
Wirfalt, 2002 BRE13504 Sweden	MDCS, Nested Case Control, Age: 50- years, W, Postmenopausal	237/ 673 controls 8 years	Partially histological - over 80%	Measured	Incidence, breast cancer, postmenopausal	(mean exposure)			Publication superseded by Lahmann, 2004a
Manjer, 2001b BRE17790 Sweden	MPP, Prospective Cohort, Age: 55 years, W	157/ 9 738 13.1 years	Partially histological - over 80%	Measured by trained personnel	Incidence, Invasive breast cancer, postmenopausal	≥168.1 vs ≤160 cm	1.78 (1.14-2.77) Ptrend:0.008	Age	Publication superseded by Wiren, 2014
Manjer, 2001a BRE80623 Sweden	MPP, Prospective Cohort, Age: 49.9 years, W, Non smokers	50/ 2 082 13.3 years	Cancer registry	Measured by trained personnel	Incidence, Invasive & In situ breast cancer, peri/postmenopause	per 1 cm	1.04 (0.99-1.09)	Age, HRT use, OC use	Publication superseded by Wiren, 2014
Palmer, 2001 BRE20603 USA	BWHS, Nested Case Control, Age: 21-69 years, W	175/ 1659 controls 2 years	Medical records + self-reported	Self-reported in questionnaire	Incidence / prevalence, Invasive & In situ breast cancer, postmenopausal	≥70 vs ≤61.9 inch	1.30 (0.60-2.50) Ptrend:0.29	Age , age at menarche, educational level	Excluded, results included incidence and prevalence cases
Berkey, 1999 BRE00743 USA	NHS, Prospective Cohort, Age: 30-55	1 485/ 65 140 16 years	Partially histological - over 80%	Self-reported in questionnaire	Incidence, breast cancer, postmenopausal	≥67 vs ≤62 inch	1.29 Ptrend:0,005	Age , age at menarche, age at menopause, alcohol, benign breast disease, family history,	Publication superseded by van den Brandy, 2000

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	years, W, Registered nurses							height, other anthropometric Index, other anthropometric Index, smoking habits, socio-economic status	
van den Brandt, 1997 BRE12717 Netherlands	NLCS, Case Cohort, Age: 55-69 years, W, Postmenopausal	553/ 4.3 years	All histology	Self-reported in questionnaire	Incidence, Invasive breast cancer, postmenopausal	per 10 cm	1.35 (1.15-1.59)	Age , age at first child, age at menarche, alcohol, parity/pregnancies	Publication superseded by van den Brandy, 2000
						≥175 vs ≤155 cm	2.06 (1.17-3.63) Ptrend:<0.001		
den Tonkelaar, 1995 BRE02224 Netherlands	DOM-project Utrecht, Prospective Cohort, Age: 40-73 years, W, Screening Program	38/ 9 491 4 years	Not specified	Measurements performed by trained personnel	Incidence, breast cancer, postmenopausal	≥1.66 vs ≤1.61 m	1.51 (0.69-3.42) Ptrend:0.18	Age	Publication superseded by Kaaks, 1998
Toniolo, 1994 BRE12398 USA	NYUWHS, Nested Case Control, Age: 35-65 years, W	101/ 465 controls 7 years	Medical records	Questionnaire self-reported	Incidence, Invasive breast cancer, postmenopausal	≥168 vs ≤157.9 cm	1.90 (0.96-3.78) Ptrend:0.07		Publication superseded by Sonnenschein, 1999
den Tonkelaar, 1994	DOM-project Utrecht,	9 746	Partially histological -	Direct measures by	Incidence, breast cancer,	≥166 vs ≤157 cm	1.00 (0.70-1.43) Ptrend:0.99	Age	Publication superseded by

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
BRE02222 Netherlands	Prospective Cohort, Age: 49-66 years, W, Postmenopausal	12.5 years	over 80%	trained assistants	postmenopausal				Kaaks, 1998
Barrett-Connor, 1993 BRE00581 USA	Rancho Bernardo, 1972, Prospective Cohort, Age: 40-79 years, W	15/ 590 15 years	Medical records + death certificate	Measured	Incidence, breast cancer, postmenopausal	(mean exposure)		Age	Excluded, mean exposure comparison only
Vatten, 1990d BRE12827 Norway	NNHSS, 1974, Prospective Cohort, Age: 35-51 years, W	99/ 23 831 12.5 years	Partially histological - over 80%	Measured	Incidence, breast cancer, postmenopausal	≥167 vs ≤158.9 cm	1.62 (0.93-2.81) Ptrend:0.06	Age	Study superseded by Wiren, 2014
London, 1989 BRE80626 USA	NHS, Prospective Cohort, Age: 30-55 years, W	420/ 115 534 743 716 person-years	Self report verified by medical record	Self-reported	Incidence, Invasive breast cancer, postmenopausal	reference error: no min from refernce			Publication superseded by van den Brandy, 2000
Le Marchand, 1988 BRE15836	Hawaii 1942, 1960, 1972, Nested Case	39/ 172 controls	All histology	From drive licence	Incidence, breast cancer, postmenopausal	q 3 vs q 1	1.18 (0.34-4.06) Ptrend:0.99	Husband occupation, other anthropometric Index	Excluded, insufficient data

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
USA	Control, W								

Figure 640 RR estimates of postmenopausal breast cancer by height

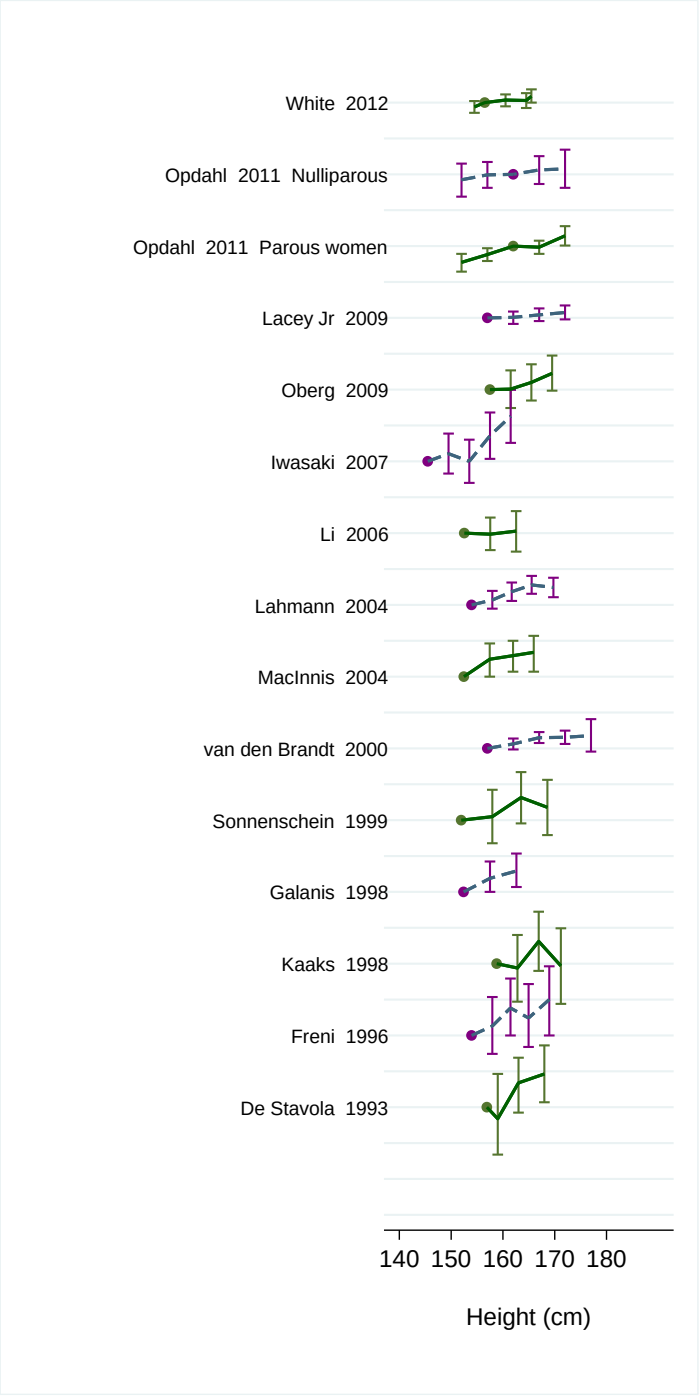


Figure 641 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest level of height

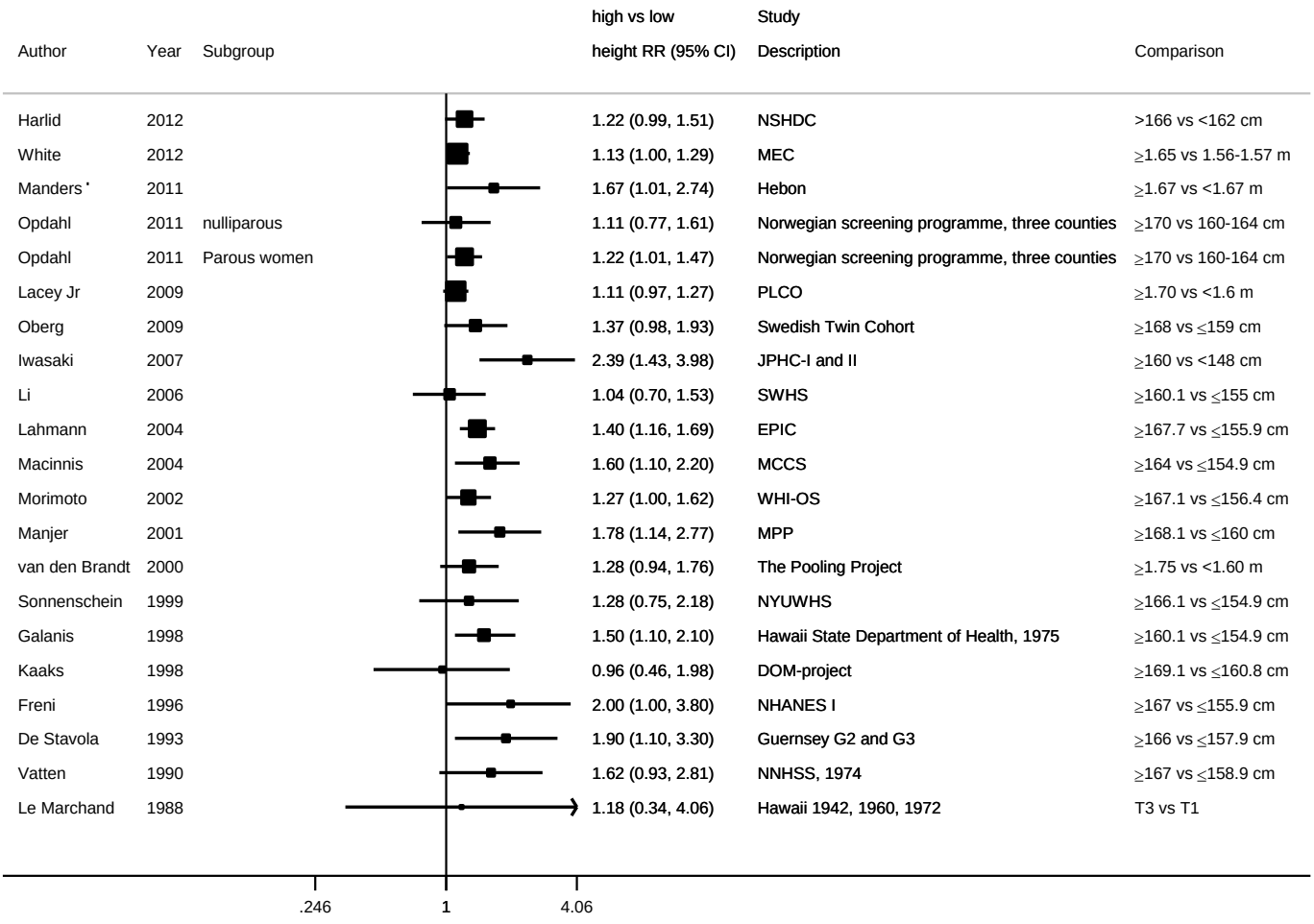


Figure 642 Relative risk of postmenopausal breast cancer for 5 cm increase of height

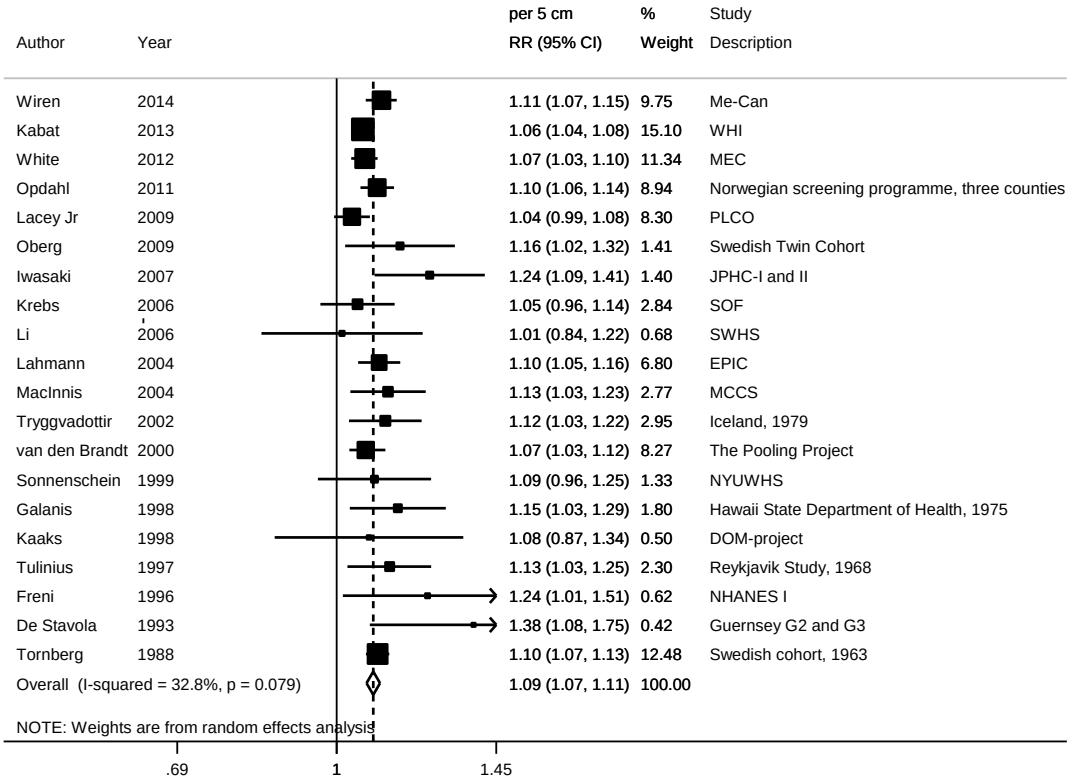


Figure 643 Funnel plot of studies included in the dose response meta-analysis of height and postmenopausal breast cancer

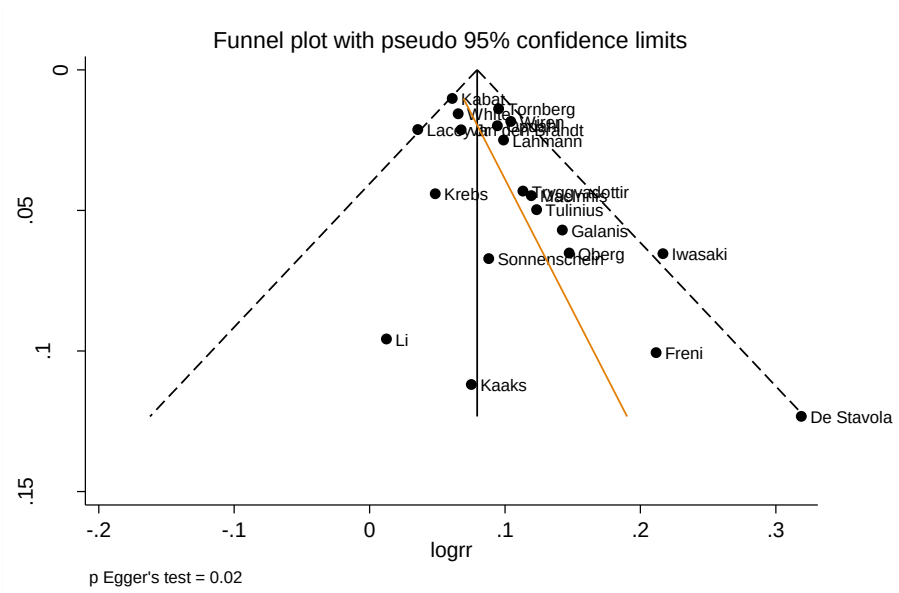


Figure 644 Relative risk of postmenopausal breast cancer for 5 cm increase of height, by geographic location

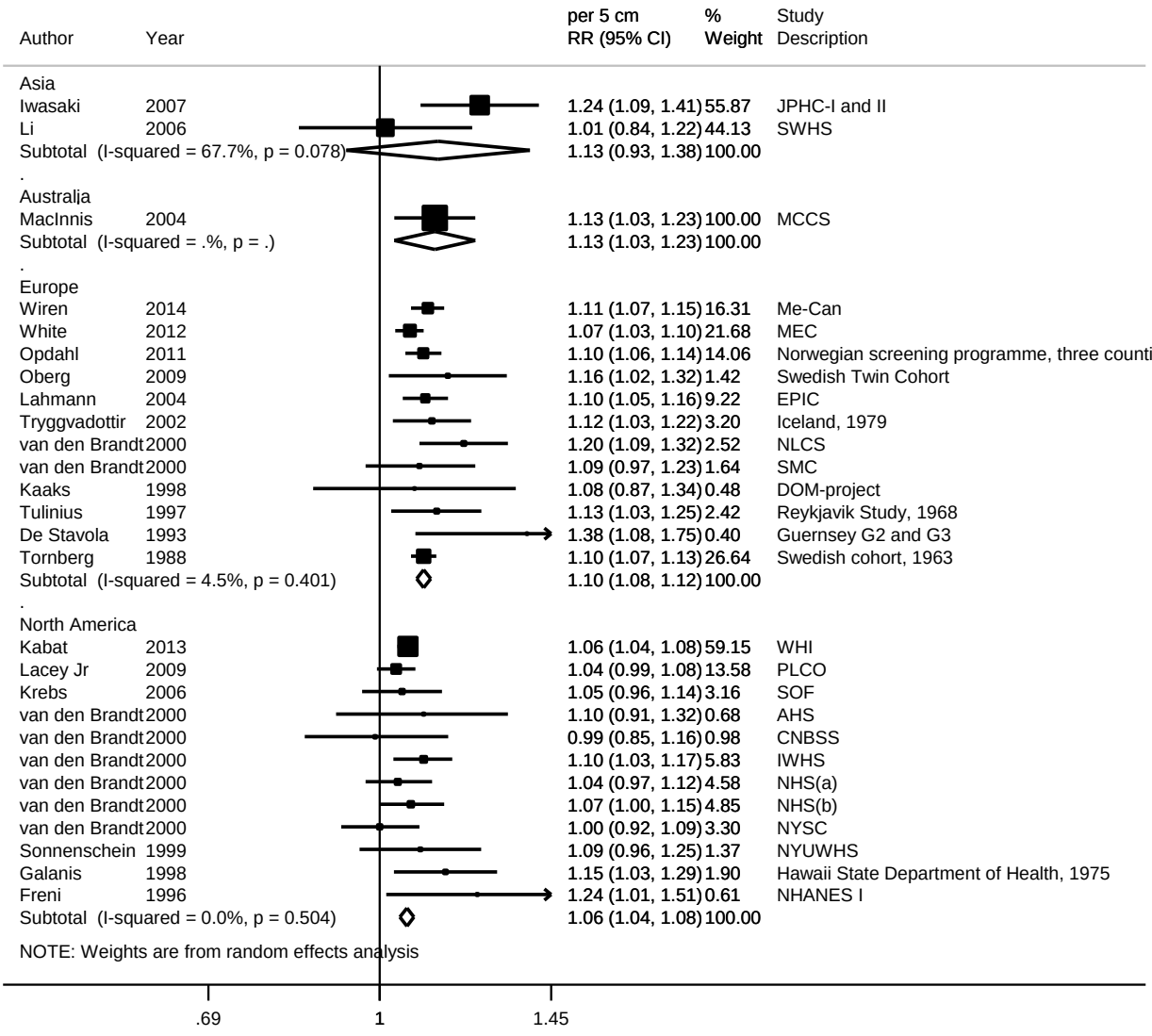


Figure 645 Relative risk of postmenopausal breast cancer for 5 cm increase of height, by anthropometric measurement methods

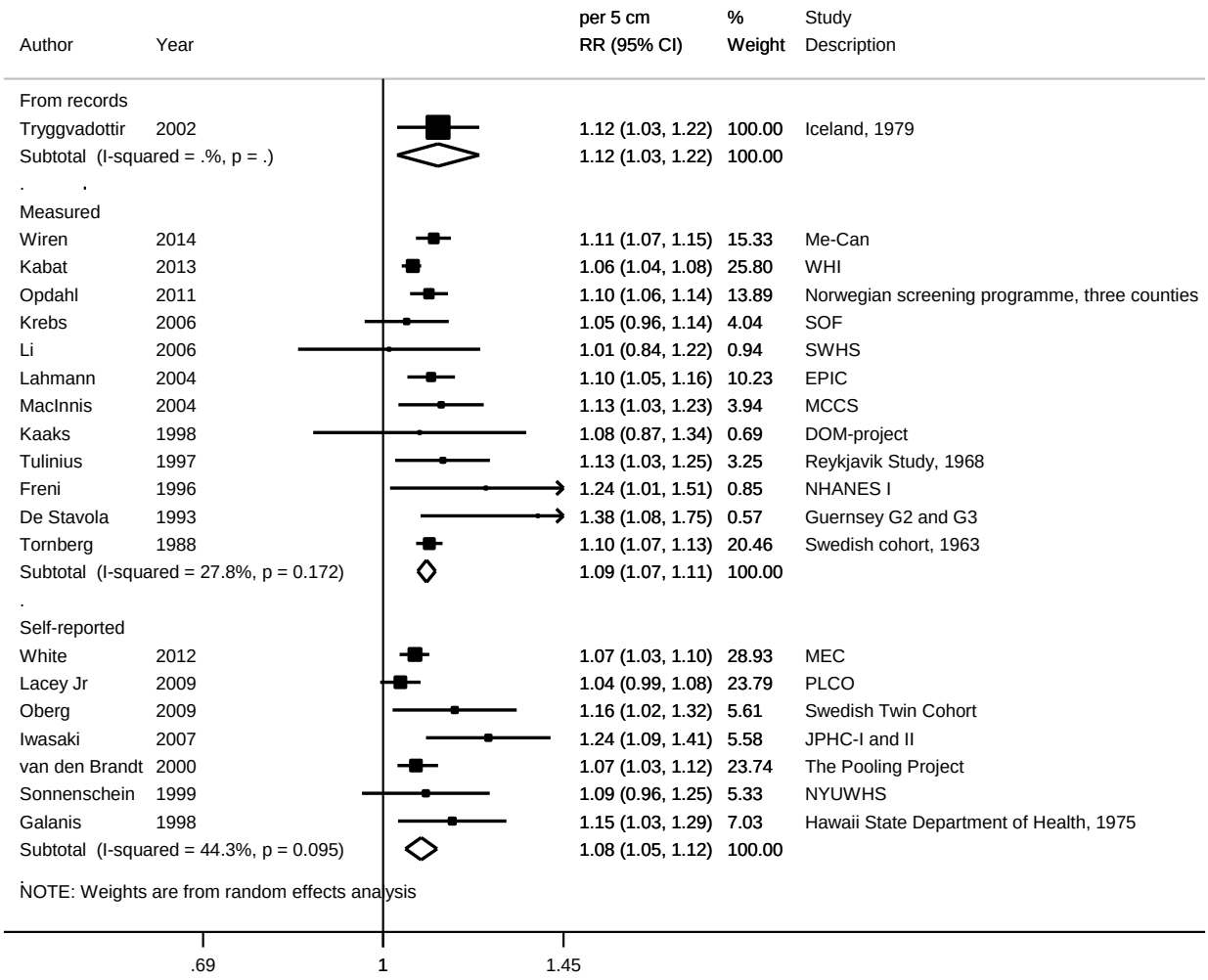
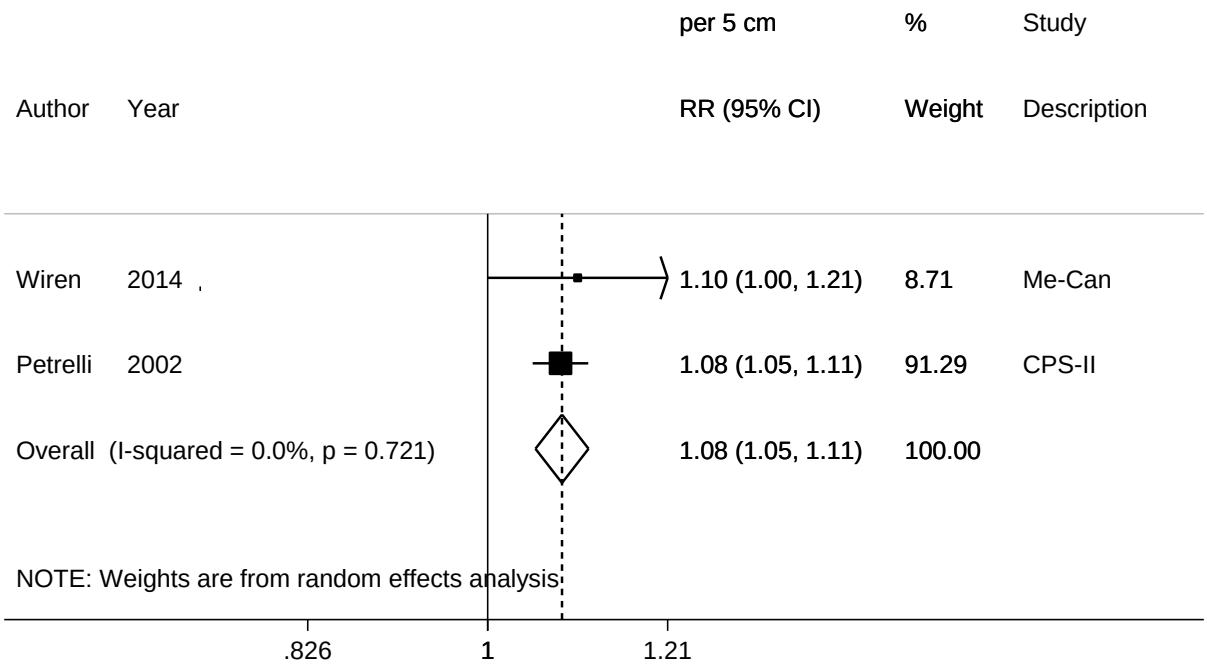


Figure 646 Relative risk of postmenopausal breast cancer mortality for 5 cm increase of height



Note: The highest versus the lowest forest plot was not produced because only Petrelli, 2002 reported categorical results (RR for ≥69 versus <60 inches=1.66, 95% CI= 1.19-2.30)

8.4.1 Birthweight

Cohort studies

Overall summary

Twenty-nine publications from 40 studies were identified. This included one pooled study on breast cancer incidence (dos Santos Silva, 2008, 32 studies).

Dose-response meta-analyses were conducted to examine the association of birthweight with risk of breast cancer, and with premenopausal and postmenopausal breast cancer.

Table 609 Summary of results of the dose-response meta-analysis in the 2016 CUP SLR

	Breast cancer	Premenopausal breast cancer	Postmenopausal breast cancer
Increment unit used	500 g	500 g	500 g
Studies (n)	19	16	14
Cases	24 904	>3 135	> 17 981
RR (95%CI)	1.01 (0.98-1.04)	1.05 (1.02-1.09)	1.00 (0.98-1.02)
Heterogeneity (I^2, p-value)	62%, 0.02	0%, 0.85	0%, 0.48
P value Egger test	0.18	-	-

Breast cancer (any)

Summary

Main results:

Nineteen out of 38 studies (21 publications) could be included in the dose-response meta-analysis. The pooled study (dos Santos, Silva, 2008) (32 studies – 16 cohorts, 13 case-control studies, 1 cohort of pre-matured babies, 2 twin studies) conducted subgroup analysis by study designs, thus only dose-response results that were derived from 13 cohorts and one nested-case control study (14 studies in total) were included in the meta-analysis.

No significant association was observed between birthweight and risk of breast cancer (summary RR per 500 g=1.01 95% CI=0.98-1.04). High heterogeneity between studies was observed (I^2=62%, P=0.02), which could be partly explained by how birthweight was assessed. A borderline significant positive association was observed in the 12 studies that used birth records (summary RR=1.04, 95% CI=1.00-1.09; I^2=0%, P=0.65), but not studies that relied on parental recalls nor self-report during adulthood (summary RRs=1.08, 95% CI=0.95-1.22, 3 studies and 0.99, 95% CI=0.97-1.01, 4 studies, respectively) (I^2=84%, P=0.01 and I^2=0%, P=0.45, respectively)

There was no significant evidence of publication or small study bias (P Egger's test=0.18). Visual inspection of the funnel plot showed asymmetry, which could be influenced by the small study with a strong positive association (dos Santos Silva, 2008, MDCS).

A total of 19 studies and 16 publications were excluded from the meta-analysis. This included 16 non-overlapping studies from the pooled study (dos Santos, Silva, 2008) and three other studies with insufficient data (Bukowski, 2012; Lof, 2007b; Mogren, 1999). Two studies reported significant positive associations for high compared with low birthweight (Bukowski, 2012; Lof, 2007b). An increased rate of breast cancer with high birthweight was observed among the Swedish cohort compared with the expected rate in the local population, but the number of cases were low (Mogren, 1999).

One study reported results by breast cancer hormone-receptor status observed similar non-significant positive associations with ER-positive and ER-negative breast cancers (Ahlgren, 2003).

Sensitivity analyses:

Summary RR remained similar when studies were omitted in turn in influence analysis. When RR estimates for the highest versus the lowest birthweight comparison were pooled in a sensitivity analysis, the summary RR was 1.08 (95% CI=0.95-1.24, 21 studies) (I^2=77%, P<0.001).

Nonlinear dose-response meta-analysis:

Nonlinear dose-response meta-analysis was not conducted due to low number of studies.

Study quality:

Most studies obtained the information on birthweight directly from birth records, which could be less prone to measurement errors. Other studies either asked the parents or the participants

to recall the information. When stratified by the sources of information, on average, studies that used birth records observed a borderline significant positive association but not in studies that used parental recalls or adult reports.

Case ascertainment was through cancer registries or confirmed through medical records. Not all studies adjusted for age, alcohol intake, reproductive factors, and adult BMI. The pooled study (dos Santos Silvea, 2008) tested several potential confounding factors including adult BMI and found RR estimates of similar magnitude.

Table 610 Birthweight and breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	38 (21 publications)
Studies included in forest plot of highest compared with lowest exposure	21 (7 publications)
Studies included in linear dose-response meta-analysis	19 (5 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 611 Birthweight and breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and 2016 CUP

	2005 SLR[1]	**CUP SLR**	
Increment unit used	1 kg	500 g	
Studies (n)	5	19	
Cases	2 658	24 904	
RR (95%CI)	1.07 (1.03-1.11)	1.01 (0.98-1.04)	
Heterogeneity (I^2, p-value)	8%	62%, 0.02	
P value Egger test	-	0.18	
Stratified analyses in the CUP SLR			
Geographic location	**North America**	**Europe**	
Studies (n)	4	15	
Cases	4 786	20 118	
RR (95%CI)	1.04 (0.93-1.16)	1.01 (0.99-1.04)	
Heterogeneity (I^2, p-value)	78%, 0.01	21%, 0.22	
Adjustment for age, adult BMI	**Adjusted**	**Not adjusted**	
Studies (n)	4	15	
Cases	19 203	5 701	
RR (95%CI)	1.02 (0.97-1.07)	1.02 (0.99-1.05)	
Heterogeneity (I^2, p-value)	79%, 0.01	0%, 0.44	

Exposure assessment methods	**Parental recalls**	**Adult reports**	**Birth records**
Studies (n)	3	4	12
Cases	3 437	19 311	2 156
RR (95%CI)	1.08 (0.95-1.22)	0.99 (0.97-1.01)	1.04 (1.00-1.09)
Heterogeneity (I^2, p-value)	84%, 0.01	0%, 0.45	0%, 0.65

[1]Meta-analysis was not conducted in the 2008 SLR.

Table 612 Birthweight and breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Xu, 2009	18 studies (7 cohorts, 11 case-control studies)	16 424	China, Europe, USA	Incidence, breast cancer (women of all ages)	Highest vs lowest (8 studies) Per 1 kg (16 studies)	1.20 (1.08-1.34) 1.07 (1.02-1.12)	0%, 0.72 40%, <0.05
Park, 2008	34 studies (15 cohorts, 19 case-control studies)	24 262 (14 579 from case-control studies, 9 683 from cohort studies)	China, Denmark, Poland, Sweden, UK, USA	Incidence, any breast cancer	Analysis by three birth weight categories: All studies (n=12): ≥4000 vs <3000 g 3000-3999 vs <3000 g Cohort studies	 1.15 (1.01-1.31) 1.06 (0.98-1.14) 1.21 (0.80-1.82)	 0.27 0.93

					(n=4): ≥4000 vs <3000 g 3000-3999 vs <3000 g Case-control studies (n=8): ≥4000 vs <3000 g 3000-3999 vs <3000 g Analysis by two birth weight categories: All studies (n=16): ≥/>3000 vs </≤3000 g	1.01 (0.79-1.31) 1.15 1.00-1.33 1.06 0.98-1.15 1.09 (1.02-1.18) 1.33 (1.09-1.61)	

					Cohort studies (n=6): ≥/>3000 vs </≤3000 g Case-control studies (n=10): ≥/>3000 vs </≤3000 g	1.06 (0.98-1.15)	

*All cohort studies identified were included in the present review. The summary RR for the highest versus the lowest birthweight was 1.08 (95% CI=0.95-1.24) (I^2=77%, P<0.001) when 21 studies in the prevent review were pooled in a sensitivity analysis.

