Diet, nutrition, physical activity and lung cancer

Revised 2018
WORLD CANCER RESEARCH FUND NETWORK

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)

The Continuous Update Project (CUP) is the World Cancer Research Fund (WCRF) Network’s ongoing programme to analyse cancer prevention and survival research related to diet, nutrition and physical activity from all over the world. Among experts worldwide it is a trusted, authoritative scientific resource which informs current guidelines and policy on cancer prevention and survival.

Scientific research from around the world is continually added to the CUP’s unique database, which is held and systematically reviewed by a team at Imperial College London. An independent panel of experts carries out ongoing evaluations of this evidence, and their findings form the basis of the WCRF Network’s Cancer Prevention Recommendations (see inside back cover).

Through this process, the CUP ensures that everyone, including policymakers, health professionals and members of the public, has access to the most up-to-date information on how to reduce the risk of developing cancer.

The launch of the WCRF Network’s Third Expert Report, Diet, Nutrition, Physical Activity and Cancer: a Global Perspective, in 2018 brings together the very latest research from the CUP’s review of the accumulated evidence on cancer prevention and survival related to diet, nutrition and physical activity. Diet, nutrition, physical activity and lung cancer is one of many parts that make up the CUP Third Expert Report: for a full list of contents, see dietandcancerreport.org.

The CUP is led and managed by World Cancer Research Fund International in partnership with the American Institute for Cancer Research, on behalf of World Cancer Research Fund UK, Wereld Kanker Onderzoek Fonds and World Cancer Research Fund HK.

HOW TO CITE THIS REPORT


KEY

References to other parts of the Third Expert Report are highlighted in purple.
EXECUTIVE SUMMARY

Background and context

Lung cancer is the third most common cancer worldwide. About 1.8 million new cases of lung cancer were recorded globally in 2012, accounting for 13 per cent of all new cases of cancer [2].

Lung cancer is the most common cause of death from cancer, estimated to be responsible for nearly one in five cancer deaths. Lung cancer survival is mostly determined by the stage at which it is diagnosed, with later-stage diagnosis having poorer survival. In the United States, the five-year survival rate is 17 per cent for lung cancer overall. However, this rises to 55 per cent for lung cancers diagnosed at an early stage.

About 58 per cent of cases of lung cancer worldwide occur in developing countries. In men lung cancer is the most common cancer diagnosed, and the highest lung cancer rates are in Central and Eastern Europe and Eastern Asia. In women lung cancer is the third most common cancer, and the highest rates are in North America, Northern Europe and Eastern Asia [2].

Rates of lung cancer incidence in many developed countries are declining because fewer people are smoking. Conversely, in some countries, including China, South Korea and several countries in Africa, smoking rates are peaking or continuing to increase and the number of new lung cancer cases continues to rise.

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 analyse global research on how certain lifestyle factors affect the risk of developing lung cancer. This research 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 lung cancer include the following:

1. **Smoking**
   - Smoking is the main cause of lung cancer. It is estimated that over 90 per cent of cases among men and over 80 per cent among women worldwide are attributable to tobacco use. Passive smoking is also a cause of lung cancer.

2. **Previous lung disease**
   - A history of emphysema, chronic bronchitis, tuberculosis or pneumonia is associated with an increased risk of lung cancer. People with antibodies to *Chlamydia pneumoniae*, a type of bacterium that can cause chest infections, have an increased risk of lung cancer.

3. **Other exposures**
   - Occupational exposure to asbestos, crystalline silica, radon, mixtures of polycyclic aromatic hydrocarbons and heavy metals are associated with an increased risk of lung cancer as well as indoor air pollution from wood and coal burning for cooking and heating.

**How the research was conducted**

The global scientific research on diet, weight, physical activity and the risk of lung 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 lung cancer.

More research has accumulated on this topic since our 2007 Second Expert Report [1]. In total, this new report analyses 124 studies from around the world, covering nearly 14 million adults and over 122,000 cases of lung cancer.

To ensure consistency, the methodology for the Continuous Update Project remains largely unchanged from that used for our 2007 Second Expert Report [1].

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

There is strong evidence that:

- There is strong evidence that drinking water containing arsenic increases the risk of lung cancer.
- In current and former smokers there is strong evidence that taking high-dose beta-carotene supplements increases the risk of lung cancer.

