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OUR VISION

We want to live in a world where no one develops a preventable cancer.

OUR MISSION

We champion the latest and most authoritative scientific research from around the world on cancer prevention and survival through diet, weight and physical activity, so that we can help people make informed choices to reduce their cancer risk.

As a network, we influence policy at the highest level and are trusted advisors to governments and to other official bodies from around the world.

OUR NETWORK

World Cancer Research Fund International is a not-for-profit organisation that leads and unifies a network of cancer charities with a global reach, dedicated to the prevention of cancer through diet, weight and physical activity.

The World Cancer Research Fund network of charities is based in Europe, the Americas and Asia, giving us a global voice to inform people about cancer prevention.
OUR CONTINUOUS UPDATE PROJECT (CUP)

World Cancer Research Fund International’s Continuous Update Project (CUP) analyses global cancer prevention and survival research linked to diet, nutrition, physical activity and weight. Among experts worldwide it is a trusted, authoritative scientific resource, which underpins current guidelines and policy for cancer prevention.

The CUP is produced in partnership with the American Institute for Cancer Research, World Cancer Research Fund UK, World Cancer Research Fund NL and World Cancer Research Fund HK.

The findings from the CUP are used to update our Cancer Prevention Recommendations, which were originally published in Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective (our Second Expert Report) [1]. These ensure that everyone – from policymakers and health professionals to members of the public – has access to the most up-to-date information on how to reduce the risk of developing the disease.

As part of the CUP, scientific research from around the world is collated and added to a database of epidemiological studies on an ongoing basis and systematically reviewed by a team at Imperial College London. An independent panel of world-renowned experts then evaluates and interprets the evidence to make conclusions based on the body of scientific evidence. Their conclusions form the basis for reviewing and, where necessary, revising our Cancer Prevention Recommendations (see inside back cover).

A review of the Cancer Prevention Recommendations is expected to be published in 2017, once an analysis of all of the cancers being assessed has been conducted. So far, new CUP reports have been published with updated evidence on breast, colorectal, pancreatic, endometrial, ovarian, prostate, liver, gallbladder and kidney cancers. In addition, our first CUP report on breast cancer survivors was published in 2014.

This CUP report on bladder cancer updates the bladder cancer section of the Second Expert Report (section 7.16) and is based on the findings of the CUP Bladder Cancer Systematic Literature Review (SLR) and the CUP Expert Panel discussion in June 2014. For further details, please see the full CUP Bladder SLR 2014 (wcrf.org/bladder-cancer-slr-2014).

HOW TO CITE THIS REPORT

World Cancer Research Fund International/American Institute for Cancer Research.
Available at: wcrf.org/bladder-cancer-2015.

All CUP reports are available at wcrf.org/cupreports.

EXEcutIve suMMary

background and context

Around 430,000 new cases of bladder cancer were recorded globally in 2012, accounting for 3 per cent of all new cases of cancer. This makes bladder cancer the ninth most common cancer worldwide [2].

Men are over four times more likely than women to develop bladder cancer, and it is more common in older adults. For example, the average age at diagnosis in the United States (US) is 73 years.

Sixty per cent of cases of bladder cancer occur in higher-income countries, with the highest incidence rates seen in North America and Europe, and the lowest in Asia, Latin America and the Caribbean.

Although bladder cancer is the 13th most common cause of death from cancer, survival rates vary across the world. The 5-year survival rate is 76 per cent in the US, and 68 per cent in Europe, but survival tends to be better in higher-income than lower-income countries.

In this report from our Continuous Update Project (CUP) – the world’s largest source of scientific research on cancer prevention and survivorship through diet, weight and physical activity – we analysed global research on how certain lifestyle factors affect the risk of developing bladder cancer. This includes new studies as well as those included in our 2007 Second Expert Report, Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective [1].

In addition to the findings in this report, other established causes of bladder cancer include:

1. Smoking:
   ◆ Smokers have up to six times the risk of bladder cancer than people who have never smoked.

2. Infection and infestation:
   ◆ Infection from parasitic worms is a major risk factor, especially for squamous cell carcinomas. This is a less common type of bladder cancer that occurs more frequently in countries with high parasitic infection rates (notably Africa and the Middle East).

3. Occupational exposure:
   ◆ People who work with metalworking fluids – such as sheet metalworkers and machine operators – have a significantly higher risk of bladder cancer, which increases with duration of employment. Exposure to aromatic amines and polyaromatic hydrocarbons (chemicals used in the plastic and chemical industries) has also been strongly associated with an elevated risk for this cancer.
How the research was conducted

The global scientific research on diet, weight, physical activity and the risk of bladder cancer was systematically gathered and analysed, and then independently assessed by a panel of leading international scientists in order to draw conclusions about which of these factors increase or decrease the risk of developing the disease.

More research has been conducted in this area since our 2007 Second Expert Report [1]. In total, this new report analysed 45 studies from around the world, comprising more than 7 million adults and nearly 37,000 cases of bladder cancer.

To ensure consistency, the methodology for the Continuous Update Project remains largely unchanged from that used for our Second Expert Report [1].

A summary of the mechanisms underpinning all the findings can be found in the Evidence and Judgements chapter of this report.

Findings

Strong evidence

◆ There is strong evidence that drinking water containing arsenic increases the risk of bladder cancer.

The findings on the link between bladder cancer and drinking water containing arsenic are now stronger than in the worldwide evidence reviewed for our 2007 Second Expert Report [1]. Therefore, the finding on drinking water containing arsenic has been upgraded to strong evidence.

Water can become contaminated by arsenic as a result of natural deposits present in the earth or from agricultural and industrial practices. Countries particularly affected by arsenic in drinking water include Bangladesh, India, Cambodia, Argentina, Chile and Mexico.

Limited evidence

◆ There is some evidence that greater consumption of vegetables and fruit decreases the risk of bladder cancer.