Table 613 Birthweight and breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Spracklen, 2014 BRE80523 USA	WHI-OS, Prospective Cohort, Age: 50-79 years, W	4 111/ 56 526 11.3 years	Self-report verified by medical record	Adult reports	Incidence, breast cancer	≥10 vs 6-7.9 lb	0.77 (0.63-0.94) Ptrend:0.54	Age, alcohol, BMI, educational level, race, smoking, socio-economic status	
Yang, 2014 BRE80521 UK	MWS, Prospective Cohort, Age: 50-64 years, W	14 542/ 453 023 9.2 years	Cancer registry	Adult reports	Incidence, breast cancer	≥4 vs ≤2.4 kg	0.95 (0.91-1.00)	Age, age at first child birth, age at menarche, alcohol, BMI, breastfeeding, exercise, height, HRT use, maternal and paternal height, parity, region, ses, smoking, smoking habbits, year of birth	
						per 1 kg	0.98 (0.92-1.03)		
Hajiebrahimi, 2013 BRE80488 Sweden	Swedish Twin Cohort, Nested Case Control, W	543/ 2715 controls 36 years	Cancer registry	Records at twin registry	Incidence, breast cancer	≥3500 vs 2500-2999 g	1.18 (0.76-1.83)	Matched by year of birth	
						per 1 kg	0.96 (0.80-1.16)		
dos Santos Silva, 2008 USA and Europe	Pooled study of 32 studies* w	5 069 cases/ 559 169 non-cases	Cancer registries, medical records, mortality	From birth records, parental reports, or adult reports	Incidence, breast cancer, Cohort studies	≥4.0 vs 3.0-<3.49	1.05 (0.96-1.15) Ptrend;0.19	Age at diagnosis, stratified by calendar year	Included in meta-analysis
		5 247 cases/			Nested case-	≥4.0 vs 3.0-	1.10 (0.90-1.33)	Matched by year	Included in

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		26 196 non-cases	registries, death certifications, self-reports		control study	<3.49	Ptrend;0.56	of birth, calendar period, recruitment centre, area of residence, or ethnicity	meta-analysis (Data from MDCS)
		2 331 cases/ 7 422 non-cases			Individual matched case-control studies	≥4.0 vs 3.0-<3.49	1.18 (1.02-1.37) Ptrend;0.02		Not used in meta-analysis
		8 736 cases/ 10 174 non-cases			Frequency matched case-control studies	≥4.0 vs 3.0-<3.49	0.98 (0.83-1.15) Ptrend;0.10		Not used in meta-analysis
	MDCS	89 cases/ 238 non-cases		Birth records		Per 0.5 kg	1.14 (0.91-1.42)		
	MRC NSHD	81 cases/ 2 085 non-cases		Birth records		Per 0.5 kg	1.10 (0.88-1.37)		
	HBCS I	174 cases/ 3 270 non-cases		Birth records		Per 0.5 kg	1.11 (0.95-1.29)		
	PSWG	38 cases/ 703 non-cases		Birth records		Per 0.5 kg	1.22 (0.93-1.62)		
	CSHRR	2 887 cases/ 107 003 non-cases		Parental recalls		Per 0.5 kg	1.02 (0.99-1.05)		
	UBCoS Multigen	384 cases/ 5 141 non-cases		Birth records		Per 0.5 kg	1.02 (0.93-1.13)		
	SOUHCB	311 cases/ 15 700 non-cases		Birth records		Per 0.5 kg	1.07 (0.95-1.19)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	NCI DES	125 cases/ 5 722 non-cases		Birth records		Per 0.5 kg	0.97 (0.83-1.14)		
	UKWCS	456 cases/ 21 415 non-cases		Adult reports		Per 0.5 kg	1.01 (0.93-1.09)		
	ACONF	66 cases/ 4 972 non-cases		Birth records		Per 0.5 kg	1.03 (0.80-1.33)		
	EPIC-Norfolk	202 cases/ 12 286 non-cases		Adult reports		Per 0.5 kg	0.92 (0.84-1.01)		
	HBCS II	199 cases/ 3 931 non-cases		Birth records		Per 0.5 kg	1.04 (0.90-1.22)		
	HBCS III	101 cases/ 1 984 non-cases		Birth records		Per 0.5 kg	1.06 (0.85-1.31)		
	SYFBC	45 cases/ 374 957 non-cases		Birth records		Per 0.5 kg	1.35 (1.01-1.81)		
*Cohort studies: MRC NSHD; HBCS I; PSWG; CSHRR; UBCoS Multigen; SOUHBC; NCI DES; UKWCS; ACONF; EPIC-Norfolk; HBCS II; HBCS III; SYFBC study; Nested case-control studies: NHS I; NHS II; MDCS; Individually-matched case-control studies: SPNFBC; NYSEOBC; TBPCCS; DPCCS; Frequency-matched case-control studies: Seattle BCYW; Seattle BCMW; Seattle PFBC; SBCS; CmsBCS; CBCS; PBCS; WEB; CARE; Twin studies: SLSTS; SOSTS; Study of premature babies: SPVLBW									
Michels, 1996b BRE80621 USA	NHS I and II, Nested Case Control, W	550/ 1478 controls 16 years	Self-report verified by medical record	Self-reported by mothers	Incidence, Invasive breast cancer	<2500 vs ≥4000 g	0.55 (0.33-0.93)	Age, age at first child birth, age at menarche, BMI, cohort, family history of breast cancer, parity	

Table 614 Birthweight and breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Andersen, 2014 BRE80511 Denmark	CSHRR, Historical Cohort, Age: 50-69 years, W	716/ 13 572 184 175 person-years	Cancer registry	Reported by parents	Incidence, breast cancer	per 1 unit	0.88 (0.74-1.05)	Age-underlying cox models, birth cohort, mammographic density	Superseded by dos Santos Silva, 2008, pooled study
Bukowski, 2012 BRE80426 USA	FHS, Prospective Cohort, W	31/ 410 14 years	Medical records and pathology reports	Self-reported	Incidence, breast cancer	highest vs lowest	2.90 (1.40-6.10) Ptrend:0.006	Age, age at first child birth, age at menarche, age at menopause, BMI, diabetes, history of breast cancer, HRT use, parity, race	Excluded, two exposure categories only
Ahlgren, 2007 BRE80132 Denmark	CSHRR, Historical Cohort, Age: 32-77 years	3 066/ 106 504 6 975 553 person-years	Cancer registry	From school records	Incidence, Invasive breast cancer	4500-5999 vs 3000-3499 g	1.07	Age, calendar period	Superseded by dos Santos Silva, 2008, pooled study
						per 1,000 g	1.05 (0.98-1.12)		
Lof, 2007b BRE80030 Sweden	WLHS, Prospective Cohort, Age: 29-49 years, W	657/ 38 566	Cancer registry	Self-reported	Incidence, breast cancer	<2.5 vs >3 kg	0.65 (0.43-0.99)	Attained age, birth cohort, BMI	Excluded, insufficient data
Troisi, 2006 BRE80119 USA	NCI-DES, Prospective Cohort, W	97/ 5 847 23.5 years	Hospital records only	From obstetrical charts	Incidence, Invasive & In situ breast cancer	≥3500 vs 3000-3499 g	1.09 (0.66-1.80) Ptrend:0.69	Age	Superseded by dos Santos Silva, 2008, pooled study
Vatten, 2005 BRE24432	SOUHBC, Prospective	311/ 16 016	Partially histological -	Measured and reported in the	Incidence, breast cancer	≥3840 vs ≤3039 g	1.50 (1.00-2.20) Ptrend:0.14	Birth cohort, marital status,	Superseded by dos Santos

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Norway	Cohort, Age: 49 years, W, Screening Program	40 years	over 80%	birth records				other reproductive Index, other reproductive Index, other reproductive Index, socio-economic status	Silva, 2008, pooled study
Ahlgren, 2004 BRE14201 Denmark	CSHRR, Historical Cohort, Age: 14-71 years, W	2 074/ 117 415 33 years	Partially histological - over 80%	Measured and registred in the school health records repeated every year.	Incidence, breast cancer	4 vs 2.5	1.17 (1.02-1.20)	Age , calendar year	Superseded by dos Santos Silva, 2008, pooled study
						per 1 kg	1.10 (1.01-1.21)	Age at peak growth, BMI, height, height	
dos Santos Silva I, 2004 BRE02399 Great Britain	MRC NSHD, Prospective Cohort, Age: 45-52 years, W, Legitimate live births	59/ 2 176 25 years	Partially histological - over 80%	From medical records	Incidence, breast cancer	4 vs ≥2.9 kg	1.57 (0.60-4.13) Ptrend:.21	Age	Superseded by dos Santos Silva, 2008, pooled study
						per 1 kg	1.46 (0.87-2.46)		
Ahlgren, 2003 BRE00198 Denmark	CSHRR, Historical Cohort, Age: 38-70 years, W	2 334/ 106 504 32 years	Partially histological - over 80%	Reported by parents	Incidence, breast cancer	per 1,000 g	1.09 (1.02-1.17)	Age , other age Indicator	Superseded by dos Santos Silva, 2008, pooled study
		1 087/			Incidence, breast cancer ER+	per 1,000 g	1.03 (0.88-1.20)		
		469/			Incidence, breast	per 1,000 g	1.01 (0.91-1.12)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
					cancer ER-				
Kaijser, 2003 BRE04537 Sweden	SPVLBW, Historical Cohort, W	7/ 1 483 30 years	Partially histological - over 80%	From birth records	Incidence, breast cance, ≥3 kg	O/E	2.55 (1.30-5.25)	Age	Excluded, standardised incidence ratio
Andersson, 2001 BRE00327 Sweden	PSWG, Age: 38-54 years, W	62/ 1 080 30 years	Partially histological - over 80%	From birth records	Incidence, breast cancer	**≥1 vs ≥-1**	1.93 (0.75-5.00) Ptrend:0,105	Age at menarche, birth cohort, other reproductive Index, other reproductive Index, other reproductive Index, parity/pregnancies	Superseded by dos Santos Silva, 2008, pooled study
Hilakivi-Clarke, 2001 BRE03903 Finland	HBCS I, Historical Cohort, W	177/ 3 447	Not specified	Recorded during periodic medical examinations	Incidence, breast cancer	per 1 kg	1.22 (0.90-1.65)		Superseded by dos Santos Silva, 2008, pooled study
						≥4001 vs ≤2500 g	1.90 (0.70-5.00)		
De Stavola BL, 2000 BRE11734 UK	MRC-NSHD, Prospective Cohort, Age: 24-51 years, W	37/ 2 221 26 years	Partially histological - over 80%	From birth records	Incidence, breast cancer	≥4 vs ≤2.9 kg	2.02 (0.59-6.90) Ptrend:0.13	Age	Superseded by dos Santos Silva, 2008, pooled study
						≥3.5 vs ≤3.5 kg	2.09 (1.06-4.12)	Socio-economic status	
Mogren, 1999 BRE80173 Sweden	SWAN, Historical Cohort,	1/ 248 701 39 years	Cancer registry	From birth records	Incidence, breast cancer	O/E	7.35 (0.10-40.87)		Excluded, standardised incidence ratio

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	W				≥4500 g				
Ekbom, 1997 BRE80172 Sweden	UBCoS, Nested Case Control, Age: 49 years, W	1 068/ 2726 controls	Cancer registry	From birth records	Incidence, breast cancer	≥4000 vs 2500-2999 g	1.04 (0.77-1.41) Ptrend:0.56	Diseases (not breast), height, maternal characteristics, twin membership	Superseded by dos Santos Silva, 2008, pooled study
Ekbom, 1992 BRE02554 Sweden	UBCoS, Nested Case Control	2 463 32 years	Partially histological - over 80%	Reported using standardized chart administered by nurses	Incidence, breast cancer	≥4000 vs 2500-2999 g	1.23 (0.75-2.00) Ptrend:0.25	Age , age at menarche, other specified factor, parity/pregnancies, socio-economic status	Superseded by dos Santos Silva, 2008, pooled study

Figure 647 RR estimates of breast cancer by birthweight

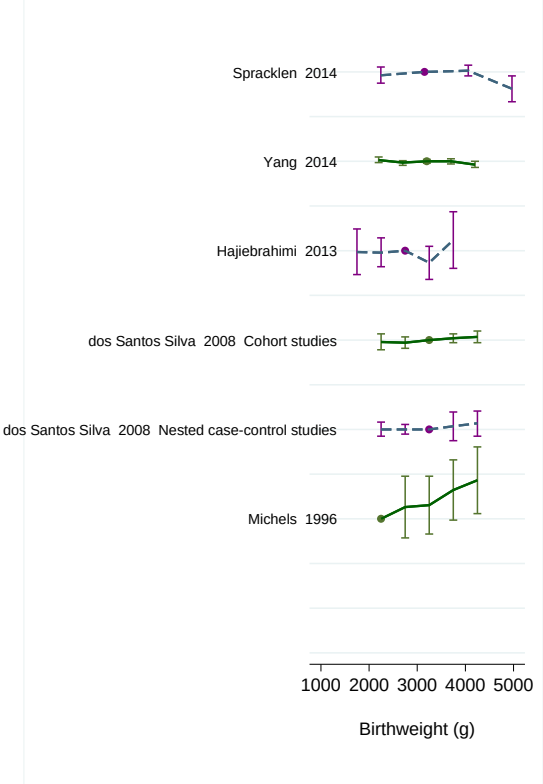
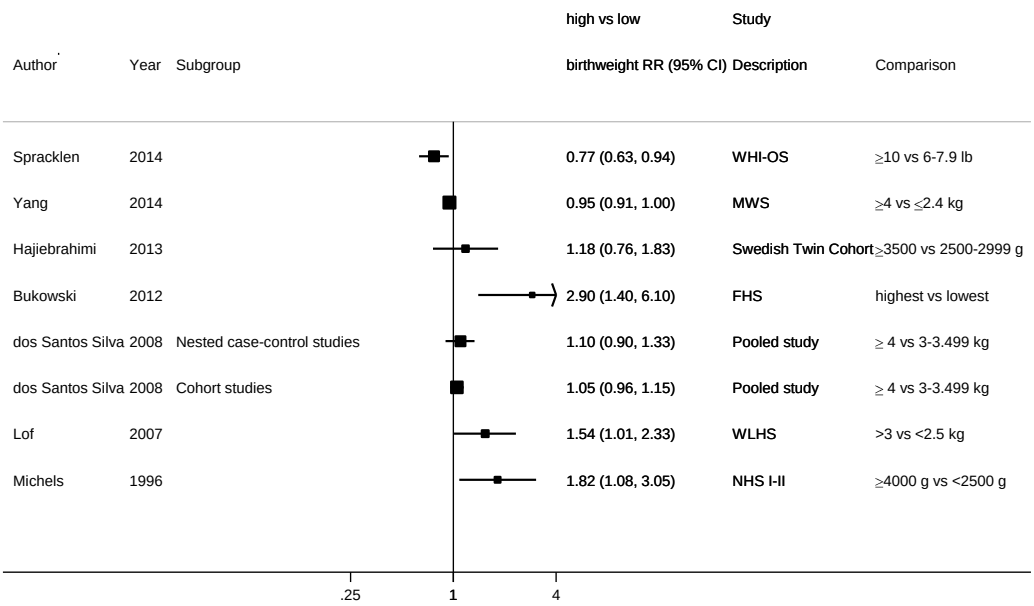


Figure 648 RR (95% CI) of breast cancer for the highest compared with the lowest level of birthweight



Note: In the sensitivity analysis, the summary RR for the highest versus the lowest birthweight was 1.08 (95% CI=0.95-1.24) (I^2=77%, P<0.001).

Figure 649 Relative risk of breast cancer for 500 g increase of birthweight

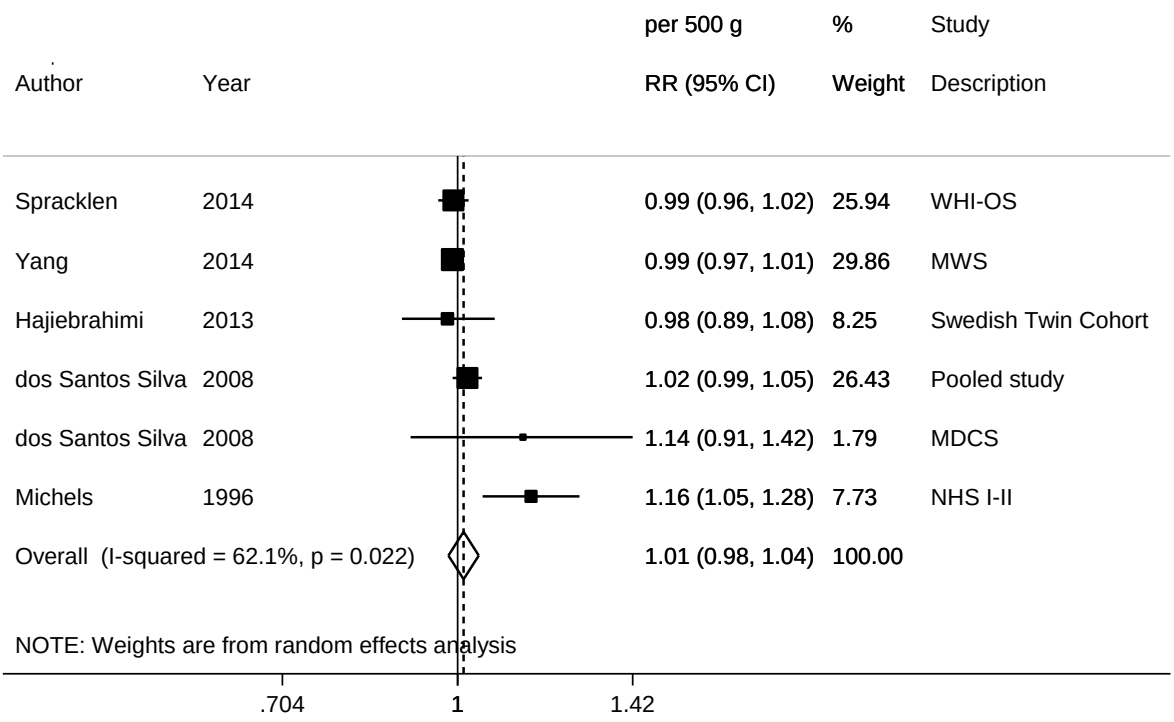


Figure 650 Funnel plot of studies included in the dose response meta-analysis of birthweight and breast cancer

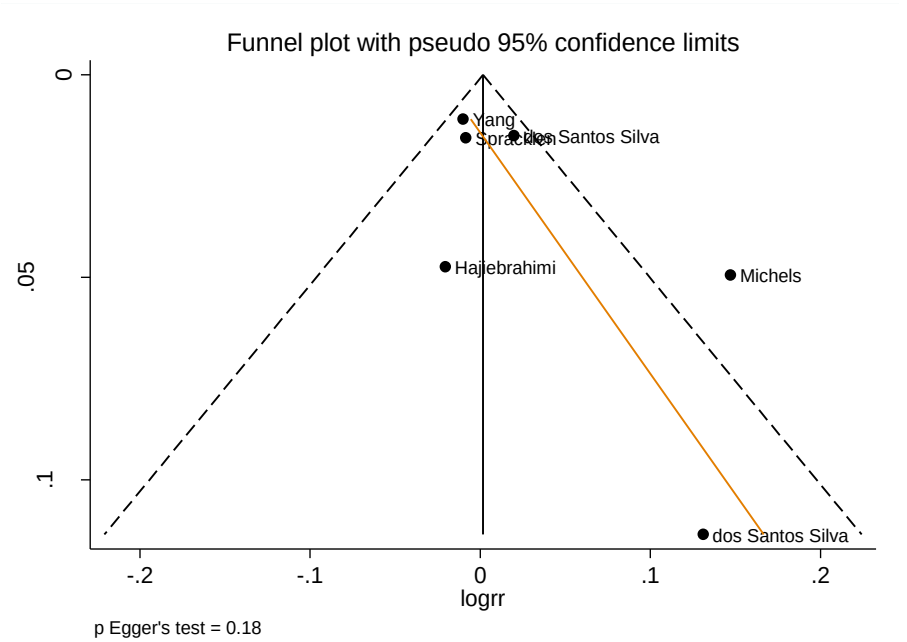
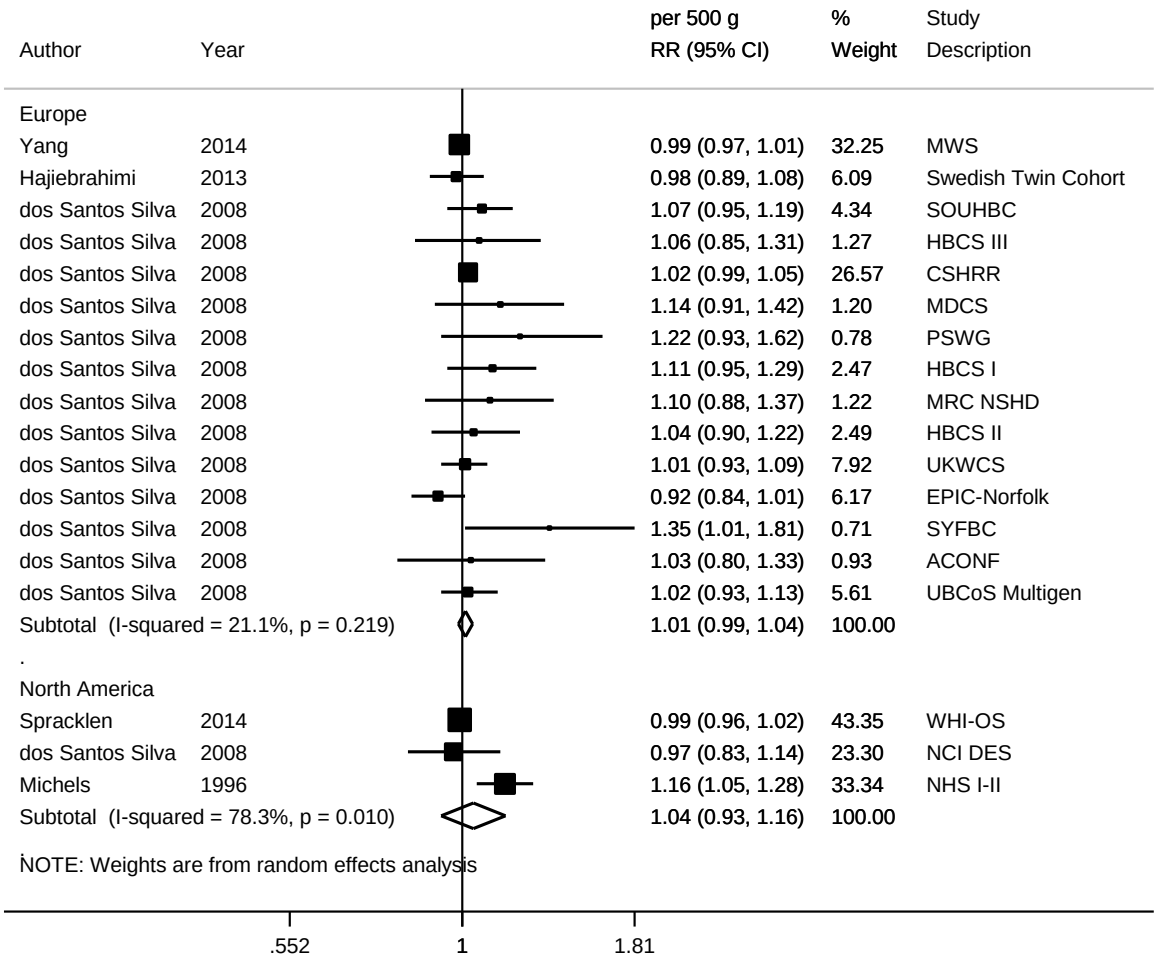
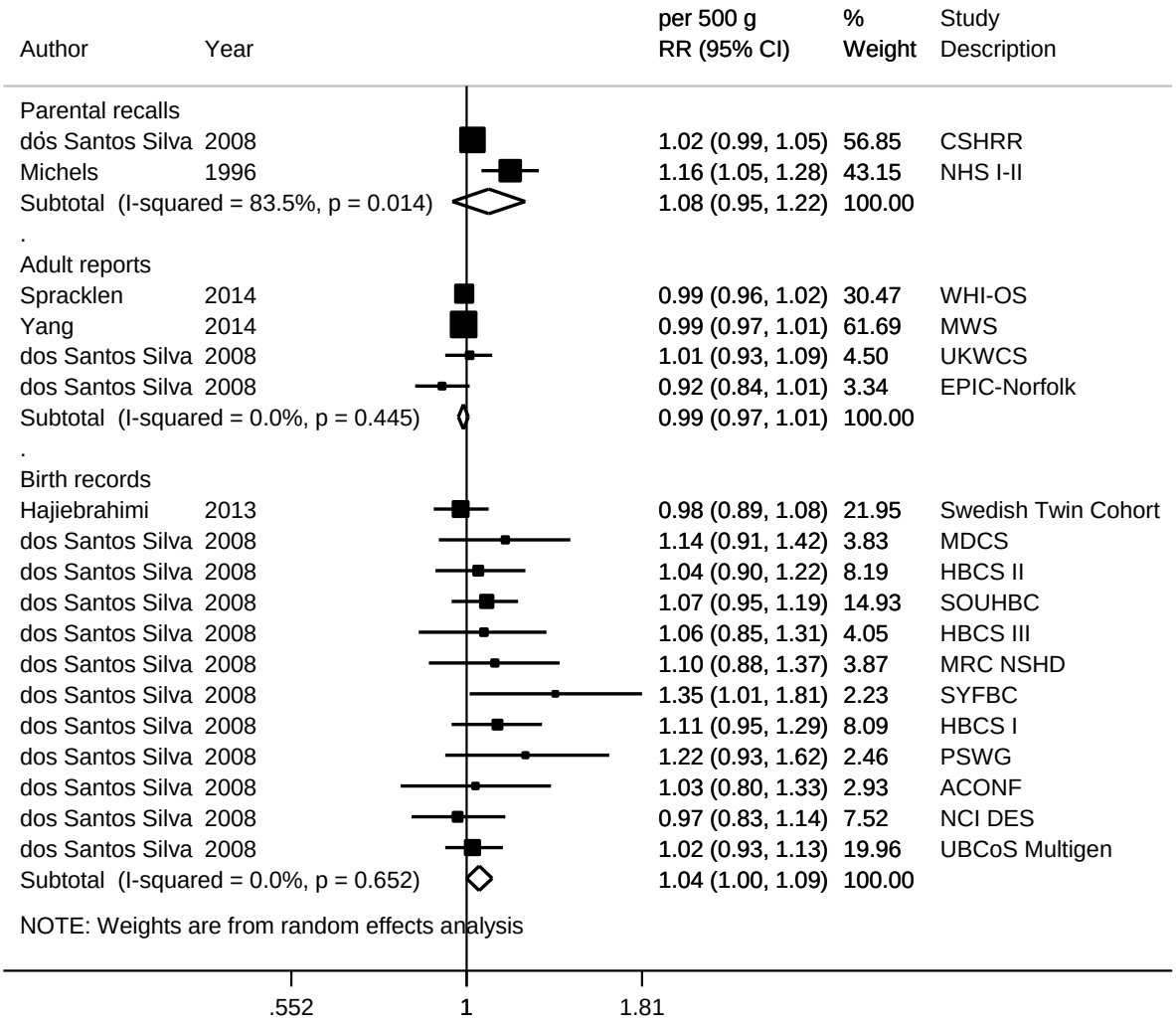


Figure 651 Relative risk of breast cancer for 500 g increase of birthweight, by geographic location



Note: Individual study results in the pooled analysis (dos Santos Silva, 2008) were used.

Figure 652 Relative risk of breast cancer for 500 g increase of birthweight, by exposure assessment methods



Note: Individual study results in the pooled study (dos Santos Silva, 2008) were used.

Premenopausal breast cancer

Summary

Main results:

Sixteen out of 25 studies (12 publications) could be included in the dose-response meta-analysis. This included three studies (Hajiebrahimi, 2013; Michels, 2006b; Ahlgren, 2004) and the study with pooled data from premenopausal women in 13 studies (8 cohorts, 5 case-control studies; results by study designs not available) (dos Santos Silva, 2008).

Birthweight was significantly positively associated with premenopausal breast cancer risk (summary RR per 500g=1.05 1.02-1.09; I^2=0%, P=0.85).

Stratified analysis and the test for publication or small studies bias were not conducted as there were only thee studies in addition to the pooled study.

Nine studies were excluded from the meta-analysis. One publication that pooled data from two studies (Michels, 1996b, NHS and NHS II) overlapped with another publication that was already included in the meta-analysis (Michels, 2006b, NHS II). The pooled study (dos Santos, Silva, 2008) excluded seven studies that were neither singleton studies nor used methods other than birth records to assess birth weight. One study of premature babies did not have sufficient data to be included in the meta-analysis (Kaijser, 2003). An increased rate of early onset (< 50 years) breast cancer with high birthweight was observed among the Swedish cohort compared to the expected rate in the local population (Kaijser, 2003).

One study reported results by breast cancer hormone-receptor status observed positive associations for the highest versus the lowest birthweight (significant for ER-positive and PR-positive breast cancers and non-significant for ER-negative and PR-negative breast cancers) (Michels, 2006b).
Sensitivity analyses:

Summary RR ranged from 1.01 (95% CI=0.84-1.21) when Hajiebrahimi, 2013 (3% weight) was omitted to 1.07 (95% CI=1.02-1.13) when Ahlgren, 2004 (36% weight) was omitted in influence analysis. When the study that pooled data from both cohort and case-control studies was excluded (dos Santos Silva, 2008) (42% weight), the summary RR was 1.04 (95% CI=0.99-1.09).

Nonlinear dose-response meta-analysis:

Nonlinear dose-response meta-analysis was not conducted due to low number of studies.

Study quality:

Most studies obtained the information on birthweight directly from birth records, which could be less prone to measurement errors. Other studies either asked the parents or the participants to recall the information. When stratified by the sources of information, the pooled study (dos Santos Silvea, 2008) observed positive associations from birth records (RR for the highest vs the lowest birthweight=1.06, 95% CI=0.95-1.18) and adult report (RR =1.02, 95% CI=0.89-1.16) and not parental recalls (RR=0.98, 95% CI=0.84-1.14). Case ascertainment was through cancer registries or confirmed through medical records. Not all studies adjusted for age,

alcohol intake, reproductive factors, and adult BMI. The pooled study (dos Santos Silvea, 2008) tested several potential confounding factors including adult BMI and found RR estimates of similar magnitude.

Table 615 Birthweight and premenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	25 (12 publications)
Studies included in forest plot of highest compared with lowest exposure	24 (3 publications)
Studies included in linear dose-response meta-analysis	16 (4 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 616 Birthweight and premenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and 2016 CUP

	2005 SLR[1]	**CUP**
Increment unit used	1 kg	500 g
Studies (n)	4	16
Cases	>93	>3 135
RR (95%CI)	1.08 (1.04-1.13)	1.05 (1.02-1.09)
Heterogeneity (I^2, p-value)	69%	0%, 0.85
P value Egger test	-	-

[1]Meta-analysis was not conducted in the 2008 SLR.

Table 617 Birthweight and premenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Xu, 2009	9 studies (3 cohorts, 6 case-control studies)	-	China, Europe, USA	Incidence, premenopausal breast cancer	Highest vs lowest	1.37 (0.98-1.92)	-	50%, 0.05

*All cohort studies identified were included in the present review.