There is some evidence that:

- There is some evidence that suggests consuming red meat, processed meat and alcoholic drinks increases the risk of lung cancer.
- In current smokers and former smokers there is some evidence that suggests consuming vegetables and fruit decreases the risk of lung cancer.
- There is some evidence that suggests consuming foods containing retinol, beta-carotene or carotenoids decreases the risk of lung cancer.
- In current smokers there is some evidence that suggests consuming foods containing vitamin C decreases the risk of lung cancer.
- In people who have never smoked there is some evidence suggesting that consuming foods containing isoflavones (constituent of plants with oestrogen-like properties) decreases the risk of lung cancer.
- There is some evidence that suggests being physically active decreases the risk of lung cancer.

Recommendations

Our Cancer Prevention Recommendations – for preventing cancer in general – include maintaining a healthy weight, being physically active and eating a healthy diet. The Cancer Prevention Recommendations are listed on the inside back cover of this report, with full details available in Recommendations and public health and policy implications.

References


## DIET, NUTRITION, PHYSICAL ACTIVITY AND LUNG CANCER

<table>
<thead>
<tr>
<th>Evidence Level</th>
<th>Decreases Risk</th>
<th>Increases Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>Convincing</td>
<td>Arsenic in drinking water&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High-dose beta-carotene supplements&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Probable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited – suggestive</td>
<td>Vegetables&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Red meat</td>
</tr>
<tr>
<td></td>
<td>Fruit&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Processed meat</td>
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<tr>
<td></td>
<td>Foods containing carotenoids</td>
<td>Alcoholic drinks</td>
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<tr>
<td></td>
<td>Foods containing beta carotene</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Foods containing retinol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Foods containing vitamin C&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Foods containing isoflavones&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Physical activity</td>
<td></td>
</tr>
<tr>
<td>Limited – no conclusion</td>
<td>Cereals (grains) and their products; starchy tubers;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>vegetables (never smokers); fruits (never smokers);</td>
<td></td>
</tr>
<tr>
<td></td>
<td>dietary fibre; pulses (legumes); citrus fruits; poultry; fish; eggs; milk and dairy products; total meat; total fat; animal fats; plant oils; soft drinks; coffee; tea; preservation, processing, and preparation; carbohydrate; protein; vitamin A; thiamin; riboflavin; niacin; vitamin B6; folate; foods containing vitamin C (former and never smokers); vitamin E; selenium; calcium; copper; iron; zinc; beta-carotene supplements (never and former smokers); alpha-carotene; lycopene; beta-cryptoxanthin, lutein and zeaxanthin; foods containing isoflavones (current and former smokers); plasma hydroxyvitamin D; vitamin C supplements; retinol supplements; multivitamin supplements; patterns of diet; body fatness; energy intake; height</td>
<td></td>
</tr>
<tr>
<td>Strong</td>
<td>Substantial effect on risk unlikely</td>
<td></td>
</tr>
</tbody>
</table>

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

<sup>2</sup> The evidence is derived from studies using high-dose supplements (20 mg/day for beta-carotene; 25,000 IU/day for retinol) in current and former smokers.

<sup>3</sup> The evidence applies to current and former smokers only.

<sup>4</sup> The evidence applies to current smokers only.

<sup>5</sup> The evidence applies only to individuals who have never smoked.
1. Summary of Panel judgements

Overall, the Panel notes the strength of the evidence that arsenic in drinking water and beta-carotene supplements (high doses in smokers) are causes of lung cancer.

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

**Convincing evidence**

Arsenic in drinking water: Consumption of arsenic in drinking water is a convincing cause of lung cancer.

Beta-carotene supplements: Consumption of high-dose beta-carotene supplements is a convincing cause of lung cancer in current and former smokers.

**Limited-suggestive evidence**

Vegetables: The evidence suggesting that consumption of vegetables decreases the risk of lung cancer in current and former smokers is limited.

Fruit: The evidence suggesting that consumption of fruit decreases the risk of lung cancer in current and former smokers is limited.

Foods containing carotenoids: The evidence suggesting that foods containing carotenoids decrease the risk of lung cancer is limited.

Foods containing beta-carotene: The evidence suggesting that foods containing beta-carotene decrease the risk of lung cancer is limited.

Foods containing retinol: The evidence suggesting that foods containing retinol decrease the risk of lung cancer is limited.

Foods containing vitamin C: The evidence suggesting that foods containing vitamin C decrease the risk of lung cancer in current smokers is limited.

Foods containing isoflavones: The evidence suggesting that foods containing isoflavones decrease the risk of lung cancer in individuals who have never smoked is limited.

Physical activity: The evidence suggesting that physical activity decreases the risk of lung cancer is limited.

Red meat: The evidence suggesting that consumption of red meat increases the risk of lung cancer is limited.

