World Cancer Research Fund

American Institute for Cancer Research

Continuous Update Project

Keeping the science current

Pancreatic Cancer 2012 Report

Food, Nutrition, Physical Activity, and the Prevention of Pancreatic Cancer

Continuous Update Project

CUP

WORLD CANCER RESEARCH FUND GLOBAL NETWORK

OUR VISION

The World Cancer Research Fund global network helps people make choices that reduce their chances of developing cancer.

OUR HERITAGE

We were the first cancer charity:

- To create awareness of the relationship between diet and cancer risk
- To focus funding on research into diet and cancer prevention
- To consolidate and interpret global research to create a practical message on cancer prevention

OUR MISSION

Today the World Cancer Research Fund global network continues:

- Funding research on the relationship of nutrition, physical activity and weight management to cancer risk
- Interpreting the accumulated scientific literature in the field
- Educating people about choices they can make to reduce their chances of developing cancer

THE WCRF GLOBAL NETWORK

The World Cancer Research Fund (WCRF) global network comprises WCRF International, which operates as the umbrella association for the global network's four charitable organisations: The American Institute for Cancer Research (AICR); World Cancer Research Fund (WCRF UK); World Cancer Research Fund Netherlands (WCRF NL); World Cancer Research Fund Hong Kong (WCRF HK).

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This report provides an updated version of section 7.6 Pancreas from the Second Expert Report: *Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective*. This section has been updated based on Panel discussions in June 2012 on the Continuous Update Project Pancreatic Cancer Systematic Literature review (SLR), prepared by the research team at Imperial College London, UK in 2011 (see acknowledgements). The SLR included research papers published until September 2011. For further details please see the full 2011 Continuous Update Project Pancreatic Cancer SLR (www.dietandcancerreport.org).

To keep the evidence current and updated into the future, WCRF/AICR is undertaking the Continuous Update Project (CUP), in collaboration with Imperial College London. The project is an ongoing review of food, nutrition, physical activity and body fatness and cancer research. The CUP builds upon the foundations of the WCRF/AICR Second Expert Report (SER) [1].

The Continuous Update Project provides a comprehensive and up to date depiction of scientific developments on the relationship between food, nutrition, physical activity, body fatness and cancer. It also provides an impartial analysis and interpretation of the data as a basis for reviewing and where necessary revising WCRF/AICR's Recommendations for Cancer Prevention based on the Second Expert Report [1].

In the same way that the Second Expert Report was informed by a process of SLRs, the Continuous Update Project systematically reviews the science. The updates to the SLRs are being conducted by a team of scientists at Imperial College London in liaison with the original SLR centres. WCRF/AICR has convened a panel of experts (the Continuous Update Project Panel (see acknowledgements)) consisting of leading scientists in the field of food, nutrition, physical activity, body fatness and cancer, who consider the updated evidence from systematic literature reviews and draw conclusions.

Once all the cancers have been updated in the CUP database in 2015, the Panel will formally review the WCRF/AICR Recommendations for Cancer Prevention, and any changes will be communicated through the WCRF global network science, education and communications programmes in 2017. From 2015 the CUP database will be continuously updated with new evidence for each cancer. Prior to 2017 the Panel will revise one or more Recommendations only if they agree there is strong evidence for a change.

Instead of periodically repeating the extensive task of conducting multiple systematic literature reviews that cover a long period of time, the continuous review process is based on a live system of scientific data. The database is updated on an ongoing basis from which, at any point in time, the most current review of scientific data (including meta-analyses where appropriate) can be performed.

Periodically WCRF/AICR will produce updated SLRs, peer reviewed by scientists, which will outline the scientific developments in the field of food, nutrition, physical activity, body weight and cancer.

Contents

Abbreviations

CUP	Continuous Update Project
SER	Second Expert Report '*Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*'
SLR	Systematic literature review

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND PANCREATIC CANCER 2012

	DECREASES RISK	INCREASES RISK
Convincing		**Body fatness**[1]
Probable		**Greater childhood growth**[2]
Limited - suggestive		Red meat[3] Processed meat[4] Alcoholic drinks (heavier drinking)[5] Foods and beverages containing fructose[6] Foods containing saturated fatty acids
Limited - no conclusion	Physical activity; fruits; vegetables; folate; fish; eggs; tea; soft drinks; carbohydrates; sucrose; glycaemic index; glycaemic load; total fat; monounsaturated fat; polyunsaturated fats; dietary cholesterol; vitamin C; and multivitamin/mineral supplements	
Substantial effect on risk unlikely	Coffee	

1 The Panel interpreted BMI, measures of abdominal girth, and adult weight gain as indicating interrelated aspects of body fatness as well as fat distribution
2 Childhood growth incorporates both linear growth and acquisition of both lean and fat tissue in childhood and adolescence (marked by adult attained height and BMI at aged ~20 years)
3 The term 'red meat' refers to beef, pork, lamb and goat from domesticated animals
4 The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives
5 Includes total alcoholic drinks and alcohol as ethanol. Limited to those drinking more than about three drinks/day (one drink contains about 10-15g ethanol)
6 Includes both foods naturally containing the constituent and foods which have the constituent added

Overall, the Panel notes the strength of the evidence that body fatness and greater childhood growth are a cause of pancreatic cancer.

The Panel judges as follows:
The evidence that body fatness (which the Panel interprets to be reflected by body mass index (BMI), measures of abdominal girth and adult weight gain) is a cause of pancreatic cancer is convincing. Greater childhood growth, which reflects factors that lead to greater linear growth and acquisition of both lean and fat tissue in childhood and adolescence (marked by adult attained height and BMI at aged ~20years) is probably a cause of pancreatic cancer. It is unlikely that coffee has any substantial effect on the risk of this cancer.

The evidence that red meat, processed meat, alcoholic drinks (heavier drinking; more than about 3 drinks/day), foods and beverages containing fructose, and foods containing saturated fatty acids, are causes of pancreatic cancer is limited. Evidence for physical activity, fruits and foods containing folate is less consistent and no conclusion could be drawn.

1. Trends, incidence, and survival

The pancreas is an elongated gland located behind the stomach. It contains two types of tissue, exocrine and endocrine. The exocrine pancreas produces digestive enzymes that are secreted into the small intestine. Cells in the endocrine pancreas produce hormones including insulin and glucagon, which influence glucose metabolism.

Cancer of the pancreas is the thirteenth most common type of cancer worldwide. About 280 000 cases were recorded in 2008, accounting for around 2 per cent of cancers overall. The incidence is somewhat higher in men than in women (144,859 and 133,825 cases in 2008 respectively). This cancer is almost always fatal and is the eighth most common cause of cancer death, accounting for somewhat over 3 per cent of all cancer deaths [2]. See Box 1.

Age-adjusted rates of pancreatic cancer have been generally stable since the 1970s, following an approximate threefold rise over the preceding 50 years in the countries for which data are available [3, 4].

Pancreatic cancer is mainly a disease of high-income countries, where overall rates are nearly three times higher than in middle-and low-income countries [2]. Around the world, age-adjusted incidence rates range from 10–15 per 100 000 people in parts of northern, central, and eastern Europe to less than 1 per 100 000 in areas of Africa and Asia, although rates are high in some of these areas, for example, Japan and Korea. In the USA, rates are higher among African-American people than in white people [5]. The risk of pancreatic cancer increases with age, with most diagnoses made in people between the ages of 60 and 80 [2].

The early stages of this cancer do not usually produce symptoms, so the disease is generally advanced when it is diagnosed. The 5-year prevalence of women globally living with pancreatic cancer is 3.5 per 100,000[1] [2].