Table 618 Birthweight and premenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Hajiebrahimi, 2013 BRE80488 Sweden	Swedish Twin Cohort, Nested Case Control, W	203/ 975 controls 36 years	Cancer registry	Records at twin registry	Incidence, breast cancer, age <=50	≥3500 vs 2500-2999 g	1.75 (0.87-3.53)	Gestational age, hypertension, maternal age, parity, socio-economic status	
						per 1 kg	1.01 (0.70-1.46)		
dos Santos Silva, 2008 USA and Europe	Pooled study of 32 studies, 22 studies with data for age <45 years*, W	2 104 cases/ 420 874 non-cases	Cancer registries, medical records, mortality registries, death certifications, self-reports	From birth records, parental reports, adult reports	Incidence, breast cancer, age < 45 years, singleton studies based on birth records (13 studies - 8 cohorts, 5 case-control studies)	per 0.5 kg	1.04 (0.99-1.09)	Cohort studies adjusted for age at diagnosis and stratified by calendar year; case-control studies matched by year of birth, calendar period, recruitment centre, area of residence, or ethnicity	Included, dose-response results pooled from 13 studies (subgroup results by study designs not available)
						>3.5 vs 3-3.5 kg	1.06 (0.95-1.18) Ptrend: 0.05		
		3 437 cases/ 7 193 non-cases			Incidence, breast cancer, age < 45 years, singleton studies based on adult reports (8 studies - 2 cohorts, 6 case-control studies)	>3.5 vs 3-3.5 kg	1.02 (0.89-1.16) Ptrend: 0.03		Excluded, missing cases and non-cases per category, could not estimate dose-response results
		826 cases/ 109 064 non-cases			Incidence, breast cancer, age < 45 years,	>3.5 vs 3-3.5 kg	0.98 (0.84-1.14) Ptrend: 0.28		Excluded, missing cases and non-cases per category,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
					singleton studies based on parental reports (1 cohort study)				could not estimate dose-response results
*Cohort studies: MRC NSHD; CSHRR; UBCoS Multigen; SOUHBC; NCI DES; UKWCS; ACONF; HBCS II; HBCS III; SYFBC study; NHS II; Case-control studies: SPNFBC; NYSEOBC; TBPCCS; DPCCS; Seattle BCYW; Seattle PFBC; SBCS; CBCS; PBCS; WEB; CARE									
Michels, 2006b BRE80120 USA	NHS II, Prospective Cohort, Age: 30-55 years	828/ 152 608 10 years	Medical records	Self-reported	Incidence, Invasive breast cancer, premenopausal	<5.5 vs >8.4 lbs	0.73 (0.51-1.03) Ptrend:0.06	Age , age at first child, age at menarche, alcohol, benign breast disease, BMI, BMI, family history, height, OC use, other reproductive Index, parity/pregnancies, physical activity	
		475/			Incidence, breast cancer ER+, premenopausal	<5.5 vs >8.4 lbs	0.56 (0.35-0.89) Ptrend:0.021		
		189/			Incidence, breast cancer ER-, premenopausal	<5.5 vs >8.4 lbs	0.75 (0.37-1.51) Ptrend:0.061		
		448/			Incidence, breast cancer PR+, premenopausal	<5.5 vs >8.4 lbs	0.55 (0.34-0.90) Ptrend:0.004		
		203/			Incidence, breast cancer PR-, premenopausal	<5.5 vs >8.4 lbs	0.85 (0.45-1.62) Ptrend:0.532		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Ahlgren, 2004 BRE14201 Denmark	CSHRR, Historical Cohort, Age: 14-71 years, W	117 415 33 years	Partially histological - over 80%	Measured and registered In the school health records, repeated every year.	Incidence, breast cancer, premenopausal	per 1 kg	1.14 (1.04-1.28)	Age at peak growth, BMI, height, height	

Table 619 Birthweight and premenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Oberg, 2009 BRE80261 Sweden	Swedish Twin Cohort, Historical Cohort, Age: 15-47 years, W	219/ 11 923 33 years	Cancer registry	From birth record	Incidence, breast cancer, age at diagnosis <=50yrs	≥3000 vs 2500-2999 g	1.58 (1.03-2.42)	Anthropometry, gestational age, zygosity	Superseded by Hajiebrahimi, 2013, BRE80488
		116/				per 500 g	1.62 (1.16-2.27)	Height, smoking status	
McCormack, 2005 BRE23366 Sweden	UBCoS, Prospective Cohort, W	5 346 37.2 years	Partially histological - over 80%	At the uppsala academic hospital, during 1915-1929 obstetrics notes data.	Incidence, Invasive breast cancer, premenopausal	per 1 SD units	1.40 (1.08-1.81)	Other specified factor, socio-economic status , socio-economic status	Superseded by dos Santos, 2008, pooled study
						≥4000 vs ≤2999 g	4.00 (1.49-10.72)		
Vatten, 2005 BRE24432 Norway	SOUHBC, Prospective Cohort, Age: 49 years, W, Screening Program	16 016 40 years	Partially histological - over 80%	Measured and reported In the birth records	Incidence, breast cancer, premenopausal	≥3840 vs ≤3039 g	1.10 (0.50-2.40)	Birth cohort, marital status, other anthropometric Index, other anthropometric Index, other reproductive Index, other reproductive Index, other reproductive	Superseded by dos Santos, 2008, pooled study

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								Index, socio-economic status	
dos Santos Silva I, 2004 BRE02399 Great Britain	NSHD (British cohort), Prospective Cohort, Age: 45-52 years, W, Legitimate live births	11/ 2 176 25 years	Partially histological - over 80%	Measured using a standardized method except birth weight obtained for medical records. repeated measures of height and weight.	Incidence, breast cancer, premenopausal	per 1 kg	1.94 (0.74-5.14)	Age , BMI, BMI, height, height	Superseded by dos Santos, 2008, pooled study
Kaijser, 2003 BRE04537 Sweden	SPVLBW, Historical Cohort, W	3/ 1 483 30 years	Partially histological - over 80%	Reported In the birth records	Incidence, breast cancer, premenopausal ≥3 kg	O/E	2.46 (0.51-7.19)	Age	Excluded, standardised incidence ratio
McCormack, 2003 BRE20357 Sweden	UBCoS, Historical Cohort, Age: 36-82 years, W	63/ 5 358 38 years	Partially histological - over 80%	Reported after measurement In the birth records.	Incidence, breast cancer, premenopausal	≥4000 vs ≤2999 g	3.48 (1.29-9.38) Ptrend:0,006	Age , birth cohort, educational level, marital status, SES indexes, other age Indicator	Superseded by dos Santos, 2008, pooled study
De Stavola BL, 2000 BRE11734 UK	MRC-NSHD, Prospective Cohort, Age: 24-51 years, W	19/ 2 221 26 years	Partially histological - over 80%	Birth records for birth weight and self-administered questionnaire for adult measurements.	Incidence, breast cancer, premenopausal	≥4 vs ≤3 kg	5.65 (0.95-33.84) Ptrend:0.03	Age	Superseded by dos Santos, 2008, pooled study
Michels, 1996b BRE80621	NHS I and II, Nested Case	202/ 1223 controls	Self-report verified by	Self-reported by mothers	Incidence, Invasive breast	≤2499 vs ≥4000 g	0.51 (0.21-1.22)	Age, age at first child birth, age	Superseded by Michels, 2006b,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
USA	Control, W	16 years	medical record		cancer, age < 45 yr			at menarche, BMI, cohort, family history of breast cancer, parity	BRE80120

Figure 653 RR estimates of premenopausal breast cancer by birthweight

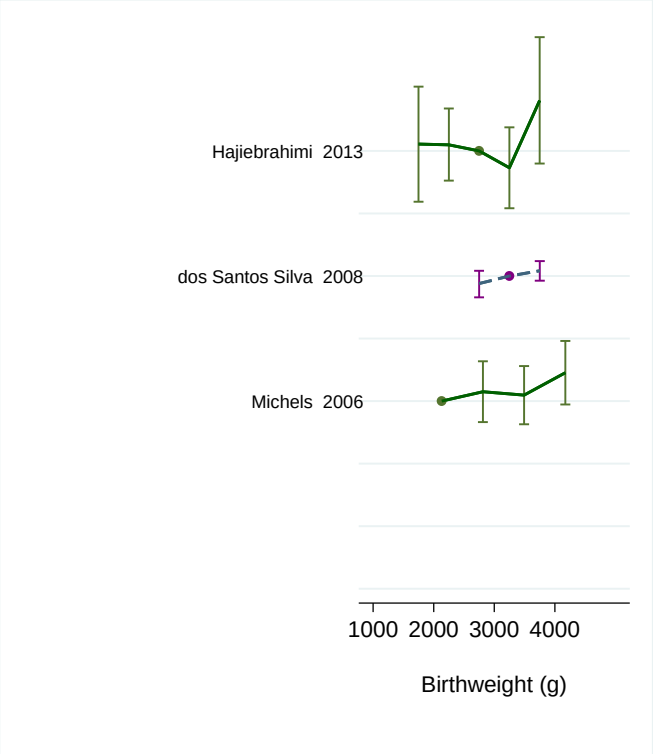


Figure 654 RR (95% CI) of premenopausal breast cancer for the highest compared with the lowest level of birthweight

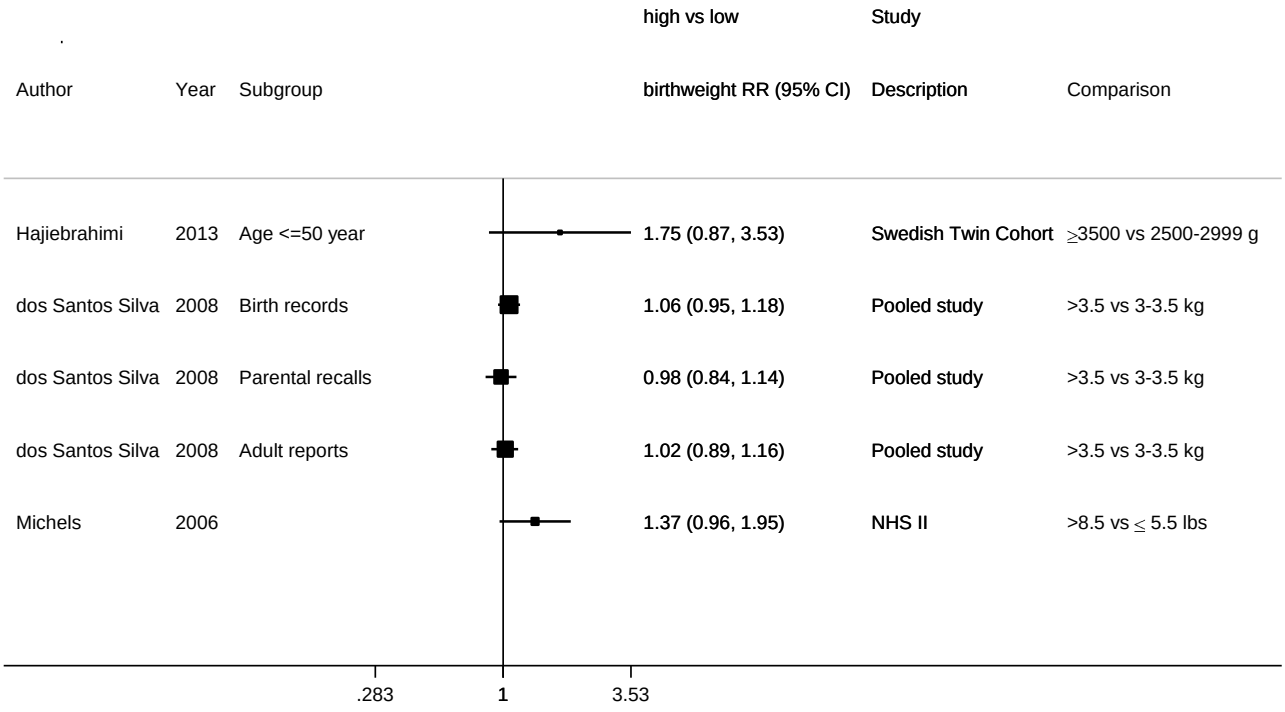
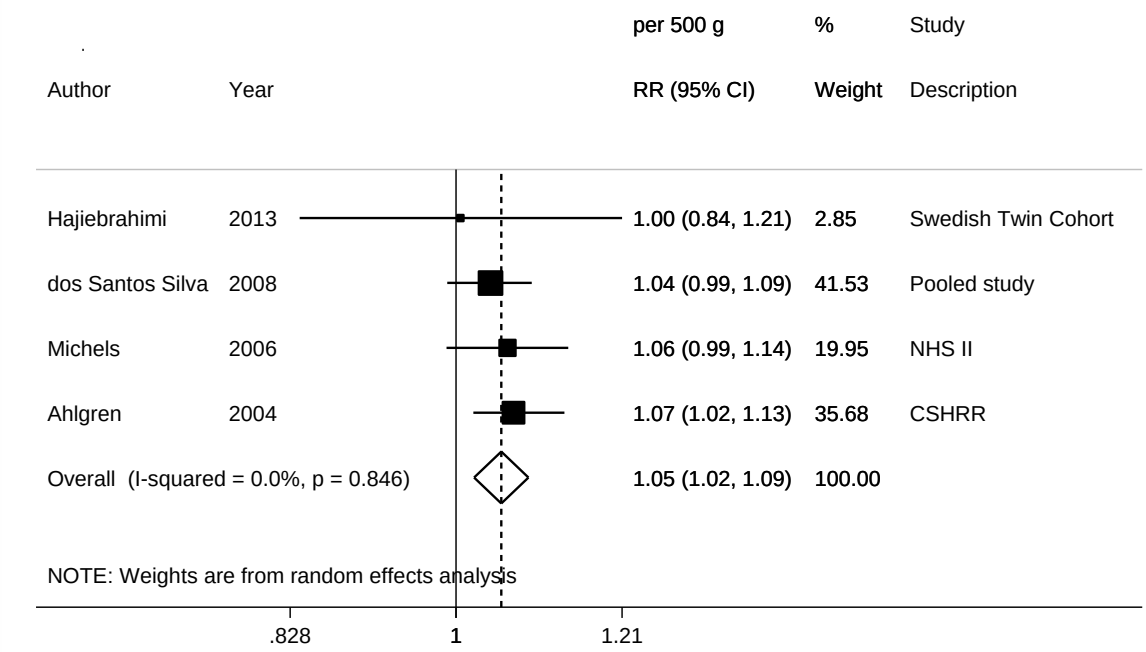


Figure 655 Relative risk of premenopausal breast cancer for 500 g increase of birthweight



Postmenopausal breast cancer

Summary

Main results:

Fourteen out of 23 studies (15 publications) could be included in the dose-response meta-analysis. This included four studies (Yang, 2014; Hajiebrahimi, 2013; Michels, 2006b; Ahlgren, 2004) and the study with pooled data from postmenopausal women in 10 studies (8 cohorts, 2 case-control studies; results by study designs not available) (dos Santos Silva, 2008).

No significant association was observed between birthweight and postmenopausal breast cancer risk (RR per 500 g=1.00, 95% CI=0.98-1.02; I^2=0%, P=0.48).

Stratified analysis was not conducted as number of studies in the strata was limited. Although full exploration of publication or small studies bias was not possible, there was evidence of borderline significant bias (P for Egger's test=0.06); and visual inspection of the funnel plot showed asymmetry, which suggested more studies with a positive association.

Nine studies were excluded from the meta-analysis. The pooled study (dos Santos Silva, 2008) excluded six studies that were not singleton studies or used methods other than birth records to assess birth weight and one study of premature babies (seven studies in total). Two excluded studies did not have sufficient data (Hartz, 2013; Rich-Edwards, 2003). One observed null association (Hartz, 2013) and the other reported a positive association (Rich-Edwards, 2003) (95% CI or P-value not available.

Sensitivity analyses:

Summary RR was materially unchanged when studies were omitted in turn in influence analysis. This included the omission of the study that pooled data from both cohort and case-control studies (dos Santos Silva, 2008) (summary RR per 500g=0.99, 95% CI=0.97-1.02).

Nonlinear dose-response meta-analysis:

Nonlinear dose-response meta-analysis was not conducted due to low number of studies.

Study quality:

Most studies obtained the information on birthweight directly from birth records, which could be less prone to measurement errors. Other studies either asked the parents or the participants to recall the information. When stratified by the sources of information, the pooled study (dos Santos Silvea, 2008) observed positive associations from birth records (RR for the highest vs the lowest birthweight=1.14, 95% CI=0.90-1.43) and parental recalls (RR =1.02, 95% CI=0.87-1.19) and not adult report (RR=0.98, 95% CI=0.89-1.09). Case ascertainment was through cancer registries or confirmed through medical records. Most studies adjusted for age, alcohol intake, reproductive factors, and adult BMI. The pooled study (dos Santos Silvea, 2008) tested several potential confounding factors including adult BMI and found RR estimates of similar magnitude.

Table 620 Birthweight and postmenopausal breast cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	23 (15 publications)
Studies included in forest plot of highest compared with lowest exposure	21 (3 publications)
Studies included in linear dose-response meta-analysis	14 (5 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 621 Birthweight and postmenopausal breast cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and 2016 CUP

	2005 SLR[1]	**2016 CUP**
Increment unit used	1 kg	500 g
Studies (n)	3	14
Cases	>88	> 17 981
RR (95%CI)	1.03 (0.97-1.10)	1.00 (0.98-1.02)
Heterogeneity (I^2, p-value)	41%	0%, 0.48
P value Egger test	-	-

[1]Meta-analysis was not conducted in the 2008 SLR.

Table 622 Birthweight and postmenopausal breast cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Xu, 2009	6 studies (2 cohorts, 4 case-control studies)	-	China, Europe, USA	Incidence, postmenopausal breast cancer	Highest vs lowest	1.13 (0.85-1.51)	-	58%, <0.05

*All cohort studies identified were included in the present review.

Table 623 Birthweight and postmenopausal breast cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Yang, 2014 BRE80521 UK	MWS, Prospective Cohort, Age: 50-64 years, W	8 662/ 453 023 9.2 years	Cancer registry	Self-reported in adulthood	Incidence, breast cancer, HRT ever	per 1 kg	0.99 (0.92-1.06)	Age, age at first child birth, age at menarche, alcohol, BMI, breastfeeding, exercise, height, HRT use, maternal and paternal height, parity, region, SES, smoking, smoking habbits, year of birth	
		5 685/			Incidence, breast cancer, never HRT users	per 1 kg	0.95 (0.88-1.04)		
		4 028/			Incidence, breast cancer, age 49-60 y	per 1 kg	0.94 (0.85-1.04)		
		9 024/			Incidence, breast cancer, 61-70 yrs	per 1 kg	1.00 (0.94-1.07)		
		1 490/			Incidence, breast cancer, 70+ yrs old	per 1 kg	0.90 (0.77-1.06)		
Hajiebrahimi, 2013 BRE80488	Swedish Twin Cohort, Nested Case	340/ 1740 controls 36 years	Cancer registry	Records at twin registry	Incidence, breast cancer, age > 50 yr	per 1 kg	1.03 (0.78-1.36)	Gestational age, hypertension, maternal age,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Sweden	Control, W							parity, socio-economic status	
						≥3500 vs 2500-2999 g	0.99 (0.54-1.80)		
dos Santos Silva, 2008 USA and Europe	Pooled study of 32 studies, 19 studies with data for age ≥55 years*, W	982 cases/ 22 468 non-cases	Cancer registries, medical records, mortality registries, death certifications, self-reports	From birth records, parental reports, adult reports	Incidence, breast cancer, age ≥55 years, singleton studies based on birth records (10 studies - 8 cohorts, 2 case-control studies)	per 0.5 kg	1.09 (0.97-1.23)	Cohort studies adjusted for age at diagnosis and stratified by calendar year; case-control studies matched by year of birth, calendar period, recruitment centre, area of residence, or ethnicity	Included, dose-response results pooled from 10 studies (subgroup results by study designs not available)
						>3.5 vs 3-3.5 kg	1.14 (0.90-1.43)		
		7 714 cases/ 35 417 non-cases			Incidence, breast cancer, age ≥55 years, singleton studies based on adult reports (8 studies - 3 cohorts, 5 case-control studies)	>3.5 vs 3-3.5 kg	0.98 (0.89-1.09)		Excluded, missing cases and non-cases per category, could not estimate dose-response results
		812 cases/ 38 387 non-cases			Incidence, breast cancer, age ≥55 years,	>3.5 vs 3-3.5 kg	1.02 (0.87-1.19)		Excluded, missing cases and non-cases

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
					singleton studies based on parental reports (1 cohort study)				per category, could not estimate dose-response results
*Cohort studies: MRC NSHD; HBCS I; PSWG; CSHRR; UBCoS Multigen; SOUHBC; UKWCS; EPIC-Norfolk; HBCS II; HBCS III; NHS I; MDCS; Case-control studies: SPNFBC; TBPCCS; Seattle BCMW; CmsBCS; PBCS; WEB; CARE									
Michels, 2006b BRE80120 USA	NHS, Prospective Cohort, Age: 30-55 years	2 312/ 152 608 10 years	Medical records	Self-reported, correlation = 0.75 with recollection by mothers of participants & 0.74 with state birth records In sub-set	Incidence, Invasive breast cancer, postmenopausal	≤5.5 vs >8.5 lbs	1.02 (0.84-1.23) Ptrend:0.89	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, BMI, family history, height, HRT use, OC use, other reproductive Index, parity/pregnancies, physical activity	
Ahlgren, 2004 BRE14201 Denmark	CSHRR, Historical Cohort, Age: 14-71 years, W	117 415 33 years	Partially histological - over 80%	Measured and registered In the school health records, repeated every year.	Incidence, breast cancer, postmenopausal	per 1 kg	1.05 (0.91-1.21)	Age at peak growth, BMI, height, height	

Table 624 Birthweight and postmenopausal breast cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Andersen, 2014 BRE80511 Denmark	CSHRR, Historical Cohort, Age: 50-69 years, W	523/ 13 572 184 175 person-years	Cancer registry	From school health records - body size at ages 7-13 years (measured) and birth weight (reported by parents)	Incidence, breast cancer, age at diagnosis >= 60 yrs	per 1 unit	0.82 (0.66-1.02)	Age-underlying cox models, birth cohort	Superseded by dos Santos, 2008, pooled study
		193/			Incidence, breast cancer, age at diagnosis 50-59y	per 1 unit	1.01 (0.75-1.36)		
Hartz, 2013 BRE80483 USA	Women's Health Initiative, Prospective Cohort, Age: 55-70 years, W, Postmenopausal	147 202 8 years	Self reported/death certificate/ medical records	Adult reports	Incidence, breast cancer, observation study	per 1 SD	1.00	Age, alcohol, family history of prostate cancer, history of cancer, history of polyp diagnosis, medication, number of cigarettes smoked, osteoporosis, psycological character, race, study, weight	Excluded, insufficient data
Oberg, 2009 BRE80261 Sweden	Swedish Twin Cohort, Historical Cohort, Age: 15-47 years, W	315/ 11 923 33 years	Cancer registry	From birth record	Incidence, breast cancer, age at diagnosis >50yrs	≥3000 vs 2500-2999 g	0.80 (0.57-1.12)	Anthropometry, gestational age, zygosity	Superseded by Hajiebrahimi, 2013, BRE80488

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Lahmann, 2005b BRE23013 Sweden	MDCS, Nested Case Control, W, Postmenopausal		Partially histological - over 80%	Birth records	Incidence, breast cancer, postmenopausal	per 100 g	1.06 (1.00-1.12)	Age , reproductive factors , reproductive factors	Superseded by dos Santos, 2008, pooled study
McCormack, 2005 BRE23366 Sweden	UBCoS, Prospective Cohort, W	5 346 37.2 years	Partially histological - over 80%	At the Uppsala academic hospital, during 1915-1929 obstetrics notes data.	Incidence, Invasive breast cancer, postmenopausal	per 1 SD units	1.00 (0.88-1.13)	Other specified factor, socio-economic status , socio-economic status	Superseded by dos Santos, 2008, pooled study
						≥4000 vs ≤2999 g	0.91 (0.57-1.46)		
Vatten, 2005 BRE24432 Norway	SOUHBC, Prospective Cohort, Age: 49 years, W, Screening Program	16 016 40 years	Partially histological - over 80%	Measured and reported In the birth records	Incidence, breast cancer, postmenopausal	≥3840 vs ≤3039 g	1.10 (0.50-2.50)	Birth cohort, marital status, other anthropometric Index, other anthropometric Index, other reproductive Index, other reproductive Index, other reproductive Index, socio-economic status	Superseded by dos Santos, 2008, pooled study
Lahmann, 2004b BRE18517 Sweden	MDCS, Nested Case Control, Age: 55- years, W, Postmenopausal	88/	All histology	Birth records	Incidence, breast cancer, postmenopausal	4001 vs ≥2999 g	2.66 (0.96-7.41)	Age , BMI, educational level, husband occupation, other reproductive Index, other reproductive Index	Superseded by dos Santos, 2008, pooled study

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
McCormack, 2003 BRE20357 Sweden	UBCoS, Historical Cohort, Age: 36-82 years, W	296/ 5 358 38 years	Partially histological - over 80%	Reported after measurement In the birth records.	Incidence, breast cancer, postmenopausal	≥4000 vs ≤2999 g	0.87 (0.56-1.36) Ptrend:0.87	Age , birth cohort, educational level, marital status, SES indexes, other age Indicator	Superseded by dos Santos, 2008, pooled study
Rich-Edwards, 2003 BRE18665 USA	NHS II, Prospective Cohort, Age: 25-42 years, W, Registered nurses		Partially histological - over 80%	Self-reported	Incidence, breast cancer, postmenopausal	per 1 kg	1.29	BMI, other specified factor, smoking habits	Excluded, insufficient data
Michels, 1996b BRE80621 USA	NHS I and II, Nested Case Control, W	178/ 1373 controls 16 years	Self report verified by medical record	Self-reported by mothers	Incidence, Invasive breast cancer, age 45 - 50 years	<2500 vs ≥4000 g	0.41 (0.16-1.05)	Age, age at first child birth, age at menarche, BMI, cohort, family history of breast cancer, parity	Superseded by Michels, 2006b, BRE80120

Figure 656 RR estimates of postmenopausal breast cancer by birthweight

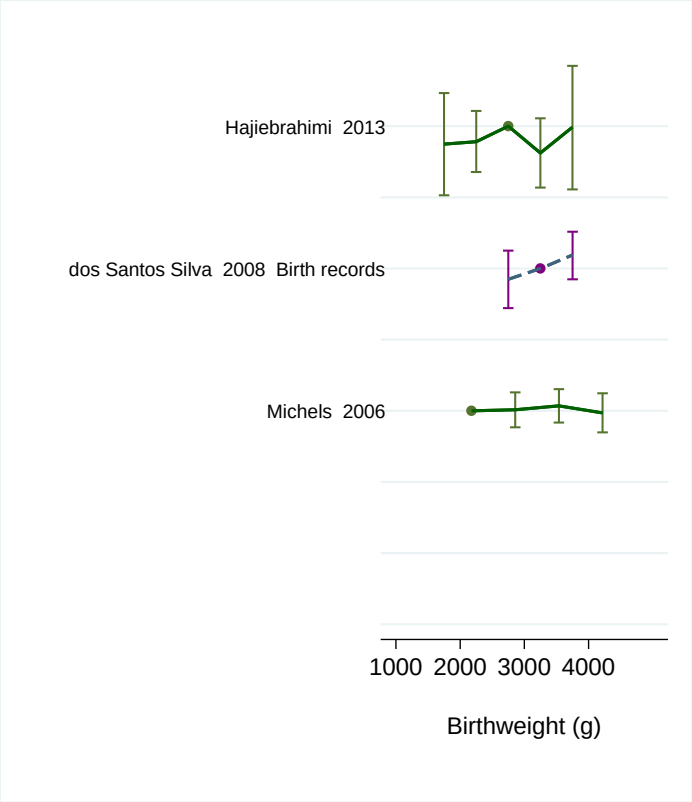


Figure 657 RR (95% CI) of postmenopausal breast cancer for the highest compared with the lowest level of birthweight

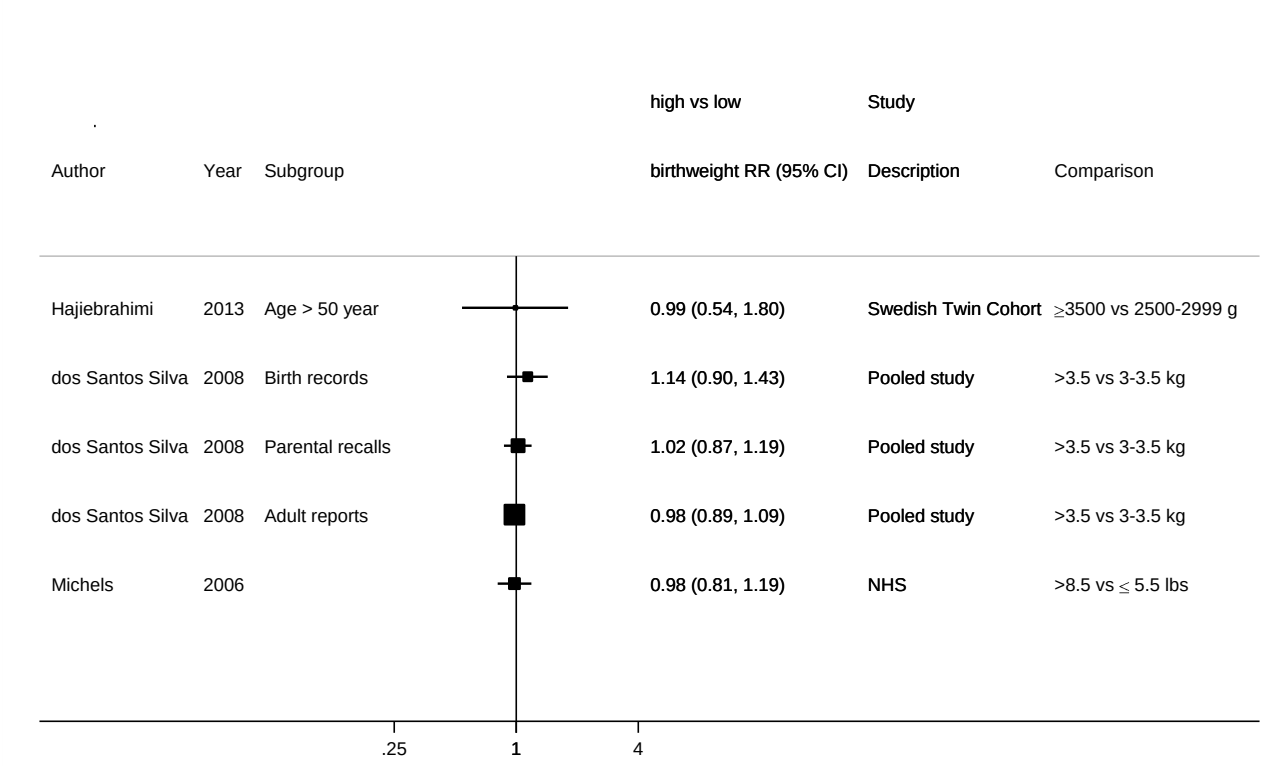


Figure 658 Relative risk of postmenopausal breast cancer for 500 g increase of birthweight

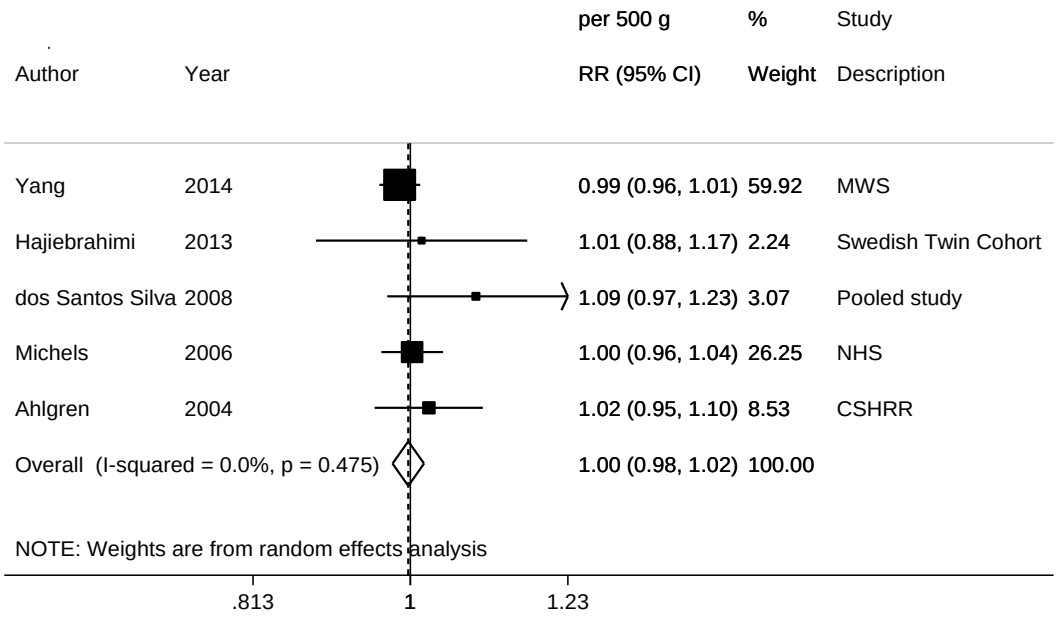
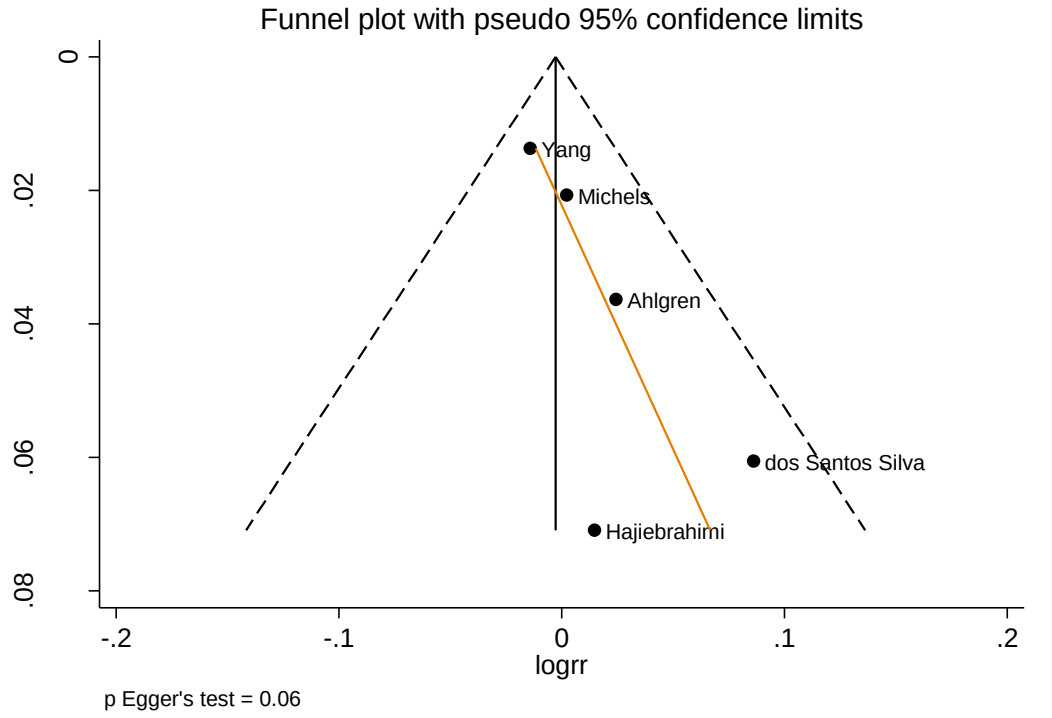


Figure 659 Funnel plot of studies included in the dose response meta-analysis of birthweight and postmenopausal breast cancer



References

1. Abbas S, Linseisen J, Rohrmann S, et al. Dietary intake of vitamin D and calcium and breast cancer risk in the European Prospective Investigation into Cancer and Nutrition. Nutr Cancer 2013;65:178-87.

2. Adebamowo CA, Hu FB, Cho E, et al. Dietary patterns and the risk of breast cancer. Ann Epidemiol 2005;15:789-95.

3. Agborsangaya CB, Surcel HM, Toriola AT, et al. Serum 25-hydroxyvitamin D at pregnancy and risk of breast cancer in a prospective study. Eur J Cancer 2010;46:467-70.

4. Agnoli C, Berrino F, Abagnato CA, et al. Metabolic syndrome and postmenopausal breast cancer in the ORDET cohort: a nested case-control study. Nutr Metab Cardiovasc Dis 2010;20:41-8.

5. Agurs-Collins T, Rosenberg L, Makambi K, et al. Dietary patterns and breast cancer risk in women participating in the Black Women's Health Study. Am J Clin Nutr 2009;90:621-8.

6. Ahlgren M, Sorensen T, Wohlfahrt J, et al. Birth weight and risk of breast cancer in a cohort of 106,504 women. Int J Cancer 2003;107:997-1000.

7. Ahlgren M, Wohlfahrt J, Olsen LW, et al. Birth weight and risk of cancer. Cancer 2007;110:412-9.

8. Ahn J, Schatzkin A, Lacey JV, Jr., et al. Adiposity, adult weight change, and postmenopausal breast cancer risk. Arch Intern Med 2007;167:2091-102.

9. Albanes D, Jones DY, Schatzkin A, et al. Adult stature and risk of cancer. Cancer Res 1988;48:1658-62.

10. Albanes D, Blair A, Taylor PR. Physical activity and risk of cancer in the NHANES I population. Am J Public Health 1989;79:744-50.

11. Allen NE, Beral V, Casabonne D, et al. Moderate alcohol intake and cancer incidence in women. J Natl Cancer Inst 2009;101:296-305.

12. Almquist M, Bondeson AG, Bondeson L, et al. Serum levels of vitamin D, PTH and calcium and breast cancer risk-a prospective nested case-control study. Int J Cancer 2010;127:2159-68.

13. Alsaker MD, Janszky I, Opdahl S, et al. Weight change in adulthood and risk of postmenopausal breast cancer: the HUNT study of Norway. Br J Cancer 2013;109:1310-7.

14. Amadou A, Ferrari P, Muwonge R, et al. Overweight, obesity and risk of premenopausal breast cancer according to ethnicity: a systematic review and dose-response meta-analysis. Obes Rev 2013;14:665-78.

15. Amir E, Cecchini RS, Ganz PA, et al. 25-Hydroxy vitamin-D, obesity, and associated variables as predictors of breast cancer risk and tamoxifen benefit in NSABP-P1. Breast Cancer Res Treat 2012;133:1077-88.

16. Andersson SW, Bengtsson C, Hallberg L, et al. Cancer risk in Swedish women: the relation to size at birth. Br J Cancer 2001;84:1193-8.

17. Andreotti G, Hou L, Beane Freeman LE, et al. Body mass index, agricultural pesticide use, and cancer incidence in the Agricultural Health Study cohort. Cancer Causes Control 2010;21:1759-75.

18. Andrieu N, Goldgar DE, Easton DF, et al. Pregnancies, breast-feeding, and breast cancer risk in the International BRCA1/2 Carrier Cohort Study (IBCCS). J Natl Cancer Inst 2006;98:535-44.

19. Arem H, Moore SC, Park Y, et al. Physical activity and cancer-specific mortality in the NIH-AARP Diet and Health Study cohort. Int J Cancer 2014;135:423-31.

20. Aune D, Chan DS, Vieira AR, et al. Dietary compared with blood concentrations of carotenoids and breast cancer risk: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr 2012;96:356-73.