Processed meat: The evidence suggesting that consumption of processed meat increases the risk of lung cancer is limited.

Alcoholic drinks: The evidence suggesting that consumption of alcoholic drinks increases the risk of lung 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 on page 67. The Panel judgements for lung cancer are shown in the matrix on page 8.

2. Trends, incidence and survival

The lungs are part of the respiratory system and lie in the thoracic cavity. Air enters the lung through the trachea which divides into two main bronchi, each of which is subdivided into several bronchioles which terminate in clusters of alveoli.

The two main types of lung cancer are small-cell lung cancer and non-small-cell lung cancer (NSCLC); NSCLC accounts for 85 to 90 per cent of all cases of lung cancer and has three major subtypes: squamous cell carcinoma, adenocarcinoma and large-cell carcinoma. Adenocarcinoma and squamous cell carcinoma are the most frequent histologic subtypes, accounting for 50 per cent and 30 per cent of NSCLC cases, respectively [3]. Small-cell lung cancer accounts for 10–15 per cent of all lung cancers; this form is a distinct pathological entity and characterised by aggressive biology, propensity for early metastasis and overall poor prognosis.

Incidence and mortality

Smoking and other exposure to tobacco smoke are the principal causes of lung cancer. Lung cancer patterns are largely determined by exposure to tobacco smoking; pooled estimates indicate over 90 per cent of cases in men are due to smoking and over 80 per cent in women [4], although there is considerable variation by world region. Age-adjusted rates of lung cancer are decreasing in many high-income countries due to decreased smoking rates; however, lung cancer remains the third most common type of cancer worldwide. There were an estimated 1.8 million new cases in 2012 (accounting for 13 per cent of all cases of cancer), 58 per cent of which occurred in less developed regions. The disease remains the most common cancer in men worldwide (1.2 million, 17 per cent of all cancers) and the third most common cancer in women (583,000, 9 per cent of all cancers). In men, the highest estimated, age-standardised, incidence rates occur in Central and Eastern Europe and Eastern Asia. Globally, the lowest incidence rates are observed in middle and western Africa. Incidence rates are generally lower in women and the geographical pattern is different, mainly due to different historical exposure to tobacco smoking. The highest estimated rates in women are in northern America and northern Europe with a relatively high rate in eastern Asia. Again, the lowest rates are observed in western and middle Africa where historically the marketing of tobacco products has been more limited.

Estimated to be responsible for nearly one in five deaths from cancer, lung cancer is the most common cause of death from cancer worldwide (1.59 million deaths, 19.4 per cent of the total) and is the leading cause of death in men in 91 countries and in women in 17 countries [5]. Smoking accounts for about 80 per cent of global lung cancer deaths in men and 50 per cent of the deaths in women [6, 7], though passive smoking may account for a further proportion in women.
Trends

Lung cancer trends are largely the product of changing patterns in prevalence of tobacco consumption, and international variations in lung cancer rates and trends largely reflect differences in the stage and degree of tobacco consumption [8, 9]. Lung cancer rates have been decreasing in men and plateauing in women [10, 11] in several Western countries where tobacco consumption was established and peaked by the middle of the last century, including the United States, the United Kingdom, Canada and Australia. In contrast, in countries where consumption is more recently established and rates of smoking have just peaked or continue to increase, including China, South Korea and several countries in Africa, lung cancer rates are increasing, and they are likely to continue to increase for at least the next few decades, barring interventions to accelerate smoking cessation [8, 12].

Lung cancer trends vary by histological subtype. Although smoking increases the risk of all subtypes of lung cancer, squamous cell carcinoma is more strongly related to smoking and rarely seen in non-smokers whereas adenocarcinoma is seen in both smokers and non-smokers, and is the most common type in never smokers [4, 13, 14]. In men, a recent change of most common cell type from squamous cell to adenocarcinoma has been observed [15], likely related to a decline in the use of unfiltered cigarettes. Adenocarcinoma is responsible for a greater proportion of lung cancer in women than in men, with increasing rates of this subtype observed in both sexes in many high-income settings [16, 17].

Survival

The geographical patterns in lung cancer mortality closely follow those in incidence, owing to the high fatality rates, which are similar across world regions. Lung cancer survival is mostly determined by the disease stage, with later-stage diagnosis having poorer prognosis [18]. Close to 70 per cent of patients with NSCLC present with locally advanced or metastatic disease at the time of diagnosis [19]. The overall prognosis is poor; in the United States the five-year survival rate is 17 per cent (rising to 55 per cent for the 16 per cent of lung cancers diagnosed at an early stage) [20], and in the United Kingdom it is 10 per cent [21]. See Box 1 for more information.
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 probably higher than the figures given here.