◆ There is some evidence that greater consumption of tea decreases the risk of bladder cancer.

The findings on consuming tea and vegetables and fruit are new. No conclusion on them was possible in our 2007 Second Expert Report [1].
Recommendations

Our Cancer Prevention Recommendations – for preventing cancer in general – include maintaining a healthy weight, being physically active and eating a healthy diet (this includes consuming a variety of vegetables, fruit, wholegrains and pulses). The Cancer Prevention Recommendations are listed on the inside back cover of this report, with full details available at wcrf.org/recommendations.

References


## DIET, NUTRITION, PHYSICAL ACTIVITY AND BLADDER CANCER

<table>
<thead>
<tr>
<th>Evidence Level</th>
<th>Risk Factor</th>
<th>Decreases Risk</th>
<th>Increases Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STRONG EVIDENCE</strong></td>
<td></td>
<td></td>
<td>Arsenic in drinking water ¹</td>
</tr>
<tr>
<td>Convincing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LIMITED EVIDENCE</strong></td>
<td>Vegetables and fruit ² Tea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited – suggestive</td>
<td>Cereals (grains) and their products, pulses (legumes), meat, poultry, fish, total fat, milk, yoghurt, cheese, dietetic foods, soft drinks, diet drinks, fruit juices, coffee, green tea, caffeine, alcohol, chlorinated surface water, total fluid intake, sweeteners, frying, carbohydrate, protein, vitamin A, vitamin C, serum 25-hydroxy vitamin D, vitamin E, calcium, folate, selenium, beta-carotene, alpha-carotene, lycopene, beta-cryptoxanthin, lutein, zeaxanthin, flavonoids, tocopherols, multivitamin supplements, physical activity, energy intake, BMI, waist circumference, height</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited – no conclusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>STRONG EVIDENCE</strong></td>
<td>Substantial effect on risk unlikely</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. The International Agency for Research on Cancer (IARC) has graded arsenic and arsenic compounds as Class 1 carcinogens [3]. The grading for this entry applies specifically to inorganic arsenic in drinking water.

2. Combined consumption of vegetables and fruit.
1. Summary of Panel judgements

Overall, the Panel notes the strength of the evidence that arsenic in drinking water is a cause of bladder cancer.

The Continuous Update Project (CUP) Panel judges as follows:

- Arsenic: Consumption of arsenic in drinking water is probably a cause of bladder cancer.
- Vegetables and fruit: The evidence suggesting that greater consumption of vegetables and fruit decreases the risk of bladder cancer is limited.
- Tea: The evidence suggesting that greater consumption of tea decreases the risk of bladder cancer is limited.

For a full description of the definitions of, and criteria for, the terminology of ‘convincing’, ‘probable’, ‘limited – suggestive’, ‘limited – no conclusion’ and ‘substantial effect on risk unlikely’, see the Appendix.

The Panel judgements for bladder cancer are shown in the matrix on page 6.
2. Trends, incidence and survival

The urinary bladder is a membranous sac that functions as a receptacle to store urine excreted by the kidneys before it is discharged through the urethra. The bladder is lined with transitional epithelial cells, known as urothelial tissue.

Urothelial carcinoma is the most common form of bladder cancer, accounting for more than 90 per cent of diagnosed cases [4]. Other types of bladder cancer include squamous cell carcinoma, adenocarcinoma and small cell cancer (in order of incidence). About 70–80 per cent of patients are diagnosed with low-grade tumours that do not tend to metastasise to surrounding tissues.

The most common symptom of bladder cancer is blood in the urine [5]. Other symptoms include increased frequency or urgency of urination, and pain or irritation during urination.

Bladder cancer is the ninth most common cancer worldwide. About 430,000 new cases were recorded in 2012, accounting for 3 per cent of all new cases of cancer. It is the 13th most common cause of death from cancer [4].

Rates of bladder cancer are more than four times higher in men than women [4]. It is most common in older adults, with a median age of diagnosis of 73 years in the United States (US) [2, 5]. About 60 per cent of bladder cancer cases are diagnosed in high-income countries. The highest incidence is seen in North America and Europe, and the lowest is in Asia, Latin America and the Caribbean [2].

Survival rates following bladder cancer diagnosis are relatively good and are more favourable in higher-income than lower-income countries. The five-year survival rate is about 76 per cent for all cancer stages combined in the US, and about 68 per cent in Europe [6, 7]. See the box below for further explanation.

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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 most probably higher than the figures given here.

The information on cancer survival shown here is for the United States of America and Europe. 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 as well as well-established treatment facilities. Survival is often a function of the stage at which a cancer is detected and diagnosed.

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3. Pathogenesis

Dietary carcinogens, as well as those from tobacco smoke or other environmental sources, are often excreted in the urine, where the lining of the bladder is exposed to these agents.

Urothelial cell carcinomas start as superficial bladder carcinomas. The majority have low rates of progression, although they can occur at multiple sites. Low-risk lesions may never progress, but if they become invasive the prognosis can be poor.

The superficial lesion that carries the highest risk is carcinoma in situ, which progresses to invasive cancer in more than 50 per cent of cases if it is not treated. These high-risk lesions are often found with multiple papillary tumours, but because they may involve different molecular changes, they are likely to have different pathways of development to low-risk lesions [8].

Squamous cell carcinoma may be caused by chronic inflammation, for instance from latent schistosomiasis, chronic infections or long-term catheter use.

Mutations in the p53 tumour suppressor gene, as well as abnormalities in chromosome 9, are common in invasive bladder cancer. Inherited mutations of two other genes, glutathione S-transferase (GSTM1) and NAT2 (N-acetyltransferase), also increase risk for bladder cancer. NAT2 is involved in detoxifying aromatic amines present in cigarette smoke, and a slow acetylation phenotype in both genes is estimated to be responsible for 20–46 per cent of bladder cancers [9, 10].