21. Avenell A, MacLennan GS, Jenkinson DJ, et al. Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D(3) and/or calcium (RECORD trial). J Clin Endocrinol Metab 2012;97:614-22.

22. Baer HJ, Rich-Edwards JW, Colditz GA, et al. Adult height, age at attained height, and incidence of breast cancer in premenopausal women. Int J Cancer 2006;119:2231-5.

23. Baglietto L, English DR, Gertig DM, et al. Does dietary folate intake modify effect of alcohol consumption on breast cancer risk? Prospective cohort study. BMJ 2005;331:807.

24. Bakker MF, Peeters PH, Klaasen VM, et al. Plasma carotenoids, vitamin C, tocopherols, and retinol and the risk of breast cancer in the European Prospective Investigation into Cancer and Nutrition cohort. Am J Clin Nutr 2016;103:454-64.

25. Bandera EV, Chandran U, Hong CC, et al. Obesity, body fat distribution, and risk of breast cancer subtypes in African American women participating in the AMBER Consortium. Breast Cancer Res Treat 2015;150:655-66.

26. Bardia A, Hartmann LC, Vachon CM, et al. Recreational physical activity and risk of postmenopausal breast cancer based on hormone receptor status. Arch Intern Med 2006;166:2478-83.

27. Barnes-Josiah D, Potter JD, Sellers TA, et al. Early body size and subsequent weight gain as predictors of breast cancer incidence (Iowa, United States). Cancer Causes Control 1995;6:112-8.

28. Barrett-Connor E, Friedlander NJ. Dietary fat, calories, and the risk of breast cancer in postmenopausal women: a prospective population-based study. J Am Coll Nutr 1993;12:390-9.

29. Bassett JK, Baglietto L, Hodge AM, et al. Dietary intake of B vitamins and methionine and breast cancer risk. Cancer Causes Control 2013;24:1555-63.

30. Batty GD, Barzi F, Woodward M, et al. Adult height and cancer mortality in Asia: the Asia Pacific Cohort Studies Collaboration. Ann Oncol 2010;21:646-54.

31. Bauer SR, Hankinson SE, Bertone-Johnson ER, et al. Plasma vitamin D levels, menopause, and risk of breast cancer: dose-response meta-analysis of prospective studies. Medicine (Baltimore) 2013;92:123-31.

32. Benzon LS, Vogel U, Christensen J, et al. Interaction between ADH1C Arg(272)Gln and alcohol intake in relation to breast cancer risk suggests that ethanol is the causal factor in alcohol related breast cancer. Cancer Lett 2010;295:191-7.

33. Berkey CS, Frazier AL, Gardner JD, et al. Adolescence and breast carcinoma risk. Cancer 1999;85:2400-9.

34. Bertone-Johnson ER, Chen WY, Holick MF, et al. Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2005;14:1991-7.

35. Bessonova L, Marshall SF, Ziogas A, et al. The association of body mass index with mortality in the California Teachers Study. Int J Cancer 2011;129:2492-501.

36. Bhaskaran K, Douglas I, Forbes H, et al. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. Lancet 2014;384:755-65.

37. Bhoo-Pathy N, Peeters P, van GC, et al. Coffee and tea intake and risk of breast cancer. Breast Cancer Res Treat 2010;121:461-7.

38. Bhoo-Pathy N, Peeters PH, Uiterwaal CS, et al. Coffee and tea consumption and risk of pre- and postmenopausal breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. Breast Cancer Res 2015;17:15.

39. Bingham SA, Luben R, Welch A, et al. Are imprecise methods obscuring a relation between fat and breast cancer? Lancet 2003;362:212-4.

40. Bjelakovic G, Gluud LL, Nikolova D, et al. Vitamin D supplementation for prevention of cancer in adults. Cochrane Database Syst Rev 2014;6:CD007469.

41. Bjerkaas E, Parajuli R, Weiderpass E, et al. Smoking duration before first childbirth: an emerging risk factor for breast cancer? Results from 302,865 Norwegian women. Cancer Causes Control 2013;24:1347-56.

42. Bjorge T, Engeland A, Tverdal A, et al. Body mass index in adolescence in relation to cause-specific mortality: a follow-up of 230,000 Norwegian adolescents. Am J Epidemiol 2008;168:30-7.

43. Bjorge T, Lukanova A, Jonsson H, et al. Metabolic syndrome and breast cancer in the me-can (metabolic syndrome and cancer) project. Cancer Epidemiol Biomarkers Prev 2010;19:1737-45.

44. Boeke CE, Eliassen AH, Chen WY, et al. Dietary fat intake in relation to lethal breast cancer in two large prospective cohort studies. Breast Cancer Res Treat 2014;146:383-392a.

45. Boeke CE, Eliassen AH, Oh H, et al. Adolescent physical activity in relation to breast cancer risk. Breast Cancer Res Treat 2014;145:715-724b.

46. Boggs DA, Palmer JR, Wise LA, et al. Fruit and vegetable intake in relation to risk of breast cancer in the Black Women's Health Study. Am J Epidemiol 2010;172:1268-1279a.

47. Boggs DA, Palmer JR, Stampfer MJ, et al. Tea and coffee intake in relation to risk of breast cancer in the Black Women's Health Study. Cancer Causes Control 2010;21:1941-1948b.

48. Boggs DA, Rosenberg L, Adams-Campbell LL, et al. Prospective approach to breast cancer risk prediction in African American women: the black women's health study model. J Clin Oncol 2015;33:1038-44.

49. Borch KB, Lund E, Braaten T, et al. Physical activity and the risk of postmenopausal breast cancer - the Norwegian Women and Cancer Study. J Negat Results Biomed 2014;13:3.

50. Borgquist S, Jirstrom K, Anagnostaki L, et al. Anthropometric factors in relation to different tumor biological subgroups of postmenopausal breast cancer. Int J Cancer 2009;124:402-11.

51. Bosco JL, Palmer JR, Boggs DA, et al. Cardiometabolic factors and breast cancer risk in U.S. black women. Breast Cancer Res Treat 2012;134:1247-56.

52. Brasky TM, Lampe JW, Potter JD, et al. Specialty supplements and breast cancer risk in the VITamins And Lifestyle (VITAL) Cohort. Cancer Epidemiol Biomarkers Prev 2010;19:1696-708.

53. Brennan SF, Cantwell MM, Cardwell CR, et al. Dietary patterns and breast cancer risk: a systematic review and meta-analysis. Am J Clin Nutr 2010;91:1294-302.

54. Breslow RA, Ballard-Barbash R, Munoz K, et al. Long-term recreational physical activity and breast cancer in the National Health and Nutrition Examination Survey I epidemiologic follow-up study. Cancer Epidemiol Biomarkers Prev 2001;10:805-8.

55. Breslow RA, Chen CM, Graubard BI, et al. Prospective study of alcohol consumption quantity and frequency and cancer-specific mortality in the US population. Am J Epidemiol 2011;174:1044-53.

56. Brinton LA, Richesson D, Leitzmann MF, et al. Menopausal hormone therapy and breast cancer risk in the NIH-AARP Diet and Health Study Cohort. Cancer Epidemiol Biomarkers Prev 2008;17:3150-60.

57. Brinton LA, Smith L, Gierach GL, et al. Breast cancer risk in older women: results from the NIH-AARP Diet and Health Study. Cancer Causes Control 2014;25:843-57.

58. Brunner RL, Wactawski-Wende J, Caan BJ, et al. The effect of calcium plus vitamin D on risk for invasive cancer: results of the Women's Health Initiative (WHI) calcium plus vitamin D randomized clinical trial. Nutr Cancer 2011;63:827-41.

59. Buckland G, Travier N, Cottet V, et al. Adherence to the mediterranean diet and risk of breast cancer in the European prospective investigation into cancer and nutrition cohort study. Int J Cancer 2013;132:2918-27.

60. Bukowski R, Chlebowski RT, Thune I, et al. Birth weight, breast cancer and the potential mediating hormonal environment. PLoS One 2012;7:e40199.

61. Burton A, Martin R, Galobardes B, et al. Young adulthood body mass index and risk of cancer in later adulthood: historical cohort study. Cancer Causes Control 2010;21:2069-77.

62. Butler LM, Wu AH, Wang R, et al. A vegetable-fruit-soy dietary pattern protects against breast cancer among postmenopausal Singapore Chinese women. Am J Clin Nutr 2010;91:1013-9.

63. Butt S, Borgquist S, Anagnostaki L, et al. Breastfeeding in relation to risk of different breast cancer characteristics. BMC Res Notes 2014;7:216.

64. Byrne C, Ursin G, Ziegler RG. A comparison of food habit and food frequency data as predictors of breast cancer in the NHANES I/NHEFS cohort. J Nutr 1996;126:2757-64.

65. Byrne C, Rockett H, Holmes MD. Dietary fat, fat subtypes, and breast cancer risk: lack of an association among postmenopausal women with no history of benign breast disease. Cancer Epidemiol Biomarkers Prev 2002;11:261-5.

66. Caan BJ, Aragaki A, Thomson CA, et al. Vasomotor symptoms, adoption of a low-fat dietary pattern, and risk of invasive breast cancer: a secondary analysis of the Women's Health Initiative randomized controlled dietary modification trial. J Clin Oncol 2009;27:4500-7.

67. Cade JE, Burley VJ, Greenwood DC. Dietary fibre and risk of breast cancer in the UK Women's Cohort Study. Int J Epidemiol 2007;36:431-8.

68. Cade JE, Taylor EF, Burley VJ, et al. Common dietary patterns and risk of breast cancer: analysis from the United Kingdom Women's Cohort Study. Nutr Cancer 2010;62:300-6.

69. Cade JE, Taylor EF, Burley VJ, et al. Does the Mediterranean dietary pattern or the Healthy Diet Index influence the risk of breast cancer in a large British cohort of women? Eur J Clin Nutr 2011;65:920-8.

70. Calle EE, Murphy TK, Rodriguez C, et al. Occupation and breast cancer mortality in a prospective cohort of US women. Am J Epidemiol 1998;148:191-7.

71. Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625-38.

72. Canchola AJ, Anton-Culver H, Bernstein L, et al. Body size and the risk of postmenopausal breast cancer subtypes in the California Teachers Study cohort. Cancer Causes Control 2012.

73. Catsburg C, Kirsh VA, Soskolne CL, et al. Associations between anthropometric characteristics, physical activity, and breast cancer risk in a Canadian cohort. Breast Cancer Res Treat 2014;145:545-552b.

74. Catsburg C, Miller AB, Rohan TE. Adherence to cancer prevention guidelines and risk of breast cancer. Int J Cancer 2014;135:2444-2452a.

75. Catsburg C, Kim RS, Kirsh VA, et al. Dietary patterns and breast cancer risk: a study in 2 cohorts. Am J Clin Nutr 2015;101:817-23.

76. Cecchini RS, Costantino JP, Cauley JA, et al. Body mass index and the risk for developing invasive breast cancer among high-risk women in NSABP P-1 and STAR breast cancer prevention trials. Cancer Prev Res (Phila) 2012;5:583-92.

77. Cerhan JR, Chiu BC, Wallace RB, et al. Physical activity, physical function, and the risk of breast cancer in a prospective study among elderly women. J Gerontol A Biol Sci Med Sci 1998;53:M251-M256.

78. Cerhan JR, Grabrick DM, Vierkant RA, et al. Interaction of adolescent anthropometric characteristics and family history on breast cancer risk in a Historical Cohort Study of 426 families (USA). Cancer Causes Control 2004;15:1-9.

79. Chang SC, Leitzmann M, Stolzenberg-Solomon R, et al. Interrelation of energy intake, body size, and physical activity with breast cancer in the PLCO screening trial. Cancer Epidemiology Biomarkers & Prevention 2003;12:138.

80. Chang SC, Ziegler RG, Dunn B, et al. Association of energy intake and energy balance with postmenopausal breast cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. Cancer Epidemiol Biomarkers Prev 2006;15:334-41.

81. Chen P, Hu P, Xie D, et al. Meta-analysis of vitamin D, calcium and the prevention of breast cancer. Breast Cancer Res Treat 2010;121:469-77.

82. Chen WY, Colditz GA, Rosner B, et al. Use of postmenopausal hormones, alcohol, and risk for invasive breast cancer. Ann Intern Med 2002;137:798-804.

83. Chen WY, Rosner B, Hankinson SE, et al. Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. JAMA 2011;306:1884-90.

84. Cheraghi Z, Poorolajal J, Hashem T, et al. Effect of body mass index on breast cancer during premenopausal and postmenopausal periods: a meta-analysis. PLoS One 2012;7:e51446.

85. Chlebowski RT, Anderson GL, Lane DS, et al. Predicting risk of breast cancer in postmenopausal women by hormone receptor status. J Natl Cancer Inst 2007;99:1695-705.

86. Chlebowski RT, Johnson KC, Kooperberg C, et al. Calcium plus vitamin D supplementation and the risk of breast cancer. J Natl Cancer Inst 2008;100:1581-91.

87. Cho E, Spiegelman D, Hunter DJ, et al. Premenopausal dietary carbohydrate, glycemic index, glycemic load, and fiber in relation to risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2003;12:1153-1158b.

88. Cho E, Spiegelman D, Hunter DJ, et al. Premenopausal intakes of vitamins A, C, and E, folate, and carotenoids, and risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2003;12:713-720c.

89. Cho E, Spiegelman D, Hunter DJ, et al. Premenopausal fat intake and risk of breast cancer. J Natl Cancer Inst 2003;95:1079-1085a.

90. Cho E, Chen WY, Hunter DJ, et al. Red meat intake and risk of breast cancer among premenopausal women. Arch Intern Med 2006;166:2253-9.

91. Cho E, Holmes M, Hankinson SE, et al. Nutrients involved in one-carbon metabolism and risk of breast cancer among premenopausal women. Cancer Epidemiol Biomarkers Prev 2007;16:2787-90.

92. Chun J, El-Tamer M, Joseph KA, et al. Predictors of breast cancer development in a high-risk population. Am J Surg 2006;192:474-7.

93. Chung M, Lee J, Terasawa T, et al. Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. Ann Intern Med 2011;155:827-38.

94. Cohen SS, Matthews CE, Bradshaw PT, et al. Sedentary behavior, physical activity, and likelihood of breast cancer among Black and White women: a report from the Southern Community Cohort Study. Cancer Prev Res (Phila) 2013;6:566-76.

95. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. Am J Epidemiol 2000;152:950-64.

96. Colditz GA, Feskanich D, Chen WY, et al. Physical activity and risk of breast cancer in premenopausal women. Br J Cancer 2003;89:847-51.

97. Colditz GA, Rosner BA, Chen WY, et al. Risk factors for breast cancer according to estrogen and progesterone receptor status. J Natl Cancer Inst 2004;96:218-28.

98. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50?302 women with breast cancer and 96?973 women without the disease. Lancet 2002;360:187-95.

99. Cottet V, Touvier M, Fournier A, et al. Postmenopausal breast cancer risk and dietary patterns in the E3N-EPIC prospective cohort study. Am J Epidemiol 2009;170:1257-67.

100. Couto E, Sandin S, Lof M, et al. Mediterranean dietary pattern and risk of breast cancer. PLoS One 2013;8:e55374.

101. Cross AJ, Leitzmann MF, Gail MH, et al. A prospective study of red and processed meat intake in relation to cancer risk. PLoS Med 2007;4:e325.

102. Cui Y, Shikany JM, Liu S, et al. Selected antioxidants and risk of hormone receptor-defined invasive breast cancers among postmenopausal women in the Women's Health Initiative Observational Study. Am J Clin Nutr 2008;87:1009-18.

103. Cust AE, Stocks T, Lukanova A, et al. The influence of overweight and insulin resistance on breast cancer risk and tumour stage at diagnosis: a prospective study. Breast Cancer Res Treat 2009;113:567-76.

104. Dai Q, Shu XO, Li H, et al. Is green tea drinking associated with a later onset of breast cancer? Ann Epidemiol 2010;20:74-81.

105. Dallal CM, Sullivan-Halley J, Ross RK, et al. Long-term recreational physical activity and risk of invasive and in situ breast cancer: the California teachers study. Arch Intern Med 2007;167:408-15.

106. Daniel CR, Cross AJ, Graubard BI, et al. Prospective investigation of poultry and fish intake in relation to cancer risk. Cancer Prev Res (Phila) 2011;4:1903-11.

107. Dartois L, Fagherazzi G, Boutron-Ruault MC, et al. Association between five lifestyle habits and cancer risk: results from the E3N cohort. Cancer Prev Res (Phila) 2014;7:516-25.

108. Davey SG, Hart C, Upton M, et al. Height and risk of death among men and women: aetiological implications of associations with cardiorespiratory disease and cancer mortality. J Epidemiol Community Health 2000;54:97-103.

109. Davey SG, Sterne JA, Fraser A, et al. The association between BMI and mortality using offspring BMI as an indicator of own BMI: large intergenerational mortality study. BMJ 2009;339:b5043.

110. de Batlle J, Ferrari P, Chajes V, et al. Dietary folate intake and breast cancer risk: European prospective investigation into cancer and nutrition. J Natl Cancer Inst 2015;107:367.

111. De Stavola BL, Wang DY, Allen DS, et al. The association of height, weight, menstrual and reproductive events with breast cancer: results from two prospective studies on the island of Guernsey (United Kingdom). Cancer Causes Control 1993;4:331-40.

112. De Stavola BL, dos SS, I, McCormack V, et al. Childhood growth and breast cancer. Am J Epidemiol 2004;159:671-82.

113. Dehal A, Garrett T, Tedders SH, et al. Body mass index and death rate of colorectal cancer among a national cohort of U.S. adults. Nutr Cancer 2011;63:1218-25.

114. den Tonkelaar I, Seidell JC, Collette HJ, et al. A prospective study on obesity and subcutaneous fat patterning in relation to breast cancer in post-menopausal women participating in the DOM project. Br J Cancer 1994;69:352-7.

115. den Tonkelaar I, Seidell JC, Collette HJ. Body fat distribution in relation to breast cancer in women participating in the DOM-project. Breast Cancer Res Treat 1995;34:55-61.

116. Deschasaux M, Zelek L, Pouchieu C, et al. Prospective association between dietary fiber intake and breast cancer risk. PLoS One 2013;8:e79718.

117. Dirx MJ, Voorrips LE, Goldbohm RA, et al. Baseline recreational physical activity, history of sports participation, and postmenopausal breast carcinoma risk in the Netherlands Cohort Study. Cancer 2001;92:1638-49.

118. Dong JY, Zhang L, He K, et al. Dairy consumption and risk of breast cancer: a meta-analysis of prospective cohort studies. Breast Cancer Res Treat 2011;127:23-31.

119. Dorgan JF, Brown C, Barrett M, et al. Physical activity and risk of breast cancer in the Framingham Heart Study. Am J Epidemiol 1994;139:662-9.

120. Dorgan JF, Sowell A, Swanson CA, et al. Relationships of serum carotenoids, retinol, alpha-tocopherol, and selenium with breast cancer risk: results from a prospective study in Columbia, Missouri (United States). Cancer Causes Control 1998;9:89-97.

121. Dorjgochoo T, Gao YT, Chow WH, et al. Plasma carotenoids, tocopherols, retinol and breast cancer risk: results from the Shanghai Women Health Study (SWHS). Breast Cancer Res Treat 2009;117:381-9.

122. dos Santos Silva I, De Stavola BL, Hardy RJ, et al. Is the association of birth weight with premenopausal breast cancer risk mediated through childhood growth? Br J Cancer 2004;91:519-24.

123. Drake DA. A longitudinal study of physical activity and breast cancer prediction. Cancer Nurs 2001;24:371-7.

124. Duffy CM, Assaf A, Cyr M, et al. Alcohol and folate intake and breast cancer risk in the WHI Observational Study. Breast Cancer Res Treat 2009;116:551-62.

125. Dumeaux V, Lund E, Hjartaker A. Use of oral contraceptives, alcohol, and risk for invasive breast cancer. Cancer Epidemiol Biomarkers Prev 2004;13:1302-7.

126. Edvardsen K, Veierod MB, Brustad M, et al. Vitamin D-effective solar UV radiation, dietary vitamin D and breast cancer risk. Int J Cancer 2011;128:1425-33.

127. Egeberg R, Olsen A, Autrup H, et al. Meat consumption, N-acetyl transferase 1 and 2 polymorphism and risk of breast cancer in Danish postmenopausal women. Eur J Cancer Prev 2008;17:39-47.

128. Ekbom A, Trichopoulos D, Adami HO, et al. Evidence of prenatal influences on breast cancer risk. Lancet 1992;340:1015-8.

129. Ekbom A, Hsieh CC, Lipworth L, et al. Intrauterine environment and breast cancer risk in women: a population-based study. J Natl Cancer Inst 1997;89:71-6.

130. Eliassen AH, Colditz GA, Rosner B, et al. Adult weight change and risk of postmenopausal breast cancer. JAMA 2006;296:193-201.

131. Eliassen AH, Hankinson SE, Rosner B, et al. Physical activity and risk of breast cancer among postmenopausal women. Arch Intern Med 2010;170:1758-64.

132. Eliassen AH, Spiegelman D, Hollis BW, et al. Plasma 25-hydroxyvitamin D and risk of breast cancer in the Nurses' Health Study II. Breast Cancer Res 2011;13:R50.

133. Eliassen AH, Hendrickson SJ, Brinton LA, et al. Circulating carotenoids and risk of breast cancer: pooled analysis of eight prospective studies. J Natl Cancer Inst 2012;104:1905-16.

134. Eliassen AH, Liao X, Rosner B, et al. Plasma carotenoids and risk of breast cancer over 20 y of follow-up. Am J Clin Nutr 2015;101:1197-205.

135. Emaus MJ, van Gils CH, Bakker MF, et al. Weight change in middle adulthood and breast cancer risk in the EPIC-PANACEA study. Int J Cancer 2014;135:2887-99.

136. Engel LS, Satagopan J, Sima CS, et al. Sun exposure, vitamin D receptor genetic variants, and risk of breast cancer in the Agricultural Health Study. Environ Health Perspect 2014;122:165-71.

137. Engel P, Fagherazzi G, Boutten A, et al. Serum 25(OH) vitamin D and risk of breast cancer: a nested case-control study from the French E3N cohort. Cancer Epidemiol Biomarkers Prev 2010;19:2341-50.

138. Engel P, Fagherazzi G, Mesrine S, et al. Joint effects of dietary vitamin D and sun exposure on breast cancer risk: results from the French E3N cohort. Cancer Epidemiol Biomarkers Prev 2011;20:187-98.

139. Engeset D, Alsaker E, Lund E, et al. Fish consumption and breast cancer risk. The European Prospective Investigation into Cancer and Nutrition (EPIC). Int J Cancer 2006;119:175-82.

140. Engeset D, Dyachenko A, Ciampi A, et al. Dietary patterns and risk of cancer of various sites in the Norwegian European Prospective Investigation into Cancer and Nutrition cohort: the Norwegian Women and Cancer study. Eur J Cancer Prev 2009;18:69-75.

141. Epplein M, Shvetsov YB, Wilkens LR, et al. Plasma carotenoids, retinol, and tocopherols and postmenopausal breast cancer risk in the Multiethnic Cohort Study: a nested case-control study. Breast Cancer Res 2009;11:R49.

142. Ericson U, Sonestedt E, Gullberg B, et al. High folate intake is associated with lower breast cancer incidence in postmenopausal women in the Malmo Diet and Cancer cohort. Am J Clin Nutr 2007;86:434-43.

143. Ericson U, Sonestedt E, Ivarsson MI, et al. Folate intake, methylenetetrahydrofolate reductase polymorphisms, and breast cancer risk in women from the Malmo Diet and Cancer cohort. Cancer Epidemiol Biomarkers Prev 2009;18:1101-10.

144. Esposito K, Chiodini P, Capuano A, et al. Metabolic syndrome and postmenopausal breast cancer: systematic review and meta-analysis. Menopause 2013;20:1301-9.

145. Fagherazzi G, Touillaud MS, Boutron-Ruault MC, et al. No association between coffee, tea or caffeine consumption and breast cancer risk in a prospective cohort study. Public Health Nutr 2011;14:1315-20.

146. Fagherazzi G, Vilier A, Boutron-Ruault MC, et al. Height, sitting height, and leg length in relation with breast cancer risk in the E3N cohort. Cancer Epidemiol Biomarkers Prev 2012;21:1171-1175b.

147. Fagherazzi G, Chabbert-Buffet N, Fabre A, et al. Hip circumference is associated with the risk of premenopausal ER-/PR- breast cancer. Int J Obes (Lond) 2012;36:431-439a.

148. Fagherazzi G, Vilier A, Boutron-Ruault MC, et al. Alcohol consumption and breast cancer risk subtypes in the E3N-EPIC cohort. Eur J Cancer Prev 2015;24:209-14.

149. Falk RT, Maas P, Schairer C, et al. Alcohol and risk of breast cancer in postmenopausal women: an analysis of etiological heterogeneity by multiple tumor characteristics. Am J Epidemiol 2014;180:705-17.

150. Farvid MS, Cho E, Chen WY, et al. Premenopausal dietary fat in relation to pre- and post-menopausal breast cancer. Breast Cancer Res Treat 2014;145:255-65.

151. Farvid MS, Cho E, Chen WY, et al. Adolescent meat intake and breast cancer risk. Int J Cancer 2015;136:1909-1920a.

152. Farvid MS, Eliassen AH, Cho E, et al. Adolescent and Early Adulthood Dietary Carbohydrate Quantity and Quality in Relation to Breast Cancer Risk. Cancer Epidemiol Biomarkers Prev 2015;24:1111-1120b.

153. Feigelson HS, Calle EE, Robertson AS, et al. Alcohol consumption increases the risk of fatal breast cancer (United States). Cancer Causes Control 2001;12:895-902.

154. Feigelson HS, Jonas CR, Robertson AS, et al. Alcohol, folate, methionine, and risk of incident breast cancer in the American Cancer Society Cancer Prevention Study II Nutrition Cohort. Cancer Epidemiol Biomarkers Prev 2003;12:161-4.

155. Feigelson HS, Jonas CR, Teras LR, et al. Weight gain, body mass index, hormone replacement therapy, and postmenopausal breast cancer in a large prospective study. Cancer Epidemiol Biomarkers Prev 2004;13:220-4.

156. Feigelson HS, Patel AV, Teras LR, et al. Adult weight gain and histopathologic characteristics of breast cancer among postmenopausal women. Cancer 2006;107:12-21.

157. Ferrari P, Rinaldi S, Jenab M, et al. Dietary fiber intake and risk of hormonal receptor-defined breast cancer in the European Prospective Investigation into Cancer and Nutrition study. Am J Clin Nutr 2013;97:344-53.

158. Ferrucci LM, Cross AJ, Graubard BI, et al. Intake of meat, meat mutagens, and iron and the risk of breast cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Br J Cancer 2009;101:178-84.

159. Folsom AR, Kaye SA, Prineas RJ, et al. Increased incidence of carcinoma of the breast associated with abdominal adiposity in postmenopausal women. Am J Epidemiol 1990;131:794-803.

160. Folsom AR, McKenzie DR, Bisgard KM, et al. No association between caffeine intake and postmenopausal breast cancer incidence in the Iowa Women's Health Study. Am J Epidemiol 1993;138:380-3.

161. Folsom AR, Kushi LH, Anderson KE, et al. Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study. Arch Intern Med 2000;160:2117-28.

162. Folsom AR, Demissie Z. Fish intake, marine omega-3 fatty acids, and mortality in a cohort of postmenopausal women. Am J Epidemiol 2004;160:1005-10.

163. Fourkala EO, Burnell M, Cox C, et al. Association of skirt size and postmenopausal breast cancer risk in older women: a cohort study within the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). BMJ Open 2014;4:e005400.

164. Fournier A, Dos SG, Guillas G, et al. Recent recreational physical activity and breast cancer risk in postmenopausal women in the E3N cohort. Cancer Epidemiol Biomarkers Prev 2014;23:1893-902.

165. Fraser GE, Shavlik D. Risk factors, lifetime risk, and age at onset of breast cancer. Ann Epidemiol 1997;7:375-82.

166. Frazier AL, Ryan CT, Rockett H, et al. Adolescent diet and risk of breast cancer. Breast Cancer Res 2003;5:R59-R64.

167. Freedman DM, Looker AC, Chang SC, et al. Prospective study of serum vitamin D and cancer mortality in the United States. J Natl Cancer Inst 2007;99:1594-602.

168. Freedman DM, Chang SC, Falk RT, et al. Serum levels of vitamin D metabolites and breast cancer risk in the prostate, lung, colorectal, and ovarian cancer screening trial. Cancer Epidemiol Biomarkers Prev 2008;17:889-94.

169. Freedman DM, Looker AC, Abnet CC, et al. Serum 25-hydroxyvitamin D and cancer mortality in the NHANES III study (1988-2006). Cancer Res 2010;70:8587-97.

170. Freedman LS, Potischman N, Kipnis V, et al. A comparison of two dietary instruments for evaluating the fat-breast cancer relationship. Int J Epidemiol 2006;35:1011-21.

171. French SA, Folsom AR, Jeffery RW, et al. Weight variability and incident disease in older women: the Iowa Women's Health Study. Int J Obes Relat Metab Disord 1997;21:217-23.

172. Freni SC, Eberhardt MS, Turturro A, et al. Anthropometric measures and metabolic rate in association with risk of breast cancer (United States). Cancer Causes Control 1996;7:358-65.

173. Friedenreich CM, Howe GR, Miller AB, et al. A cohort study of alcohol consumption and risk of breast cancer. Am J Epidemiol 1993;137:512-20.

174. Frisch RE, Wyshak G, Albright NL, et al. Lower prevalence of breast cancer and cancers of the reproductive system among former college athletes compared to non-athletes. Br J Cancer 1985;52:885-91.

175. Frisch RE, Wyshak G, Witschi J, et al. Lower lifetime occurrence of breast cancer and cancers of the reproductive system among former college athletes. Int J Fertil 1987;32:217-25.

176. Fuchs CS, Stampfer MJ, Colditz GA, et al. Alcohol consumption and mortality among women. N Engl J Med 1995;332:1245-50.

177. Fujino Y. Anthropometry, development history and mortality in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). Asian Pac J Cancer Prev 2007;8 Suppl:105-12.

178. Fung TT, Hu FB, Holmes MD, et al. Dietary patterns and the risk of postmenopausal breast cancer. Int J Cancer 2005;116:116-21.

179. Fung TT, Hu FB, McCullough ML, et al. Diet quality is associated with the risk of estrogen receptor-negative breast cancer in postmenopausal women. J Nutr 2006;136:466-72.

180. Fung TT, Hu FB, Hankinson SE, et al. Low-carbohydrate diets, dietary approaches to stop hypertension-style diets, and the risk of postmenopausal breast cancer. Am J Epidemiol 2011;174:652-60.

181. Fung TT, Schulze MB, Hu FB, et al. A dietary pattern derived to correlate with estrogens and risk of postmenopausal breast cancer. Breast Cancer Res Treat 2012;132:1157-62.

182. Fung TT, Chiuve SE, Willett WC, et al. Intake of specific fruits and vegetables in relation to risk of estrogen receptor-negative breast cancer among postmenopausal women. Breast Cancer Res Treat 2013;138:925-30.

183. Gaard M, Tretli S, Urdal P. Risk of breast cancer in relation to blood lipids: a prospective study of 31,209 Norwegian women. Cancer Causes Control 1994;5:501-9.

184. Gaard M, Tretli S, Loken EB. Dietary fat and the risk of breast cancer: a prospective study of 25,892 Norwegian women. Int J Cancer 1995;63:13-7.

185. Gago-Dominguez M, Yuan JM, Sun CL, et al. Opposing effects of dietary n-3 and n-6 fatty acids on mammary carcinogenesis: The Singapore Chinese Health Study. Br J Cancer 2003;89:1686-92.

186. Galanis DJ, Kolonel LN, Lee J, et al. Anthropometric predictors of breast cancer incidence and survival in a multi-ethnic cohort of female residents of Hawaii, United States. Cancer Causes Control 1998;9:217-24.

187. Gallicchio L, McSorley MA, Newschaffer CJ, et al. Body mass, polymorphisms in obesity-related genes, and the risk of developing breast cancer among women with benign breast disease. Cancer Detect Prev 2007;31:95-101.

188. Gandini S, Boniol M, Haukka J, et al. Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma. Int J Cancer 2011;128:1414-24.

189. Ganmaa D, Willett WC, Li TY, et al. Coffee, tea, caffeine and risk of breast cancer: a 22-year follow-up. Int J Cancer 2008;122:2071-6.

190. Gapstur SM, Potter JD, Sellers TA, et al. Increased risk of breast cancer with alcohol consumption in postmenopausal women. Am J Epidemiol 1992;136:1221-31.

191. Garland M, Hunter DJ, Colditz GA, et al. Alcohol consumption in relation to breast cancer risk in a cohort of United States women 25-42 years of age. Cancer Epidemiol Biomarkers Prev 1999;8:1017-21.

192. Gaudet MM, Falk RT, Gierach GL, et al. Do adipokines underlie the association between known risk factors and breast cancer among a cohort of United States women? Cancer Epidemiol 2010;34:580-6.

193. Gaudet MM, Patel AV, Teras LR, et al. Obesity-related markers and breast cancer in CPS-II Nutrition Cohort. Int J Mol Epidemiol Genet 2013;4:156-66.

194. Gaudet MM, Carter BD, Patel AV, et al. Waist circumference, body mass index, and postmenopausal breast cancer incidence in the Cancer Prevention Study-II Nutrition Cohort. Cancer Causes Control 2014;25:737-45.

195. Genkinger JM, Makambi KH, Palmer JR, et al. Consumption of dairy and meat in relation to breast cancer risk in the Black Women's Health Study. Cancer Causes Control 2013;24:675-84.

196. George SM, Park Y, Leitzmann MF, et al. Fruit and vegetable intake and risk of cancer: a prospective cohort study. Am J Clin Nutr 2009;89:347-353a.

197. George SM, Mayne ST, Leitzmann MF, et al. Dietary glycemic index, glycemic load, and risk of cancer: a prospective cohort study. Am J Epidemiol 2009;169:462-472b.

198. George SM, Irwin ML, Matthews CE, et al. Beyond recreational physical activity: examining occupational and household activity, transportation activity, and sedentary behavior in relation to postmenopausal breast cancer risk. Am J Public Health 2010;100:2288-95.

199. Gertig DM, Hankinson SE, Hough H, et al. N-acetyl transferase 2 genotypes, meat intake and breast cancer risk. Int J Cancer 1999;80:13-7.

200. Gibson LJ, Hery C, Mitton N, et al. Risk factors for breast cancer among Filipino women in Manila. Int J Cancer 2010;126:515-21.

201. Gierach GL, Freedman ND, Andaya A, et al. Coffee intake and breast cancer risk in the NIH-AARP diet and health study cohort. Int J Cancer 2012;131:452-60.

202. Giles GG, Simpson JA, English DR, et al. Dietary carbohydrate, fibre, glycaemic index, glycaemic load and the risk of postmenopausal breast cancer. Int J Cancer 2006;118:1843-7.

203. Giovannucci E, Stampfer MJ, Colditz GA, et al. Recall and selection bias in reporting past alcohol consumption among breast cancer cases. Cancer Causes Control 1993;4:441-448b.