Most information on cancer survival is for the United States 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.

3. Pathogenesis

Carcinogens in tobacco smoke and other inhaled particles, such as coal tar or asbestos, can interact directly with the DNA of lung cells. Because the whole lung is exposed to inhaled carcinogens, several sites may accumulate different cancerous changes, leading to multiple cancers originating in different types of cells. Chronic inflammation may also play a role in the development of lung cancer, with cancerous changes occurring as a response to exposure to irritants and repeated injury.

Molecular changes in the mucosa of smokers that predispose to cancer are now being identified. Dysplasia and carcinoma in situ are histopathologic changes predictive of future development of invasive carcinoma.

This process may take many years or decades depending upon the exposure to cancer-initiating and cancer-promoting components. People with lung adenocarcinomas may have an associated history of chronic lung disease, such as scleroderma, rheumatoid disease, sarcoidosis or tuberculosis.
4. Other established causes

**Tobacco use**

Smoking is the principal cause of lung cancer; it is estimated to be responsible for over 90 per cent of cases among men and over 80 per cent among women [4]. Involuntary exposure to tobacco smoke in people who have never smoked (‘passive smoking’) is also a cause of lung cancer [22].

**Environmental exposures**

The most important occupational and environmental lung carcinogens include asbestos, crystalline silica, radon, mixtures of polycyclic aromatic hydrocarbons and heavy metals [23], as well as indoor air pollution from burning wood and coal for cooking and heating [24].

**Previous lung disease**

A history of emphysema (144 per cent increased risk), chronic bronchitis (47 per cent), tuberculosis (48 per cent) or pneumonia (57 per cent) is associated with an increased risk of lung cancer [25].

5. Interpretation of the evidence

**5.1 General**

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

‘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 lung cancer include the following:

Confounding

Smoking tobacco is the predominant cause of lung cancer. Smokers tend to have less healthy diets, more sedentary ways of life and lower body weight than non-smokers. Therefore a central task in assessing the results of dietary studies is to evaluate the degree to which observed associations in smokers may be due to residual confounding by cigarette smoking; that is, not a direct result of the dietary exposure examined. For most exposures, studies included in these analyses adjusted for smoking, though this may not completely mitigate the problem. Stratification by smoking status can be useful, but typically the number of lung cancers in never smokers is limited. Moreover, if an association is observed in current smokers but not in never smokers, residual confounding in smokers may be an explanation, but it is also plausible that the factor is only operative in ameliorating or enhancing the effects of cigarette smoke. It is also important to differentiate residual confounding from a true effect limited to smokers. Because smoking is such a strong risk factor for lung cancer, residual confounding remains a likely explanation, especially when the estimated risks are of moderate magnitudes.

The relationship between smoking and body composition presents particular problems in interpretation of observational data in relation to lung cancer. Smokers tend to have lower body mass index (BMI) than non-smokers (except for very heavy smokers), and so lower BMI may appear to be associated with increased risk (and conversely, higher BMI with decreased risk) of smoking-related cancers because of confounding by smoking, and imprecision in ascertainment of exposure to smoking makes residual confounding a likely consequence. Furthermore, despite the tendency toward lower BMI among smokers, they also tend to have greater waist circumference. These anthropometric measures are valuable markers of body composition in observational epidemiology but are not able to precisely characterise the proportions of lean and fat tissue, nor the distribution of body fat. The metabolic consequences of greater body fatness (which are responsible for associations between body composition and cancer risk) may be more pronounced in relation to visceral adiposity, which is not marked by BMI. Furthermore, low BMI may reflect predominant loss of lean rather than fat mass, and this may be a consequence of pre-existing disease or a marker of disease severity. Therefore, current evidence is insufficient to elucidate the complex interactions between body size, shape and composition, and metabolic state (including inflammation and hormonal status) in relation to smoking, other related behaviours and lung cancer risk.
6. Methodology

To ensure consistency with evidence collected and analysed for the Second Expert Report [1], the methodology for reviewing the epidemiological evidence in the Continuous Update Project (CUP) remains largely unchanged. However, on the basis of 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, and cohort and nested case-control studies. Owing to their methodological limitations, and because of the copious prospective data, case-control studies were not analysed in the CUP Lung SLR 2015.

Where possible for this update, meta-analyses for incidence and mortality were conducted separately. However, analyses combining studies on lung cancer incidence and mortality were also conducted to explore whether this outcome could explain any heterogeneity in the results. Separate meta-analyses were also conducted for men and women, and by geographical location, where possible. Separate estimates were provided for former, current and never smokers when possible; however, this was not possible for all exposures.