4. Other established causes

Tobacco use

Smoking increases the risk of bladder cancer [11, 12]. The risk of developing bladder cancer is between two and six times higher in smokers compared with non-smokers.

Infection and infestation

Chronic inflammation of the bladder is a major risk factor, especially for squamous cell carcinomas. Chronic infection with the parasitic trematode Schistosoma haematobium, causing schistosomiasis, is associated with bladder cancer development in countries with high infection rates (notably in Africa and the Middle East). There is a two- to five-fold increased risk of this cancer in infected compared with non-infected individuals [4].

Occupational exposure

Male precision metalworkers, operators of metalworking or textile machines, mechanics and those working in electronic component manufacturing are at significantly elevated risk of bladder cancer. Estimates of increased risk range from 30 to 220 per cent, increasing with duration of employment [13]. Occupational exposure to aromatic amines and polyaromatic hydrocarbons has been causally linked to bladder cancer, with exposure to metalworking fluids strongly implicated [13].
5. Interpretation of the evidence

5.1 General

For general considerations that may affect interpretation of the evidence, see sections 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’.

5.2 Specific

Considerations specific to cancer of the bladder include:

Confounding

Tobacco smoking is a potential confounder or effect modifier. Most studies included in this report controlled for smoking. All studies on vegetables and fruit, and all studies on tea except one, adjusted for smoking duration and intensity. Three of the studies identified on arsenic and bladder cancer did not report adjustment for smoking.

6. Methodology

To ensure consistency with evidence collected and analysed for the Second Expert Report [1], the methodology for the CUP remains largely unchanged. However, based upon the experience of conducting the systematic literature reviews (SLRs) for the Second Expert Report, some modifications to the methodology were made. The updated literature search was restricted to Medline and included only randomised controlled trials, cohort and nested case-control studies. Due to their methodological limitations, case-control studies were not analysed in the CUP Bladder SLR 2014, unlike in the 2005 SLR used for the Second Expert Report.

Where possible for this update, meta-analyses for incidence and mortality were conducted separately. However, analyses combining studies on bladder cancer incidence and mortality were also conducted to explore whether the outcome could explain any heterogeneity in the results. Separate meta-analyses were also conducted for men and women, and by geographical location, where possible.

Studies reporting mean difference as a measure of association were not included in the CUP Bladder SLR 2014, as relative risks estimated from mean differences are not adjusted for confounders and thus are not comparable with adjusted relative risks from other studies.

Non-linear meta-analysis was applied when the data suggested that the dose-response curve was non-linear and when detecting a threshold of exposure might be of interest. Details on the non-linear meta-analyses can be found in the CUP Bladder SLR 2014.

The CUP Bladder SLR 2014 included studies published up to 31 July 2013. For more
information on methodology, see the full CUP Bladder SLR 2014 at wcrf.org/bladder-cancer-slr-2014.

6.1 Mechanistic evidence

Where relevant, mechanistic reviews previously conducted for the Second Expert Report are included in this report (more details can be found in chapters 2 and 4 of the Second Expert Report). These reviews have not been updated here, but will be updated in the future as part of a systematic literature review for the CUP of the mechanistic evidence (see below). A brief summary is given of possible mechanisms linking arsenic from drinking water, vegetables and fruit, and tea with bladder cancer. Plausible mechanisms identified by CUP Panel members and published reviews are included in this report.

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

7. Evidence and judgements

The following sections summarise the evidence identified in the CUP Bladder SLR 2014 and provide a comparison with the findings from the Second Expert Report [1] and the Panel’s conclusions. They also include a brief description of potential biological mechanisms for each exposure.

For information on the criteria for grading the epidemiological evidence, see the Appendix in this report. References to studies added as part of the CUP have been included; for details of references to other studies from the Second Expert Report, see the CUP Bladder SLR 2014.

7.1 Vegetables and fruit

(Also see CUP Bladder SLR 2014: Section 2.2)

This section relates to the evidence from vegetables and fruit combined. Evidence on vegetables and fruit separately did not show statistically significant associations with bladder cancer risk; see Table 1 for a summary of meta-analyses of vegetable and fruit subtypes. The Panel advised that the evidence relating to vegetable and fruit subtypes considered separately was limited and that no specific conclusions could be drawn.
The CUP identified three new studies [14, 15] on consumption of vegetables and fruit combined, giving a total of nine studies (eight publications; see CUP Bladder SLR 2014 Table 5 for a full list of references). All nine studies (eight estimates) reported on bladder cancer incidence. When comparing the highest and lowest categories of intake, five estimates reported an inverse association, of which one was significant; two reported a non-significant positive association; and one reported no effect (see CUP Bladder SLR 2014 Figure 1).

Eight of the nine studies were included in the dose-response meta-analysis (n = 2,508), which showed a statistically significant 3 per cent decreased risk per 1 serving (80 grams) of vegetables and fruit consumed per day (RR = 0.97 (95% CI 0.95–0.99); see CUP Bladder SLR 2014 Figure 2). No heterogeneity was observed (I² = 0%).

After stratification by sex, no significant association was observed in men (RR = 0.99 (95% CI 0.96–1.01)) or women (RR = 0.93 (95% CI 0.81–1.07)). Stratified analysis by smoking status was not possible.

All studies adjusted for smoking status, intensity and duration, except one study that adjusted for smoking status only and reported similar results. Four studies were carried out in the US and five in Europe.