204. Giovannucci E, Stampfer MJ, Colditz GA, et al. A comparison of prospective and retrospective assessments of diet in the study of breast cancer. Am J Epidemiol 1993;137:502-511a.

205. Gissel T, Rejnmark L, Mosekilde L, et al. Intake of vitamin D and risk of breast cancer--a meta-analysis. J Steroid Biochem Mol Biol 2008;111:195-9.

206. Goldbohm RA, Hertog MG, Brants HA, et al. Consumption of black tea and cancer risk: a prospective cohort study. J Natl Cancer Inst 1996;88:93-100.

207. Goodman MT, Cologne JB, Moriwaki H, et al. Risk factors for primary breast cancer in Japan: 8-year follow-up of atomic bomb survivors. Prev Med 1997;26:144-53.

208. Graham S, Zielezny M, Marshall J, et al. Diet in the epidemiology of postmenopausal breast cancer in the New York State Cohort. Am J Epidemiol 1992;136:1327-37.

209. Green J, Cairns BJ, Casabonne D, et al. Height and cancer incidence in the Million Women Study: prospective cohort, and meta-analysis of prospective studies of height and total cancer risk. Lancet Oncol 2011;12:785-94.

210. Grenier D, Cooke AL, Lix L, et al. Bone mineral density and risk of postmenopausal breast cancer. Breast Cancer Res Treat 2011;126:679-86.

211. Gunter MJ, Hoover DR, Yu H, et al. Insulin, insulin-like growth factor-I, and risk of breast cancer in postmenopausal women. J Natl Cancer Inst 2009;101:48-60.

212. Guo L, Li N, Wang G, et al. [Body mass index and cancer incidence:a prospective cohort study in northern China]. Zhonghua Liu Xing Bing Xue Za Zhi 2014;35:231-6.

213. Hajiebrahimi M, Bahmanyar S, Oberg S, et al. Breast cancer risk in opposite-sexed twins: influence of birth weight and co-twin birth weight. J Natl Cancer Inst 2013;105:1833-6.

214. Han J, Hankinson SE, De V, I, et al. A prospective study of XRCC1 haplotypes and their interaction with plasma carotenoids on breast cancer risk. Cancer Res 2003;63:8536-41.

215. Han X, Stevens J, Truesdale KP, et al. Body mass index at early adulthood, subsequent weight change and cancer incidence and mortality. Int J Cancer 2014;135:2900-9.

216. Harding JL, Shaw JE, Anstey KJ, et al. Comparison of anthropometric measures as predictors of cancer incidence: A pooled collaborative analysis of 11 Australian cohorts. Int J Cancer 2015;137:1699-708.

217. Harlid S, Butt S, Ivarsson MI, et al. Interactive effect of genetic susceptibility with height, body mass index, and hormone replacement therapy on the risk of breast cancer. BMC Womens Health 2012;12:17.

218. Harnack L, Nicodemus K, Jacobs DR, Jr., et al. An evaluation of the Dietary Guidelines for Americans in relation to cancer occurrence. Am J Clin Nutr 2002;76:889-96.

219. Harris HR, Tamimi RM, Willett WC, et al. Body size across the life course, mammographic density, and risk of breast cancer. Am J Epidemiol 2011;174:909-918a.

220. Harris HR, Willett WC, Terry KL, et al. Body fat distribution and risk of premenopausal breast cancer in the Nurses' Health Study II. J Natl Cancer Inst 2011;103:273-278b.

221. Hartz A, He T, Rimm A. Comparison of adiposity measures as risk factors in postmenopausal women. J Clin Endocrinol Metab 2012;97:227-33.

222. Hartz AJ, He T. Cohort study of risk factors for breast cancer in post menopausal women. Epidemiol Health 2013;35:e2013003.

223. Harvie M, Howell A, Vierkant RA, et al. Association of gain and loss of weight before and after menopause with risk of postmenopausal breast cancer in the Iowa women's health study. Cancer Epidemiol Biomarkers Prev 2005;14:656-61.

224. Hastert TA, Beresford SA, Patterson RE, et al. Adherence to WCRF/AICR cancer prevention recommendations and risk of postmenopausal breast cancer. Cancer Epidemiol Biomarkers Prev 2013;22:1498-508.

225. Hedelin M, Lof M, Olsson M, et al. Dietary phytoestrogens are not associated with risk of overall breast cancer but diets rich in coumestrol are inversely associated with risk of estrogen receptor and progesterone receptor negative breast tumors in Swedish women. J Nutr 2008;138:938-45.

226. Heo M, Kabat GC, Strickler HD, et al. Optimal cutoffs of obesity measures in relation to cancer risk in postmenopausal women in the Women's Health Initiative Study. J Womens Health (Larchmt) 2015;24:218-27.

227. Hiatt RA, Klatsky AL, Armstrong MA. Alcohol consumption and the risk of breast cancer in a prepaid health plan. Cancer Res 1988;48:2284-2287a.

228. Hiatt RA, Krieger N, Lobaugh B, et al. Prediagnostic serum vitamin D and breast cancer. J Natl Cancer Inst 1998;90:461-463b.

229. Higginbotham S, Zhang ZF, Lee IM, et al. Dietary glycemic load and breast cancer risk in the Women's Health Study. Cancer Epidemiol Biomarkers Prev 2004;13:65-70.

230. Hilakivi-Clarke L, Forsen T, Eriksson JG, et al. Tallness and overweight during childhood have opposing effects on breast cancer risk. Br J Cancer 2001;85:1680-4.

231. Hildebrand JS, Gapstur SM, Campbell PT, et al. Recreational physical activity and leisure-time sitting in relation to postmenopausal breast cancer risk. Cancer Epidemiol Biomarkers Prev 2013;22:1906-12.

232. Hines LM, Hankinson SE, Smith-Warner SA, et al. A prospective study of the effect of alcohol consumption and ADH3 genotype on plasma steroid hormone levels and breast cancer risk. Cancer Epidemiol Biomarkers Prev 2000;9:1099-105.

233. Hippisley-Cox J, Coupland C. Development and validation of risk prediction algorithms to estimate future risk of common cancers in men and women: prospective cohort study. BMJ Open 2015;5:e007825.

234. Hirvonen T, Mennen LI, de BA, et al. Consumption of antioxidant-rich beverages and risk for breast cancer in French women. Ann Epidemiol 2006;16:503-8.

235. Hjartaker A, Laake P, Lund E. Childhood and adult milk consumption and risk of premenopausal breast cancer in a cohort of 48,844 women - the Norwegian women and cancer study. Int J Cancer 2001;93:888-93.

236. Hjartaker A, Thoresen M, Engeset D, et al. Dairy consumption and calcium intake and risk of breast cancer in a prospective cohort: the Norwegian Women and Cancer study. Cancer Causes Control 2010;21:1875-85.

237. Holmberg L, Baron JA, Byers T, et al. Alcohol intake and breast cancer risk: effect of exposure from 15 years of age. Cancer Epidemiol Biomarkers Prev 1995;4:843-7.

238. Holmes MD, Hunter DJ, Colditz GA, et al. Association of dietary intake of fat and fatty acids with risk of breast cancer. JAMA 1999;281:914-20.

239. Holmes MD, Colditz GA, Hunter DJ, et al. Meat, fish and egg intake and risk of breast cancer. Int J Cancer 2003;104:221-7.

240. Holmes MD, Liu S, Hankinson SE, et al. Dietary carbohydrates, fiber, and breast cancer risk. Am J Epidemiol 2004;159:732-9.

241. Hong Z, Tian C, Zhang X. Dietary calcium intake, vitamin D levels, and breast cancer risk: a dose-response analysis of observational studies. Breast Cancer Res Treat 2012;136:309-12.

242. Horn-Ross PL, Hoggatt KJ, West DW, et al. Recent diet and breast cancer risk: the California Teachers Study (USA). Cancer Causes Control 2002;13:407-15.

243. Horn-Ross PL, Canchola AJ, West DW, et al. Patterns of alcohol consumption and breast cancer risk in the California Teachers Study cohort. Cancer Epidemiol Biomarkers Prev 2004;13:405-11.

244. Horn-Ross PL, Canchola AJ, Bernstein L, et al. Alcohol consumption and breast cancer risk among postmenopausal women following the cessation of hormone therapy use: the California Teachers Study. Cancer Epidemiol Biomarkers Prev 2012;21:2006-13.

245. Horn J, Opdahl S, Engstrom MJ, et al. Reproductive history and the risk of molecular breast cancer subtypes in a prospective study of Norwegian women. Cancer Causes Control 2014;25:881-889a.

246. Horn J, Alsaker MD, Opdahl S, et al. Anthropometric factors and risk of molecular breast cancer subtypes among postmenopausal Norwegian women. Int J Cancer 2014;135:2678-2686b.

247. Howard RA, Leitzmann MF, Linet MS, et al. Physical activity and breast cancer risk among pre- and postmenopausal women in the U.S. Radiologic Technologists cohort. Cancer Causes Control 2009;20:323-33.

248. Howe GR, Friedenreich CM, Jain M, et al. A cohort study of fat intake and risk of breast cancer. J Natl Cancer Inst 1991;83:336-40.

249. Hoyer AP, Engholm G. Serum lipids and breast cancer risk: a cohort study of 5,207 Danish women. Cancer Causes Control 1992;3:403-8.

250. Hoyer AP, Grandjean P, Jorgensen T, et al. Organochlorine exposure and risk of breast cancer. Lancet 1998;352:1816-20.

251. Huang Z, Hankinson SE, Colditz GA, et al. Dual effects of weight and weight gain on breast cancer risk. JAMA 1997;278:1407-11.

252. Huang Z, Willett WC, Colditz GA, et al. Waist circumference, waist:hip ratio, and risk of breast cancer in the Nurses' Health Study. Am J Epidemiol 1999;150:1316-24.

253. Hulten K, Van Kappel AL, Winkvist A, et al. Carotenoids, alpha-tocopherols, and retinol in plasma and breast cancer risk in northern Sweden. Cancer Causes Control 2001;12:529-37.

254. Hunter DJ, Spiegelman D, Adami HO, et al. Cohort studies of fat intake and the risk of breast cancer--a pooled analysis. N Engl J Med 1996;334:356-61.

255. Hvidtfeldt UA, Tjonneland A, Keiding N, et al. Risk of breast cancer in relation to combined effects of hormone therapy, body mass index, and alcohol use, by hormone-receptor status. Epidemiology 2015;26:353-61.

256. Inoue M, Yamamoto S, Kurahashi N, et al. Daily total physical activity level and total cancer risk in men and women: results from a large-scale population-based cohort study in Japan. Am J Epidemiol 2008;168:391-403b.

257. Inoue M, Robien K, Wang R, et al. Green tea intake, MTHFR/TYMS genotype and breast cancer risk: the Singapore Chinese Health Study. Carcinogenesis 2008;29:1967-1972a.

258. Ishitani K, Lin J, Manson JE, et al. Caffeine consumption and the risk of breast cancer in a large prospective cohort of women. Arch Intern Med 2008;168:2022-31.

259. Iwasaki M, Otani T, Inoue M, et al. Role and impact of menstrual and reproductive factors on breast cancer risk in Japan. Eur J Cancer Prev 2007;16:116-123a.

260. Iwasaki M, Otani T, Inoue M, et al. Body size and risk for breast cancer in relation to estrogen and progesterone receptor status in Japan. Ann Epidemiol 2007;17:304-312b.

261. Iwasaki M, Inoue M, Otani T, et al. Plasma isoflavone level and subsequent risk of breast cancer among Japanese women: a nested case-control study from the Japan Public Health Center-based prospective study group. J Clin Oncol 2008;26:1677-83.

262. Iwasaki M, Inoue M, Sasazuki S, et al. Green tea drinking and subsequent risk of breast cancer in a population-based cohort of Japanese women. Breast Cancer Res 2010;12:R88.

263. Jain MG, Ferrenc RG, Rehm JT, et al. Alcohol and breast cancer mortality in a cohort study. Breast Cancer Res Treat 2000;64:201-9.

264. Jarvinen R, Knekt P, Seppanen R, et al. Diet and breast cancer risk in a cohort of Finnish women. Cancer Lett 1997;114:251-3.

265. Jee SH, Yun JE, Park EJ, et al. Body mass index and cancer risk in Korean men and women. Int J Cancer 2008;123:1892-6.

266. John EM, Schwartz GG, Dreon DM, et al. Vitamin D and breast cancer risk: the NHANES I Epidemiologic follow-up study, 1971-1975 to 1992. National Health and Nutrition Examination Survey. Cancer Epidemiol Biomarkers Prev 1999;8:399-406.

267. Jonas CR, McCullough ML, Teras LR, et al. Dietary glycemic index, glycemic load, and risk of incident breast cancer in postmenopausal women. Cancer Epidemiol Biomarkers Prev 2003;12:573-7.

268. Jones DY, Schatzkin A, Green SB, et al. Dietary fat and breast cancer in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. J Natl Cancer Inst 1987;79:465-71.

269. Jonsson F, Wolk A, Pedersen NL, et al. Obesity and hormone-dependent tumors: cohort and co-twin control studies based on the Swedish Twin Registry. Int J Cancer 2003;106:594-9.

270. Jumaan AO, Holmberg L, Zack M, et al. Beta-carotene intake and risk of postmenopausal breast cancer. Epidemiology 1999;10:49-53.

271. Jung S, Spiegelman D, Baglietto L, et al. Fruit and vegetable intake and risk of breast cancer by hormone receptor status. J Natl Cancer Inst 2013;105:219-36.

272. Jung S, Wang M, Anderson K, et al. Alcohol consumption and breast cancer risk by estrogen receptor status: in a pooled analysis of 20 studies. Int J Epidemiol 2015.

273. Kaaks R, Van Noord PA, den Tonkelaar I, et al. Breast-cancer incidence in relation to height, weight and body-fat distribution in the Dutch "DOM" cohort. Int J Cancer 1998;76:647-51.

274. Kabat GC, Miller AB, Jain M, et al. Dietary iron and heme iron intake and risk of breast cancer: a prospective cohort study. Cancer Epidemiol Biomarkers Prev 2007;16:1306-8.

275. Kabat GC, Miller AB, Jain M, et al. Dietary intake of selected B vitamins in relation to risk of major cancers in women. Br J Cancer 2008;99:816-21.

276. Kabat GC, Kim M, Chlebowski RT, et al. A longitudinal study of the metabolic syndrome and risk of postmenopausal breast cancer. Cancer Epidemiol Biomarkers Prev 2009;18:2046-2053b.

277. Kabat GC, Cross AJ, Park Y, et al. Meat intake and meat preparation in relation to risk of postmenopausal breast cancer in the NIH-AARP diet and health study. Int J Cancer 2009;124:2430-2435a.

278. Kabat GC, Kim M, Adams-Campbell LL, et al. Longitudinal study of serum carotenoid, retinol, and tocopherol concentrations in relation to breast cancer risk among postmenopausal women. Am J Clin Nutr 2009;90:162-9.

279. Kabat GC, Kim M, Wactawski-Wende J, et al. Recreational physical activity, anthropometric factors, and risk of ductal carcinoma in situ of the breast in a cohort of postmenopausal women. Cancer Causes Control 2010;21:2173-81.

280. Kabat GC, Kim M, Phipps AI, et al. Smoking and alcohol consumption in relation to risk of triple-negative breast cancer in a cohort of postmenopausal women. Cancer Causes Control 2011;22:775-83.

281. Kabat GC, Anderson ML, Heo M, et al. Adult stature and risk of cancer at different anatomic sites in a cohort of postmenopausal women. Cancer Epidemiol Biomarkers Prev 2013;22:1353-1363b.

282. Kabat GC, Heo M, Kamensky V, et al. Adult height in relation to risk of cancer in a cohort of Canadian women. Int J Cancer 2013;132:1125-1132a.

283. Kabat GC, Kim MY, Hollenbeck AR, et al. Attained height, sex, and risk of cancer at different anatomic sites in the NIH-AARP diet and health study. Cancer Causes Control 2014;25:1697-706.

284. Kabat GC, Xue X, Kamensky V, et al. Risk of breast, endometrial, colorectal, and renal cancers in postmenopausal women in association with a body shape index and other anthropometric measures. Cancer Causes Control 2015;26:219-229b.

285. Kabat GC, Matthews CE, Kamensky V, et al. Adherence to cancer prevention guidelines and cancer incidence, cancer mortality, and total mortality: a prospective cohort study. Am J Clin Nutr 2015;101:558-569a.

286. Kaijser M, Akre O, Cnattingius S, et al. Preterm birth, birth weight, and subsequent risk of female breast cancer. Br J Cancer 2003;89:1664-6.

287. Kawai M, Minami Y, Kuriyama S, et al. Adiposity, adult weight change and breast cancer risk in postmenopausal Japanese women: the Miyagi Cohort Study. Br J Cancer 2010;103:1443-1447b.

288. Kawai M, Minami Y, Kuriyama S, et al. Reproductive factors, exogenous female hormone use and breast cancer risk in Japanese: the Miyagi Cohort Study. Cancer Causes Control 2010;21:135-145a.

289. Kawai M, Minami Y, Kakizaki M, et al. Alcohol consumption and breast cancer risk in Japanese women: the Miyagi Cohort study. Breast Cancer Res Treat 2011;128:817-25.

290. Keinan-Boker L, van Der Schouw YT, Grobbee DE, et al. Dietary phytoestrogens and breast cancer risk. Am J Clin Nutr 2004;79:282-8.

291. Keogh RH, Park JY, White IR, et al. Estimating the alcohol-breast cancer association: a comparison of diet diaries, FFQs and combined measurements. Eur J Epidemiol 2012;27:547-59.

292. Kerlikowske K, Walker R, Miglioretti DL, et al. Obesity, mammography use and accuracy, and advanced breast cancer risk. J Natl Cancer Inst 2008;100:1724-33.

293. Kesse-Guyot E, Bertrais S, Duperray B, et al. Dairy products, calcium and the risk of breast cancer: results of the French SU.VI.MAX prospective study. Ann Nutr Metab 2007;51:139-45.

294. Key TJ, Thorogood M, Appleby PN, et al. Dietary habits and mortality in 11,000 vegetarians and health conscious people: results of a 17 year follow up. BMJ 1996;313:775-9.

295. Key TJ, Sharp GB, Appleby PN, et al. Soya foods and breast cancer risk: a prospective study in Hiroshima and Nagasaki, Japan. Br J Cancer 1999;81:1248-56.

296. Key TJ, Appleby PN, Spencer EA, et al. Cancer incidence in vegetarians: results from the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford). Am J Clin Nutr 2009;89:1620S-6S.

297. Key TJ, Appleby PN, Cairns BJ, et al. Dietary fat and breast cancer: comparison of results from food diaries and food-frequency questionnaires in the UK Dietary Cohort Consortium. Am J Clin Nutr 2011;94:1043-52.

298. Kilkkinen A, Virtamo J, Vartiainen E, et al. Serum enterolactone concentration is not associated with breast cancer risk in a nested case-control study. Int J Cancer 2004;108:277-80.

299. Kim EH, Willett WC, Colditz GA, et al. Dietary fat and risk of postmenopausal breast cancer in a 20-year follow-up. Am J Epidemiol 2006;164:990-7.

300. Kim MK, Ko MJ, Han JT. Alcohol consumption and mortality from all-cause and cancers among 1.34 million Koreans: the results from the Korea national health insurance corporation's health examinee cohort in 2000. Cancer Causes Control 2010;21:2295-302.

301. Kim Y, Je Y. Vitamin D intake, blood 25(OH)D levels, and breast cancer risk or mortality: a meta-analysis. Br J Cancer 2014;110:2772-2784b.

302. Kim Y, Franke AA, Shvetsov YB, et al. Plasma 25-hydroxyvitamin D3 is associated with decreased risk of postmenopausal breast cancer in whites: a nested case-control study in the multiethnic cohort study. BMC Cancer 2014;14:29a.

303. Klatsky AL, Udaltsova N, Li Y, et al. Moderate alcohol intake and cancer: the role of underreporting. Cancer Causes Control 2014;25:693-9.

304. Klatsky AL, Li Y, Nicole TH, et al. Alcohol intake, beverage choice, and cancer: a cohort study in a large kaiser permanente population. Perm J 2015;19:28-34.

305. Knekt P, Albanes D, Seppanen R, et al. Dietary fat and risk of breast cancer. Am J Clin Nutr 1990;52:903-8.

306. Knekt P, Jarvinen R, Seppanen R, et al. Intake of dairy products and the risk of breast cancer. Br J Cancer 1996;73:687-91.

307. Kotsopoulos J, Chen WY, Gates MA, et al. Risk factors for ductal and lobular breast cancer: results from the nurses' health study. Breast Cancer Res 2010;12:R106.

308. Krebs EE, Taylor BC, Cauley JA, et al. Measures of adiposity and risk of breast cancer in older postmenopausal women. J Am Geriatr Soc 2006;54:63-9.

309. Krishnan K, Bassett JK, MacInnis RJ, et al. Associations between weight in early adulthood, change in weight, and breast cancer risk in postmenopausal women. Cancer Epidemiol Biomarkers Prev 2013;22:1409-16.

310. Kuhn T, Kaaks R, Becker S, et al. Plasma 25-hydroxyvitamin D and the risk of breast cancer in the European prospective investigation into cancer and nutrition: a nested case-control study. Int J Cancer 2013;133:1689-700.

311. Kuper H, Yang L, Sandin S, et al. Prospective study of solar exposure, dietary vitamin D intake, and risk of breast cancer among middle-aged women. Cancer Epidemiol Biomarkers Prev 2009;18:2558-61.

312. Kuriyama S, Tsubono Y, Hozawa A, et al. Obesity and risk of cancer in Japan. Int J Cancer 2005;113:148-57.

313. Kushi LH, Sellers TA, Potter JD, et al. Dietary fat and postmenopausal breast cancer. J Natl Cancer Inst 1992;84:1092-9.

314. Kushi LH, Potter JD, Bostick RM, et al. Dietary fat and risk of breast cancer according to hormone receptor status. Cancer Epidemiol Biomarkers Prev 1995;4:11-9.

315. Kvale G, Heuch I. Lactation and cancer risk: is there a relation specific to breast cancer? J Epidemiol Community Health 1988;42:30-7.

316. Kwan K, Chlebowski RT, McTiernan A, et al. Walking speed, physical activity, and breast cancer in postmenopausal women. Eur J Cancer Prev 2014;23:49-52.

317. Lacey JV, Jr., Kreimer AR, Buys SS, et al. Breast cancer epidemiology according to recognized breast cancer risk factors in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial Cohort. BMC Cancer 2009;9:84.

318. Lahmann P. Birth weight and postmenopausal breast cancer risk (Sweden). 2005:985.

319. Lahmann P. Adult weight change and postmenopausal breast cancer risk: Findings from the European Prospective Investigation into Cancer and nutrition (epic). Int J Obes 2004;-c.

320. Lahmann PH, Lissner L, Gullberg B, et al. A prospective study of adiposity and postmenopausal breast cancer risk: the Malmo Diet and Cancer Study. Int J Cancer 2003;103:246-52.

321. Lahmann PH, Hoffmann K, Allen N, et al. Body size and breast cancer risk: findings from the European Prospective Investigation into Cancer And Nutrition (EPIC). Int J Cancer 2004;111:762-771a.

322. Lahmann PH, Gullberg B, Olsson H, et al. Birth weight is associated with postmenopausal breast cancer risk in Swedish women. Br J Cancer 2004;91:1666-1668b.

323. Lahmann PH, Schulz M, Hoffmann K, et al. Long-term weight change and breast cancer risk: the European prospective investigation into cancer and nutrition (EPIC). Br J Cancer 2005;93:582-9.

324. Lahmann PH, Friedenreich C, Schuit AJ, et al. Physical activity and breast cancer risk: the European Prospective Investigation into Cancer and Nutrition. Cancer Epidemiol Biomarkers Prev 2007;16:36-42.

325. Lajous M, Romieu I, Sabia S, et al. Folate, vitamin B12 and postmenopausal breast cancer in a prospective study of French women. Cancer Causes Control 2006;17:1209-13.

326. Lajous M, Boutron-Ruault MC, Fabre A, et al. Carbohydrate intake, glycemic index, glycemic load, and risk of postmenopausal breast cancer in a prospective study of French women. Am J Clin Nutr 2008;87:1384-91.

327. Land SR, Liu Q, Wickerham DL, et al. Cigarette smoking, physical activity, and alcohol consumption as predictors of cancer incidence among women at high risk of breast cancer in the NSABP P-1 trial. Cancer Epidemiol Biomarkers Prev 2014;23:823-32.

328. Lappe JM, Travers-Gustafson D, Davies KM, et al. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr 2007;85:1586-91.

329. Larsen T, Mose FH, Bech JN, et al. Effect of cholecalciferol supplementation during winter months in patients with hypertension: a randomized, placebo-controlled trial. Am J Hypertens 2012;25:1215-22.

330. Larsson SC, Bergkvist L, Wolk A. Folate intake and risk of breast cancer by estrogen and progesterone receptor status in a Swedish cohort. Cancer Epidemiol Biomarkers Prev 2008;17:3444-9.

331. Larsson SC, Bergkvist L, Wolk A. Long-term meat intake and risk of breast cancer by oestrogen and progesterone receptor status in a cohort of Swedish women. Eur J Cancer 2009;45:3042-3046a.

332. Larsson SC, Bergkvist L, Wolk A. Long-term dietary calcium intake and breast cancer risk in a prospective cohort of women. Am J Clin Nutr 2009;89:277-282d.

333. Larsson SC, Bergkvist L, Wolk A. Coffee and black tea consumption and risk of breast cancer by estrogen and progesterone receptor status in a Swedish cohort. Cancer Causes Control 2009;20:2039-2044b.

334. Larsson SC, Bergkvist L, Wolk A. Glycemic load, glycemic index and breast cancer risk in a prospective cohort of Swedish women. Int J Cancer 2009;125:153-157c.

335. Larsson SC, Bergkvist L, Wolk A. Dietary carotenoids and risk of hormone receptor-defined breast cancer in a prospective cohort of Swedish women. Eur J Cancer 2010;46:1079-85.

336. Le ML, Kolonel LN, Earle ME, et al. Body size at different periods of life and breast cancer risk. Am J Epidemiol 1988;128:137-52.

337. Lee CP, Irwanto A, Salim A, et al. Breast cancer risk assessment using genetic variants and risk factors in a Singapore Chinese population. Breast Cancer Res 2014;16:R64.

338. Lee HJ, Wu K, Cox DG, et al. Polymorphisms in xenobiotic metabolizing genes, intakes of heterocyclic amines and red meat, and postmenopausal breast cancer. Nutr Cancer 2013;65:1122-31.

339. Lee IM, Rexrode KM, Cook NR, et al. Physical activity and breast cancer risk: the Women's Health Study (United States). Cancer Causes Control 2001;12:137-45.

340. Lee KH, Shu XO, Gao YT, et al. Breast cancer and urinary biomarkers of polycyclic aromatic hydrocarbon and oxidative stress in the Shanghai Women's Health Study. Cancer Epidemiol Biomarkers Prev 2010;19:877-83.

341. Lee SA, Shu XO, Li H, et al. Adolescent and adult soy food intake and breast cancer risk: results from the Shanghai Women's Health Study. Am J Clin Nutr 2009;89:1920-6.

342. Lee SY, Kim MT, Kim SW, et al. Effect of lifetime lactation on breast cancer risk: a Korean women's cohort study. Int J Cancer 2003;105:390-3.

343. Leitzmann MF, Moore SC, Peters TM, et al. Prospective study of physical activity and risk of postmenopausal breast cancer. Breast Cancer Res 2008;10:R92.

344. Lew JQ, Freedman ND, Leitzmann MF, et al. Alcohol and risk of breast cancer by histologic type and hormone receptor status in postmenopausal women: the NIH-AARP Diet and Health Study. Am J Epidemiol 2009;170:308-17.

345. Li CI, Chlebowski RT, Freiberg M, et al. Alcohol consumption and risk of postmenopausal breast cancer by subtype: the women's health initiative observational study. J Natl Cancer Inst 2010;102:1422-31.

346. Li HL, Gao YT, Li Q, et al. [Anthropometry and female breast cancer: a prospective cohort study in urban Shanghai]. Zhonghua Liu Xing Bing Xue Za Zhi 2006;27:488-93.

347. Li J, Koh WP, Jin AZ, et al. Calcium intake is not related to breast cancer risk among Singapore Chinese women. Int J Cancer 2013;133:680-6.

348. Li K, Kaaks R, Linseisen J, et al. Dietary calcium and magnesium intake in relation to cancer incidence and mortality in a German prospective cohort (EPIC-Heidelberg). Cancer Causes Control 2011;22:1375-82.

349. Li W, Ray RM, Lampe JW, et al. Dietary and other risk factors in women having fibrocystic breast conditions with and without concurrent breast cancer: a nested case-control study in Shanghai, China. Int J Cancer 2005;115:981-93.

350. Li XJ, Ren ZJ, Qin JW, et al. Coffee consumption and risk of breast cancer: an up-to-date meta-analysis. PLoS One 2013;8:e52681.

351. Li Y, Baer D, Friedman GD, et al. Wine, liquor, beer and risk of breast cancer in a large population. Eur J Cancer 2009;45:843-50.

352. Lin J, Manson JE, Lee IM, et al. Intakes of calcium and vitamin D and breast cancer risk in women. Arch Intern Med 2007;167:1050-9.

353. Lin J, Lee IM, Cook NR, et al. Plasma folate, vitamin B-6, vitamin B-12, and risk of breast cancer in women. Am J Clin Nutr 2008;87:734-43.

354. Lin Y, Kikuchi S, Tamakoshi K, et al. Prospective study of alcohol consumption and breast cancer risk in Japanese women. Int J Cancer 2005;116:779-83.

355. Lin YS, Caffrey JL, Lin JW, et al. Increased risk of cancer mortality associated with cadmium exposures in older Americans with low zinc intake. J Toxicol Environ Health A 2013;76:1-15.

356. Link LB, Canchola AJ, Bernstein L, et al. Dietary patterns and breast cancer risk in the California Teachers Study cohort. Am J Clin Nutr 2013;98:1524-32.

357. Linos E, Willett WC, Cho E, et al. Adolescent diet in relation to breast cancer risk among premenopausal women. Cancer Epidemiol Biomarkers Prev 2010;19:689-96.

358. Liu Y, Colditz GA, Rosner B, et al. Alcohol intake between menarche and first pregnancy: a prospective study of breast cancer risk. J Natl Cancer Inst 2013;105:1571-8.

359. Lof M, Sandin S, Lagiou P, et al. Dietary fat and breast cancer risk in the Swedish women's lifestyle and health cohort. Br J Cancer 2007;97:1570-1576b.

360. Lof M, Sandin S, Hilakivi-Clarke L, et al. Birth weight in relation to endometrial and breast cancer risks in Swedish women. Br J Cancer 2007;96:134-136a.

361. Lof M, Sandin S, Lagiou P, et al. Fruit and vegetable intake and risk of cancer in the Swedish women's lifestyle and health cohort. Cancer Causes Control 2011;22:283-9.

362. Loft S, Olsen A, Moller P, et al. Association between 8-oxo-7,8-dihydro-2'-deoxyguanosine excretion and risk of postmenopausal breast cancer: nested case-control study. Cancer Epidemiol Biomarkers Prev 2013;22:1289-96.

363. London SJ, Colditz GA, Stampfer MJ, et al. Prospective study of relative weight, height, and risk of breast cancer. JAMA 1989;262:2853-8.

364. London SJ, Colditz GA, Stampfer MJ, et al. Lactation and risk of breast cancer in a cohort of US women. Am J Epidemiol 1990;132:17-26.

365. Lubinski J, Huzarski T, Byrski T, et al. The risk of breast cancer in women with a BRCA1 mutation from North America and Poland. Int J Cancer 2012;131:229-34.

366. Lukanova A, Bjor O, Kaaks R, et al. Body mass index and cancer: results from the Northern Sweden Health and Disease Cohort. Int J Cancer 2006;118:458-66.

367. Lundqvist E, Kaprio J, Verkasalo PK, et al. Co-twin control and cohort analyses of body mass index and height in relation to breast, prostate, ovarian, corpus uteri, colon and rectal cancer among Swedish and Finnish twins. Int J Cancer 2007;121:810-8.

368. Luoto R, Latikka P, Pukkala E, et al. The effect of physical activity on breast cancer risk: a cohort study of 30,548 women. Eur J Epidemiol 2000;16:973-80.

369. Ma H, Henderson KD, Sullivan-Halley J, et al. Pregnancy-related factors and the risk of breast carcinoma in situ and invasive breast cancer among postmenopausal women in the California Teachers Study cohort. Breast Cancer Res 2010;12:R35.

370. Ma J, Flanders WD, Ward EM, et al. Body mass index in young adulthood and premature death: analyses of the US National Health Interview Survey linked mortality files. Am J Epidemiol 2011;174:934-44.

371. MacInnis RJ, English DR, Gertig DM, et al. Body size and composition and risk of postmenopausal breast cancer. Cancer Epidemiol Biomarkers Prev 2004;13:2117-25.

372. Mai V, Kant AK, Flood A, et al. Diet quality and subsequent cancer incidence and mortality in a prospective cohort of women. Int J Epidemiol 2005;34:54-60.

373. Maillard V, Kuriki K, Lefebvre B, et al. Serum carotenoid, tocopherol and retinol concentrations and breast cancer risk in the E3N-EPIC study. Int J Cancer 2010;127:1188-96.

374. Makarem N, Lin Y, Bandera EV, et al. Concordance with World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) guidelines for cancer prevention and obesity-related cancer risk in the Framingham Offspring cohort (1991-2008). Cancer Causes Control 2015;26:277-86.

375. Manders P, Pijpe A, Hooning MJ, et al. Body weight and risk of breast cancer in BRCA1/2 mutation carriers. Breast Cancer Res Treat 2011;126:193-202.

376. Manjer J, Malina J, Berglund G, et al. Breast cancer incidence in ex-smokers in relation to body mass index, weight gain and blood lipid levels. Eur J Cancer Prev 2001;10:281-287a.

377. Manjer J, Kaaks R, Riboli E, et al. Risk of breast cancer in relation to anthropometry, blood pressure, blood lipids and glucose metabolism: a prospective study within the Malmo Preventive Project. Eur J Cancer Prev 2001;10:33-42b.

378. Mannisto S, Dixon LB, Balder HF, et al. Dietary patterns and breast cancer risk: results from three cohort studies in the DIETSCAN project. Cancer Causes Control 2005;16:725-33.

379. Margolis KL, Mucci L, Braaten T, et al. Physical activity in different periods of life and the risk of breast cancer: the Norwegian-Swedish Women's Lifestyle and Health cohort study. Cancer Epidemiol Biomarkers Prev 2005;14:27-32.

380. Martin LJ, Li Q, Melnichouk O, et al. A randomized trial of dietary intervention for breast cancer prevention. Cancer Res 2011;71:123-33.

381. Maruti SS, Lampe JW, Potter JD, et al. A prospective study of bowel motility and related factors on breast cancer risk. Cancer Epidemiol Biomarkers Prev 2008;17:1746-1750a.