Studies reporting mean difference as a measure of association were not included in the CUP Lung SLR 2015, 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 used 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 Lung SLR 2015.

The CUP Lung SLR 2015 included studies published up to 30 September 2014. For more information on the methodology, see the full CUP Lung SLR 2015 at wcrf.org/lung-cancer-slr.
6.1 Mechanistic evidence

The evidence for mechanisms is summarised under each exposure. These summaries were developed from mechanistic reviews conducted for the Second Expert Report [1], updates from CUP Panel members and published reviews.

Update: The evidence for site specific mechanisms of carcinogenesis has been updated for the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report 2018 (our Third Expert Report, available at dietandcancerreport.org). The evidence is based on both human and animal studies. It covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature. A signpost to the relevant section in the Third Expert Report which summarises the updated mechanisms evidence can be found under each exposure within this report.

7. Evidence and judgements

The following sections summarise the evidence identified in the CUP Lung SLR 2015 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 on page 67 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 Lung SLR 2015.
7.1 Arsenic in drinking water

(Also see CUP Lung SLR 2015: Section 4.1.2.7.2)

The CUP identified four new publications [26-29]. Ten publications from five studies on arsenic and lung cancer were identified in total (summarised in Table 1; see CUP Lung SLR Table 98). From the four recent publications, three were on arsenic in drinking water [26, 28, 29] and one was on dietary arsenic intake from foods [27]. Two studies on arsenic in drinking water were on populations with high exposure to arsenic [26, 28] and one study was from an area with low exposure [29]. The measurement of exposure to arsenic in drinking water was based on arsenic levels in well water. Cumulative exposure was calculated from the amount of water consumed and the years of residence in the area. In one study [27], exposure to dietary arsenic was based on questionnaire data. Four of the studies did not adjust for smoking status [30–33].

The studies from areas with high exposure to arsenic [26, 28] showed a significant increased risk of lung cancer with increasing levels of cumulative exposure to arsenic from drinking water. No significant association with risk of lung cancer was observed in the Danish Cohort Study, which is in a population with low levels of exposure to arsenic in drinking water [29]. One study on arsenic from foods [27] reported a borderline significant dose-response association of total arsenic and inorganic arsenic intake and risk of lung cancer in males. Due to the variability in median arsenic exposure and outcomes across studies, it was not possible to conduct meta-analyses. See Table 1 (CUP Lung SLR 2015 Table 98).
<table>
<thead>
<tr>
<th>Study description</th>
<th>No. cases (No. participants) years of follow-up</th>
<th>Sex</th>
<th>RR (95% CI)</th>
<th>Exposure / Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIGH-EXPOSURE AREAS</strong></td>
<td></td>
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<tr>
<td>Chung, 2013 (Taiwan, Arsenic Study) [26]</td>
<td>71 (1,563) 20 years</td>
<td>Mixed</td>
<td>1.47 (0.66–3.31)</td>
<td>≥ 19.5 vs. &lt; 9.1 (μg/L * year)</td>
</tr>
<tr>
<td></td>
<td>43 cases Men *SMR 6.05 (4.38–8.15)</td>
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<tr>
<td></td>
<td>28 cases Women *SMR 7.18 (4.77–10.38)</td>
<td></td>
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<tr>
<td>Chen, 2010 Taiwan (North-eastern Taiwan cohort) [28]</td>
<td>178 (6,888) 11 years</td>
<td>Mixed</td>
<td>2.08 (1.33–3.27) Ptrend: &lt; 0.01</td>
<td>≥ 10,000 vs. &lt; 400 (μg/L year)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.25 (1.43–3.55) Ptrend: &lt; 0.01</td>
<td>≥ 300 vs. &lt; 10 μg/L</td>
</tr>
<tr>
<td>Chen, 2004 (South-western and north-eastern Taiwan) [34]</td>
<td>139 (10,591) 8 years</td>
<td>Mixed</td>
<td>3.29 (1.60–6.78)</td>
<td>≥ 700 vs. &lt; 10 μg/L</td>
</tr>
<tr>
<td>Nakadaira, 2002 (Nakajo Town Study, Japan) [30]</td>
<td>7 (86) 34 years</td>
<td>Men</td>
<td>11.01</td>
<td>Observed deaths vs. expected</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women</td>
<td>5.34</td>
<td>Observed deaths vs. expected</td>
</tr>
<tr>
<td>Chiou, 1995 (South-western Taiwan cohort) [35]</td>
<td>17 (2,256) 5 years</td>
<td>Mixed</td>
<td>4.01 (1.00–16.12)</td>
<td>High vs. unexposed mg/L</td>
</tr>
<tr>
<td>Tsuda, 1995 (Japan 1959-1992) [31]</td>
<td>9 (454) 33 years</td>
<td>Mixed</td>
<td>*SMR 15.69 (7.38–31.02)</td>
<td>≥ 1 ppm</td>
</tr>
<tr>
<td>Tsuda, 1989 (Nakajo Japan) [32]</td>
<td>6 (281) 28 years</td>
<td>Mixed</td>
<td>*SMR 1,641 (715–3,634)</td>
<td>≥ 0.5 ppm</td>
</tr>
<tr>
<td>Chen, 1988 (Taiwan study) [33]</td>
<td>27 (1,008) 16 years</td>
<td>Mixed</td>
<td>*SMR 1,049</td>
<td>***BFD patients vs. general population</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>*SMR 284</td>
<td>***BFD patients vs. residents in BFD-endemic area</td>
</tr>
<tr>
<td><strong>LOW-EXPOSURE AREAS</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Baastrup, 2008 (Danish Diet Cancer and Health cohort) [29]</td>
<td>402 (56,378) 10 years</td>
<td>Mixed</td>
<td>**IRR 0.99 (0.90–1.08)</td>
<td>Per 1 μg/L</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>**IRR 1.00 (0.98–1.03)</td>
<td>Per 5 mg/L</td>
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<tr>
<td><strong>ARSENIC IN FOODS</strong></td>
<td></td>
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<tr>
<td>Sawada, 2013 (Japan Public Health Centre study) [27]</td>
<td>685 men, 254 women (90,378) 11 years</td>
<td>Men</td>
<td>1.28 (1.00–1.62) Ptrend: 0.05</td>
<td>102.2 vs. 36.5 μg/day (inorganic arsenic)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women</td>
<td>1.37 (0.95–1.98) Ptrend: 0.08</td>
<td>107.6 vs. 37.1 μg/day (inorganic arsenic)</td>
</tr>
</tbody>
</table>