Table 1: Summary of CUP 2014 of dose-response meta-analyses of intake of vegetable and fruit subtypes and bladder cancer risk

<table>
<thead>
<tr>
<th>EXPOSURE</th>
<th>INCREMENT</th>
<th>RR (95% CI)</th>
<th>I²</th>
<th>NO. STUDIES</th>
<th>NO. CASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined vegetables &amp; fruit</td>
<td>Per 1 serving/day</td>
<td>0.97 (0.95–0.99)</td>
<td>0%</td>
<td>8</td>
<td>2,508</td>
</tr>
<tr>
<td>Non-starchy vegetables</td>
<td>Per 1 serving/day</td>
<td>0.97 (0.94–1.00)</td>
<td>10%</td>
<td>10</td>
<td>5,119</td>
</tr>
<tr>
<td>Cruciferous vegetables</td>
<td>Per 1 serving/week</td>
<td>0.98 (0.94–1.02)</td>
<td>58%</td>
<td>7</td>
<td>2,437</td>
</tr>
<tr>
<td>Green leafy vegetables</td>
<td>Per 1 serving/week</td>
<td>0.98 (0.95–1.01)</td>
<td>0%</td>
<td>6</td>
<td>2,310</td>
</tr>
<tr>
<td>Fruit</td>
<td>Per 1 serving/day</td>
<td>0.98 (0.96–1.00)</td>
<td>0%</td>
<td>12</td>
<td>5,329</td>
</tr>
<tr>
<td>Citrus fruit</td>
<td>Per 1 serving/day</td>
<td>0.96 (0.91–1.02)</td>
<td>0%</td>
<td>6</td>
<td>1,968</td>
</tr>
</tbody>
</table>
One study [15] contributed 55 per cent of the weight of the meta-analysis. When this study was removed in sensitivity analysis, the overall association was no longer significant (RR = 0.98 (95% CI 0.95–1.01)).

The CUP 2014 findings were different from the dose-response meta-analysis in the 2005 SLR, which reported no effect (RR = 1.00 (95% CI 0.95–1.03) per 1 serving per day). The CUP Bladder SLR 2014 included more cohort studies, and more cases of bladder cancer.

**Published pooled analyses and meta-analyses**

No published meta-analysis or pooled analysis was identified on consumption of vegetables and fruit combined.

**Mechanisms**

*Note: This section is adapted from sections 2.2, 2.3 and 4.2 of the Second Expert Report. In the future, a full review of mechanisms for this exposure will form part of a larger review of mechanisms (see section 6.1 in this report).*

Vegetables and fruit contain several substances that are potentially protective against cancer, and it is difficult to unravel the relative importance of each constituent. It is likely that any preventative effect may result from a combination of influences on several pathways involved in carcinogenesis.

Many vegetables and fruit include several antioxidant nutrients (such as carotenoids and vitamin C), minerals, dietary fibre, phenols, flavonoids and phytochemicals [16-18], which may reduce oxidative stress and DNA damage caused by free radicals, and also affect pathways controlling cell proliferation and apoptosis [19]. Antioxidants may also protect against the damage caused by free radicals found in cigarette smoke.

Cruciferous vegetables in particular contain glucosinolates. During food preparation, these are transformed into isothiocyanates, which alter the metabolism of carcinogens. The particular isoform of the enzyme induced may protect against bladder cancer [20].

**CUP Panel’s conclusion:**

The evidence for consumption of vegetables and fruit was generally consistent in the direction of an inverse association, with a significant inverse association overall between consumption of vegetables and fruit and risk of bladder cancer. However, the association was strongly influenced by a single study, and the association was not significant after stratification by sex. The CUP Panel concluded:

> The evidence suggesting that greater consumption of vegetables and fruit decreases the risk of bladder cancer is limited.
7.2 Tea

(Also see CUP Bladder SLR 2014: Section 3.6.2)

The CUP identified one new study (one publication) [21], giving a total of four studies (four publications; see CUP Bladder SLR 2014 Table 75 for a full list of references). All four studies (four estimates) reporting on bladder cancer incidence reported a non-significant inverse association when comparing the highest and lowest categories of intake (see CUP Bladder SLR 2014 Figure 71).

All four studies were included in the dose-response meta-analysis (n = 1,446), which showed a statistically significant 6 per cent decreased risk per 1 cup per day (RR = 0.94 (95% CI 0.89–0.98); see CUP Bladder SLR 2014 Figure 72). No heterogeneity was observed (I² = 0%). There were not enough data available to conduct stratified analyses.

All studies except one adjusted for smoking status, duration or dose. The unadjusted study reported a lower risk estimate and wider confidence intervals than the other studies. Two studies were conducted in the US, and two in Europe. Type of tea was not specified.

The CUP Bladder SLR 2014 findings were similar to the dose-response meta-analysis from the 2005 SLR, which also reported a significant inverse association (RR = 0.95 (95% CI 0.90–0.99) per 1 cup per day). The CUP Bladder SLR 2014 included an additional cohort study and more cases of bladder cancer.

Published pooled analyses and meta-analyses

One published meta-analysis on tea and bladder cancer risk was identified (see Table 2).

Table 2: Summary of published meta-analysis of tea intake and bladder cancer risk

<table>
<thead>
<tr>
<th>PUBLICATION</th>
<th>NO. STUDIES</th>
<th>COMPARISON</th>
<th>RR (95% CI)</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qin (2012) [22]</td>
<td>6</td>
<td>Tea consumption vs. no tea consumption</td>
<td>0.94 (0.78-1.09)</td>
<td>0%</td>
</tr>
</tbody>
</table>

Mechanisms

Note: This is adapted from sections 2.4 and 4.7 of the Second Expert Report. In the future, a full review of mechanisms for this exposure will form part of a larger review of mechanisms (see section 6.1 in this report).

Animal studies have shown that certain compounds present in tea may have inhibitory effects on bladder tumour formation and growth [23]. This inhibitory activity is believed to be due mainly to the anti-oxidative and possibly anti-proliferative effect of polyphenol compounds, through inhibition of metabolic or signal-transduction pathways [23].
CUP Panel’s conclusion:

The evidence was sparse but generally consistent. Overall, there was a significant inverse association between consumption of tea and risk of bladder cancer. Not enough data were available for stratified analyses. The CUP Panel concluded:

The evidence suggesting that greater consumption of tea decreases the risk of bladder cancer is limited.