Over 95 per cent of pancreatic cancers are adenocarcinomas of the exocrine pancreas, the type included in the CUP analyses.

Box 1 Cancer incidence and survival

The cancer incidence rates and figures given here are those reported by cancer registries, now established in many countries. These registries record cases of cancer that have been diagnosed. However, many cases of cancer are not identified or recorded: some countries do not have cancer registries; regions of some countries have few or no records; records in countries suffering war or other disruption are bound to be incomplete; and some people with cancer do not consult a physician. Altogether, this means that the actual incidence of cancer is higher than the figures given here. The cancer survival rates given here and elsewhere are usually overall global averages. Survival rates are generally higher in high-income countries and other parts of the world where there are established services for screening and early detection of cancer and well established treatment facilities. Survival also is often a function of the stage at which a cancer is detected and diagnosed. The symptoms of some internal cancers are often evident only at a late stage, which accounts for relatively low survival rates. In this context, 'survival' means that the person with diagnosed cancer has not died 5 years after diagnosis.

[1] 5-year prevalence is estimated from incidence estimates and observed survival by cancer and age group.

2. Pathogenesis

The ductal cells in the head of the pancreas are exposed to pancreatic secretions, as well as bile, and environmental carcinogens can reach these cells through these fluids or the blood, through which endogenous factors may also act (see chapter 7.7 in the Second Expert Report).

The pancreas is relatively inaccessible to routine medical examination, so the progression of this cancer through precursor lesions is not well understood. However, inflammation is implicated in this process through chronic pancreatitis, which is a risk factor for pancreatic cancer. The role of infection with *H pylori* (see box 7.5.1, Second Expert Report) is the subject of ongoing research [6]. Conditions characterised by high insulin secretion, such as insulin resistance and type 2 diabetes, are associated with the risk of this cancer [7].

More than 90 per cent of pancreatic cancer cases are sporadic (due to spontaneous rather than inherited mutations), although a family history increases risk, particularly where more than one family member is involved [6]. Around 75–90 per cent of pancreatic cancer cases involve a point mutation in the K-ras oncogene [8] (see box 2.2 in chapter 2, Second Expert Report).

3. Other established causes

(Also see chapters 2.4 and 7.1.3.1, Second Expert Report)

Tobacco use. Tobacco use is an established cause of pancreatic cancer [9] and approximately 25 per cent of cases of pancreatic cancer are attributable to tobacco smoking [10].

4. Interpretation of the evidence

4.1 General

For general considerations that may affect interpretation of the evidence, see chapters 3.3 and 3.5, and boxes 3.1, 3.2, 3.6 and 3.7 in the Second Expert Report.

'Relative risk' (RR) is used in this report to denote ratio measures of effect, including 'risk ratios', 'rate ratios', 'hazard ratios', and 'odds ratios'.

4.2 Specific

Considerations specific to cancer of the pancreas include:

Measurement. Owing to very low survival rates, both incidence and mortality can be assessed.

Confounding. High-quality studies adjust for smoking.

5. Methodology

To ensure consistency with evidence collected and analysed for the Second Expert Report, much of the methodology for the Continuous Update Project remains unchanged from that used previously. However, based upon the experience of conducting the systematic literature reviews for the Second Expert Report, some modifications to the methodology were made. The literature search was restricted to Medline and included only randomised controlled trials, cohort and case-control studies. The reference lists of all review articles identified in the search were also checked, as a result of the relatively high number of articles (30) identified in this way during the

SLR of pancreatic cancer. The search was not limited to "human studies" as it was not guaranteed that all studies on PubMed would be coded as human. The CUP Pancreatic Cancer SLR included studies published up to September 2011. Publications in foreign languages were not included.

Due to the large number of cohort studies, analysis and interpretation of case-control studies was not included in the Continuous Update Project SLR. Given that pancreatic cancer is most often diagnosed at a very advanced stage, survival rates beyond a few months are extremely low. There is, therefore, very little difference between cancer incidence and mortality rates, and study results on incidence and mortality have been presented and analysed together in the CUP SLR. If there were sufficient studies, meta-analyses and forest plots of highest versus lowest categories were prepared for pancreatic cancer incidence and mortality separately. Studies reporting mean difference as a measure of association are not included in the 2011 Continuous Update Project SLR, as relative risks estimated from the mean differences are not adjusted for possible confounders, and thus not comparable to adjusted relative risks from other studies. For more information on methodology see the full CUP Pancreatic Cancer SLR.

5.1 Mechanistic evidence

With regard to mechanisms involved in the development of pancreatic cancer, mechanistic reviews previously conducted for the SER are included in this report (more details can be found in chapters 2, 4 and 6 of the SER). These mechanisms have not been updated here, and will be updated as part of a larger review of the mechanistic evidence for the CUP (see below). Where an exposure presented in this report was not judged as 'limited-suggestive' or above previously in the SER (and therefore was no previous review of the mechanisms), a brief summary of possible mechanisms for that particular exposure is given. This includes the following exposures:

- Processed meat
- Foods containing saturated fatty acids
- Alcoholic drinks
- Foods and beverages containing fructose

Work is under way to develop a methodology for systematically reviewing the animal, human and other experimental studies, and will be used to conduct mechanistic reviews for all cancer sites (see www.dietandcancerreport.org for further information). A full review of the mechanistic evidence for pancreatic cancer will form part of this larger review.

6. Evidence and judgements

The updated search identified 79 new articles from cohort studies and randomised controlled trials, added to the 129 pancreatic cancer articles included in the SER.

The CUP Panel's conclusions will be reviewed again after 2015, when the CUP database is up to date, in preparation for the review of the 10 Recommendations for Cancer Prevention in 2017. This report includes the conclusions of the SER, with an updated description of the epidemiological evidence and revised conclusions. It also includes a brief description of potential mechanisms for each exposure.

For information on the criteria for grading the epidemiological evidence see Appendix 1 in this report. References to studies added as part of the CUP have been included in the following

sections; for details of references to other studies see the SER. Summary estimates from dose-response meta-analyses were regarded as non-significant if the 95% confidence interval included 1.0. A study reporting a summary estimate of 1.0 was considered to observe no effect.

6.1 Red meat

(Also see CUP Pancreatic Cancer SLR 2011: Section 2.5.1.3)

The CUP identified four new papers (from three cohort studies) [11-14] giving a total of 10 studies (including studies from the SER). Overall, the CUP found three of seven studies on pancreatic cancer incidence reported an increased risk for the highest intake group compared to the lowest, two of which were statistically significant. For pancreatic cancer mortality, two of three studies showed an increased risk, one of which was statistically significant.

Eight studies (three new) were included in the dose-response meta-analyses for red meat and pancreatic cancer (incidence and mortality combined). The CUP analyses were conducted per 100g/day compared to 20g/day in the SER. Overall, the analyses showed a non-significant positive association between red meat intake and pancreatic cancer risk (RR 1.19 (95% CI 0.98-1.45) with moderate heterogeneity (I^2= 52%) (see CUP 2011 Figure 25). In the SER, there was no clear association from the meta-analysis (RR 1.00 (95% CI 0.95-1.05)) and based on this meta-analysis of two cohort studies (incidence only) and review of five additional studies not included in the meta-analysis, it was concluded that the evidence suggesting an increased risk was limited.

The CUP dose-response meta-analysis showed an overall statistically significant increased risk of pancreatic cancer (incidence and mortality combined) in men, but not women (RRs 1.43 (95% CI 1.10-1.86) and 1.06 (95% CI 0.86-1.30) respectively (see CUP 2011 Figure 28). In women, most studies showed an increased risk, but these were not statistically significant.