The CUP Lung SLR 2015 findings were similar to the findings from the 2005 SLR. The CUP Lung SLR 2015 included more cohort studies and more cases of lung cancer.

**Mechanisms**

The International Agency for Research on Cancer (IARC) has judged arsenic and arsenic compounds to be carcinogenic to humans [36]. 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. 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 United States [37].

*Update: As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see Exposures: Non-alcoholic drinks (Appendix – Mechanisms) for the updated mechanisms summary.*

**CUP Panel’s conclusion:**

The overall evidence was generally consistent, showing an increased risk of lung cancer with consumption of drinking water containing arsenic. No meta-analysis was possible. There is robust evidence for plausible mechanisms operating in humans. The CUP Panel concluded the following:

*Consumption of arsenic in drinking water is a convincing cause of lung cancer.*

**7.2 Beta-carotene supplements**

*(Also see CUP Lung SLR 2015: Section 5.5.1.2.2)*

The CUP identified one new randomised controlled trial (RCT) [38] and two cohort studies [39, 40], giving a total of six RCTs and five cohort studies.

The new RCT [38] reported no significant effect of 50 mg of beta-carotene every other day (RR 1.26 (95% CI 0.80–1.99)) during an average of 9.4 years of treatment.

Five other RCTs were identified in the 2005 SLR. A summary of the results is presented in Table 2 (CUP Lung SLR 2015 Table 136).
Table 2: Summary of RCTs – beta-carotene supplements

<table>
<thead>
<tr>
<th>Study name and intervention</th>
<th>No. cases</th>
<th>RR (95% CI)</th>
<th>Trial period</th>
<th>Post-trial period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women's Antioxidant Cardiovascular Study [38]</td>
<td>41</td>
<td>1.26</td>
<td>June 1995–Jan 2005</td>
<td></td>
</tr>
<tr>
<td>β-carotene 50 mg every other day vs. placebo</td>
<td>33</td>
<td>1.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily 20 mg β-carotene vs. no β-carotene in male smokers</td>
<td>209</td>
<td>1.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARET study, lung cancer incidence [42]</td>
<td></td>
<td>1.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily β-carotene (30 mg) and retinyl palmitate (25,000 IU) current or former smokers</td>
<td>5.92/ 1,000 person years</td>
<td>4.62/ 1,000 person years</td>
<td>1985–Jan 1996</td>
<td>Feb 1996–Dec 2001</td>
</tr>
<tr>
<td>30 mg/day β-carotene vs. 25,000 IU/day retinol</td>
<td>4</td>
<td>1.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physicians Health Study (PHS) [44]</td>
<td></td>
<td>0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 mg β-carotene on alternate days vs. placebo group</td>
<td>85</td>
<td>0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women’s Health Study [45]</td>
<td>93</td>
<td>0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 mg of β-carotene every other day for 2 years (women)</td>
<td>21</td>
<td>1.43</td>
<td>Apr 1993–Jan 1996</td>
<td>Feb 1998</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>1.43</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Both the ATBC and CARET studies reported significant increased risk of lung cancer during the supplementation period, but at follow-up the effect was reduced and no longer statistically significant.