7.3 Arsenic in drinking water

(Also see CUP Bladder SLR 2014: Section 4.1.2.7.1)

The CUP identified three new or updated studies (five publications) [24–28] giving a total of eight studies (11 publications; summarised in Table 3, see CUP Bladder SLR 2014 Table 82 for a full list of references).

Of six studies reporting on bladder cancer incidence, three reported a significant positive association and two reported a non-significant positive association when comparing the highest and the lowest categories of cumulative exposure; one reported no effect from average exposure levels. Of three studies reporting on bladder cancer mortality, one reported a significant positive association for the highest exposure levels compared with the lowest; the other two reported no significant association for either men or women. Meta-analysis was not possible due to variability in arsenic exposure assessment across studies.

Four studies were conducted in high-exposure areas, and four were conducted in low-exposure areas. All except one of the risk estimates for studies carried out in high-exposure areas reported a large and significant increased risk of bladder or urothelial cancer with increasing levels of cumulative exposure to arsenic from drinking water.

Seven studies assessed arsenic concentration in drinking water, and one assessed toenail arsenic concentration. Four studies were carried out in Asia, three were in Europe and one in the US. Two studies included more than 200 cases. Three studies did not report adjustment for smoking. Of these studies, two were conducted in areas of high exposure to arsenic and reported data on smoking status; the third was conducted in a low-exposure area and estimated a low prevalence of smoking.

The CUP Bladder SLR 2014 findings were similar to the findings from the 2005 SLR. The CUP Bladder SLR 2014 included more cohort studies and more cases of bladder cancer.
Table 3: Summary of studies on arsenic and bladder cancer risk

<table>
<thead>
<tr>
<th>PUBLICATION</th>
<th>NO. CASES</th>
<th>SEX</th>
<th>RR (95% CI)</th>
<th>INCREMENT/CONTRAST</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIGH-EXPOSURE AREAS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chung (2013)</td>
<td>43</td>
<td>Men and women</td>
<td>7.74 (0.97–61.51)</td>
<td>Cumulative exposure ≥19.5 vs. &lt;9.1 μg/L/year</td>
</tr>
<tr>
<td>South-western Taiwan cohort, 1989–1996 [28]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hsu (2011)</td>
<td>41</td>
<td>Men and women</td>
<td>19.31 (2.46–151.24)</td>
<td>Cumulative exposure (well water) 20 vs. 0–9.9 mg/L/year</td>
</tr>
<tr>
<td>South-western Taiwan cohort, 1989–1996 [26]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huang (2008)</td>
<td>37</td>
<td>Men and women</td>
<td>7.9 (1.7–37.9)</td>
<td>Cumulative exposure (well water) ≥20 mg/L/year vs. none</td>
</tr>
<tr>
<td>South-western Taiwan cohort, 1989–2001 [25]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen (2010)</td>
<td>45</td>
<td>Men and women</td>
<td>12.6 (3.40–46.8)</td>
<td>Cumulative exposure (well water) ≥10000 vs. &lt;400 μg/L</td>
</tr>
<tr>
<td>Chiang (2001)</td>
<td>11</td>
<td>Men and women</td>
<td>15.10 (1.70–138.50)</td>
<td>Concentration in well water collected at enrolment &gt;100 vs. 0–10 μg/L</td>
</tr>
<tr>
<td>Tsuda (1995)</td>
<td>3</td>
<td>Men and women</td>
<td>SMR 31.18 (8.62–91.75)</td>
<td>Drinking water ≥1 ppm</td>
</tr>
<tr>
<td>Chiou (1995)</td>
<td>29</td>
<td>Men and women</td>
<td>5.1 (1.5–17.3)</td>
<td>Cumulative exposure (well water) ≥20 mg/L/year vs. none</td>
</tr>
<tr>
<td>South-western Taiwan cohort [31]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LOW-EXPOSURE AREAS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baastrup (2008)</td>
<td>214</td>
<td>Men and women</td>
<td>1.00 (0.91–1.11)</td>
<td>Time-weighted average exposure (drinking water) Per μg/L</td>
</tr>
<tr>
<td>Danish Diet, Cancer and Health cohort [24]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michaud (2004)</td>
<td>280</td>
<td>Men</td>
<td>1.13 (0.70–1.81)</td>
<td>Toenail arsenic level &gt;0.161 vs. &lt;0.05 μg/g</td>
</tr>
<tr>
<td>ATBC study [32]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lewis (1999)</td>
<td>–</td>
<td>Men</td>
<td>SMR 0.95</td>
<td>Drinking water ≥5000 ppb-year</td>
</tr>
<tr>
<td>Cohort of Mormons, USA* [33]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kurttio (1999)</td>
<td>61</td>
<td>Men and women</td>
<td>1.00 (0.91–1.11)</td>
<td>Cumulative exposure (well water), 3 to 9 years before cancer diagnosis ≥2.0 vs &lt;0.5 mg</td>
</tr>
<tr>
<td>Finnish cohort, 1981–1995 [34]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: SMR = standardised mortality ratio; ppb = parts per billion; ppm = parts per million.
* Retrospective cohort study of mortality.
Published pooled analyses and meta-analyses

No pooled analysis was identified. Two published meta-analyses containing cohort studies have reported on arsenic intake and bladder cancer risk, summarised in Table 4.