382. Maruti SS, Willett WC, Feskanich D, et al. A prospective study of age-specific physical activity and premenopausal breast cancer. J Natl Cancer Inst 2008;100:728-737b.

383. Maruti SS, Ulrich CM, White E. Folate and one-carbon metabolism nutrients from supplements and diet in relation to breast cancer risk. Am J Clin Nutr 2009;89:624-33.

384. Masala G, Assedi M, Bendinelli B, et al. Fruit and vegetables consumption and breast cancer risk: the EPIC Italy study. Breast Cancer Res Treat 2012;132:1127-36.

385. Mattisson I, Wirfalt E, Wallstrom P, et al. High fat and alcohol intakes are risk factors of postmenopausal breast cancer: a prospective study from the Malmo diet and cancer cohort. Int J Cancer 2004;110:589-597a.

386. Mattisson I, Wirfalt E, Johansson U, et al. Intakes of plant foods, fibre and fat and risk of breast cancer--a prospective study in the Malmo Diet and Cancer cohort. Br J Cancer 2004;90:122-127b.

387. McCarty CA, Reding DJ, Commins J, et al. Alcohol, genetics and risk of breast cancer in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Breast Cancer Res Treat 2012;133:785-92.

388. McCormack VA, dos SS, I, De Stavola BL, et al. Fetal growth and subsequent risk of breast cancer: results from long term follow up of Swedish cohort. BMJ 2003;326:248.

389. McCormack VA, dos SS, I, Koupil I, et al. Birth characteristics and adult cancer incidence: Swedish cohort of over 11,000 men and women. Int J Cancer 2005;115:611-7.

390. McCullough ML, Rodriguez C, Diver WR, et al. Dairy, calcium, and vitamin D intake and postmenopausal breast cancer risk in the Cancer Prevention Study II Nutrition Cohort. Cancer Epidemiol Biomarkers Prev 2005;14:2898-904.

391. McCullough ML, Stevens VL, Patel R, et al. Serum 25-hydroxyvitamin D concentrations and postmenopausal breast cancer risk: a nested case control study in the Cancer Prevention Study-II Nutrition Cohort. Breast Cancer Res 2009;11:R64.

392. McKenzie F, Ferrari P, Freisling H, et al. Healthy lifestyle and risk of breast cancer among postmenopausal women in the European Prospective Investigation into Cancer and Nutrition cohort study. Int J Cancer 2015;136:2640-8.

393. McTiernan A, Kooperberg C, White E, et al. Recreational physical activity and the risk of breast cancer in postmenopausal women: the Women's Health Initiative Cohort Study. JAMA 2003;290:1331-6.

394. Mellemkjaer L, Bigaard J, Tjonneland A, et al. Body composition and breast cancer in postmenopausal women: a Danish prospective cohort study. Obesity (Silver Spring) 2006;14:1854-62.

395. Mellemkjaer L, Christensen J, Frederiksen K, et al. Leg length, sitting height and postmenopausal breast cancer risk. Br J Cancer 2012;107:165-8.

396. Mertens AJ, Sweeney C, Shahar E, et al. Physical activity and breast cancer incidence in middle-aged women: a prospective cohort study. Breast Cancer Res Treat 2006;97:209-14.

397. Miao JJ, Cederholm J, Gudbjornsdottir S. Excess body weight and cancer risk in patients with type 2 diabetes who were registered in Swedish National Diabetes Register--register-based cohort study in Sweden. PLoS One 2014;9:e105868.

398. Michels KB, Willett WC, Rosner BA, et al. Prospective assessment of breastfeeding and breast cancer incidence among 89,887 women. Lancet 1996;347:431-436a.

399. Michels KB, Trichopoulos D, Robins JM, et al. Birthweight as a risk factor for breast cancer. Lancet 1996;348:1542-1546b.

400. Michels KB, Holmberg L, Bergkvist L, et al. Dietary antioxidant vitamins, retinol, and breast cancer incidence in a cohort of Swedish women. Int J Cancer 2001;91:563-7.

401. Michels KB, Holmberg L, Bergkvist L, et al. Coffee, tea, and caffeine consumption and breast cancer incidence in a cohort of Swedish women. Ann Epidemiol 2002;12:21-6.

402. Michels KB, Terry KL, Willett WC. Longitudinal study on the role of body size in premenopausal breast cancer. Arch Intern Med 2006;166:2395-2402a.

403. Michels KB, Xue F, Terry KL, et al. Longitudinal study of birthweight and the incidence of breast cancer in adulthood. Carcinogenesis 2006;27:2464-2468b.

404. Michels KB, Rosner BA, Chumlea WC, et al. Preschool diet and adult risk of breast cancer. Int J Cancer 2006;118:749-754c.

405. Michels KB, Terry KL, Eliassen AH, et al. Adult weight change and incidence of premenopausal breast cancer. Int J Cancer 2012;130:902-9.

406. Mills PK, Annegers JF, Phillips RL. Animal product consumption and subsequent fatal breast cancer risk among Seventh-day Adventists. Am J Epidemiol 1988;127:440-53.

407. Mills PK, Beeson WL, Phillips RL, et al. Dietary habits and breast cancer incidence among Seventh-day Adventists. Cancer 1989;64:582-90.

408. Missmer SA, Smith-Warner SA, Spiegelman D, et al. Meat and dairy food consumption and breast cancer: a pooled analysis of cohort studies. Int J Epidemiol 2002;31:78-85.

409. Modugno F, Kip KE, Cochrane B, et al. Obesity, hormone therapy, estrogen metabolism and risk of postmenopausal breast cancer. Int J Cancer 2006;118:1292-301.

410. Mogren I, Damber L, Tavelin B, et al. Characteristics of pregnancy and birth and malignancy in the offspring (Sweden). Cancer Causes Control 1999;10:85-94.

411. Mohr SB, Gorham ED, Alcaraz JE, et al. Serum 25-hydroxyvitamin D and breast cancer in the military: a case-control study utilizing pre-diagnostic serum. Cancer Causes Control 2013;24:495-504.

412. Moore DB, Folsom AR, Mink PJ, et al. Physical activity and incidence of postmenopausal breast cancer. Epidemiology 2000;11:292-6.

413. Moradi T, Adami HO, Bergstrom R, et al. Occupational physical activity and risk for breast cancer in a nationwide cohort study in Sweden. Cancer Causes Control 1999;10:423-30.

414. Moradi T, Adami HO, Ekbom A, et al. Physical activity and risk for breast cancer a prospective cohort study among Swedish twins. Int J Cancer 2002;100:76-81.

415. Morch LS, Johansen D, Thygesen LC, et al. Alcohol drinking, consumption patterns and breast cancer among Danish nurses: a cohort study. Eur J Public Health 2007;17:624-9.

416. Morimoto LM, White E, Chen Z, et al. Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). Cancer Causes Control 2002;13:741-51.

417. Morimoto Y, Maskarinec G, Park SY, et al. Dietary isoflavone intake is not statistically significantly associated with breast cancer risk in the Multiethnic Cohort. Br J Nutr 2014;112:976-83.

418. Munsell MF, Sprague BL, Berry DA, et al. Body mass index and breast cancer risk according to postmenopausal estrogen-progestin use and hormone receptor status. Epidemiol Rev 2014;36:114-36.

419. Murdoch DR, Slow S, Chambers ST, et al. Effect of vitamin D3 supplementation on upper respiratory tract infections in healthy adults: the VIDARIS randomized controlled trial. JAMA 2012;308:1333-9.

420. Muti P, Stanulla M, Micheli A, et al. Markers of insulin resistance and sex steroid hormone activity in relation to breast cancer risk: a prospective analysis of abdominal adiposity, sebum production, and hirsutism (Italy). Cancer Causes Control 2000;11:721-30.

421. Nagel G, Linseisen J, van Gils CH, et al. Dietary beta-carotene, vitamin C and E intake and breast cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). Breast Cancer Res Treat 2010;119:753-65.

422. Neuhouser ML, Manson JE, Millen A, et al. The influence of health and lifestyle characteristics on the relation of serum 25-hydroxyvitamin D with risk of colorectal and breast cancer in postmenopausal women. Am J Epidemiol 2012;175:673-84.

423. Nielsen NR, Gronbaek M. Interactions between intakes of alcohol and postmenopausal hormones on risk of breast cancer. Int J Cancer 2008;122:1109-13.

424. Nielsen TG, Olsen A, Christensen J, et al. Dietary carbohydrate intake is not associated with the breast cancer incidence rate ratio in postmenopausal Danish women. J Nutr 2005;135:124-8.

425. Nilsen TI, Vatten LJ. Adult height and risk of breast cancer: a possible effect of early nutrition. Br J Cancer 2001;85:959-61.

426. Nilsson LM, Johansson I, Lenner P, et al. Consumption of filtered and boiled coffee and the risk of incident cancer: a prospective cohort study. Cancer Causes Control 2010;21:1533-44.

427. Nilsson LM, Winkvist A, Johansson I, et al. Low-carbohydrate, high-protein diet score and risk of incident cancer; a prospective cohort study. Nutr J 2013;12:58.

428. Nyante SJ, Dallal CM, Gierach GL, et al. Risk factors for specific histopathological types of postmenopausal breast cancer in the NIH-AARP Diet and Health Study. Am J Epidemiol 2013;178:359-71.

429. Oberg S, Cnattingius S, Sandin S, et al. Birth weight-breast cancer revisited: is the association confounded by familial factors? Cancer Epidemiol Biomarkers Prev 2009;18:2447-52.

430. Ogunleye AA, Xue F, Michels KB. Green tea consumption and breast cancer risk or recurrence: a meta-analysis. Breast Cancer Res Treat 2010;119:477-84.

431. Oh JK, Sandin S, Strom P, et al. Prospective study of breast cancer in relation to coffee, tea and caffeine in Sweden. Int J Cancer 2015;137:1979-89.

432. Okasha M, Davey SG, McCarron P, et al. Adolescent BMI and cancer risk. IARC Sci Publ 2002;156:263-265b.

433. Okasha M, McCarron P, McEwen J, et al. Body mass index in young adulthood and cancer mortality: a retrospective cohort study. J Epidemiol Community Health 2002;56:780-784a.

434. Olsen A, Tjonneland A, Thomsen BL, et al. Fruits and vegetables intake differentially affects estrogen receptor negative and positive breast cancer incidence rates. J Nutr 2003;133:2342-7.

435. Onitilo AA, Stankowski RV, Berg RL, et al. Breast cancer incidence before and after diagnosis of type 2 diabetes mellitus in women: increased risk in the prediabetes phase. Eur J Cancer Prev 2014;23:76-83.

436. Opdahl S, Alsaker MD, Janszky I, et al. Joint effects of nulliparity and other breast cancer risk factors. Br J Cancer 2011;105:731-6.

437. Ordonez-Mena JM, Schottker B, Haug U, et al. Serum 25-hydroxyvitamin d and cancer risk in older adults: results from a large German prospective cohort study. Cancer Epidemiol Biomarkers Prev 2013;22:905-16.

438. Osaki Y, Taniguchi S, Tahara A, et al. Metabolic syndrome and incidence of liver and breast cancers in Japan. Cancer Epidemiol 2012;36:141-7.

439. Overvad K, Wang DY, Olsen J, et al. Selenium in human mammary carcinogenesis: a case-cohort study. Eur J Cancer 1991;27:900-2.

440. Ozasa K. Alcohol use and mortality in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). Asian Pac J Cancer Prev 2007;8 Suppl:81-8.

441. Paffenbarger RS, Jr., Hyde RT, Wing AL. Physical activity and incidence of cancer in diverse populations: a preliminary report. Am J Clin Nutr 1987;45:312-7.

442. Pala V, Krogh V, Berrino F, et al. Meat, eggs, dairy products, and risk of breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Am J Clin Nutr 2009;90:602-12.

443. Palmer JR, Rao RS, Adams-Campbell LL, et al. Height and breast cancer risk: results from the Black Women's Health Study (United States). Cancer Causes Control 2001;12:343-8.

444. Palmer JR, Adams-Campbell LL, Boggs DA, et al. A prospective study of body size and breast cancer in black women. Cancer Epidemiol Biomarkers Prev 2007;16:1795-802.

445. Pantavos A, Ruiter R, Feskens EF, et al. Total dietary antioxidant capacity, individual antioxidant intake and breast cancer risk: the Rotterdam Study. Int J Cancer 2015;136:2178-86.

446. Parekh N, Lin Y, Vadiveloo M, et al. Metabolic dysregulation of the insulin-glucose axis and risk of obesity-related cancers in the Framingham heart study-offspring cohort (1971-2008). Cancer Epidemiol Biomarkers Prev 2013;22:1825-36.

447. Park SY, Kolonel LN, Henderson BE, et al. Dietary fat and breast cancer in postmenopausal women according to ethnicity and hormone receptor status: the Multiethnic Cohort Study. Cancer Prev Res (Phila) 2012;5:216-28.

448. Park SY, Kolonel LN, Lim U, et al. Alcohol consumption and breast cancer risk among women from five ethnic groups with light to moderate intakes: the Multiethnic Cohort Study. Int J Cancer 2014;134:1504-10.

449. Park Y, Brinton LA, Subar AF, et al. Dietary fiber intake and risk of breast cancer in postmenopausal women: the National Institutes of Health-AARP Diet and Health Study. Am J Clin Nutr 2009;90:664-671a.

450. Park Y, Leitzmann MF, Subar AF, et al. Dairy food, calcium, and risk of cancer in the NIH-AARP Diet and Health Study. Arch Intern Med 2009;169:391-401b.

451. Parr CL, Batty GD, Lam TH, et al. Body-mass index and cancer mortality in the Asia-Pacific Cohort Studies Collaboration: pooled analyses of 424,519 participants. Lancet Oncol 2010;11:741-52.

452. Patel AV, Callel EE, Bernstein L, et al. Recreational physical activity and risk of postmenopausal breast cancer in a large cohort of US women. Cancer Causes Control 2003;14:519-29.

453. Peters TM, Moore SC, Gierach GL, et al. Intensity and timing of physical activity in relation to postmenopausal breast cancer risk: the prospective NIH-AARP diet and health study. BMC Cancer 2009;9:349b.

454. Peters TM, Schatzkin A, Gierach GL, et al. Physical activity and postmenopausal breast cancer risk in the NIH-AARP diet and health study. Cancer Epidemiol Biomarkers Prev 2009;18:289-296a.

455. Petrelli JM, Calle EE, Rodriguez C, et al. Body mass index, height, and postmenopausal breast cancer mortality in a prospective cohort of US women. Cancer Causes Control 2002;13:325-32.

456. Petri AL, Tjonneland A, Gamborg M, et al. Alcohol intake, type of beverage, and risk of breast cancer in pre- and postmenopausal women. Alcohol Clin Exp Res 2004;28:1084-90.

457. Pezzotti A, Kraft P, Hankinson SE, et al. The mitochondrial A10398G polymorphism, interaction with alcohol consumption, and breast cancer risk. PLoS One 2009;4:e5356.

458. Phipps AI, Chlebowski RT, Prentice R, et al. Body size, physical activity, and risk of triple-negative and estrogen receptor-positive breast cancer. Cancer Epidemiol Biomarkers Prev 2011;20:454-63.

459. Pierobon M, Frankenfeld CL. Obesity as a risk factor for triple-negative breast cancers: a systematic review and meta-analysis. Breast Cancer Res Treat 2013;137:307-14.

460. Pijpe A, Manders P, Brohet RM, et al. Physical activity and the risk of breast cancer in BRCA1/2 mutation carriers. Breast Cancer Res Treat 2010;120:235-44.

461. Pike MC, Kolonel LN, Henderson BE, et al. Breast cancer in a multiethnic cohort in Hawaii and Los Angeles: risk factor-adjusted incidence in Japanese equals and in Hawaiians exceeds that in whites. Cancer Epidemiol Biomarkers Prev 2002;11:795-800.

462. Pot GK, Stephen AM, Dahm CC, et al. Dietary patterns derived with multiple methods from food diaries and breast cancer risk in the UK Dietary Cohort Consortium. Eur J Clin Nutr 2014;68:1353-8.

463. Potter JD, Cerhan JR, Sellers TA, et al. Progesterone and estrogen receptors and mammary neoplasia in the Iowa Women's Health Study: how many kinds of breast cancer are there? Cancer Epidemiol Biomarkers Prev 1995;4:319-26.

464. Pouchieu C, Deschasaux M, Hercberg S, et al. Prospective association between red and processed meat intakes and breast cancer risk: modulation by an antioxidant supplementation in the SU.VI.MAX randomized controlled trial. Int J Epidemiol 2014;43:1583-92.

465. Pouchieu C, Galan P, Ducros V, et al. Plasma carotenoids and retinol and overall and breast cancer risk: a nested case-control study. Nutr Cancer 2014;66:980-8.

466. Poynter JN, Inoue-Choi M, Ross JA, et al. Reproductive, lifestyle, and anthropometric risk factors for cancer in elderly women. Cancer Epidemiol Biomarkers Prev 2013;22:681-7.

467. Prentice RL, Caan B, Chlebowski RT, et al. Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA 2006;295:629-42.

468. Prentice RL, Thomson CA, Caan B, et al. Low-fat dietary pattern and cancer incidence in the Women's Health Initiative Dietary Modification Randomized Controlled Trial. J Natl Cancer Inst 2007;99:1534-43.

469. Prentice RL, Shaw PA, Bingham SA, et al. Biomarker-calibrated energy and protein consumption and increased cancer risk among postmenopausal women. Am J Epidemiol 2009;169:977-89.

470. Prentice RL, Pettinger MB, Jackson RD, et al. Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. Osteoporos Int 2013;24:567-580b.

471. Prentice RL, Pettinger M, Tinker LF, et al. Regression calibration in nutritional epidemiology: example of fat density and total energy in relationship to postmenopausal breast cancer. Am J Epidemiol 2013;178:1663-1672a.

472. Pronk A, Ji BT, Shu XO, et al. Physical activity and breast cancer risk in Chinese women. Br J Cancer 2011;105:1443-50.

473. Pudrovska T, Carr D, McFarland M, et al. Higher-status occupations and breast cancer: a life-course stress approach. Soc Sci Med 2013;89:53-61.

474. Pukkala E, Poskiparta M, Apter D, et al. Life-long physical activity and cancer risk among Finnish female teachers. Eur J Cancer Prev 1993;2:369-76.

475. Radimer KL, Ballard-Barbash R, Miller JS, et al. Weight change and the risk of late-onset breast cancer in the original Framingham cohort. Nutr Cancer 2004;49:7-13.

476. Rapp K, Schroeder J, Klenk J, et al. Obesity and incidence of cancer: a large cohort study of over 145,000 adults in Austria. Br J Cancer 2005;93:1062-7.

477. Ravn-Haren G, Olsen A, Tjonneland A, et al. Associations between GPX1 Pro198Leu polymorphism, erythrocyte GPX activity, alcohol consumption and breast cancer risk in a prospective cohort study. Carcinogenesis 2006;27:820-5.

478. Redaniel MT, Jeffreys M, May MT, et al. Associations of type 2 diabetes and diabetes treatment with breast cancer risk and mortality: a population-based cohort study among British women. Cancer Causes Control 2012;23:1785-95.

479. Reeves GK, Pirie K, Beral V, et al. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. BMJ 2007;335:1134.

480. Reeves KW, McLaughlin V, Fredman L, et al. Components of metabolic syndrome and risk of breast cancer by prognostic features in the study of osteoporotic fractures cohort. Cancer Causes Control 2012;23:1241-51.

481. Reinier KS, Vacek PM, Geller BM. Risk factors for breast carcinoma in situ versus invasive breast cancer in a prospective study of pre- and post-menopausal women. Breast Cancer Res Treat 2007;103:343-8.

482. Rejnmark L, Tietze A, Vestergaard P, et al. Reduced prediagnostic 25-hydroxyvitamin D levels in women with breast cancer: a nested case-control study. Cancer Epidemiol Biomarkers Prev 2009;18:2655-60.

483. Rich-Edwards JW, Michels KB, Wright R, et al. Own birthweight, offspring birthweight, and risk of subsequent hypertension, diabetes, and breast cancer in maturity. 2003:21-2.

484. Rinaldi S, Key TJ, Peeters PH, et al. Anthropometric measures, endogenous sex steroids and breast cancer risk in postmenopausal women: a study within the EPIC cohort. Int J Cancer 2006;118:2832-9.

485. Rintala b, Pukkala E, Paakkulainen HT, et al. Self-experienced physical workload and risk of breast cancer. Scand J Work Environ Health 2002;28:158-62.

486. Rintala P, Pukkala E, Laara E, et al. Physical activity and breast cancer risk among female physical education and language teachers: a 34-year follow-up. Int J Cancer 2003;107:268-70.

487. Rissanen H, Knekt P, Jarvinen R, et al. Serum fatty acids and breast cancer incidence. Nutr Cancer 2003;45:168-75.

488. Ritte R, Lukanova A, Berrino F, et al. Adiposity, hormone replacement therapy use and breast cancer risk by age and hormone receptor status: a large prospective cohort study. Breast Cancer Res 2012;14:R76.

489. Ritte R, Tikk K, Lukanova A, et al. Reproductive factors and risk of hormone receptor positive and negative breast cancer: a cohort study. BMC Cancer 2013;13:584a.

490. Ritte R, Lukanova A, Tjonneland A, et al. Height, age at menarche and risk of hormone receptor-positive and -negative breast cancer: a cohort study. Int J Cancer 2013;132:2619-2629b.

491. Robien K, Cutler GJ, Lazovich D. Vitamin D intake and breast cancer risk in postmenopausal women: the Iowa Women's Health Study. Cancer Causes Control 2007;18:775-82.

492. Robsahm TE, Hestvik UE, Veierod MB, et al. Cancer risk in Norwegian world class athletes. Cancer Causes Control 2010;21:1711-9.

493. Rockhill B, Willett WC, Hunter DJ, et al. Physical activity and breast cancer risk in a cohort of young women. J Natl Cancer Inst 1998;90:1155-60.

494. Rockhill B, Willett WC, Hunter DJ, et al. A prospective study of recreational physical activity and breast cancer risk. Arch Intern Med 1999;159:2290-6.

495. Rod NH, Hansen AM, Nielsen J, et al. Low-risk factor profile, estrogen levels, and breast cancer risk among postmenopausal women. Int J Cancer 2009;124:1935-40.

496. Rohan TE, Howe GR, Friedenreich CM, et al. Dietary fiber, vitamins A, C, and E, and risk of breast cancer: a cohort study. Cancer Causes Control 1993;4:29-37.

497. Rohan TE, Jain M, Howe GR, et al. Alcohol consumption and risk of breast cancer: a cohort study. Cancer Causes Control 2000;11:239-247a.

498. Rohan TE, Jain MG, Howe GR, et al. Dietary folate consumption and breast cancer risk. J Natl Cancer Inst 2000;92:266-269b.

499. Rohan TE, Heo M, Choi L, et al. Body fat and breast cancer risk in postmenopausal women: a longitudinal study. J Cancer Epidemiol 2013;2013:754815.

500. Romaguera D, Vergnaud AC, Peeters PH, et al. Is concordance with World Cancer Research Fund/American Institute for Cancer Research guidelines for cancer prevention related to subsequent risk of cancer? Results from the EPIC study. Am J Clin Nutr 2012;96:150-63.

501. Romieu I, Ferrari P, Rinaldi S, et al. Dietary glycemic index and glycemic load and breast cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). Am J Clin Nutr 2012;96:345-55.

502. Romieu I, Scoccianti C, Chajes V, et al. Alcohol intake and breast cancer in the European prospective investigation into cancer and nutrition. Int J Cancer 2015;137:1921-30.

503. Rosenberg L, Palmer JR, Bethea TN, et al. A prospective study of physical activity and breast cancer incidence in African-American women. Cancer Epidemiol Biomarkers Prev 2014;23:2522-31.

504. Rosner B, Eliassen AH, Toriola AT, et al. Short-term weight gain and breast cancer risk by hormone receptor classification among pre- and postmenopausal women. Breast Cancer Res Treat 2015;150:643-53.

505. Roswall N, Olsen A, Christensen J, et al. Micronutrient intake and breast cancer characteristics among postmenopausal women. Eur J Cancer Prev 2010;19:360-5.

506. Saadatian-Elahi M, Toniolo P, Ferrari P, et al. Serum fatty acids and risk of breast cancer in a nested case-control study of the New York University Women's Health Study. Cancer Epidemiol Biomarkers Prev 2002;11:1353-60.

507. Sant M, Allemani C, Sieri S, et al. Salad vegetables dietary pattern protects against HER-2-positive breast cancer: a prospective Italian study. Int J Cancer 2007;121:911-4.

508. Sato R, Helzlsouer KJ, Alberg AJ, et al. Prospective study of carotenoids, tocopherols, and retinoid concentrations and the risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2002;11:451-7.

509. Sauvaget C, Nagano J, Hayashi M, et al. Vegetables and fruit intake and cancer mortality in the Hiroshima/Nagasaki Life Span Study. Br J Cancer 2003;88:689-94.

510. Scarmo S, Afanasyeva Y, Lenner P, et al. Circulating levels of 25-hydroxyvitamin D and risk of breast cancer: a nested case-control study. Breast Cancer Res 2013;15:R15.

511. Schairer C, Li Y, Frawley P, et al. Risk factors for inflammatory breast cancer and other invasive breast cancers. J Natl Cancer Inst 2013;105:1373-84.

512. Schatzkin A, Jones DY, Hoover RN, et al. Alcohol consumption and breast cancer in the epidemiologic follow-up study of the first National Health and Nutrition Examination Survey. N Engl J Med 1987;316:1169-73.

513. Schatzkin A, Carter CL, Green SB, et al. Is alcohol consumption related to breast cancer? Results from the Framingham Heart Study. J Natl Cancer Inst 1989;81:31-5.

514. Schmid D, Leitzmann MF. Television viewing and time spent sedentary in relation to cancer risk: a meta-analysis. J Natl Cancer Inst 2014;106.

515. Schnohr P, Gronbaek M, Petersen L, et al. Physical activity in leisure-time and risk of cancer: 14-year follow-up of 28,000 Danish men and women. Scand J Public Health 2005;33:244-9.

516. Schonfeld SJ, Pfeiffer RM, Lacey JV, Jr., et al. Hormone-related risk factors and postmenopausal breast cancer among nulliparous versus parous women: An aggregated study. Am J Epidemiol 2011;173:509-17.

517. Schulz M, Hoffmann K, Weikert C, et al. Identification of a dietary pattern characterized by high-fat food choices associated with increased risk of breast cancer: the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. Br J Nutr 2008;100:942-6.

518. Schutze M, Boeing H, Pischon T, et al. Alcohol attributable burden of incidence of cancer in eight European countries based on results from prospective cohort study. BMJ 2011;342:d1584.

519. Schwingshackl L, Hoffmann G. Adherence to Mediterranean diet and risk of cancer: a systematic review and meta-analysis of observational studies. Int J Cancer 2014;135:1884-97.

520. Sczaniecka AK, Brasky TM, Lampe JW, et al. Dietary intake of specific fatty acids and breast cancer risk among postmenopausal women in the VITAL cohort. Nutr Cancer 2012;64:1131-42.

521. Sellers TA, Gapstur SM, Potter JD, et al. Association of body fat distribution and family histories of breast and ovarian cancer with risk of postmenopausal breast cancer. Am J Epidemiol 1993;138:799-803.

522. Sellers TA, Sprafka JM, Gapstur SM, et al. Does body fat distribution promote familial aggregation of adult onset diabetes mellitus and postmenopausal breast cancer? Epidemiology 1994;5:102-8.

523. Sellers TA, Kushi LH, Cerhan JR, et al. Dietary folate intake, alcohol, and risk of breast cancer in a prospective study of postmenopausal women. Epidemiology 2001;12:420-8.

524. Sellers TA, Davis J, Cerhan JR, et al. Interaction of waist/hip ratio and family history on the risk of hormone receptor-defined breast cancer in a prospective study of postmenopausal women. Am J Epidemiol 2002;155:225-33.

525. Sellers TA, Grabrick DM, Vierkant RA, et al. Does folate intake decrease risk of postmenopausal breast cancer among women with a family history? Cancer Causes Control 2004;15:113-20.

526. Sesso HD, Paffenbarger RS, Jr., Lee IM. Physical activity and breast cancer risk in the College Alumni Health Study (United States). Cancer Causes Control 1998;9:433-9.

527. Sesso HD, Buring JE, Zhang SM, et al. Dietary and plasma lycopene and the risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2005;14:1074-81.

528. Setiawan VW, Monroe KR, Wilkens LR, et al. Breast cancer risk factors defined by estrogen and progesterone receptor status: the multiethnic cohort study. Am J Epidemiol 2009;169:1251-9.

529. Shen C, Schooling CM, Chan WM, et al. Alcohol intake and death from cancer in a prospective Chinese elderly cohort study in Hong Kong. J Epidemiol Community Health 2013;67:813-20.

530. Shen D, Mao W, Liu T, et al. Sedentary behavior and incident cancer: a meta-analysis of prospective studies. PLoS One 2014;9:e105709.

531. Shibata A, Paganini-Hill A, Ross RK, et al. Intake of vegetables, fruits, beta-carotene, vitamin C and vitamin supplements and cancer incidence among the elderly: a prospective study. Br J Cancer 1992;66:673-9.

532. Shikany JM, Redden DT, Neuhouser ML, et al. Dietary glycemic load, glycemic index, and carbohydrate and risk of breast cancer in the Women's Health Initiative. Nutr Cancer 2011;63:899-907.

533. Shin MH, Holmes MD, Hankinson SE, et al. Intake of dairy products, calcium, and vitamin d and risk of breast cancer. J Natl Cancer Inst 2002;94:1301-11.

534. Shrubsole MJ, Shu XO, Li HL, et al. Dietary B vitamin and methionine intakes and breast cancer risk among Chinese women. Am J Epidemiol 2011;173:1171-82.

535. Sieri S, Krogh V, Muti P, et al. Fat and protein intake and subsequent breast cancer risk in postmenopausal women. Nutr Cancer 2002;42:10-7.

536. Sieri S, Krogh V, Pala V, et al. Dietary patterns and risk of breast cancer in the ORDET cohort. Cancer Epidemiol Biomarkers Prev 2004;13:567-72.

537. Sieri S, Pala V, Brighenti F, et al. Dietary glycemic index, glycemic load, and the risk of breast cancer in an Italian prospective cohort study. Am J Clin Nutr 2007;86:1160-6.

538. Sieri S, Krogh V, Ferrari P, et al. Dietary fat and breast cancer risk in the European Prospective Investigation into Cancer and Nutrition. Am J Clin Nutr 2008;88:1304-12.

539. Sieri S, Pala V, Brighenti F, et al. High glycemic diet and breast cancer occurrence in the Italian EPIC cohort. Nutr Metab Cardiovasc Dis 2013;23:628-34.

540. Sieri S, Chiodini P, Agnoli C, et al. Dietary fat intake and development of specific breast cancer subtypes. J Natl Cancer Inst 2014;106.

541. Silva IS, De SB, McCormack V. Birth size and breast cancer risk: re-analysis of individual participant data from 32 studies. PLoS Med 2008;5:e193.

542. Silvera SA, Jain M, Howe GR, et al. Dietary carbohydrates and breast cancer risk: a prospective study of the roles of overall glycemic index and glycemic load. Int J Cancer 2005;114:653-8.

543. Silvera SA, Jain M, Howe GR, et al. Energy balance and breast cancer risk: a prospective cohort study. Breast Cancer Res Treat 2006;97:97-106.

544. Sisti JS, Lindstrom S, Kraft P, et al. Premenopausal plasma carotenoids, fluorescent oxidation products, and subsequent breast cancer risk in the nurses' health studies. Breast Cancer Res Treat 2015;151:415-25.

545. Skaaby T, Husemoen LL, Thuesen BH, et al. Prospective population-based study of the association between serum 25-hydroxyvitamin-D levels and the incidence of specific types of cancer. Cancer Epidemiol Biomarkers Prev 2014;23:1220-9.

546. Smith-Warner SA, Spiegelman D, Adami HO, et al. Types of dietary fat and breast cancer: a pooled analysis of cohort studies. Int J Cancer 2001;92:767-774b.

547. Smith-Warner SA, Spiegelman D, Yaun SS, et al. Intake of fruits and vegetables and risk of breast cancer: a pooled analysis of cohort studies. JAMA 2001;285:769-776a.

548. Snowdon DA, Phillips RL. Coffee consumption and risk of fatal cancers. Am J Public Health 1984;74:820-3.

549. Sonestedt E, Gullberg B, Wirfalt E. Both food habit change in the past and obesity status may influence the association between dietary factors and postmenopausal breast cancer. Public Health Nutr 2007;10:769-79.

550. Sonestedt E, Borgquist S, Ericson U, et al. Plant foods and oestrogen receptor alpha- and beta-defined breast cancer: observations from the Malmo Diet and Cancer cohort. Carcinogenesis 2008;29:2203-2209a.

551. Sonestedt E, Ericson U, Gullberg B, et al. Do both heterocyclic amines and omega-6 polyunsaturated fatty acids contribute to the incidence of breast cancer in postmenopausal women of the Malmo diet and cancer cohort? Int J Cancer 2008;123:1637-1643b.

552. Song X, Pukkala E, Dyba T, et al. Body mass index and cancer incidence: the FINRISK study. Eur J Epidemiol 2014;29:477-87.

553. Song YM, Sung J, Ha M. Obesity and risk of cancer in postmenopausal Korean women. J Clin Oncol 2008;26:3395-402.

554. Sonnenschein E, Toniolo P, Terry MB, et al. Body fat distribution and obesity in pre- and postmenopausal breast cancer. Int J Epidemiol 1999;28:1026-31.

555. Sperati F, Vici P, Maugeri-Sacca M, et al. Vitamin D supplementation and breast cancer prevention: a systematic review and meta-analysis of randomized clinical trials. PLoS One 2013;8:e69269.

556. Spracklen CN, Wallace RB, Sealy-Jefferson S, et al. Birth weight and subsequent risk of cancer. Cancer Epidemiol 2014;38:538-43.

557. Stavola BL, Hardy R, Kuh D, et al. Birthweight, childhood growth and risk of breast cancer in a British cohort. Br J Cancer 2000;83:964-8.

558. Steenland K, Nowlin S, Palu S. Cancer incidence in the National Health and Nutrition Survey I. Follow-up data: diabetes, cholesterol, pulse and physical activity. Cancer Epidemiol Biomarkers Prev 1995;4:807-11.

559. Steindorf K, Ritte R, Tjonneland A, et al. Prospective study on physical activity and risk of in situ breast cancer. Cancer Epidemiol Biomarkers Prev 2012;21:2209-19.

560. Steindorf K, Ritte R, Eomois PP, et al. Physical activity and risk of breast cancer overall and by hormone receptor status: the European prospective investigation into cancer and nutrition. Int J Cancer 2013;132:1667-78.

561. Stendell-Hollis NR, Thompson PA, Thomson CA, et al. Investigating the association of lactation history and postmenopausal breast cancer risk in the Women's Health Initiative. Nutr Cancer 2013;65:969-81.