Results from two other published meta-analysis were similar to the CUP analysis, both finding a non-significant positive association between red meat intake and pancreatic cancer risk [15, 16].

Mechanisms

Note: This is taken from Chapters 2 and 4 of the SER. An updated review of mechanisms for this exposure will form part of a larger review of mechanisms for the CUP (see 5.1 in this report).

High intake of red meat may result in more absorption of haem iron, greater oxidative stress, and potential for DNA damage [17, 18]. In addition, iron overload can also activate oxidative responsive transcription factors and inflammation in the colon [19]. Iron metabolism and transport are strictly regulated to reduce the likelihood of cells being exposed to free iron and so to oxidative damage; most iron in living tissues is bound to proteins, such as transferrin and ferritin, which prevent its involvement in free radical generation.

Red meat consumption is also associated with the formation of *N*-nitroso compounds. Some *N*-nitroso compounds are carcinogens, and are formed in foods containing added nitrates or nitrites; examples include fish and meat preserved with salting or preservatives, and smoking or drying. These carcinogens can also be generated from ingested foods containing nitrate or nitrite. *N*-nitroso compounds are also produced endogenously in the stomach and colon of people who eat large amounts of red meat [20].

When cooked at high temperatures, red meat can also contain heterocyclic amines and polycyclic aromatic hydrocarbons. Heterocyclic amines are formed when muscle meats such as beef, pork, fowl, and fish are cooked. High cooking temperatures cause amino acids and creatine (a chemical found in muscles) to react together to form these chemicals. So far, different heterocyclic amines have been identified as being formed by cooking muscle meats and which may pose a cancer risk [21, 22].

CUP Panel's conclusion:
More studies were available for the CUP analysis. Overall the evidence is not considered to have changed since the SER, and the Panel therefore concludes:

The evidence is inconsistent. The evidence suggesting that red meat is a cause of pancreatic cancer is limited.

6.2 Processed meat

(Also see CUP Pancreatic Cancer SLR 2011: Section 2.5.1.2)

The CUP identified three new papers (from two cohort studies) [12-14], giving a total of eight studies (including studies from the SER). Overall, the CUP found four of six studies on pancreatic cancer incidence reported an increased risk for the highest intake group compared to the lowest, one of which was statistically significant. For pancreatic cancer mortality, one of two studies reported a non-significant increased risk. The other reported a non-significant decreased risk.

Seven studies (two new) were included in the dose-response meta-analyses for processed meat and pancreatic cancer (incidence and mortality combined). The CUP analyses were conducted per 50g/day compared to 20g/day in the SER. Overall, the analyses showed a 17% increased risk per 50g processed meat per day, and this was statistically significant (RR 1.17 (95% CI 1.01-1.34)) (see CUP 2011 Figure 21). No heterogeneity was observed compared to high heterogeneity in the SER (I^2= 0 vs. 63%). In the SER, there was limited and inconclusive evidence for an association based on three cohort studies (incidence only) (RR 0.93 (95% CI 0.82-1.05)).

In the CUP, when stratified by sex, the effect was significant in men but not in women (RRs 1.21 (95% CI 1.01-1.45) and 1.09 (95% CI 0.69-1.73) respectively)) (see CUP 2011 Figure 23). There was no indication of publication bias and no evidence of significant heterogeneity in the analyses overall, although study results in women were inconsistent with moderate heterogeneity (I^2= 43%).

Results from the CUP analysis are consistent with that from another published meta-analysis, which also found a statistically significant increased risk per 50g/day increase in processed meat consumption [16].

Epidemiological evidence evaluating the relation of nitrate and nitrite to pancreatic cancer risk is limited and inconsistent [23-26].

Mechanisms

Note: A full review of mechanisms for this exposure will form part of a larger review of mechanisms for the CUP (see 5.1 in this report).

Human exposure to *N*-nitroso compounds through tobacco smoking is an established risk factor for pancreatic cancer [27]. Aside from tobacco smoking, humans are exposed to *N*-nitroso compounds mainly through intestinal absorption of dietary sources, which can be ingested preformed or endogenously produced. *N*-nitrosoamines form in foods containing protein that are preserved with nitrite (cured, smoked or pickled) or dried at high temperatures [27]. *N*-nitroso compounds can be further formed in the stomach from nitrite and ingested amides in foods of animal origin [28], and importantly, are α-hydroxylated to their proximate reactive forms in hepatocytes and pancreatic ductal epithelium and acini. These reach the pancreas via the bloodstream and are potent carcinogens that can induce pancreatic cancer in animal models [27].

CUP Panel's conclusion:

The evidence for processed meat and pancreatic cancer risk remains limited but is now stronger with more studies included in the CUP analysis, and no heterogeneity compared to the SER. In the SER, the Panel judged the evidence as too limited to draw a conclusion. In the CUP, a statistically significant positive association was observed and is supported by results from another published meta-analysis, which also found a significant positive association. Overall the evidence is limited, but suggests that processed meat increases risk of pancreatic cancer. The Panel therefore concludes:

The evidence is inconsistent. The evidence suggesting that processed meat is a cause of pancreatic cancer is limited.

6.3 Foods containing total fat and saturated fatty acids

(Also see CUP Pancreatic Cancer SLR 2011: Sections 5.2.1 and 5.2.2)

The CUP identified four new papers (from four cohort studies) [12, 29-31], giving a total of six studies. Overall, the CUP found four of six studies on pancreatic cancer incidence showed an increased risk of pancreatic cancer when comparing the highest versus lowest intakes of saturated fatty acids, one of which was significant. Two studies reported a non-significant decreased risk.

Five studies (four new) were included in the dose-response meta-analyses for saturated fatty acids and pancreatic cancer incidence. Overall, the CUP analysis found an 11% statistically significant increased risk of pancreatic cancer per 10g saturated fatty acids per day (RR 1.11 (95% CI 1.01-1.21)) with moderate heterogeneity observed (see CUP 2011 Figure 130). A non-significant increased risk was previously reported in the SER (RR 1.08 (95% CI 0.89-1.31) and the SER Panel judged the evidence too limited to draw a conclusion.

The CUP meta-analysis for total fat intake (including 8 studies) (see CUP 2011 Section 5.2.1) showed a marginally significant positive association (RR 1.05 (95% CI 1.00-1.12), with no evidence of heterogeneity. However, the evidence for total fat intake is limited and inconsistent, with four of seven studies reporting a non-significant decreased risk when comparing the highest intakes versus the lowest, and three reporting an increased risk (two of which were significant).

Mechanisms

Note: A full review of mechanisms for this exposure will form part of a larger review of mechanisms for the CUP (see 5.1 in this report).

The involvement of total dietary fat in pancreatic carcinogenesis through promotion of tumour formation in animal models is well established [32] and several mechanisms have been suggested to play a role. In animal models, pancreatic hypertrophy or hyperplasia can result from long-term exposure to large amounts of free fatty acids, which in turn causes the pancreas to become more vulnerable to carcinogens and lead to uncontrolled growth of abnormal cells [33].

In addition, it is suggested that increased bile acids may promote pancreatic cancer [34]. Higher intake of fat may stimulate bile acid secretion into the pancreatic duct and in turn stimulate the tumour promoter cyclooxygenase-2 (COX-2). Expression of COX-2 is greater in pancreatic cancer patients, and both conjugated and unconjugated bile acids induce COX-2 in pancreatic cancer cell lines [34].

Saturated fatty acids have been linked with insulin resistance in several randomised controlled trials, and diabetes or insulin resistance may be associated with pancreatic cancer via metabolic, immunological and hormonal alterations in the body [33].