Table 4: Summary of published meta-analyses of arsenic exposure and bladder cancer risk

<table>
<thead>
<tr>
<th>PUBLICATION</th>
<th>NO. STUDIES</th>
<th>NO. CASES</th>
<th>COMPARISON</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mink (2008)</strong>* [35]</td>
<td>8 (2 cohort, 6 case-control)</td>
<td>1105</td>
<td>HvL &lt;100–200 μg/L</td>
<td>1.11 (0.95–1.30)</td>
</tr>
<tr>
<td></td>
<td>6 (1 cohort, 5 case-control)</td>
<td>182</td>
<td>HvL: never-smokers &lt;100–200 μg/L</td>
<td>0.81 (0.60–1.08)</td>
</tr>
<tr>
<td></td>
<td>6 (1 cohort, 5 case-control)</td>
<td>182</td>
<td>HvL: ever-smokers &lt;100–200 μg/L</td>
<td>1.24 (0.99–1.56)</td>
</tr>
<tr>
<td><strong>Chu (2006)</strong> [36]</td>
<td>7 (2 cohort, 5 case-control)</td>
<td>—</td>
<td>Dose-response Per μg/L from high- and low-arsenic areas</td>
<td>Slope = 0.004 (-0.03–0.01)</td>
</tr>
</tbody>
</table>

* Low-level arsenic exposure in drinking water. Study funded by the Wood Preservative Science Council, Virginia, USA: a trade association of manufacturers of wood preservatives, some of which may contain arsenic.
Mechanisms

Note: This section is adapted from sections 2.4.2.4 and 4.7.5 of the Second Expert Report. In the future, a full review of mechanisms for this exposure will form part of a larger review of mechanisms (see section 6.1 in this report).

The International Agency for Research on Cancer (IARC) has judged arsenic and arsenic compounds to be carcinogenic to humans [3]. Arsenic is genotoxic in humans and acts as a chromosomal mutagen, and can also act as a synergistic co-mutagen. Arsenic can result in changes in the methylation of oncogenes or tumour-suppressor genes, and also interferes with several enzymes of the haem biosynthetic pathway.

In laboratory animals and human cells, exposure to arsenite or arsenate results in generation of reduced oxygen species (free radicals). Arsenic biotransformation is thought to deplete cells of reduced glutathione, leading to a state of oxidative stress characterised by decreased scavenging of free radicals, which can directly damage DNA and induce cell proliferation.

Arsenic in drinking water is absorbed from the gastrointestinal tract and excreted in urine, where it comes into contact with the lining of the bladder. Studies have shown that it can modify the urinary excretion of porphyrins in animals and humans. The joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Committee on Food Additives has set a provisional tolerable weekly intake of 0.015 mg arsenic per kg body weight [37]. Regions where arsenic contamination in drinking water leads to high levels of exposure include some southern Asian countries such as Bangladesh, Cambodia and India; areas in South America including Argentina and Chile; and some parts of China and the US [38].

CUP Panel’s conclusion:

There was generally consistent evidence of a significant positive association between arsenic in drinking water and bladder cancer in high-exposure areas. In these areas, risk estimates were particularly large, indicating a strong effect. In addition, arsenic is a recognised carcinogen. There is strong evidence for plausible mechanisms operating in humans. The CUP Panel concluded:

**Consumption of arsenic in drinking water is probably a cause of bladder cancer.**
7.4 Other

Other exposures were evaluated. However, data were of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. The list of exposures judged as ‘limited – no conclusion’ is summarised in the matrix on page 6.

The evidence for milk, previously judged as ‘limited – suggestive’ in the Second Expert Report, was less consistent and the Panel could not draw any conclusions from the updated evidence on milk or dairy produce.

Evidence for the following exposures previously judged as ‘limited – no conclusion’ in the Second Expert Report remains unchanged after updating the analyses with new data identified in the CUP Bladder SLR 2014: vitamin C, vitamin E, selenium, total meat, poultry, fish, cheese, yoghurt, total fluid intake, coffee, alcohol, multivitamin supplements, physical activity, energy intake and body fatness.

Evidence for the following exposures that was also previously too limited to draw conclusions in the Second Expert Report, and not updated as part of the CUP Bladder SLR 2014 due to a lack of new evidence, remains ‘limited – no conclusion’: cereals (grains) and their products, pulses (legumes), eggs, total fat, butter, dietetic foods, soft drinks, diet drinks, fruit juices, caffeine, chlorinated surface water, sweeteners, frying, carbohydrate, protein, vitamin A, folate, beta-carotene, alpha-carotene, lycopene, beta-cryptoxanthin, lutein, zeaxanthin and flavonoids.

In addition, evidence for the following new exposures for which no judgement was made in the Second Expert Report is too limited to draw any conclusions: height, red meat, processed meat, folic acid supplements, calcium, serum 25-hydroxy vitamin D, vitamin E supplements and tocopherols.

8. Comparison with the Second Expert Report

The evidence from the additional cohort studies identified by the CUP on arsenic in drinking water strengthened the evidence reported in the Second Expert Report, and the conclusion was upgraded from ‘limited – suggestive’ to ‘probable’. Much of the new evidence in the CUP related to vegetables and fruit, and tea, for which no conclusion was possible in the Second Expert Report. New evidence for milk and dairy was less consistent than previously, and a conclusion could not be drawn.
9. Conclusions

The CUP Panel concluded:

◆ Arsenic: Consumption of arsenic in drinking water is probably a cause of bladder cancer.

◆ Vegetables and fruit: The evidence suggesting that greater consumption of vegetables and fruit decreases the risk of bladder cancer is limited.

◆ Tea: The evidence suggesting that greater consumption of tea decreases the risk of bladder cancer is limited.

For a full description of the definitions of, and criteria for, the terminology of ‘convincing’, ‘probable’, ‘limited – suggestive’, ‘limited – no conclusion’ and ‘substantial effect on risk unlikely’, see the Appendix.