562. Stensvold I, Jacobsen BK. Coffee and cancer: a prospective study of 43,000 Norwegian men and women. Cancer Causes Control 1994;5:401-8.

563. Stevens VL, McCullough ML, Sun J, et al. Folate and other one-carbon metabolism-related nutrients and risk of postmenopausal breast cancer in the Cancer Prevention Study II Nutrition Cohort. Am J Clin Nutr 2010;91:1708-15.

564. Stolzenberg-Solomon RZ, Chang SC, Leitzmann MF, et al. Folate intake, alcohol use, and postmenopausal breast cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Am J Clin Nutr 2006;83:895-904.

565. Stripp C, Overvad K, Christensen J, et al. Fish intake is positively associated with breast cancer incidence rate. J Nutr 2003;133:3664-9.

566. Stuebe AM, Willett WC, Xue F, et al. Lactation and incidence of premenopausal breast cancer: a longitudinal study. Arch Intern Med 2009;169:1364-71.

567. Sue LY, Schairer C, Ma X, et al. Energy intake and risk of postmenopausal breast cancer: an expanded analysis in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) cohort. Cancer Epidemiol Biomarkers Prev 2009;18:2842-50.

568. Sugiyama K, Kuriyama S, Akhter M, et al. Coffee consumption and mortality due to all causes, cardiovascular disease, and cancer in Japanese women. J Nutr 2010;140:1007-13.

569. Sung J, Song YM, Lawlor DA, et al. Height and site-specific cancer risk: A cohort study of a korean adult population. Am J Epidemiol 2009;170:53-64.

570. Suzuki K. Health conditions and mortality in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). Asian Pac J Cancer Prev 2007;8 Suppl:25-34.

571. Suzuki R, Ye W, Rylander-Rudqvist T, et al. Alcohol and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status: a prospective cohort study. J Natl Cancer Inst 2005;97:1601-8.

572. Suzuki R, Rylander-Rudqvist T, Ye W, et al. Body weight and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status among Swedish women: A prospective cohort study. Int J Cancer 2006;119:1683-9.

573. Suzuki R, Rylander-Rudqvist T, Ye W, et al. Dietary fiber intake and risk of postmenopausal breast cancer defined by estrogen and progesterone receptor status--a prospective cohort study among Swedish women. Int J Cancer 2008;122:403-412a.

574. Suzuki R, Rylander-Rudqvist T, Saji S, et al. Dietary lignans and postmenopausal breast cancer risk by oestrogen receptor status: a prospective cohort study of Swedish women. Br J Cancer 2008;98:636-640b.

575. Suzuki R, Orsini N, Saji S, et al. Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status--a meta-analysis. Int J Cancer 2009;124:698-712.

576. Suzuki R, Iwasaki M, Inoue M, et al. Alcohol consumption-associated breast cancer incidence and potential effect modifiers: the Japan Public Health Center-based Prospective Study. Int J Cancer 2010;127:685-95.

577. Suzuki R, Iwasaki M, Yamamoto S, et al. Leisure-time physical activity and breast cancer risk defined by estrogen and progesterone receptor status--the Japan Public Health Center-based Prospective Study. Prev Med 2011;52:227-233a.

578. Suzuki R, Iwasaki M, Inoue M, et al. Body weight at age 20 years, subsequent weight change and breast cancer risk defined by estrogen and progesterone receptor status--the Japan public health center-based prospective study. Int J Cancer 2011;129:1214-1224b.

579. Suzuki R, Iwasaki M, Hara A, et al. Fruit and vegetable intake and breast cancer risk defined by estrogen and progesterone receptor status: the Japan Public Health Center-based Prospective Study. Cancer Causes Control 2013;24:2117-28.

580. Suzuki S, Kojima M, Tokudome S, et al. Effect of physical activity on breast cancer risk: findings of the Japan collaborative cohort study. Cancer Epidemiol Biomarkers Prev 2008;17:3396-3401c.

581. Suzuki S, Kojima M, Tokudome S, et al. Obesity/weight gain and breast cancer risk: findings from the Japan collaborative cohort study for the evaluation of cancer risk. J Epidemiol 2013;23:139-45.

582. Suzuki Y, Tsubono Y, Nakaya N, et al. Green tea and the risk of breast cancer: pooled analysis of two prospective studies in Japan. Br J Cancer 2004;90:1361-3.

583. Swanson CA, Jones DY, Schatzkin A, et al. Breast cancer risk assessed by anthropometry in the NHANES I epidemiological follow-up study. Cancer Res 1988;48:5363-7.

584. Sweeney C, Blair CK, Anderson KE, et al. Risk factors for breast cancer in elderly women. Am J Epidemiol 2004;160:868-75.

585. Taghizadeh N, Boezen HM, Schouten JP, et al. BMI and lifetime changes in BMI and cancer mortality risk. PLoS One 2015;10:e0125261.

586. Tamimi RM, Hankinson SE, Spiegelman D, et al. Manganese superoxide dismutase polymorphism, plasma antioxidants, cigarette smoking, and risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2004;13:989-96.

587. Tamimi RM, Hankinson SE, Campos H, et al. Plasma carotenoids, retinol, and tocopherols and risk of breast cancer. Am J Epidemiol 2005;161:153-60.

588. Tamimi RM, Colditz GA, Hankinson SE. Circulating carotenoids, mammographic density, and subsequent risk of breast cancer. Cancer Res 2009;69:9323-9.

589. Taylor EF, Burley VJ, Greenwood DC, et al. Meat consumption and risk of breast cancer in the UK Women's Cohort Study. Br J Cancer 2007;96:1139-46.

590. Tehard B, Lahmann PH, Riboli E, et al. Anthropometry, breast cancer and menopausal status: use of repeated measurements over 10 years of follow-up-results of the French E3N women's cohort study. Int J Cancer 2004;111:264-9.

591. Tehard B, Friedenreich CM, Oppert JM, et al. Effect of physical activity on women at increased risk of breast cancer: results from the E3N cohort study. Cancer Epidemiol Biomarkers Prev 2006;15:57-64.

592. Tehard B, Clavel-Chapelon F. Several anthropometric measurements and breast cancer risk: results of the E3N cohort study. Int J Obes (Lond) 2006;30:156-63.

593. Terry P, Suzuki R, Hu FB, et al. A prospective study of major dietary patterns and the risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2001;10:1281-5.

594. Terry P, Jain M, Miller AB, et al. No association among total dietary fiber, fiber fractions, and risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2002;11:1507-8.

595. Terry P, Jain M, Miller AB, et al. Dietary carotenoids and risk of breast cancer. Am J Clin Nutr 2002;76:883-8.

596. Thiebaut AC, Clavel-Chapelon F. [Fat consumption and breast cancer: preliminary results from the E3N-Epic cohort]. Bull Cancer 2001;88:954-8.

597. Thiebaut AC, Kipnis V, Chang SC, et al. Dietary fat and postmenopausal invasive breast cancer in the National Institutes of Health-AARP Diet and Health Study cohort. J Natl Cancer Inst 2007;99:451-62.

598. Thomson CA, Van HL, Caan BJ, et al. Cancer incidence and mortality during the intervention and postintervention periods of the Women's Health Initiative dietary modification trial. Cancer Epidemiol Biomarkers Prev 2014;23:2924-2935a.

599. Thomson CA, McCullough ML, Wertheim BC, et al. Nutrition and physical activity cancer prevention guidelines, cancer risk, and mortality in the women's health initiative. Cancer Prev Res (Phila) 2014;7:42-53b.

600. Thun MJ, Peto R, Lopez AD, et al. Alcohol consumption and mortality among middle-aged and elderly U.S. adults. N Engl J Med 1997;337:1705-14.

601. Thune I, Brenn T, Lund E, et al. Physical activity and the risk of breast cancer. N Engl J Med 1997;336:1269-75.

602. Tjonneland A, Thomsen BL, Stripp C, et al. Alcohol intake, drinking patterns and risk of postmenopausal breast cancer in Denmark: a prospective cohort study. Cancer Causes Control 2003;14:277-84.

603. Tjonneland A, Christensen J, Thomsen BL, et al. Lifetime alcohol consumption and postmenopausal breast cancer rate in Denmark: a prospective cohort study. J Nutr 2004;134:173-8.

604. Tjonneland A, Christensen J, Olsen A, et al. Folate intake, alcohol and risk of breast cancer among postmenopausal women in Denmark. Eur J Clin Nutr 2006;60:280-6.

605. Tjonneland A, Christensen J, Olsen A, et al. Alcohol intake and breast cancer risk: the European Prospective Investigation into Cancer and Nutrition (EPIC). Cancer Causes Control 2007;18:361-73.

606. Tognon G, Nilsson LM, Lissner L, et al. The Mediterranean diet score and mortality are inversely associated in adults living in the subarctic region. J Nutr 2012;142:1547-53.

607. Toniolo P, Riboli E, Shore RE, et al. Consumption of meat, animal products, protein, and fat and risk of breast cancer: a prospective cohort study in New York. Epidemiology 1994;5:391-7.

608. Toniolo P, Van Kappel AL, Akhmedkhanov A, et al. Serum carotenoids and breast cancer. Am J Epidemiol 2001;153:1142-7.

609. Torio CM, Klassen AC, Curriero FC, et al. The modifying effect of social class on the relationship between body mass index and breast cancer incidence. Am J Public Health 2010;100:146-51.

610. Tornberg SA, Holm LE, Carstensen JM. Breast cancer risk in relation to serum cholesterol, serum beta-lipoprotein, height, weight, and blood pressure. Acta Oncol 1988;27:31-7.

611. Tornberg SA, Carstensen JM. Relationship between Quetelet's index and cancer of breast and female genital tract in 47,000 women followed for 25 years. Br J Cancer 1994;69:358-61.

612. Touillaud MS, Thiebaut AC, Niravong M, et al. No association between dietary phytoestrogens and risk of premenopausal breast cancer in a French cohort study. Cancer Epidemiol Biomarkers Prev 2006;15:2574-6.

613. Travis RC, Allen NE, Appleby PN, et al. A prospective study of vegetarianism and isoflavone intake in relation to breast cancer risk in British women. Int J Cancer 2008;122:705-10.

614. Trichopoulou A, Bamia C, Lagiou P, et al. Conformity to traditional Mediterranean diet and breast cancer risk in the Greek EPIC (European Prospective Investigation into Cancer and Nutrition) cohort. Am J Clin Nutr 2010;92:620-5.

615. Troisi R, Hatch EE, Titus-Ernstoff L, et al. Birth weight and breast cancer risk. Br J Cancer 2006;94:1734-7.

616. Tryggvadottir L, Tulinius H, Eyfjord JE, et al. Breastfeeding and reduced risk of breast cancer in an Icelandic cohort study. Am J Epidemiol 2001;154:37-42.

617. Tryggvadottir L, Tulinius H, Eyfjord JE, et al. Breast cancer risk factors and age at diagnosis: an Icelandic cohort study. Int J Cancer 2002;98:604-8.

618. Tulinius H, Sigfusson N, Sigvaldason H, et al. Risk factors for malignant diseases: a cohort study on a population of 22,946 Icelanders. Cancer Epidemiol Biomarkers Prev 1997;6:863-73.

619. Turner LB. A meta-analysis of fat intake, reproduction, and breast cancer risk: an evolutionary perspective. Am J Hum Biol 2011;23:601-8.

620. Ursin G, Bjelke E, Heuch I, et al. Milk consumption and cancer incidence: a Norwegian prospective study. Br J Cancer 1990;61:454-9.

621. Vacek PM, Skelly JM, Geller BM. Breast cancer risk assessment in women aged 70 and older. Breast Cancer Res Treat 2011;130:291-9.

622. van den Brandt PA, van't Veer P, Goldbohm RA, et al. A prospective cohort study on dietary fat and the risk of postmenopausal breast cancer. Cancer Res 1993;53:75-82.

623. van den Brandt PA, Goldbohm RA, van ', V. Alcohol and breast cancer: results from The Netherlands Cohort Study. Am J Epidemiol 1995;141:907-15.

624. van den Brandt PA, Dirx MJ, Ronckers CM, et al. Height, weight weight change, and postmenopausal breast cancer risk: The Netherlands Cohort Study. Cancer Causes Control 1997;8:39-47.

625. van den Brandt PA, Spiegelman D, Yaun SS, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. Am J Epidemiol 2000;152:514-27.

626. van der Hel OL, Peeters PH, Hein DW, et al. GSTM1 null genotype, red meat consumption and breast cancer risk (The Netherlands). Cancer Causes Control 2004;15:295-303.

627. van der Pols JC, Bain C, Gunnell D, et al. Childhood dairy intake and adult cancer risk: 65-y follow-up of the Boyd Orr cohort. Am J Clin Nutr 2007;86:1722-9.

628. van Gils CH, Peeters PH, Bueno-de-Mesquita HB, et al. Consumption of vegetables and fruits and risk of breast cancer. JAMA 2005;293:183-93.

629. van Kruijsdijk RC, van der Graaf Y, Peeters PH, et al. Cancer risk in patients with manifest vascular disease: effects of smoking, obesity, and metabolic syndrome. Cancer Epidemiol Biomarkers Prev 2013;22:1267-77.

630. Vatten LJ, Solvoll K, Loken EB. Coffee consumption and the risk of breast cancer. A prospective study of 14,593 Norwegian women. Br J Cancer 1990;62:267-270b.

631. Vatten LJ, Kvinnsland S. Body height and risk of breast cancer. A prospective study of 23,831 Norwegian women. Br J Cancer 1990;61:881-885d.

632. Vatten LJ, Kvinnsland S. Body mass index and risk of breast cancer. A prospective study of 23,826 Norwegian women. Int J Cancer 1990;45:440-444c.

633. Vatten LJ, Solvoll K, Loken EB. Frequency of meat and fish intake and risk of breast cancer in a prospective study of 14,500 Norwegian women. Int J Cancer 1990;46:12-15a.

634. Vatten LJ, Kvinnsland S. Prospective study of height, body mass index and risk of breast cancer. Acta Oncol 1992;31:195-200.

635. Vatten LJ, Nilsen TI, Tretli S, et al. Size at birth and risk of breast cancer: prospective population-based study. Int J Cancer 2005;114:461-4.

636. Velie E, Kulldorff M, Schairer C, et al. Dietary fat, fat subtypes, and breast cancer in postmenopausal women: a prospective cohort study. J Natl Cancer Inst 2000;92:833-9.

637. Velie EM, Schairer C, Flood A, et al. Empirically derived dietary patterns and risk of postmenopausal breast cancer in a large prospective cohort study. Am J Clin Nutr 2005;82:1308-19.

638. Vena JE, Graham S, Zielezny M, et al. Occupational exercise and risk of cancer. Am J Clin Nutr 1987;45:318-27.

639. Verhoeven DT, Assen N, Goldbohm RA, et al. Vitamins C and E, retinol, beta-carotene and dietary fibre in relation to breast cancer risk: a prospective cohort study. Br J Cancer 1997;75:149-55.

640. Vihko VJ, Apter DL, Pukkala EI, et al. Risk of breast cancer among female teachers of physical education and languages. Acta Oncol 1992;31:201-4.

641. Visvanathan K, Crum RM, Strickland PT, et al. Alcohol dehydrogenase genetic polymorphisms, low-to-moderate alcohol consumption, and risk of breast cancer. Alcohol Clin Exp Res 2007;31:467-76.

642. Vogel U, Christensen J, Nexo BA, et al. Peroxisome proliferator-activated [corrected] receptor-gamma2 [corrected] Pro12Ala, interaction with alcohol intake and NSAID use, in relation to risk of breast cancer in a prospective study of Danes. Carcinogenesis 2007;28:427-34.

643. Voorrips LE, Brants HA, Kardinaal AF, et al. Intake of conjugated linoleic acid, fat, and other fatty acids in relation to postmenopausal breast cancer: the Netherlands Cohort Study on Diet and Cancer. Am J Clin Nutr 2002;76:873-82.

644. Wada K, Nakamura K, Tamai Y, et al. Soy isoflavone intake and breast cancer risk in Japan: from the Takayama study. Int J Cancer 2013;133:952-60.

645. Wada K, Nagata C, Tamakoshi A, et al. Body mass index and breast cancer risk in Japan: a pooled analysis of eight population-based cohort studies. Ann Oncol 2014;25:519-24.

646. Wakai K, Tamakoshi K, Date C, et al. Dietary intakes of fat and fatty acids and risk of breast cancer: a prospective study in Japan. Cancer Sci 2005;96:590-9.

647. Wang J, Eliassen AH, Spiegelman D, et al. Plasma free 25-hydroxyvitamin D, vitamin D binding protein, and risk of breast cancer in the Nurses' Health Study II. Cancer Causes Control 2014;25:819-27.

648. Wang Y, Gapstur SM, Gaudet MM, et al. Evidence for an association of dietary flavonoid intake with breast cancer risk by estrogen receptor status is limited. J Nutr 2014;144:1603-11.

649. Ward HA, Kuhnle GG, Mulligan AA, et al. Breast, colorectal, and prostate cancer risk in the European Prospective Investigation into Cancer and Nutrition-Norfolk in relation to phytoestrogen intake derived from an improved database. Am J Clin Nutr 2010;91:440-8.

650. Warner ET, Colditz GA, Palmer JR, et al. Reproductive factors and risk of premenopausal breast cancer by age at diagnosis: are there differences before and after age 40? Breast Cancer Res Treat 2013;142:165-75.

651. Weiderpass E, Braaten T, Magnusson C, et al. A prospective study of body size in different periods of life and risk of premenopausal breast cancer. Cancer Epidemiol Biomarkers Prev 2004;13:1121-7.

652. Wen W, Shu XO, Li H, et al. Dietary carbohydrates, fiber, and breast cancer risk in Chinese women. Am J Clin Nutr 2009;89:283-9.

653. White KK, Park SY, Kolonel LN, et al. Body size and breast cancer risk: the Multiethnic Cohort. Int J Cancer 2012;131:E705-E716.

654. Whitlock G, Lewington S, Sherliker P, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet 2009;373:1083-96.

655. Whittemore AS, Paffenbarger RS, Jr., Anderson K, et al. Early precursors of site-specific cancers in college men and women. J Natl Cancer Inst 1985;74:43-51.

656. Wie GA, Cho YA, Kang HH, et al. Red meat consumption is associated with an increased overall cancer risk: a prospective cohort study in Korea. Br J Nutr 2014;112:238-47.

657. Willett WC, Browne ML, Bain C, et al. Relative weight and risk of breast cancer among premenopausal women. Am J Epidemiol 1985;122:731-40.

658. Willett WC, Stampfer MJ, Colditz GA, et al. Moderate alcohol consumption and the risk of breast cancer. N Engl J Med 1987;316:1174-1180a.

659. Willett WC, Stampfer MJ, Colditz GA, et al. Dietary fat and the risk of breast cancer. N Engl J Med 1987;316:22-28b.

660. Willett WC, Hunter DJ, Stampfer MJ, et al. Dietary fat and fiber in relation to risk of breast cancer. An 8-year follow-up. JAMA 1992;268:2037-44.

661. Williams PT. Breast cancer mortality vs. exercise and breast size in runners and walkers. PLoS One 2013;8:e80616.

662. Wilson KM, Willett WC, Michels KB. Mothers' pre-pregnancy BMI and weight gain during pregnancy and risk of breast cancer in daughters. Breast Cancer Res Treat 2011;130:273-9.

663. Wiren S, Haggstrom C, Ulmer H, et al. Pooled cohort study on height and risk of cancer and cancer death. Cancer Causes Control 2014;25:151-9.

664. Wirfalt E, Mattisson I, Gullberg B, et al. Postmenopausal breast cancer is associated with high intakes of omega6 fatty acids (Sweden). Cancer Causes Control 2002;13:883-93.

665. Wirfalt E, Vessby B, Mattisson I, et al. No relations between breast cancer risk and fatty acids of erythrocyte membranes in postmenopausal women of the Malmo Diet Cancer cohort (Sweden). Eur J Clin Nutr 2004;58:761-70.

666. Wirfalt E, Mattisson I, Gullberg B, et al. Fat from different foods show diverging relations with breast cancer risk in postmenopausal women. Nutr Cancer 2005;53:135-43.

667. Witham MD, Price RJ, Struthers AD, et al. Cholecalciferol treatment to reduce blood pressure in older patients with isolated systolic hypertension: the VitDISH randomized controlled trial. JAMA Intern Med 2013;173:1672-9.

668. Wolk A, Bergstrom R, Hunter D, et al. A prospective study of association of monounsaturated fat and other types of fat with risk of breast cancer. Arch Intern Med 1998;158:41-5.

669. Wood AD, Secombes KR, Thies F, et al. Vitamin D3 supplementation has no effect on conventional cardiovascular risk factors: a parallel-group, double-blind, placebo-controlled RCT. J Clin Endocrinol Metab 2012;97:3557-68.

670. Wu AH, Koh WP, Wang R, et al. Soy intake and breast cancer risk in Singapore Chinese Health Study. Br J Cancer 2008;99:196-200.

671. Wu K, Helzlsouer KJ, Comstock GW, et al. A prospective study on folate, B12, and pyridoxal 5'-phosphate (B6) and breast cancer. Cancer Epidemiol Biomarkers Prev 1999;8:209-17.

672. Wu K, Sinha R, Holmes MD, et al. Meat mutagens and breast cancer in postmenopausal women--a cohort analysis. Cancer Epidemiol Biomarkers Prev 2010;19:1301-10.

673. Wu MH, Chou YC, Yu JC, et al. Hormonal and body-size factors in relation to breast cancer risk: a prospective study of 11,889 women in a low-incidence area. Ann Epidemiol 2006;16:223-9.

674. Wyrwich KW, Wolinsky FD. Physical activity, disability, and the risk of hospitalization for breast cancer among older women. J Gerontol A Biol Sci Med Sci 2000;55:M418-M421.

675. Wyshak G, Frisch RE. Breast cancer among former college athletes compared to non-athletes: a 15-year follow-up. Br J Cancer 2000;82:726-30.

676. Xia X, Chen W, Li J, et al. Body mass index and risk of breast cancer: a nonlinear dose-response meta-analysis of prospective studies. Sci Rep 2014;4:7480.

677. Yang L, Veierod MB, Lof M, et al. Prospective study of UV exposure and cancer incidence among Swedish women. Cancer Epidemiol Biomarkers Prev 2011;20:1358-67.

678. Yang TO, Reeves GK, Green J, et al. Birth weight and adult cancer incidence: large prospective study and meta-analysis. Ann Oncol 2014;25:1836-43.

679. Yang XR, Chang-Claude J, Goode EL, et al. Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. J Natl Cancer Inst 2011;103:250-63.

680. Yin L, Grandi N, Raum E, et al. Meta-analysis: serum vitamin D and breast cancer risk. Eur J Cancer 2010;46:2196-205.

681. Yu F, Jin Z, Jiang H, et al. Tea consumption and the risk of five major cancers: a dose-response meta-analysis of prospective studies. BMC Cancer 2014;14:197.

682. Yu X, Bao Z, Zou J, et al. Coffee consumption and risk of cancers: a meta-analysis of cohort studies. BMC Cancer 2011;11:96.

683. Yuan JM, Koh WP, Sun CL, et al. Green tea intake, ACE gene polymorphism and breast cancer risk among Chinese women in Singapore. Carcinogenesis 2005;26:1389-94.

684. Zamora-Ros R, Ferrari P, Gonzalez CA, et al. Dietary flavonoid and lignan intake and breast cancer risk according to menopause and hormone receptor status in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study. Breast Cancer Res Treat 2013;139:163-76.

685. Zhang S, Hunter DJ, Hankinson SE, et al. A prospective study of folate intake and the risk of breast cancer. JAMA 1999;281:1632-1637c.

686. Zhang S, Hunter DJ, Forman MR, et al. Dietary carotenoids and vitamins A, C, and E and risk of breast cancer. J Natl Cancer Inst 1999;91:547-556a.

687. Zhang SM, Willett WC, Selhub J, et al. Plasma folate, vitamin B6, vitamin B12, homocysteine, and risk of breast cancer. J Natl Cancer Inst 2003;95:373-80.

688. Zhang SM, Hankinson SE, Hunter DJ, et al. Folate intake and risk of breast cancer characterized by hormone receptor status. Cancer Epidemiol Biomarkers Prev 2005;14:2004-8.

689. Zhang SM, Lee IM, Manson JE, et al. Alcohol consumption and breast cancer risk in the Women's Health Study. Am J Epidemiol 2007;165:667-76.

690. Zhang X, Spiegelman D, Baglietto L, et al. Carotenoid intakes and risk of breast cancer defined by estrogen receptor and progesterone receptor status: a pooled analysis of 18 prospective cohort studies. Am J Clin Nutr 2012;95:713-25.

691. Zhang X, Eliassen AH, Tamimi RM, et al. Adult body size and physical activity in relation to risk of breast cancer according to tumor androgen receptor status. Cancer Epidemiol Biomarkers Prev 2015;24:962-8.

692. Zhang Y, Kreger BE, Dorgan JF, et al. Alcohol consumption and risk of breast cancer: the Framingham Study revisited. Am J Epidemiol 1999;149:93-101b.

693. Zhang YF, Xu Q, Lu J, et al. Tea consumption and the incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Eur J Cancer Prev 2015;24:353-62.

694. Zheng W, Shu XO, McLaughlin JK, et al. Occupational physical activity and the incidence of cancer of the breast, corpus uteri, and ovary in Shanghai. Cancer 1993;71:3620-4.

695. Zheng W, Doyle TJ, Kushi LH, et al. Tea consumption and cancer incidence in a prospective cohort study of postmenopausal women. Am J Epidemiol 1996;144:175-82.

Appendix 1 Breast cancer continuous update protocol

Continuous update of the WCRF-AICR report on diet and cancer

Protocol: Breast Cancer

Prepared by: Imperial College Team

The current protocol for the continuous update should ensure consistency of approach to the evidence, common approach to the analysis and format for displaying the evidence used as in the literature reviews for the Second Expert Report.

The starting point for this protocol are:

- The judgement of the Panel of the WCRF-AICR Second Expert Report on the evidence of the relationship of food, nutrition, physical activity and breast cancer (Second Expert Report Part 2 Chapter 7.10 pp 289).
- The convention for conducting systematic reviews developed by WCRF International for the Second Expert Report (SLR Specification Manual –version 15).
- The protocol developed by the SLR group on breast cancer for the Second Expert Report (National Cancer Institute, Milan, Version October 29, 2004).

The protocol will represent the agreed plan for the Continuous Update. Should departure from the agreed plan be considered necessary at a later stage, this must be agreed by the Continuous Update Panel (CUP) and the reasons documented.

Judgement of the Panel of the WCRF-AICR Second Expert Report:

The following summary has been extracted from the WCRF-AICR Second Expert Report:

CANCER OF THE BREAST (PREMENOPAUSE)
In the judgement of the Panel, the factors listed below modify the risk of

cancer of the breast (premenopause). Judgements are graded according to the strength of the evidence.		
	DECREASES RISK	**INCREASES RISK**
Convincing	Lactation	Alcoholic drinks
Probable	Body fatness	Adult attained height[1] Greater birth weight
Limited –suggestive	Physical activity[2]	
Limited –no conclusion	Cereals (grains) and their products; (grains) and their products; potatoes; vegetables; fruits; pulses (legumes); soya and soya products; meat; poultry; fish; eggs; fats and oils; vegetable fat; sugar; sugary foods and drinks; milk and dairy products; coffee; tea; carbohydrate; starch; dietary fibre; sugars; total fat; fatty acid composition; *trans*-fatty acids; cholesterol; protein; vitamin A; carotenoids; folate; riboflavin; vitamin B6; cobalamin; vitamin C; vitamin D; vitamin E; iron; calcium; selenium; isoflavones; dieldrin; *trans*-nonachlor; dichlorodiphenyltrichloroethane; dichlorodiphenyldichloroethylene; polychlorinated biphenyls; hexachlorocyclohexane; hexachlorobenzene; energy intake; adult weight gain; adult attained height; dietary patterns; culturally defined diets; glycaemic index; and being breastfed.	
Substantial effect on risk unlikely	None identified	

CANCER OF THE BREAST (POSTMENOPAUSE)		
In the judgement of the Panel, the factors listed below modify the risk of cancer of the breast (postmenopause). Judgements are graded according to the strength of the evidence.		
	DECREASES RISK	**INCREASES RISK**
Convincing	Lactation	Alcoholic drinks Body fatness Adult attained height[1]
Probable	Physical activity[2]	Abdominal fatness Adult weight gain
Limited –suggestive		Total fat
Limited –no conclusion	Cereals (grains) and their products; potatoes; vegetables and fruits; pulses; soya and soya products; meat; poultry; fish; eggs; fats and oils; sugar; sugary drinks and foods; milk and dairy products; coffee; tea; carbohydrate; starch; dietary fibre; vegetable fat; fatty acid composition; cholesterol; protein; vitamin A and carotenoids; riboflavin; vitamin B6; vitamin B12; folate; vitamin C; vitamin D; vitamin E; isoflavones; iron; calcium; selenium; dieldrin; *trans*-nonachlor; dichlorodiphenyltrichloroethane; dichlorodiphenyldichloroethylene; polychlorinated biphenyls; hexachlorocyclohexane; hexachlorobenzene; energy intake; birth length; culturally defined diets; dietary patterns; glycaemic index; being breastfed; and birth weight.	
Substantial effect on risk	None identified	

unlikely	

Extent of the continuous update.

The extent of the update has to be adequate to time and resources. The determination of priorities for the update will be based on:

- **Study type**
- **Grade of evidence of the association of exposures with breast cancer**
- **Recommendations from the CUP and the ICL team**

Study type: the study types that will be included in the update are:

- Randomized controlled trial
- Group randomized controlled trial (Community trial)
- Prospective cohort study
- Nested case-control study
- Case-cohort study
- **Population based case-control study with more than 1000 cases**

Factors: In this initial phase the ICL team will update the factors for which the strength of the evidence of association to breast cancer was graded as convincing, probable, limited-suggestive and limited –no conclusion by the Panel of **Second WCRF-AICR Expert Report. :**

- **Lactation**
- **Greater birth weight**
- Adult attained height
- **Alcoholic drinks**
- Body fatness
- Abdominal fatness
- Adult weight gain
- Physical activity
- **Total fat intake**

1. Research question

The research topic is:

The associations between food, nutrition and physical activity and the risk of breast cancer.

2. Review team

Name	Current position at ICL	Role within team
Teresa Norat	Research Fellow	Principal investigator
Rui Veira	Data manager	Responsible of the data management, the design and architecture of the database
Doris Chan	Research Assistant	Nutritional epidemiologist, reviewer

3. Timeline

The update will include the articles added to Medline after January 1st 2006. The review for the Second Expert Report ended in December 30th 2005. A pre publication update extended the search to May 30th 2006 for exposures and cancer sites with suggestive, probable, convincing associations with the exposure of interest.

Task	Deadline
Preliminary output from search strategy	1st July, 2007
Review abstracts and citations identified in initial electronic search. Select papers for complete review	1st August, 2007
Review relevant papers. Select papers for data extraction*	15 September, 2007
Data extraction	30 December, 2007
Production of preliminary tables	30 January, 2007
Production of tables.	March 30, 2007
Preparation of forrests plot with relevant data	
Preparation of report to WCRF-AICR	April 15, 2007
Transfer copy of database, Endnote files to WCRF	April 15, 2007

** It is intended to continue tasks 1, 2, 3 with a monthly periodicity*

4. Search strategy

The WCRF-PubMed search strategy and search terms used in the SLR for the Second Expert Report will be the core for this literature search.

5. Selection of articles:

5.1 Inclusion criteria

The articles to be included in the review:

- **Have to be included in Medline after January 1st 2006 (closure date of the database for the Second Report).**
- Have to present results from an epidemiologic study of one of the following types:
    - Randomized controlled trial
    - Group randomized controlled trial (Community trial)
    - Prospective cohort study
    - Nested case-control study
    - Case-cohort study
    - Population based case-control study with more than 1000 cases
    -
- Must have as outcome of interest breast cancer (*in situ*, invasive) incidence or mortality in women.
- Have to present results on the relevant exposures
- Published in English language
- Included in Medline

5.2 Exclusion criteria

The articles to be excluded from the review:

1. Are out of the research topic
2. Do not report measure of relationship
3. The measure of relationship is only the mean difference of exposure
4. Are supplement to the main manuscript (e.g. Authors' Reply).
5. Are in-press
6. Are not in English language

Pooled analysis will be used as support for interpretation, but the data will not be included in the database.

6. Exposures

The continuous update will use the same labels as used in the SLR for the Second Expert Report.

Surrogate exposures of diet at early age, such as attained height at age at menarche and height velocity, have been included as exposures in the database during the SLR for the Second Expert Report and will be included in the continuous update.

Biomarkers of dietary intake was coded under the Main exposure corresponding to the dietary exposure and specified in a sub-exposure. We propose to use the same list of biomarkers used by the SLR teams of Bristol and Leeds (Attachment 1).

7. Outcome

The outcome of interest is breast cancer encompassing incidence and mortality (except for case-control studies, for which the outcome of interest is incidence). Separate analyses for incidence and mortality will be provided.

The information of all the papers reporting outcome for more than one cancer site, will be extracted and the information inputted in the database.

8. Databases

Only the Medline database will be searched. Data provided from the SLR Breast cancer for the Second Expert Report indicates that 95% of the articles included in the review have been retrieved from the Medline database (See Apendix 2).

9. Hand searching for cited references

For feasibility reasons, journals will not be hand searched in the continuous update.

However, hand searching, and searching in other databases should be done when a formal meta-analysis will be done after recommendation of the CUP.

10. Retrieving papers

The abstracts from the initial search results from PubMed will be reviewed by one person to assess each reference as to whether it is relevant and potentially relevant.

Complete papers will be retrieved for all relevant and potentially relevant references, and for references that cannot be excluded upon reading the title and abstracts.

A second assessment will be done after review of the complete papers.

The ICL team uses resources at Imperial College to retrieve the papers identified as satisfying the inclusion criteria. This should cover most of the online journal. For articles not accessible through the ICL library, funds provided by WCRF-AICR will be required.

The assessment of trials and cohort studies will be checked by a second reviewer.

11. Labelling of references

For consistency with the previous data collected during the SLR process for the Second Expert Report, the Imperial College team will use the same labelling of references: the unique identifier for a particular reference will be constructed using a 3-letter code to represent the cancer site (e.g. BRE for breast cancer), followed by a 5-digit number that will be allocated in sequence.

12. Reference Manager files

Reference Manager databases are generated in the continuous update containing the references of the initial search.

1) One of the customized fields (custom 1) is named 'inclusion' and this field is marked 'in', 'out' for each paper, thereby indicating which papers are deemed potentially relevant based on an assessment of the title and abstract.
2) One of the customized fields (custom 2) is named 'reasons' and this field should include the reason for exclusion for each paper.
3) The study identifier should be entered under the field titled 'label'.
4) One of the customized fields (custom 3) is named "study design". This field should include a letter (A-Q) representing the study design of each paper.

13. Data extraction

Ideally, data extraction should be performed in duplicate for all papers. This is not feasible with the available resources. Instead, the extracted data of 10% of the prospective cohort studies and trials in the database will be checked by a second reviewer at Imperial College.