CUP Panel's conclusion:

Overall the evidence on saturated fatty acids and pancreatic cancer risk is limited and inconsistent. However, a significant positive association was observed compared to the non-significant positive association observed in the SER. A marginally significant positive association was observed for total fat intake, although generally the evidence is limited and inconsistent. It is not clear whether total fat intake has any effect independent of the association with saturated fatty acids. The Panel therefore concludes for foods containing saturated fatty acids:

The evidence is limited and inconsistent. The evidence suggesting that intake of saturated fatty acids is a cause of pancreatic cancer is limited. It is uncertain whether total fat intake has any independent effect.

6.4 Coffee

(Also see CUP Pancreatic Cancer SLR 2011: Section 3.6.1)

The CUP identified two new papers (from two cohort studies) [35, 36], giving a total of 20 studies. Overall, the CUP found eight of 12 studies on pancreatic cancer incidence showed a decreased risk when comparing the highest versus lowest intakes of coffee (one of which was significant) and four reported an increased risk (two of which were significant). For pancreatic cancer mortality, three of five studies showed a decreased risk (one of which was significant) when comparing highest versus lowest intakes and two showed a non-significant increased risk.

A total of 13 studies (two new) were included in the dose-response meta-analyses. The CUP analysis found an overall small positive association between coffee and pancreatic cancer (incidence and mortality combined) but this was not significant (RR 1.02 (95% CI 0.95-1.09) and (see CUP 2011 Figure 53). This finding is similar to that reported in the SER (RR 1.00 (95% CI 0.94-1.07). When stratified by outcome, meta-analysis on three studies reporting on mortality showed a slight non-significant decreased risk (RR 0.99 (95% CI 0.76-1.28), but the summary

estimate for studies on incidence only was similar to the overall estimate (RR 1.03 (95% CI 0.95-1.11).

Published pooled analyses
Results from one pooled analysis have been published [37], reporting no significant association between coffee and pancreatic cancer risk. The results are presented in the table below.

Summary of pooled analyses and CUP meta-analyses – Coffee

		RR (95% CI)	I^2	No. studies	No. cases	Factors adjusted for
CUP 2011	Per 240ml/d	1.02 (0.95-1.09)	29	13	1460	
Harvard Pooling Project [37]	Per 237g/d	1.01 (0.97-1.04)	38	11	1595	Smoking status, alcohol intake, diabetes, BMI and energy intake

CUP Panel's conclusion:
Overall, the CUP result is similar to that in the SER. The evidence is strong, with more studies included in the CUP analysis. The finding is also similar to that from the Harvard Pooling Project, which also reported no significant association. The CUP Panel concludes:

There is substantial evidence which is consistent, with low heterogeneity, and which fails to show an association. It is unlikely that coffee has any substantial effect on the risk of pancreatic cancer.

6.5 Alcoholic drinks

(Also see CUP Pancreatic Cancer SLR 2011: Sections 3.7.1 and 5.4)

The evidence for total alcoholic drinks and alcohol (as ethanol) is presented in the following section, and is followed by an overall conclusion that incorporates both these exposures.

Total alcohol drinks
The CUP identified four new papers (from three cohort studies) [38-41], giving a total of nine studies (including studies from the SER). Overall, the CUP found five of six studies on pancreatic cancer incidence showed an increased risk of pancreatic cancer when comparing the highest versus lowest consumers, one of which was significant. For studies of pancreatic cancer mortality, all three studies showed an increased risk, two of which were significant.

Six studies (three new) were included in the dose-response meta-analyses for total alcoholic drinks and pancreatic cancer (incidence and mortality combined). The CUP analyses were conducted per drink/week. Overall, the CUP analyses found no clear association between total alcoholic drinks and pancreatic cancer risk (RR 1.00 (95% CI 0.99-1.01)) (see CUP 2011 Figure 64). In the SER, a marginally significant decreased risk was observed (RR 0.98 (95% CI 0.97-0.99)). In the CUP analyses, high heterogeneity was observed overall (I^2= 93 vs. 0% in the SER), most likely explained by one small study in men [42] that reported a strong positive association. There was evidence of a nonlinear association between total alcoholic drinks and pancreatic cancer risk, but this was only significant for those consuming 17.6 or more drinks per week (see CUP 2011 Figure 69 and Table 62).

In a stratified analysis by sex (for incidence and mortality combined), there was no clear association in women (RR 1.00 (95% CI 0.98-1.01)), but in men there was a marginally significant increased risk (RR 1.01 (95% CI 1.00-1.02)) (see CUP 2011 Figure 67).

A published meta-analysis [43] reported an overall significant inverse association of low to moderate alcohol intake (<3 drinks/day) and pancreatic cancer risk (RR 0.92 (95% CI: 0.86–0.97) and a significant increased association for higher levels of alcohol intake (RR 1.22 (95% CI: 1.12–1.34) compared with non-drinking. This meta-analysis included studies that reported on alcoholic drinks and on ethanol from alcoholic drinks. A pooled analysis of the PanScan project investigated ethanol from alcoholic drinks (see below).

Alcohol (as ethanol)

The CUP identified four new papers (from four cohort studies) [31, 40, 44, 45], giving a total of 10 studies (including studies from the SER). All studies reported pancreatic cancer incidence. Overall, the CUP found five of nine studies showed an increased risk of pancreatic cancer when comparing the highest versus lowest consumers, two of which were significant. Three studies reported a non-significant decreased risk. One study reported no effect.

Nine studies (four new) were included in the dose-response meta-analyses for alcohol (as ethanol) and pancreatic cancer. Overall, the CUP analyses found no clear linear association between alcohol (as ethanol) (per 10g a day) and pancreatic cancer risk (RR 1.00 (95% CI 0.99-1.01)) with no heterogeneity observed (see CUP 2011 Figure 149). This is similar to that reported in the SER (RR 1.00 (95% CI 0.98-1.02)). A summary estimate from a highest versus lowest comparison did result in a statistically significant increased risk (RR 1.30 (95% CI 1.09-1.54)). There was also evidence of a nonlinear association between alcohol (as ethanol) and pancreatic cancer risk. The risk was significant for those consuming 53.4g ethanol or more a day (see CUP 2011 Figure 153 and Table 132).

In a stratified analysis by sex, a non-significant increased risk in men and a non-significant decreased risk in women were observed (RRs 1.02 (95% CI 0.99-1.04) and 0.99 (95% CI 0.95-1.02) respectively) (see CUP 2011 Figure 152), and in a separate analysis stratified by smoking, the summary estimates were similar to the overall finding (see CUP 2011 Table 130).

Published pooled analyses

Results from two separate pooled analyses on alcohol (as ethanol) and pancreatic cancer risk have been published [46, 47]. In the PanScan [46], no overall significant association was observed between total alcohol (ethanol) intake and pancreatic cancer risk for 60g/d vs 0-5g/day, although a statistically significant increase in risk was observed among men consuming 45 or more grams of alcohol from liquor per day. Similar to the CUP finding for the highest versus lowest categories, the Harvard Pooling Project [47] found a statistically significant increased risk for 30g or more per day vs no alcohol. Only three single studies were included in all three analyses. In a CUP sensitivity analysis, adding in studies from PanScan and Harvard pooling projects, a statistically significant increased risk was observed (see CUP 2011 Figure 155). The results are presented in the following table.