The CUP database is being continually updated for all cancers. The Cancer Prevention Recommendations will be reviewed in 2017 when the Panel has reviewed the conclusions for the other cancers.
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Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AICR</td>
<td>American Institute for Cancer Research</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CUP</td>
<td>Continuous Update Project</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>HvL</td>
<td>Highest vs. lowest analysis</td>
</tr>
<tr>
<td>I²</td>
<td>Heterogeneity</td>
</tr>
<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
</tr>
<tr>
<td>n</td>
<td>Number of cases</td>
</tr>
<tr>
<td>No.</td>
<td>Number</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SLR</td>
<td>Systematic literature review</td>
</tr>
<tr>
<td>WCRF</td>
<td>World Cancer Research Fund</td>
</tr>
</tbody>
</table>
Glossary

Adenocarcinoma
Cancer of glandular epithelial cells.

Adjustment
A statistical tool for taking into account the effect of known confounders (see confounder).

Antioxidant
Any substance that inhibits oxidation or traps or quenches reactive oxygen species generated during metabolism.

Apoptosis
The regulated process of programmed cell death that occurs during an organism’s life cycle. A lack of apoptosis can result in uncontrolled cell proliferation.

Bias
In epidemiology, deviation of an observed result from the true value in a particular direction (systematic error) due to factors pertaining to the observer or to study design or analysis. See also selection bias.

Body mass index (BMI)
Body weight expressed in kilograms divided by the square of height expressed in metres (BMI = kg/m²). It provides an indirect measure of body fatness. Also called Quetelet’s Index.

Carcinogen
Any substance or agent capable of causing cancer.

Carcinoma
A malignant tumour derived from epithelial cells, usually with the ability to spread into surrounding tissue (invasion) and produce secondary tumours (metastases).

Carcinoma in situ
The first stage of carcinoma, in which the malignant tumour has not spread beyond the epithelium.

Case-control study
An epidemiological study in which the participants are chosen based on their disease or condition (cases) or lack of it (controls), to test whether distant or recent history of an exposure such as smoking, genetic profile, alcohol consumption or dietary intake is associated with the risk of disease.

Cell proliferation
An increase in cell numbers as a result of cell growth and division.

Chromosomal mutagen
An agent that induces mutations involving more than one gene, typically large deletions or rearrangements.

Cohort study
A study of a (usually large) group of people whose characteristics are recorded at recruitment (and sometimes later), followed up for a period of time during which outcomes of interest are noted. Differences in the frequency of outcomes (such as disease) within the cohort are calculated in relation to different levels of exposure to factors of interest for example, smoking, alcohol consumption, diet and exercise. Differences in the likelihood of a particular outcome are presented as the relative risk, comparing one level of exposure to another.
**Confidence interval (CI)**  
A measure of the uncertainty in an estimate, usually reported as 95 per cent confidence interval (CI), which is the range of values within which there is a 95 per cent chance that the true value lies. For example, the effect of smoking on the relative risk of lung cancer in one study may be expressed as 10 (95% CI 5–15). This means that in this particular analysis, the estimate of the relative risk was calculated as 10, and that there is a 95 per cent chance that the true value lies between 5 and 15.

**Confounder**  
A variable that is associated both with an exposure and a disease, but is not in the causal pathway from the exposure to the disease. If not adjusted for within a specific epidemiological study, this factor may distort the apparent exposure–disease relationship. An example is that smoking is related both to coffee drinking and to risk of lung cancer, and thus unless accounted for (controlled) in studies, might make coffee drinking appear falsely as a cause of lung cancer.

**Deoxyribonucleic acid (DNA)**  
The double-stranded, helical molecular chain found within the nucleus of each cell that carries the genetic information.

**Dietary fibre**  
Constituents of plant cell walls that are not digested in the small intestine. Several methods of analysis are used, which identify different components. The many constituents that are variously included in the definitions have different chemical and physiological features that are not easily defined under a single term. The different analytical methods do not generally characterise the physiological impact of foods or diets. Non-starch polysaccharides are a consistent feature and are fermented by colonic bacteria to produce energy and short-chain fatty acids, including butyrate. The term ‘dietary fibre’ is increasingly seen as a concept describing a particular aspect of some dietary patterns (see Second Expert Report Box 4.1.2).

**Dose-response**  
A term derived from pharmacology that describes the degree to which an effect changes with the level of an exposure, for instance, intake of a drug or food (see Second Expert Report Box 3.2).

**Exposure**  
A factor to which an individual may be exposed to varying degrees, such as intake of a food, level or type of physical activity, or aspect of body composition.

**Heterogeneity**  
A measure of difference between the results of different studies addressing a similar question. In meta-analysis, the degree of heterogeneity may be calculated statistically using the I^2 test.

**High-income countries**  
As defined by the World Bank, countries with a gross average annual national product of more than an agreed figure per head (in 2006 this was more than US$ 10,726). This term is more precise than, and used in preference to, ‘economically developed countries’.

**Incidence rates**  
The number of new cases of a condition appearing during a specified period of time expressed relative to the size of the population; for example, 60 new cases of breast cancer per 100,000 women per year.
Inflammation
The immunologic response of tissues to injury or infection. Inflammation is characterised by accumulation of white blood cells that produce several bioactive chemicals (cytokines), causing redness, heat, pain and swelling.

Lesion
A general term for any abnormality of cells or tissues, including those due to cancer.

Low-income countries
As defined by the World Bank, countries with a gross average annual national product of less than an agreed figure per head (in 2006, this was US$ 875). This term is more precise than and used in preference to ‘economically developing countries’.

Malignant
The capacity of a tumour to spread to surrounding tissue (invasion) or to other sites in the body (metastasis).

Meta-analysis
The process of using statistical methods to combine the results of different studies.

Metastasis
The spread of malignant cancer cells to locations around the body remote from the original site.

Mutation
In biology, a mutation is a permanent change of the nucleotide sequence of the genome (an organism’s complete set of DNA).