The ICL team will update the merged MySQL database using a new interface created at Imperial College. This contains the same fields included in the Access database for the SLR for the Second Expert Report, including quality characteristics and results.

The study design algorithm devised (SLR specification manual –version 15) for use of the SLR centres for the Second Expert Report will be used to allocate study designs to papers. In some cases it will be appropriate to assign more than one design to a particular paper because the methods for assessment of different exposures may vary, because the data analyses correspond to more than one study design (e.g. analyses in the entire cohort and nested case-control).

Important overall aspects of the study that need attention are the strategy of analysis, the variables for which the exposure – disease association was adjusted for, the information given on the validity of the measurements and whether analyses were performed that attempted to correct for the likely effect of measurement error in the exposure variable. These variables were programmed in the Access database and are included in the MySQL database used by the continuous update by the ICL team.

The effect measures estimated with all the models reported in the paper should be extracted. The models should be labelled as not adjusted, minimally adjusted and intermediately adjusted. In addition, the ICL reviewer should indicate a "best model" for inclusion in reports. Where the same exposure was analyzed in more than one way with different levels of adjustment, the best model was taken to be the one with the most appropriate adjustment for confounding. Sometimes, some of the potential risk factors are not kept in the model because its inclusion does not modify the risk estimates. This model should also be considered the "best model". The most appropriate model should adjust for:

- Age
- Socio-economic status, educational attainment
- Alcohol intake
- Anthropometric variables (BMI, weight, height, WHR)
- Total energy intake (if exposure is a dietary variable)
- Menstrual characteristics (including age at menarche, menopausal status, age at menopause, among others)
- Reproductive and hormonal factors (including parity, HRT use, OC use)
- Genetic factors (e.g. family history)
- Previous breast disease
- Factors related to laboratory determinations (e.g. batch)

In relation to effect modification, the ICL team should report whether interaction terms were included in models and extract the results, in particular any statistical tests of heterogeneity across strata.

Data should also be abstracted for sub-groups corresponding to the list of potential effect modifiers. Where the data permit, the following sub-groups must be reported:

- Age
- Obesity
- Physical activity
- Oral contraceptive use
- Menopausal status
- Hormone replacement therapy
- Ethnicity
- Family history

- Smoking
- Genetic polymorphism
- Blood levels of nutrients/hormones

Data should be extracted for each individual paper, even if there is more than one from any one study, unless the information is identical. The extracted information should only be used once per analysis. To facilitate the detection of multiple reports from the same study, the study name in each article should be extracted .

If needed, the CU team should contact the authors to confirm, refute these suspicions. If the matter remains unresolved the coordinator of the continuous update will then seek advice from the CUP if necessary.

14. Reports

14.1 Content of the report:

Results of the search

Information on number of records downloaded, number of papers thought potentially relevant after reading titles and abstracts and number of included relevant papers. The reasons for excluding papers should also be described.

Description of studies identified in the continuous update

Amount of data and study types (i.e. numbers of different types of studies)
Populations studied
Exposures identified
Outcomes identified

Summary of number of studies by exposure and study type, separated on new (studies identified in the continuous update) and total.

14.2. Tabulation of study characteristics

Information on the characteristics (e.g. population, exposure, outcome, study design) and results of the study (e.g. direction and magnitude) of the new studies should be summarised in tables using the same format as for the SLR for the Second Expert Report.

Within this table the studies should be ordered according to design (e.g. trials, cohort studies, case-control studies).

The results will be presented separately for premenopausal and postmenopausal breast cancer. Studies that did not differentiate pre and post menopausal breast cancer will be analyzed separately in the meta-analyses.

14.3 Data analysis

A meta-analysis for a particular exposure and outcome will be conducted when more than 2 trials or 2 cohort studies or 3 case-control studies has been published in the year, and if the new and the previous results totalize more than 3 trials, 5 cohort studies or 5 case-control studies.

The meta-analysis will include also the study results extracted during the SLR and included in the merged database. Special care will be taken to avoid including more than once the results of the same study (e.g. previous analyses and re-analyses after a longer follow-up).

Results of pooled analyses will be presented to the CUP to support the evaluation, but they will not be included in the meta-analyses.

The first stage of the analysis will be to investigate whether any variations in estimates of effects exist between studies. Forest plots will be used to assess and display heterogeneity. These should be presented in the report using the standard format for the presentation used in the SLR for the Second Expert Report. Heterogeneity will be formally assessed by using the I^2 statistic.

If sufficient homogeneity exists, an overall summary of effect should be determined. If there is significant heterogeneity, it should be characterised as clearly as possible. If possible meta-regression should be performed to investigate sources of heterogeneity.

The list of characteristics to be explored as possible causes of heterogeneity is:

Method of measurement, assessment of the exposure

Definition of exposure

Exposure range

Adjustment for confounders

Age at recruitment

Duration of follow-up

Geographical region

Outcome

Study design

From this identification, it may be possible for studies to be grouped according to a particular characteristic and separate analysis performed within each sub-group.

Meta-regression analysis will be used when appropriate and possible. In addition, sensitivity analysis and influence analyses could be done when possible and appropriate.

Summary estimates should be prepared for each study design separately but not combined, and these should be displayed on the same forest plot. The studies should be ordered by study design: randomised controlled trials, cohort and then case-control studies.

Formal quality grading should not be performed on an individual study basis. Instead, study characteristics (such as aspects of study design, methods of exposure assessment etc.) will be used to explore potential sources of bias and the robustness of conclusions. This approach has the following uses:

1) To explore the reasons for heterogeneity in study results

2) To guide interpretation of findings and to aid determining the strength of inferences

3) To guide recommendations for future research

The recommended method for presenting the results of the meta-analyses is in terms of *log, per unit increase in exposure*. If it is not possible, the meta-analyses will summarize the comparison of extreme categories. The analyses will be conducted using STATA.

Appendix 2 Search Strategy

WCRF - PUBMED SEARCH STRATEGY (with modifications implemented by the SLR centre Milan)

a) Searching for all studies relating to breast cancer:

#1 Breast Neoplasms [MeSH Terms]

#2 Breast AND (cancer* OR neoplasm* OR tumour* OR tumor* OR carcinoma* OR adenocarcinoma*)

#3 mammary AND (cancer* OR neoplasm* OR tumour* OR tumor* OR carcinoma* OR adenocarcinoma*)

#4 #1 OR #2 OR #3

b) Searching for all studies relating to food, nutrition and physical activity:

#5 weight loss[tiab] or weight gain[tiab] OR anthropometry[tiab] OR birth weight[tiab] OR birthweight[tiab] OR birth-weight[tiab] OR child development[tiab] OR height[tiab] OR body composition[tiab] OR body mass[tiab] OR BMI[tiab] OR obesity[tiab] OR obese[tiab] OR overweight[tiab] OR over-weight[tiab] OR over weight[tiab] OR skinfold measurement*[tiab] OR skinfold thickness[tiab] OR DEXA[tiab] OR bio-impedence[tiab] OR waist circumference[tiab] OR hip circumference[tiab] OR waist hip ratio*[tiab]

#6 recreational activit*[tiab] OR household activit*[tiab] OR occupational activit*[tiab] OR physical activit*[tiab] OR physical inactivit*[tiab] OR exercise[tiab] OR exercising[tiab] OR energy intake[tiab] OR energy expenditure[tiab] OR energy balance[tiab] OR energy density[tiab]

#7 body composition[MeSH Terms] OR body constitution[MeSH Terms] OR growth[MeSH Terms] OR anthropometry[MeSH Terms] OR physical fitness[MeSH Terms] OR exertion[MeSH Terms] OR physical endurance[MeSH Terms] or walking[MeSH Terms]

#8 pesticides[MeSH Terms] OR fertilizers[MeSH Terms] OR "veterinary drugs"[MeSH Terms]

#9 supplements[tiab] OR supplement[tiab] OR vitamin*[tiab] OR retinol[tiab] OR carotenoid*[tiab] OR tocopherol[tiab] OR folate*[tiab] OR folic acid[tiab] OR methionine[tiab] OR riboflavin[tiab] OR thiamine[tiab] OR niacin[tiab] OR pyridoxine[tiab] OR cobalamin[tiab] OR mineral*[tiab] OR sodium[tiab] OR iron[tiab] OR calcium[tiab] OR selenium[tiab] OR iodine[tiab] OR magnesium[tiab] OR potassium[tiab] OR zinc[tiab] OR copper[tiab] OR phosphorus[tiab] OR manganese[tiab] OR chromium[tiab] OR phytochemical[tiab] OR allium[tiab] OR isothiocyanate*[tiab] OR glucosinolate*[tiab] OR indoles[tiab] OR polyphenol*[tiab] OR phytoestrogen*[tiab] OR genistein[tiab] OR saponin*[tiab] OR coumarin*[tiab]

#10 vitamins[MeSH Terms]

#11 salt[tiab] OR salting[tiab] OR salted[tiab] OR fibre[tiab] OR fibre[tiab] OR polysaccharide*[tiab] OR starch[tiab] OR starchy[tiab] OR carbohydrate*[tiab] OR lipid*[tiab] OR linoleic acid*[tiab] OR sterols[tiab] OR stanols[tiab] OR sugar*[tiab] OR sweetener*[tiab] OR saccharin*[tiab] OR aspartame[tiab] OR acesulfame[tiab] OR cyclamates[tiab] OR maltose[tiab] OR mannitol[tiab] OR sorbitol[tiab] OR sucrose[tiab] OR xylitol[tiab] OR

cholesterol[tiab] OR diet*protein*[tiab] OR hydrogenated dietary oils[tiab] OR hydrogenated lard[tiab] OR hydrogenated oils[tiab]

#12 dietary carbohydrates[MeSH Terms] OR dietary proteins[MeSH Terms] OR sweetening agents[MeSH Terms]

#13 cooking[tiab] OR cooked[tiab] OR grill[tiab] OR grilled[tiab] OR fried[tiab] OR fry[tiab] OR roast[tiab] OR bake[tiab] OR baked[tiab] OR stewing[tiab] OR stewed[tiab] OR casserol*[tiab] OR broil[tiab] OR broiled[tiab] OR boiled[tiab] OR microwave[tiab] OR microwaved[tiab] OR re-heating[tiab] OR reheating[tiab] OR heating[tiab] OR re-heated[tiab] OR heated[tiab] OR poach[tiab] OR poached[tiab] OR steamed[tiab] OR barbecue*[tiab] OR chargrill*[tiab] OR heterocyclic amines[tiab] OR polycyclic aromatic hydrocarbons[tiab]

#14 cookery[MeSH Terms]

#15 mycotoxin*[tiab] OR aflatoxin*[tiab] OR pickled[tiab] OR bottled[tiab] OR bottling[tiab] OR canned[tiab] OR canning[tiab] OR vacuum pack*[tiab] OR refrigerate*[tiab] OR refrigeration[tiab] OR cured[tiab] OR smoked[tiab] OR preserved[tiab] OR preservatives[tiab] OR nitrosamine[tiab] OR hydrogenation[tiab] OR fortified[tiab] OR additive*[tiab] OR colouring*[tiab] OR coloring*[tiab] OR flavouring*[tiab] OR flavoring*[tiab] OR nitrates[tiab] OR nitrites[tiab] OR solvent[tiab] OR solvents[tiab] OR ferment*[tiab] OR processed[tiab] OR antioxidant*[tiab] OR genetic modif*[tiab] OR genetically modif*[tiab] OR vinyl chloride[tiab] OR packaging[tiab] OR labelling[tiab] OR phthalates[tiab]

#16 food preservation[MeSH Terms]

#17 diet therapy[MeSH Terms] OR nutrition[MeSH Terms] OR Food Habits[MeSH Terms] OR Micronutrients[MeSH Terms]

#18 pesticide*[tiab] OR herbicide*[tiab] OR DDT[tiab] OR fertiliser*[tiab] OR fertilizer*[tiab] OR organic[tiab] OR contaminants[tiab] OR contaminate*[tiab] OR veterinary drug*[tiab] OR polychlorinated dibenzofuran*[tiab] OR PCDF*[tiab] OR polychlorinated dibenzodioxin*[tiab] OR PCDD*[tiab] OR polychlorinated biphenyl*[tiab] OR PCB*[tiab] OR cadmium[tiab] OR arsenic[tiab] OR chlorinated hydrocarbon*[tiab] OR microbial contamination*[tiab]

#19 fluid intake[tiab] OR water[tiab] OR drinks[tiab] OR drinking[tiab] OR tea[tiab] OR coffee[tiab] OR caffeine[tiab] OR juice[tiab] OR beer[tiab] OR spirits[tiab] OR liquor[tiab] OR wine[tiab] OR alcohol[tiab] OR alcoholic[tiab] OR beverage*[tiab] OR ethanol[tiab] OR yerba mate[tiab] OR ilex paraguariensis[tiab]

#20 food*[tiab] OR cereal*[tiab] OR grain*[tiab] OR granary[tiab] OR wholegrain[tiab] OR wholewheat[tiab] OR roots[tiab] OR plantain*[tiab] OR tuber[tiab] OR tubers[tiab] OR vegetable*[tiab] OR fruit*[tiab] OR pulses[tiab] OR beans[tiab] OR lentils[tiab] OR chickpeas[tiab] OR legume*[tiab] OR soy[tiab] OR soya[tiab] OR nut[tiab] OR nuts[tiab] OR peanut*[tiab] OR groundnut*[tiab] OR seeds[tiab] OR meat[tiab] OR beef[tiab] OR pork[tiab] OR lamb[tiab] OR poultry[tiab] OR chicken[tiab] OR turkey[tiab] OR duck[tiab] OR fish[tiab] OR fat[tiab] OR fats[tiab] OR fatty[tiab] OR egg[tiab] OR eggs[tiab] OR bread[tiab] OR oils[tiab] OR shellfish[tiab] OR seafood[tiab] OR sugar[tiab] OR syrup[tiab] OR dairy[tiab] OR milk[tiab] OR herbs[tiab] OR spices[tiab] OR chilli[tiab] OR chillis[tiab] OR pepper*[tiab] OR condiments[tiab] OR Potato*[tiab] OR Cabbage*[tiab] OR Brassica[tiab] OR Cruciferous[tiab] OR Radish[tiab] OR Carrot*[tiab] OR Lettuce*[tiab] OR Spinach[tiab] OR Onion*[tiab] OR Tomato*[tiab] OR Soybean[tiab]

#21 food and beverages[MeSH Terms]

#22 diet[tiab] OR diets[tiab] OR dietetic[tiab] OR dietary[tiab] OR eating[tiab] OR intake[tiab] OR nutrient*[tiab] OR nutrition[tiab] OR vegetarian*[tiab] OR vegan*[tiab] OR "seventh day adventist"[tiab] OR macrobiotic[tiab] OR breastfeed*[tiab] OR breast feed*[tiab] OR breastfed[tiab] OR breast fed[tiab] OR breastmilk[tiab] OR breast milk[tiab] OR Lactose[tiab] OR Galactose[tiab] OR Cheese[tiab] OR Sausage[tiab] OR Ham[tiab]

#23 diet therapy[MeSH Terms] OR nutrition[MeSH Terms]

#24 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23

Combining searches on breast cancer (a) and searches on all studies relating to food, nutrition and physical activity (b):

#4 AND **#24**

Appendix 3 Exposure codes

1 Patterns of diet

1.1 Regionally defined diets

*1.1.1 Mediterranean diet

Include all regionally defined diets, evident in the literature. These are likely to include Mediterranean, Mesoamerican, oriental, including Japanese and Chinese, and "western type".

1.2 Socio-economically defined diets

To include diets of low-income, middle-income and high-income countries (presented, when available in this order). Rich and poor populations within low-income, middle-income and high-income countries should also be considered. This section should also include the concept of poverty diets (monotonous diets consumed by impoverished populations in the economically-developing world mostly made up of one starchy staple, and may be lacking in micronutrients).

1.3 Culturally defined diets

To include dietary patterns such as vegetarianism, vegan diets, macrobiotic diets and diets of Seventh-day Adventists.

1.4 Individual level dietary patterns

To include work on factor and cluster analysis, and various scores and indexes (e.g. diet diversity indexes) that do not fit into the headings above.

1.5 Other dietary patterns

Include under this heading any other dietary patterns present in the literature, that are not regionally, socio-economically, culturally or individually defined.

1.6 Breastfeeding

1.6.1 Mother

Include here also age at first lactation, duration of breastfeeding, number of children breast-fed

1.6.2 Child

Results concerning the effects of breastfeeding on the development of cancer should be disaggregated into effects on the mother and effects on the child. Wherever possible detailed information on duration of total and exclusive breastfeeding, and of complementary feeding should be included.

1.7 Other issues

For example results related to diet diversity, meal frequency, frequency of snacking, dessert-eating and breakfast-eating should be reported here. Eating out of home should be reported here.

2 Foods

*2.0.1 Plant foods

2.1 Starchy foods

2.1.1 Cereals (grains)

* 2.1.1.0.1 Rice, pasta, noodles

* 2.1.1.0.2 Bread

* 2.1.1.0.3 Cereal

** Report under this subheading the cereals when it is not specified if they are wholegrain or refined cereals (e.g. fortified cereals)*

2.1.1.1 Wholegrain cereals and cereal products

* 2.1.1.1.1 Wholegrain rice, pasta, noodles

* 2.1.1.1.2 Wholegrain bread

* 2.1.1.1.3 Wholegrain cereal

2.1.1.2 Refined cereals and cereal products

* 2.1.1.2.1 Refined rice, pasta, noodles

* 2.1.1.2.2 Refined bread

* 2.1.1.2.3 Refined cereal

2.1.2 Starchy roots, tubers and plantains

* 2.1.2.1 Potatoes

2.1.3 Other starchy foods

**Report polenta under this heading*

2.2 Fruit and (non-starchy) vegetables

Results for "fruit and vegetables" and "fruits, vegetables and fruit juices" should be reported here. If the definition of vegetables used here is different from that used in the first report, this should be highlighted.

2.2.1 Non-starchy vegetables

This heading should be used to report total non-starchy vegetables. If results about specific vegetables are reported they should be recorded under one of the sub-headings below or if not covered, they should be recorded under '2.2.1.5 other'.

2.2.1.1 Non-starchy root vegetables and tubers

*2.2.1.1.1 Carrots

2.2.1.2 Cruciferous vegetables
2.2.1.3 Allium vegetables
2.2.1.4 Green leafy vegetables (not including cruciferous vegetables)
2.2.1.5 Other non-starchy vegetables

*2.2.1.5.13 Tomatoes
*2.2.1.5.1 Fresh beans (e.g. string beans, French beans) and peas

Other non-starchy vegetables' should include foods that are botanically fruits but are eaten as vegetables, e.g. courgettes. In addition vegetables such as French beans that do not fit into the other categories, above.

If there is another sub-category of vegetables that does not easily fit into a category above eg salted root vegetables (ie you do not know if it is starchy or not) then report under 2.2.1.5. and note the precise definition used by the study. If in doubt, enter the exposure more than once in this way.

2.2.1.6 Raw vegetables

This section should include any vegetables specified as eaten raw. Results concerning specific groups and type of raw vegetable should be reported twice i.e. also under the relevant headings 2.2.1.1 –2.2.1.5.

2.2.2 Fruits

*2.2.2.0.1 Fruit, dried

*2.2.2.0.2 Fruit, canned

*2.2.2.0.3 Fruit, cooked

2.2.2.1 Citrus fruit

2.2.2.1.1 Oranges
2.2.2.1.2 Other citrus fruits (e.g. grapefruits)

2.2.2.2 Other fruits

*2.2.2.2.1 Bananas

*2.2.2.2.4 Melon

*2.2.2.2.5 Papaya

*2.2.2.2.7 Blueberries, strawberries and other berries

*2.2.2.2.8 Apples, pears

*2.2.2.2.10 Peaches, apricots, plums

*2.2.2.2.11 Grapes

If results are available that consider other groups of fruit or a particular fruit please report under 'other', specifying the grouping/fruit used in the literature.

2.3 Pulses (legumes)

*2.3.1 Soya, soya products

*2.3.1.1 Miso, soya paste soup

*2.3.1.2 Soya juice

*2.3.1.4 Soya milk

*2.3.1.5 Tofu

*2.3.2 Dried beans, chickpeas, lentiles

*2.3.4 Peanuts, peanut products

Where results are available for a specific pulse/legume, please report under a separate heading.

2.4 Nuts and Seeds

To include all tree nuts and seeds, but not peanuts (groundnuts). Where results are available for a specific nut/seed, e.g. brazil nuts, please report under a separate heading.

2.5 Meat, poultry, fish and eggs

Wherever possible please differentiate between farmed and wild meat, poultry and fish.

2.5.1 Meat

This heading refers only to red meat: essentially beef, lamb, pork from farmed domesticated animals either fresh or frozen, or dried without any other form of preservation. It does not refer to poultry or fish.

Where there are data for offal (organs and other non-flesh parts of meat) and also when there are data for wild and non-domesticated animals, please show these separately under this general heading as a subcategory.

2.5.1.1 Fresh Meat
2.5.1.2 Processed meat

*2.5.1.2.1 Ham

*2.5.1.2.1.7 Burgers

*2.5.1.2.8 Bacon

*2.5.1.2.9 Hot dogs

*2.5.1.2.10 Sausages

Repeat results concerning processed meat here and under the relevant section under 4. Food Production and Processing. Please record the definition of 'processed meat' used by each study.

2.5.1.3 Red meat

*2.5.1.3.1 Beef

*2.5.1.3.2 Lamb

*2.5.1.3.3 Pork

*2.5.1.3.6 Horse, rabbit, wild meat (game)

Where results are available for a particular type of meat, e.g. beef, pork or lamb, please report under a separate heading.

Show any data on wild meat (game) under this heading as a separate sub-category.

2.5.1.4 Poultry

Show any data on wild birds under this heading as a separate sub-category.

*2.5.1.5 Offals, offal products (organ meats)

2.5.2 Fish

*2.5.2.3 Fish, processed (dried, salted, smoked)

*2.5.2.5 Fatty Fish

*2.5.2.7 Dried Fish

*2.5.2.9 White fish, lean fish

2.5.3 Shellfish and other seafood

2.5.4 Eggs

2.6 Fats, oils and sugars

2.6.1 Animal fats

*2.6.1.1 Butter
*2.6.1.2 Lard
*2.6.1.3 Gravy
*2.6.1.4 Fish oil

2.6.2 Plant oils
2.6.3 Hydrogenated fats and oils

*2.6.3.1 Margarine

Results concerning hydrogenated fats and oils should be reported twice, here and under 4.3.2 Hydrogenation

2.6.4 Sugars

This heading refers to added (extrinsic) sugars and syrups as a food, that is refined sugars, such as table sugar, or sugar used in bakery products.

2.7 Milk and dairy products

Results concerning milk should be reported twice, here and under 3.3 Milk

*2.7.1 Milk, fresh milk, dried milk

*2.7.1.1 Whole milk, full-fat milks

*2.7.1.2 Semi skimmed milk, skimmed milk, low fat milk, 2% Milk

*2.7.2 Cheese

*2.7.2.1 Cottage cheese

*2.7.2.2 Cheese, low fat

*2.7.3 Yoghurt, buttermilk, sour milk, fermented milk drinks

*2.7.3.1 Fermented whole milk

*2.7.3.2 Fermented skimmed milk

*2.7.7 Ice cream

2.8 Herbs, spices, condiments

*2.8.1 Ginseng

*2.8.2 Chili pepper, green chili pepper, red chili pepper

2.9 Composite foods

Eg, snacks, crisps, desserts, pizza. Also report any mixed food exposures here ie if an exposure is reported as a combination of 2 or more foods that cross categories (eg bacon and eggs). Label each mixed food exposure.

*2.9.1 Cakes, biscuits and pastry

*2.9.2 Cookies

*2.9.3 Confectionery

*2.9.4 Soups

*2.9.5 Pizza

*2.9.6 Chocolate, candy bars

*2.9.7 Snacks

3 Beverages

3.1 Total fluid intake

3.2 Water

3.3 Milk

For results concerning milk please report twice, here and under 2.7 Milk and Dairy Products.

3.4 Soft drinks

Soft drinks that are both carbonated and sugary should be reported under this general heading. Drinks that contain artificial sweeteners should be reported separately and labelled as such.

3.4.1 Sugary (not carbonated)
3.4.2 Carbonated (not sugary)

The precise definition used by the studies should be highlighted, as definitions used for various soft drinks vary greatly.

*3.5 Fruit and vegetable juices

*3.5.1 Citrus fruit juice

*3.5.2 Fruit juice

*3.5.3 Vegetable juice

*3.5.4 Tomato juice

3.6 Hot drinks

3.6.1 Coffee
3.6.2 Tea

Report herbal tea as a sub-category under tea.

3.6.2.1 Black tea
3.6.2.2 Green tea
3.6.3 Maté
3.6.4 Other hot drinks

3.7 Alcoholic drinks

3.7.1 Total

3.7.1.1 Beers
3.7.1.2 Wines
3.7.1.3 Spirits
3.7.1.4 Other alcoholic drinks

4 Food production, preservation, processing and preparation

4.1 Production

4.1.1 Traditional methods (*to include 'organic')*
4.1.2 Chemical contaminants

Only results based on human evidence should be reported here (see instructions for dealing with mechanistic studies). Please be comprehensive and cover the exposures listed below:

4.1.2.1 Pesticides
4.1.2.2 DDT

4.1.2.3 Herbicides
4.1.2.4 Fertilisers
4.1.2.5 Veterinary drugs
4.1.2.6 Other chemicals

4.1.2.6.1 Polychlorinated dibenzofurans (PCDFs)
4.1.2.6.2 Polychlorinated dibenzodioxins (PCDDs)
4.1.2.6.3 Polychlorinated biphenyls (PCBs)

4.1.2.7 Heavy metals

4.1.2.7.1 Cadmium
4.1.2.7.2 Arsenic

4.1.2.8 Waterborne residues

4.1.2.8.1 Chlorinated hydrocarbons

4.1.2.9 Other contaminants

Please also report any results that cover the cumulative effect of low doses of contaminants in this section.

4.2 Preservation

4.2.1 Drying

4.2.2 Storage

4.2.2.1 Mycotoxins
4.2.2.1.1 Aflatoxins
4.2.2.1.2 Others

4.2.3 Bottling, canning, vacuum packing
4.2.4 Refrigeration
4.2.5 Salt, salting

4.2.5.1 Salt
4.2.5.2 Salting
4.2.5.3 Salted foods

4.2.5.3.1 Salted animal food
4.2.5.3.2 Salted plant food

4.2.6 Pickling
4.2.7 Curing and smoking

4.2.7.1 Cured foods

4.2.7.1.1 Cured meats

4.2.7.1.2 Smoked foods

For some cancers e.g. colon, rectum, stomach and pancreas, it may be important to report results about specific cured foods, cured meats and smoked meats. N-*nitrososamines should also be covered here.*

4.3 Processing

4.3.1 Refining

Results concerning refined cereals and cereal products should be reported twice, here and under 2.1.1.2 refined cereals and cereal products.

4.3.2 Hydrogenation

Results concerning hydrogenated fats and oils should be reported twice, here and under 2.6.3 Hydrogenated fats and oils

4.3.3 Fermenting
4.3.4 Compositional manipulation

4.3.4.1 Fortification
4.3.4.2 Genetic modification
4.3.4.3 Other methods

4.3.5 Food additives

4.3.5.1 Flavours

Report results for monosodium glutamate as a separate category under 4.3.5.1 Flavours.

4.3.5.2 Sweeteners (non-caloric)
4.3.5.3 Colours
4.3.5.4 Preservatives

4.3.5.4.1 Nitrites and nitrates

4.3.5.5 Solvents
4.3.5.6 Fat substitutes
4.3.5.7 Other food additives

Please also report any results that cover the cumulative effect of low doses of additives.

Please also report any results that cover synthetic antioxidants

4.3.6 Packaging

4.3.6.1 Vinyl chloride
4.3.6.2 Phthalates

4.4 Preparation

4.4.1 Fresh food

4.4.1.1 Raw

Report results regarding all raw food other than fruit and vegetables here. There is a separate heading for raw fruit and vegetables (2.2.1.6).

4.4.1.2 Juiced

4.4.2 Cooked food

4.4.2.1 Steaming, boiling, poaching
4.4.2.2 Stewing, casseroling
4.4.2.3 Baking, roasting
4.4.2.4 Microwaving
4.4.2.5 Frying
4.4.2.6 Grilling (broiling) and barbecuing
4.4.2.7 Heating, re-heating

Some studies may have reported methods of cooking in terms of temperature or cooking medium, and also some studies may have indicated whether the food was cooked in a direct or indirect flame. When this information is available, it should be included in the SLR report.

Results linked to mechanisms e.g. heterocyclic amines, acrylamides and polycyclic aromatic hydrocarbons should also be reported here. There may also be some literature on burned food that should be reported in this section.

5 Dietary constituents

Food constituents' relationship to outcome needs to be considered in relation to dose and form including use in fortified foods, food supplements, nutrient supplements and specially formulated foods. Where relevant and possible these should be disaggregated.

5.1 Carbohydrate

5.1.1 Total carbohydrate
5.1.2 Non-starch polysaccharides/dietary fibre

5.1.2.1 Cereal fibre
5.1.2.2 Vegetable fibre
5.1.2.3 Fruit fibre

5.1.3 Starch

5.1.3.1 Resistant starch

5.1.4 Sugars
*5.1.5 Glycemic index, glycemic load

This heading refers to intrinsic sugars that are naturally incorporated into the cellular structure of foods, and also extrinsic sugars not incorporated into the cellular structure of foods. Results for intrinsic and extrinsic sugars should be presented separately. Count honey and sugars in fruit juices as extrinsic. They can be natural and unprocessed, such as honey, or refined such as table sugar. Any results related to specific sugars e.g. fructose should be reported here.

5.2 Lipids

5.2.1 Total fat
5.2.2 Saturated fatty acids
5.2.3 Monounsaturated fatty acids
5.2.4 Polyunsaturated fatty acids

5.2.4.1 n-3 fatty acids

Where available, results concerning alpha linolenic acid and long chain n-3 PUFA should be reported here, and if possible separately.

5.2.4.2 n-6 fatty acids
5.2.4.3 Conjugated linoleic acid

5.2.5 Trans fatty acids
5.2.6 Other dietary lipids, cholesterol, plant sterols and stanols.

For certain cancers, e.g. endometrium, lung, and pancreas, results concerning dietary cholesterol may be available. These results should be reported under this section.

5.3 Protein

5.3.1 Total protein
5.3.2 Plant protein
5.3.3 Animal protein

5.4 Alcohol

This section refers to ethanol the chemical. Results related to specific alcoholic drinks should be reported under 3.7 Alcoholic drinks. Past alcohol refers, for example, to intake at age 18, during adolescence, etc.

*5.4.1 Total Alcohol (as ethanol)

*5.4.1.1Alcohol (as ethanol) from beer
*5.4.1.2Alcohol (as ethanol) from wine
*5.4.1.3Alcohol (as ethanol) from spirits
*5.4.1.4Alcohol (as ethanol) from other alcoholic drinks
* 5.4.1.5 Total alcohol (as ethanol), lifetime exposure

* 5.4.1.6 Total alcohol (as ethanol), past

5.5 Vitamins

*5.5.0 Vitamin supplements
*5.5.0.1 Vitamin and mineral supplements
*5.5.0.2 Vitamin B supplement

5.5.1 Vitamin A

5.5.1.1 Retinol
5.5.1.2 Provitamin A carotenoids

5.5.2 Non-provitamin A carotenoids

Record total carotenoids under 5.5.2 as a separate category marked Total Carotenoids.

5.5.3 Folates and associated compounds

*5.5.3.1 Total folate

*5.5.3.2 Dietary folate

*5.5.3.3 Folate from supplements

Examples of the associated compounds are lipotropes, methionine and other methyl donors.

5.5.4 Riboflavin
5.5.5 Thiamin (vitamin B1)
5.5.6 Niacin
5.5.7 Pyridoxine (vitamin B6)
5.5.8 Cobalamin (vitamin B12)
5.5.9 Vitamin C
5.5.10 Vitamin D (and calcium)
5.5.11 Vitamin E
5.5.12 Vitamin K
5.5.13 Other

If results are available concerning any other vitamins not listed here, then these should be reported at the end of this section. In addition, where information is available concerning multiple vitamin deficiencies, these should be reported at the end of this section under 'other'.

5.6 Minerals

5.6.1 Sodium
5.6.2 Iron
5.6.3 Calcium (and Vitamin D)
5.6.4 Selenium
5.6.5 Iodine
5.6.6 Other

Results are likely to be available on other minerals e.g. magnesium, potassium, zinc, copper, phosphorus, manganese and chromium for certain cancers. These should be reported at the end of this section when appropriate under 'other'.

5.7 Phytochemicals

5.7.1 Allium compounds
5.7.2 Isothiocyanates
5.7.3 Glucosinolates and indoles
5.7.4 Polyphenols
5.7.5 Phytoestrogens eg genistein
5.7.6 Caffeine
5.7.7 Other

Where available report results relating to other phytochemicals such as saponins and coumarins. Results concerning any other bioactive compounds, which are not phytochemicals should be reported under the separate heading 'other bioactive compounds'. Eg flavonoids, isoflavonoids, glycoalkaloids, cyanogens, oligosaccharides and anthocyanins should be reported separately under this heading.

5.8 Other bioactive compounds

6 Physical activity

6.1 Total physical activity (overall summary measures)

6.1.1 Type of activity

6.1.1.1 Occupational
6.1.1.2 Recreational
6.1.1.3 Household
6.1.1.4 Transportation

6.1.2 Frequency of physical activity

*6.1.2.1 Frequency of occupational physical activity

*6.1.2.2 Frequency of recreational physical activity

6.1.3 Intensity of physical activity

*6.1.3.1 Intensity of occupational physical activity

*6.1.3.2 Intensity of recreational physical activity

6.1.4 Duration of physical activity

*6.1.4.1Duration of occupational physical activity
*6.1.4.2Duration of recreational physical activity

6.2 Physical inactivity
6.3 Surrogate markers for physical activity e.g. occupation

7 Energy balance

7.1 Energy intake

*7.1.0.1 Energy from fats

*7.1.0.2 Energy from protein

*7.1.0.3 Energy from carbohydrates

*7.1.0.4 Energy from alcohol

*7.1.0.5 Energy from all other sources

7.1.1 Energy density of diet

7.2 Energy expenditure

8 Anthropometry

8.1 Markers of body composition

8.1.1 BMI
8.1.2 Other weight adjusted for height measures
8.1.3 Weight
8.1.4 Skinfold measurements
8.1.5 Other (e.g. DEXA, bio- impedance, etc)
8.1.6 Change in body composition (including weight gain)

8.2 Markers of distribution of fat

8.2.1 Waist circumference
8.2.2 Hips circumference
8.2.3 Waist to hip ratio
8.2.4 Skinfolds ratio
8.2.5 Other e.g. CT, ultrasound

8.3 Skeletal size

8.3.1 Height (and proxy measures)
8.3.2 Other (e.g. leg length)

8.4 Growth in fetal life, infancy or childhood

8.4.1 Birthweight,
8.4.2 Weight at one year