Summary of pooled analyses and CUP meta-analyses– Alcohol (as ethanol)

		RR (95% CI)	I^2	No. studies	No. cases	Factors adjusted for
CUP 2011	Per 10g/d	1.00 (0.99-1.01)	0	9	3096	
CUP 2011	Highest vs lowest	1.30 (1.09-1.54)		9	3096	
CUP Sensitivity analysis	Highest vs lowest	1.29 (1.13-1.48)		25	4795	
PanScan [46]	≥60g/d vs. 0-5g/d	1.38 (0.86-2.23)		12	1530	Smoking status, diabetes, BMI, and energy intake
Harvard Pooling Project [47]	≥30g/d vs. 0g/d	1.22 (1.03-1.45)		14	2187	Smoking status, diabetes, BMI and energy intake

Mechanisms

Note: A full review of mechanisms for this exposure will form part of a larger review of mechanisms for the CUP (see 5.1 in this report).

Alcohol (ethanol) is classified as a Group 1 carcinogen [48]. It is thought that ethanol metabolites, such as acetaldehyde, might be more important carcinogens [49]. The risk of pancreatic cancer may be increased with heavy alcohol consumption via mechanisms that promote the effects of other risk factors such as tobacco smoking. Heavy alcohol consumption may also alter metabolic pathways involved in the inflammatory response and carcinogenesis, for example increased production of reactive oxygen species resulting in oxidative DNA damage, and dysregulation of proliferation and apoptosis, and there may also be other independent genetic and epigenetic effects [49, 50].

CUP Panel's conclusion:

Overall, findings are similar to that reported in the SER, with no clear linear association between alcohol and risk of pancreatic cancer. However, dose-response analyses revealed a suggestion of an increased risk in heavier drinkers (more than about 3 drinks/day). The Panel therefore concludes:

There is ample evidence, but this is inconsistent across the range of intakes. At higher levels of consumption, there is evidence of an increased risk of pancreatic cancer. There is limited evidence of a nonlinear association between alcohol and pancreatic cancer, suggesting an increased risk limited to those consuming more than about 3 drinks a day.

6.6 Foods and beverages containing fructose

(Also see CUP Pancreatic Cancer SLR 2011: Sections 5.1.4)

The CUP identified five new papers (from five cohort studies) [51-55], giving a total of seven studies (including studies from the SER). Overall, the CUP found five of seven studies on pancreatic cancer incidence showed an increased risk of pancreatic cancer when comparing the highest versus lowest intakes of fructose, two of which were significant. One study reported a non-significant decreased risk and one reported no effect.

Six studies (four new) were included in the dose-response meta-analyses for foods and beverages containing fructose and pancreatic cancer incidence. Overall, the CUP analysis found a 22% statistically significant increased risk of pancreatic cancer per 25g fructose per day (RR 1.22 (95% CI 1.08-1.37)) with no heterogeneity observed (see CUP 2011 Figure 97). No

differences were observed between men and women. No meta-analysis was conducted in the SER. Of the two studies identified in the SER, one reported a non-significant positive association and one reported no effect. The SER Panel judged the evidence too limited to draw a conclusion.

For other related exposures (total carbohydrate, sucrose and soft drinks) there were no clear associations with pancreatic cancer risk and the CUP Panel judged the evidence too limited to draw any conclusions (see CUP 2011 SLR Sections 5.1, 5.1.4 and 3.4).

Mechanisms

Note: A full review of mechanisms for this exposure will form part of a larger review of mechanisms for the CUP (see 5.1 in this report).

Fructose is known to increase postprandial plasma glucose levels, which may have a direct effect on pancreatic cancer risk, given that glucose intolerance and insulin resistance are related to pancreatic cancer [56]. Fructose has also been shown to contribute directly to oxidative stress in hamster islet tumour cells, by inhibiting glutathione peroxidase activity [57]. Metabolism of glucose and fructose are different, and cancer cells readily metabolise fructose to increase cell proliferation. Fructose induces thiamine-dependent transketolase flux and is preferentially used in the non-oxidative pentose phosphate pathway to produce nucleotides essential for DNA synthesis and cell proliferation [58].

CUP Panel's conclusion:

More evidence was available for the CUP analysis and the evidence is generally consistent. Overall a significant positive association was observed between fructose intake and pancreatic cancer risk, and there was no heterogeneity. However, fructose comes from many sources (e.g. soft drinks, fruit juices and sucrose), which may differ between population groups, and makes it difficult to interpret. It is also unclear whether fructose may be acting as a marker for other linked exposures. The Panel therefore concludes:

Although there is ample evidence, which is generally consistent and there is some evidence for a dose-response relationship, fructose comes from many sources making the evidence difficult to interpret. The evidence suggesting that foods and beverages containing fructose are a cause of pancreatic cancer is limited.

6.7 Body fatness

(Also see CUP Pancreatic Cancer SLR 2011: Sections 8.1.1, 8.1.6, 8.2.1 and 8.2.3)

The Panel interpreted body mass index (BMI), measures of abdominal girth, and adult weight gain as indicating interrelated aspects of body fatness and fat distribution. Anthropometric measures are imperfect and cannot distinguish reliably between lean and fat, between total and abdominal fat, or between visceral and subcutaneous fat. Increases in body weight during adulthood depend on accumulation of fat more than lean tissue, and therefore any change may better reflect fatness than adult weight itself, which is more dependent on lean mass.

The evidence for BMI, weight gain (including increase in BMI), waist circumference and waist-to-hip ratio is presented in the following section, and is followed by an overall conclusion that incorporates all these exposures.

Body mass index (BMI)

The CUP identified 23 new papers (from 17 cohort studies) [31, 39, 41, 59-79] giving a total of 30 studies (including studies from the SER). Overall, the CUP found 19 of 23 studies on pancreatic cancer incidence, and four of seven studies on pancreatic cancer mortality, showed an increased risk for the highest BMI groups compared to the lowest.

Dose-response meta-analyses for pancreatic cancer incidence and mortality were conducted separately. A total of 23 studies (12 of which were new) were included in the dose-response meta-analysis for BMI and pancreatic cancer incidence, and seven studies (five of which were new) were included in the dose-response meta-analysis of BMI and pancreatic cancer mortality.

The analyses showed, for both incidence and mortality separately, a 10% statistically significant increased risk per 5 BMI units (RRs 1.10 (95% CI 1.07-1.14) and 1.10 (95% CI 1.02-1.19) respectively)) (see CUP 2011 Figures 181 and 188). With more studies and lower heterogeneity (I^2= 23 vs. 51%), this is consistent with the finding from the SER, which gave an estimate for incidence and mortality combined (RR 1.14 (95% CI 1.07-1.22)). No differences were observed between men and women. There was evidence of a nonlinear dose-response with an increased risk apparent for BMI of 25 kg/m^2 or more (see CUP 2011 Figures 185 and 191).

Published pooled analyses

Results from four separate pooled analyses on BMI and pancreatic cancer risk have been published [80-83], three of which are consistent with the CUP findings [80-82] (results from the PanScan only gave an estimate for the highest versus lowest categories). The fourth pooled analysis of studies in the Asia-Pacific Cohort Studies Collaboration was not consistent with the CUP result, but had fewer cases than the other pooled analyses and CUP meta-analysis. These results are presented in the table below with the CUP result for pancreatic cancer incidence.

Summary of pooled analyses and CUP meta-analyses - BMI

		RR (95% CI)	I^2	No. studies	No. cases	Factors adjusted for
CUP 2011	Per 5 units	1.10 (1.07-1.14)	19	23	9504	
Harvard Pooling Project [80]	Per 5 units	1.14 (1.07-1.21)		14	2135	Smoking status, diabetes, alcohol intake, energy intake
NCI pooled analysis [82]	Per 5 units	1.08 (1.03-1.14)	0	7	2454	Age, sex, cohort, smoking status
Asia-Pacific Cohort Studies Collaboration [83]	Per 5 units	1.02 (0.83-1.25)		39	301	Age, smoking status
PanScan [81]*	BMI ≥35 vs. 18.5-24.9 kg/m^2	1.55 (1.16-2.07)**		13	2095	Cohort, age, sex, anthropometric factor source (self-reported or measured), smoking status

*Includes 12 cohort studies and 1 case-control study

** This was attenuated when adjusting for history of diabetes mellitus (RR 1.26 (95% CI 0.93-1.71))

Weight change (including an increase in BMI)

The CUP identified three new papers on weight change [64, 70, 72], and one on change in BMI [84], giving a total of nine studies (including studies from the SER). None of these studies reported a statistically significant association. Meta-analysis was not possible because weight change was reported inconsistently.