Odds ratio (OR)
A measure of the risk of an outcome such as cancer, associated with an exposure of interest, used in case-control studies; approximately equivalent to the relative risk (RR).

Oncogene
A gene that has the potential to cause cancer. Normal genes may become oncogenes through mutations or altered expression, usually in combination with other genetic changes. Oncogenes can halt apoptosis in cells, causing uncontrolled cell proliferation.

Oxidative stress
A state whereby levels of reactive oxygen species (chemically reactive molecules containing oxygen) surpass an organism’s ability to detoxify or repair resultant damage. Some oxidants are generated in the normal course of metabolism; however, excessive oxidation results in damage to cells or structures in cells, including DNA, which can induce cell proliferation.

p53
A protein central to the regulation of cell growth. Mutations of the p53 gene are important causes of cancer (see oncogene and Second Expert Report Box 2.2).

Pathogenesis
The origin and development of disease. The mechanisms by which causal factors increase the risk of disease.

Physical activity
Any movement using skeletal muscles.

Phytochemicals
Compounds found in plants not required for normal structure or function in humans, which may modify physiological functions and influence health (see Second Expert Report Box 4.2.2).
Polyphenol
Molecules produced by plants as secondary metabolites. Flavonoids and phenolic acids are types of polyphenols. Dietary sources include fruit and vegetables and beverages such as tea, coffee and red wine. Certain polyphenols have antioxidant properties and may protect against damage from oxidative stress, including cellular and genetic damage predisposing cancer.

Pooled analysis
In epidemiology, a type of study in which original individual-level data from two or more original studies are obtained, combined and re-analysed.

Processed meat
Meat (usually red meat) that is preserved by smoking, curing or salting, or by the addition of preservatives. Definitions vary between countries and studies as to what precisely is included (see Second Expert Report Box 4.3.1).

Randomised controlled trial (RCT)
A study in which a comparison is made between one intervention (often a treatment or prevention strategy) and another (control). Sometimes the control group receives an inactive agent (a placebo). Groups are randomised to one intervention or the other, so that any difference in outcome between the two groups can be ascribed with confidence to the intervention. Neither investigators nor subjects usually know to which intervention they have been randomised; this is called ‘double-blinding’ (see Second Expert Report section 3.1.6).

Reactive oxygen species
An oxygen-containing radical or reactive ion that oxidises DNA (removes electrons); may be hydroxyl radical (HO•), hydrogen peroxide (H₂O₂) or superoxide radical (O₂•–).

Relative risk (RR)
The ratio of the rate of disease (incidence) or death (mortality) among people exposed to a factor to the rate among the unexposed, usually used in cohort studies (see ‘odds ratio’).

Selection bias
Bias arising from the procedures used to select study participants and from factors influencing participation.

Standardised mortality ratio
Ratio of observed deaths in the studied group to expected deaths in the general population.

Statistical significance
The probability that any observed result has or has not occurred by chance. Conventionally, a probability of less than 5 per cent (p < 0.05) that a study result has occurred by chance is considered ‘statistically significant’ (see confidence interval).

Systematic literature review (SLR)
A means of compiling and assessing published evidence that addresses a scientific question with a predefined protocol and transparent methods (see Second Expert Report Box 3.4).

Tocopherol
The generic chemical term for the several forms of vitamin E.

Tumour suppressor gene
A gene that protects a cell from one step on the path to cancer. When this gene mutates to cause a loss of, or reduction in, its function, the cell can progress to cancer, usually in combination with other genetic changes.
References


Appendix – Criteria for grading evidence
(Taken from Chapter 3 of the Second Expert Report [1])

This appendix lists the criteria 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 (STRONG EVIDENCE)
This judgement is 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 are 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, from either human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes.

PROBABLE (STRONG EVIDENCE)
This judgement is 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 are 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

This judgement is for evidence that is too limited to permit a probable or convincing causal judgement, but is 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 judgement almost always does not justify recommendations designed to reduce the incidence of cancer. Any exceptions require special explicit justification.

All of the following are 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 judgement represents an entry level and is intended to encompass 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 World Cancer Research Fund International website (wcrf.org). However, such evidence is usually not included in the summaries.

SUBSTANTIAL EFFECT ON RISK UNLIKELY (STRONG EVIDENCE)

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 are 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 and 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. An exposure that might be deemed a ‘limited – suggestive’ causal factor in the absence, for example, of a biological gradient, might be upgraded to ‘probable’ if it were present. 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.

*Factors may include:*

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.
Our Cancer Prevention Recommendations

Be a healthy weight
Keep your weight as low as you can within the healthy range

Move more
Be physically active for at least 30 minutes every day, and sit less

Avoid high-calorie foods and sugary drinks
Limit high-calorie foods (particularly processed foods high in fat or added sugar, or low in fibre) and avoid sugary drinks

Enjoy more grains, veg, fruit and beans
Eat a wide variety of whole grains, vegetables, fruit and pulses such as beans

Limit red meat and avoid processed meat
Eat no more than 500g (cooked weight) a week of red meat, such as beef, pork and lamb. Eat little, if any, processed meat such as ham and bacon

For cancer prevention, don’t drink alcohol
For cancer prevention, it’s best not to drink alcohol. If you do, limit alcoholic drinks to two for men and one for women a day

Eat less salt and avoid mouldy grains & cereals
Limit your salt intake to less than 6g (2.4g sodium) a day by adding less salt and eating less food processed with salt
Avoid mouldy grains and cereals as they may be contaminated by aflatoxins

For cancer prevention, don’t rely on supplements
Eat a healthy diet rather than relying on supplements to protect against cancer

If you can, breastfeed your baby
If you can, breastfeed your baby for six months before adding other liquids and foods

Cancer survivors should follow our Recommendations (where possible)
After cancer treatment, the best advice is to follow the Cancer Prevention Recommendations. Check with your health professional