In the ATBC study, beta-carotene supplementation in those smoking 20+ cigarettes daily was associated with a 25 per cent increased risk of lung cancer (RR = 1.25 (95% CI, 1.07–1.46)) over those smoking 5–19 cigarettes daily, in whom no significant association was observed (RR = 0.97 (95% CI, 0.76–1.33)). Similarly, beta-carotene supplementation in those who consumed 11 grams of ethanol or more was associated with a significant increased risk of lung cancer (RR = 1.35 (95% CI, 1.01–1.81)) compared with the effect of supplementation in lower-alcohol consumers.
In the CARET study, risk of lung cancer was especially elevated in those who had the intervention as well as exposure to either asbestos or smoking (at least 20 pack-years), although neither subgroup was statistically significant.

In the PHS, the risk related to beta-carotene consumption was similar for each smoking category in subgroup analyses.

Four of five cohort studies reported non-significant associations. One [39], a Danish prospective study in men and women, showed a significant increase in lung cancer risk per 5,000 µg/day of beta-carotene supplement (the comparison of > 13,500 vs. 0 µg/day was not significant). A summary of the results from the cohort studies is presented in Table 3 (CUP Lung 2015 SLR Table 137).

### Table 3: Summary of cohort studies – beta-carotene supplements

<table>
<thead>
<tr>
<th>Study</th>
<th>Increment/ Contrast</th>
<th>RR (95% CI)</th>
<th>No. cases</th>
<th>Factors adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virtamo, 2014 ATBC [46]</td>
<td>Beta-carotene vs. no beta-carotene</td>
<td>1.04 (0.96–1.11)</td>
<td>2,881</td>
<td>Age, smoking (number cigarettes/day), alcohol consumption, BMI</td>
</tr>
<tr>
<td>Roswall, 2009 Denmark Cohort [39]</td>
<td>Per 5,000 µg/day</td>
<td>1.64 (1.20–2.23)</td>
<td>721</td>
<td>Age; sex; supplements of folate, vitamin C and vitamin E; smoking status, intensity, duration; passive smoking; smoking cessation; work exposure to carcinogenic substances</td>
</tr>
<tr>
<td></td>
<td>&gt; 13,500 vs. 0 µg/day</td>
<td>1.56 (0.58–4.25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satia, 2009 Vitamins And Lifestyle (VITAL) cohort Study [40]</td>
<td>&gt; 1,200 µg/day vs no use men</td>
<td>1.10 (0.71–1.70)</td>
<td>297</td>
<td>Age; sex; BMI; years of smoking, pack-years and pack-years squared; fruit and vegetable intake; physical activity; supplemental vitamin E use</td>
</tr>
<tr>
<td></td>
<td>&gt; 1,200 µg/day vs no use women</td>
<td>1.49 (0.76–2.58)</td>
<td>224</td>
<td></td>
</tr>
<tr>
<td>Michaud, 2000 Health Professionals Follow-up Study [47]</td>
<td>Use vs. non-use</td>
<td>0.82 (0.36–1.85)</td>
<td>275</td>
<td>Age (5-year categories), smoking status, time since quitting, age at start of smoking quintiles of energy intake, time period</td>
</tr>
<tr>
<td>Michaud, 2000 Nurses’ Health Study [47]</td>
<td></td>
<td>1.23 (0.55–2.76)</td>
<td>519</td>
<td></td>
</tr>
</tbody>
</table>

### Genotype and beta-carotene

As reported in the Second Expert Report [1] there is an interaction between beta-carotene, smoking and genotype. Glutathione-S transferase 1 and 2 are carcinogen-detoxifying enzymes. People without or with less active forms of these enzymes are less able to metabolise certain toxins than others and have higher risk of some cancers, particularly if they are smokers. In the ATBC study, among those not supplemented with beta-carotene, the relative risk of lung cancer among those with the glutathione-
S-transferase variant GSTM1 who smoked more than 42 cigarettes per day compared with those who smoked fewer than 37 cigarettes per day was not significant, while in those without the GSTM1 variant the relative risk for higher compared with lower smoking was RR = 8.2 (95% CI 2.2–29.8). In those who received beta-carotene supplements, the relative risk of lung cancer from smoking more than 42 compared with fewer than 37 cigarettes daily was RR = 3.6 (95% CI 1.1–11.1) in those with the GSTM 1 variant, compared with RR = 6.0 (95% CI 1.9–19.1) among those without.