Published pooled analyses

The result from one pooled analysis on increase in BMI and pancreatic cancer risk has been published [80], reporting a statistically significant increased risk with increasing BMI from <25 in early adulthood to >30 at recruitment (RR 1.38 (95% CI 1.14-1.66)). This adjusted for smoking status, diabetes, alcohol intake and energy intake.

Waist circumference

The CUP identified three new papers (from 3 cohort studies) [68, 70, 76], giving a total of five studies (including studies from the SER). All five studies reported on pancreatic cancer incidence and showed a non-significant increased risk when comparing the highest versus lowest groups for waist circumference.

All five studies were included in the CUP meta-analysis. The CUP analysis was conducted per 10cm compared to per 1cm in the SER. The meta-analysis showed an 11% statistically significant increased risk per 10cm (RR 1.11 (95% CI 1.05-1.18)) with no heterogeneity (see CUP 2011 Figure 201). In a stratified analysis, the effect was statistically significant in women, but not in men (RRs 1.14 (95% CI 1.02-1.28) and 1.13 (95% CI 0.89-1.44) respectively) (see CUP 2011 Figure 204). The risk estimate for the SER was a 2% increased risk per 1cm (RR 1.02 (95% CI 1.00-1.04)) (this approximately equates to a 20% increased risk per 10cm).

Published pooled analyses

Results from two separate pooled analyses on waist circumference and pancreatic cancer risk have been published [80, 81]. Both analyses reported positive associations when comparing the highest versus lowest categories, but these were not statistically significant. However, the PanScan [81] reported a statistically significant positive trend with greater waist circumference (p_{trend}= 0.04). No single study was included in all three analyses. These results are presented in the table below.

Summary of pooled analyses and CUP meta-analyses – Waist circumference

		RR (95% CI)	I^2	No. studies	No. cases	Factors adjusted for
CUP 2011	Per 10cm	1.11 (1.05-1.18)	0	5	949	
Harvard Pooling Project [80]	H vs. L	1.16 (0.92-1.46)	10	7	743	Smoking status, diabetes, alcohol intake, energy intake
	H vs. L (additionally adjusted for BMI)	1.04 (0.73-1.47)	26			
PanScan [81]*	H vs. L	1.23 (0.94-1.62)** p_{trend}= 0.04		6	812	Cohort, age, sex, anthropometric factor source (self-reported or measured), smoking status and height

*Includes 12 cohort studies and 1 case-control study

** There was no difference when adjusting for diabetes mellitus history (RR 1.21 (95% CI 0.91-1.60))

Waist-to-hip ratio

The CUP identified three new papers (from three cohort studies) [68, 70, 76], giving a total of four studies (including studies from the SER). All four studies reported on pancreatic cancer incidence and showed a non-significant increased risk when comparing the highest versus lowest groups for waist-to-hip ratio.

All four studies were included in the CUP meta-analysis. The meta-analysis showed a 19% statistically significant increased risk per 0.1 units (RR 1.19 ((95% CI 1.09-1.31)) with little heterogeneity (I^2 = 11%) (see CUP 2011 Figure 211). No meta-analysis was conducted in the SER.

Published pooled analyses

Results from two separate pooled analyses on waist-to-hip ratio and pancreatic cancer risk have been published [80, 81]. Both reported statistically significant positive associations for the highest versus lowest categories, and results are presented in the table below with the CUP result. No single study was included in all three analyses.

Summary of pooled analyses and CUP meta-analyses – Waist-to-hip ratio

		RR (95% CI)	I^2	No. studies	No. cases	Factors adjusted for
CUP 2011	Per 0.1 units	1.19 (1.09-1.31)	11	4	1047	
Harvard Pooling Project [80]	H vs. L	1.35 (1.03-1.78)	0	6	552	Smoking status, diabetes, alcohol intake, energy intake
	H vs. L (additionally adjusted for BMI)	1.34 (1.00-1.79)	0			
PanScan [81]*	H vs. L	1.71 (1.27-2.30)**		6	750	Cohort, age, sex, anthropometric factor source (self-reported or measured), smoking status and height

* Includes 12 cohort studies and 1 case-control study

** There was no difference when adjusting for diabetes mellitus history (RR 1.69 (95% CI 1.24-2.30))

Mechanisms

Note: This is taken from Chapters 2 and 6 of the SER. An updated review of mechanisms for this exposure will form part of a larger review of mechanisms for the CUP (see 5.1 in this report).

It is biologically plausible that body fatness is a cause of pancreatic cancer. There is an established connection between increasing BMI or body fatness and insulin resistance and diabetes. The risk of this cancer is increased in people with insulin resistance or diabetes. It also directly affects levels of many circulating hormones, such as insulin, insulin-like growth factors, and oestrogens, creating an environment that encourages carcinogenesis and discourages apoptosis. Body fatness stimulates the inflammatory response, which may contribute to the initiation and progression of several cancers.

Obesity influences the levels of a number of hormones and growth factors [85]. Insulin-like growth factor 1 (IGF-1), insulin, and leptin are all elevated in obese people, and can promote the growth of cancer cells. In addition, insulin resistance is increased, in particular by abdominal fatness, and the pancreas compensates by increasing insulin production. This hyperinsulinaemia

increases the risk of cancers of the colon and endometrium, and possibly of the pancreas and kidney [86].

Obesity is characterised by a low-grade chronic inflammatory state, with up to 40 per cent of fat tissue comprising macrophages. The adipocyte (fat cell) produces pro-inflammatory factors, and obese individuals have elevated concentrations of circulating tumour necrosis factor (TNF)-alpha [86] interleukin (IL)-6, and C-reactive protein, compared with lean people [87], as well as of leptin, which also functions as an inflammatory cytokine [88]. Such chronic inflammation can promote cancer development.

CUP Panel's conclusion:
The SER Panel judged the evidence that greater body fatness (as BMI) is a cause of pancreatic cancer as convincing, and that abdominal fatness (incorporating waist circumference and waist-to-hip ratio) is a probable cause of pancreatic cancer.

Overall the evidence from the CUP for an association between body fatness (which the CUP Panel interprets to be reflected by BMI, measures of abdominal girth and weight gain) is stronger, with more studies available than the SER, and results from several pooled analyses generally consistent with the CUP findings. The evidence for abdominal fatness and weight gain is less robust than that where BMI is used as the measure of body fatness, but supports the evidence for an association between overall body fatness and pancreatic cancer risk. The Panel therefore concludes:

Body fatness is reflected by BMI, measures of abdominal girth, and adult weight gain. There is ample evidence for an association between various measures of body fatness and pancreatic cancer incidence and mortality. The evidence is generally consistent, and there is a dose-response relationship. There is evidence for plausible mechanisms that operate in humans. The evidence that greater body fatness, including abdominal fatness and adult weight gain, is a cause of pancreatic cancer is convincing.

6.8 Greater childhood growth

(Also see CUP Pancreatic Cancer SLR 2011: Sections 8.1.1 and 8.3.1)

The Panel interpreted measures of adult attained height as representing greater linear growth during childhood and adolescence, and BMI at aged ~20years as accumulation of both lean and fat tissue over the same period. Both these measures reflect factors relating to development and maturation that influence later risk of cancer. The current evidence does not allow identification of particular aspects of the growth trajectory up to 20 years that may play a role, but these may include age of BMI rebound (also referred to as 'adiposity rebound') and age of pubertal maturation. Although much is known about nutritional and other factors which affect the pattern and tempo of growth and development, it is not yet clear precisely how these may influence later susceptibility to cancer.

The evidence for BMI at aged ~20 years and adult attained height is presented in the following section, and is followed by an overall conclusion that incorporates both these exposures.

BMI at aged ~20years

The CUP identified three new papers (from three cohort studies) [59, 71, 72], giving a total of six studies (including studies from the SER). Overall, the evidence was generally consistent with all five studies on pancreatic cancer incidence reporting a non-significant increased risk, and the one study on pancreatic cancer mortality reporting a non-significant decreased risk when comparing the highest versus lowest groups.

Four studies (three of which were new) were included in the dose-response meta-analysis for BMI at aged ~20 years and pancreatic cancer (incidence and mortality combined). The meta-analysis showed a non-significant increased risk per 5 BMI units (RR 1.12 (95% CI 0.97-1.29)) and no heterogeneity was observed (see CUP 2011 Figure 194). No meta-analysis was conducted in the SER.

Published pooled analyses

Results from the Harvard Pooling Project on BMI in young adulthood and pancreatic cancer risk [80] showed a statistically significant increased risk of pancreatic cancer, even after adjustment for BMI in adulthood. This analysis was able to include 11 studies, compared to four in the CUP. Only two studies were included in both CUP and Harvard Pooling Project analyses. The results are presented in the table below.

Summary of pooled analyses and CUP meta-analyses – BMI aged ~20years

		RR (95% CI)	I^2	No. studies	No. cases	Factors adjusted for
CUP 2011	Per 5 units	1.12 (0.97-1.29)	0	4	900	
Harvard Pooling Project [80]	Per 5 units	1.20 (1.10-1.30)		11	1598	Smoking status, diabetes, alcohol intake, energy intake
	BMI ≥30 vs. 23-24.9	1.30 (1.09-1.56)	6			
	BMI ≥30 vs. 23-24.9 (adjusted for BMI in adulthood)	1.21 (1.01-1.45)				

Adult attained height

The CUP identified 12 new papers (from 8 cohort studies) [31, 39, 66, 70, 76, 84, 89-94], giving a total of 14 studies (including studies from the SER). Overall, the evidence was generally consistent with eight of 10 studies on pancreatic cancer incidence showing an increased risk (three of which were statistically significant) and one study on pancreatic cancer mortality showing a non-significant increased risk when comparing the highest versus lowest groups.

Ten studies (seven of which were new) were included in the dose-response meta-analysis for height and pancreatic cancer (incidence and mortality combined). The meta-analysis showed a 7% statistically significant increased risk per 5cm (RR 1.07 (95% CI 1.03-1.12)) with considerably greater heterogeneity observed compared with the SER (I^2= 57 vs. 8%), which could be due to one study [70] reporting a risk in the opposite direction (see CUP 2011 Figure 216). The CUP analysis included more studies. The summary estimate is consistent with the SER, which reported an 11% statistically significant increased risk per 5cm (RR 1.11 (95% CI 1.05-1.17)).

Published pooled analyses

Results from three separate pooled analyses on height and pancreatic cancer risk have been published [80, 81, 83], none of which found a statistically significant association, in contrast to the CUP. However, the CUP included several large cohort studies that were not included in the pooled analyses, and had 2-3 times as many cases. This may have provided more statistical power to detect a modest association. Only three of the same studies were included in all three pooled analyses. The results are presented in the table below.

Summary of pooled analyses and CUP meta-analyses - Height

		RR (95% CI)	I^2	No. studies	No. cases	Factors adjusted for
CUP 2011	Per 5cm	1.07 (1.03-1.12)	57	10	6147	
Harvard Pooling Project [80]	≥180 vs. <170cm Men	1.18 (0.93-1.49)	11	14	1019 (M) 1115 (F)	Smoking status, diabetes, alcohol intake, energy intake
	≥180 vs. <170cm Men (adjusted for BMI)	1.20 (0.96-1.51)	9			
	≥170 vs. <160cm Women	1.03 (0.84-1.25)	0			
	≥170 vs. <160cm Women (adjusted for BMI)	1.06 (0.87-1.29)	1			
PanScan [81]*	H vs. L	0.99 (0.83-1.18)		13	2095	Cohort, age, sex, anthropometric factor source and smoking status
Asia-Pacific Cohort Studies Collaboration [83]	Per 6cm Men	1.08 (0.94-1.24)		38	294	Age, study and year of birth
	Per 6cm Women	0.99 (0.82-1.21)				

* Includes 12 cohort studies and 1 case-control study

Mechanisms

Note: This is taken from Chapter 6 of the SER. An updated review of mechanisms related to this exposure will form part of a larger review of mechanisms for the CUP (see 5.1 in this report).

Factors that lead to greater adult attained height, or its consequences, are a cause of a number of cancers. Adult height is related to the rate of growth during fetal life and childhood. The number of cell divisions in fetal life and childhood, health and nutrition status in childhood, and age of sexual maturity can alter the hormonal microenvironment, and affect circulating levels of growth factors, insulin, and oestrogens. Taller people have undergone more cell divisions stimulated by IGF-1 and pituitary derived growth hormone [95], and there is therefore more potential for error during DNA replication, which may result in cancer development.

CUP Panel's conclusion:

The SER Panel judged the evidence that factors leading to greater adult attained height, or its consequences, are probably a cause of pancreatic cancer. No judgement was made for BMI at aged ~20years in the SER. The CUP Panel concludes:

Developmental factors that lead to greater linear growth and acquisition of both lean and fat tissue in childhood and adolescence (marked by adult attained height and BMI at aged ~20 years) are a probable cause of pancreatic cancer.

6.9 Other

Other exposures were evaluated. However, data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached.

The evidence that foods containing folate protect against pancreatic cancer risk is weak. More studies were available for the CUP analysis, but summary estimates were not significant in contrast to the SER, which found a marginally significant association for dietary folate. Higher heterogeneity was observed overall in the CUP. Results from the Harvard Pooling Project strengthen the null association. Overall, the Panel concluded the evidence is too inconsistent to allow a conclusion to be drawn (see CUP Pancreatic Cancer SLR 2011: Section 5.5.3).

The evidence for a protective effect of fruits and physical activity is also weak and the evidence failed to demonstrate a significant association for either exposure. Overall, the Panel concluded the evidence for fruits and for physical activity is too limited and inconsistent to allow a conclusion to be reached (see CUP Pancreatic Cancer SLR 2011: Sections 2.2.2 and 6).

Evidence for the following exposures previously judged as 'limited-no conclusion' in the SER, remain unchanged: Fish, eggs, vegetables, tea, total dietary fat, dietary cholesterol, carbohydrates, sucrose, and vitamin C.

In addition, evidence for the following exposures, for which no judgement was made in the SER, is too limited to draw any conclusions: Soft drinks (including diet soft drinks and fruit juice), monounsaturated fat, polyunsaturated fats (including linolenic and linoleic acid), glycaemic index, glycaemic load, and multivitamin/mineral supplements.

7. Comparison with the Second Expert Report

Overall, the evidence from the additional cohort studies identified in the CUP was consistent with those reviewed as part of the SER for exposures graded convincing or probable. The CUP Panel grouped several individual anthropometric exposures to reflect 'body fatness' (BMI, measures of abdominal girth and adult weight gain), where previously these exposures were judged individually in the SER. The Panel also combined two exposures under 'greater childhood growth' to reflect factors relating to development and maturation that influence later risk of cancer. These include BMI in early adulthood (at aged ~20 years), and factors leading to adult attained height. In the SER, an individual judgement was made for adult attained height, and no judgement was made for BMI at aged ~20 years.

The evidence for a protective effect of fruits, foods containing folate, and physical activity, has weakened, and the Panel could not draw any conclusions on the updated evidence. The evidence

for higher consumers of alcoholic drinks has strengthened, and is suggestive of a causal effect in this group (for those consuming more than approximately 3 drinks per day).

More data for additional exposures was available for inclusion in the CUP analyses. New exposures for which the Panel could make a judgement with regard to risk of pancreatic cancer, included processed meat, foods containing saturated fatty acids, and foods and beverages containing fructose, all of which there was limited evidence suggesting a causal effect.

8. Conclusions

The CUP Panel will review the evidence relating to pancreatic cancer again after 2015 once the CUP database is being continuously updated for all cancers. The Recommendations for Cancer Prevention will be reviewed in 2017 when the Panel have reviewed the conclusions for the other cancers.

The Continuous Update Project Panel concludes:

The evidence that body fatness (reflected by BMI, measures of abdominal girth and adult weight gain) is a cause of pancreatic cancer is convincing. Greater childhood growth, reflecting factors that lead to greater linear growth and acquisition of both lean and fat tissue in childhood and adolescence (marked by adult attained height and BMI at aged ~20 years) is probably a cause of pancreatic cancer. It is unlikely that coffee has any substantial effect on the risk of this cancer.

There is limited evidence suggesting that consumption of red meat, processed meat, alcoholic drinks (heavier drinking; more than about 3 drinks/day), foods and beverages containing fructose, and foods containing saturated fatty acids, are causes of pancreatic cancer.

Evidence for fruits, foods containing folate and physical activity is less consistent and was too limited to draw a conclusion.

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Appendix 1 Criteria for grading evidence

(Taken from Chapter 3 of the Second Expert Report)

This box lists the criteria finally agreed by the Panel that were necessary to support the judgements shown in the matrices. The grades shown here are 'convincing', 'probable', 'limited — suggestive', 'limited — no conclusion', and 'substantial effect on risk unlikely'. In effect, the criteria define these terms.

Convincing

These criteria are for evidence strong enough to support a judgement of a convincing causal relationship, which justifies goals and recommendations designed to reduce the incidence of cancer. A convincing relationship should be robust enough to be highly unlikely to be modified in the foreseeable future as new evidence accumulates.

All of the following were generally required:

- Evidence from more than one study type.
- Evidence from at least two independent cohort studies.
- No substantial unexplained heterogeneity within or between study types or in different populations relating to the presence or absence of an association, or direction of effect.
- Good quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error, and selection bias.
- Presence of a plausible biological gradient ('dose response') in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.
- Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes.

Probable

These criteria are for evidence strong enough to support a judgement of a probable causal relationship, which would generally justify goals and recommendations designed to reduce the incidence of cancer.

All the following were generally required:

- Evidence from at least two independent cohort studies, or at least five case control studies.
- No substantial unexplained heterogeneity between or within study types in the presence or absence of an association, or direction of effect.
- Good quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error, and selection bias.
- Evidence for biological plausibility.

Limited — suggestive

These criteria are for evidence that is too limited to permit a probable or convincing causal judgement, but where there is evidence suggestive of a direction of effect. The evidence may have methodological flaws, or be limited in amount, but shows a generally consistent direction of effect. This almost always does not justify recommendations designed to reduce the incidence of cancer. Any exceptions to this require special explicit justification.

All the following were generally required:

- Evidence from at least two independent cohort studies or at least five case control studies.
- The direction of effect is generally consistent though some unexplained heterogeneity may be present.
- Evidence for biological plausibility.

Limited — no conclusion

Evidence is so limited that no firm conclusion can be made. This category represents an entry level, and is intended to allow any exposure for which there are sufficient data to warrant Panel consideration, but where insufficient evidence exists to permit a more definitive grading. This does not necessarily mean a limited quantity of evidence. A body of evidence for a particular exposure might be graded 'limited — no conclusion' for a number of reasons. The evidence might be limited by the amount of evidence in terms of the number of studies available, by inconsistency of direction of effect, by poor quality of studies (for example, lack of adjustment for known confounders), or by any combination of these factors.

When an exposure is graded 'limited — no conclusion', this does not necessarily indicate that the Panel has judged that there is evidence of no relationship. With further good quality research, any exposure graded in this way might in the future be shown to increase or decrease the risk of cancer. Where there is sufficient evidence to give confidence that an exposure is unlikely to have an effect on cancer risk, this exposure will be judged 'substantial effect on risk unlikely'.

There are also many exposures for which there is such limited evidence that no judgement is possible. In these cases, evidence is recorded in the full CUP SLRs on the Diet and Cancer Report website (www.dietandcancerreport.org). However, such evidence is usually not included in the summaries.

Substantial effect on risk unlikely

Evidence is strong enough to support a judgement that a particular food, nutrition, or physical activity exposure is unlikely to have a substantial causal relation to a cancer outcome. The evidence should be robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates.

All of the following were generally required:

- Evidence from more than one study type.
- Evidence from at least two independent cohort studies.
- Summary estimate of effect close to 1.0 for comparison of high versus low exposure categories.
- No substantial unexplained heterogeneity within or between study types or in different populations.
- Good quality studies to exclude, with confidence, the possibility that the absence of an observed association results from random or systematic error, including inadequate power, imprecision or error in exposure measurement, inadequate range of exposure, confounding, and selection bias.
- Absence of a demonstrable biological gradient ('dose response').
- Absence of strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures lead to relevant cancer outcomes.

Factors that might misleadingly imply an absence of effect include imprecision of the exposure assessment, an insufficient range of exposure in the study population, and inadequate statistical power. Defects in these and other study design attributes might lead to a false conclusion of no effect.

The presence of a plausible, relevant biological mechanism does not necessarily rule out a judgement of 'substantial effect on risk unlikely'. But the presence of robust evidence from appropriate animal models or in humans that a specific mechanism exists, or that typical exposures can lead to cancer outcomes, argues against such a judgement.

Because of the uncertainty inherent in concluding that an exposure has no effect on risk, the criteria used to judge an exposure 'substantial effect on risk unlikely' are roughly equivalent to the criteria used with at least a 'probable' level of confidence. Conclusions of 'substantial effect on risk unlikely' with a lower confidence than this would not be helpful, and could overlap with judgements of 'limited — suggestive' or 'limited — no conclusion'.

Special upgrading factors

These are factors that form part of the assessment of the evidence that, when present, can upgrade the judgement reached. So an exposure that might be deemed a 'limited — suggestive' causal factor in the absence, say, of a biological gradient, might be upgraded to 'probable' in its presence. The application of these factors (listed below) requires judgement, and the way in which these judgements affect the final conclusion in the matrix are stated.

- Presence of a plausible biological gradient ('dose response') in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.
- A particularly large summary effect size (an odds ratio or relative risk of 2.0 or more, depending on the unit of exposure) after appropriate control for confounders.
- Evidence from randomised trials in humans.
- Evidence from appropriately controlled experiments demonstrating one or more plausible and specific mechanisms actually operating in humans.
- Robust and reproducible evidence from experimental studies in appropriate animal models showing that typical human exposures can lead to relevant cancer outcomes.

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