In another study of Chinese tin miners at high risk of lung cancer, after adjusting for age and smoking habits, those with the wild-type Arg/Arg genotype in the XRCC1 gene had a RR of lung cancer of 3.0 (95% CI 1.3–7.1) comparing the highest and lowest tertiles of serum beta-carotene (190–900 μg/l compared with < 90 μg/l), while no significant association between lung cancer risk and serum beta-carotene was seen in those with the heterozygous or homozygous Arg/Trp or Trp/Trp variants [48].

**Mechanisms**

An adverse effect of higher than physiological blood or tissue concentrations of beta-carotene is plausible. In one animal study, low-dose beta-carotene was protective against smoking-induced changes in p53, whereas high doses promoted these changes [49]. In addition, the complex nature of naturally occurring carotenoids raises the possibility that the protective associations are not due simply to the specific agent, but rather to interactions with other carotenoids present in dietary exposure [50], or other associated dietary or health-related behaviours.

*Update: As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see Exposures: Other dietary exposures (Appendix – Mechanisms) for the updated mechanisms summary.*

**CUP Panel’s conclusion:**

There is strong evidence from good-quality trials, generally consistent with cohort studies. An interaction between smoking, genetics and beta-carotene is apparent; the adverse effect of beta-carotene supplements is seen mainly among heavy smokers, and in particular a subgroup characterised by genetic variation in GSTM. The evidence that high-dose beta-carotene supplements cause lung cancer in current and former smokers is convincing. There is robust evidence for mechanisms operating in humans. The CUP Panel concluded the following:

**High-dose beta-carotene supplements are a convincing cause of lung cancer in current and former smokers.**
7.3 Vegetables

(Also see CUP Lung SLR 2015: Sections 2.2.1, 2.2.1.2 and 2.2.1.4)

The CUP identified five new or updated studies (10 publications) [51-57], giving a total of 24 studies (32 publications) reviewing the evidence for vegetables and lung cancer (see CUP Lung SLR 2015 Tables 15 and 16 for a full list of references). Of 16 studies reporting on lung cancer incidence, 11 reported inverse associations, three of which were significant, three reported non-significant positive associations and two reported inconsistent results for men and women when comparing the highest and lowest categories of intake. Of five studies reporting on lung cancer mortality, three showed inverse associations and one showed a positive association; none of these results were significant. One study reported inconsistent results for men and women when comparing the highest and lowest categories of intake (see CUP Lung SLR 2015 Figure 11).

Twenty of the 24 studies were included in the dose-response meta-analysis (\( n = 12,563 \) cases), which showed a statistically significant six per cent decreased risk per 100 grams of vegetables per day (RR 0.94 (95% CI 0.89–0.98); see CUP Lung SLR 2015, Figure 13). Moderate heterogeneity (\( I^2 = 48\% \)) was observed that was not explained in analyses stratified by sex, smoking or geographic location, but appears to be due to the size of the effect.

There was evidence of a non-linear relationship (\( p < 0.01 \)), with decreasing risks for intakes up to 300–400 grams per day and no further decrease for higher intake levels (CUP Lung SLR 2015 Figure 20 and Table 17). There was evidence of small study bias with Egger’s test (\( p < 0.01 \)). The asymmetry was driven by a small Japanese study reporting on very low intakes (see CUP Lung SLR 2015 Figure 14).

When stratified by smoking status, the dose-response meta-analysis showed a 12 per cent decreased risk per 100 grams per day in current smokers (RR = 0.88 (95% CI 0.79–0.99)). No significant associations were observed for former or never smokers (see Table 4 and CUP Lung SLR 2015 Figure 18).

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Increment</th>
<th>RR (95% CI)</th>
<th>( I^2 )</th>
<th>No. Studies</th>
<th>No. Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smokers</td>
<td>Per 100 g/day</td>
<td>0.88 (0.79–0.99)</td>
<td>81%</td>
<td>6</td>
<td>6,520</td>
</tr>
<tr>
<td>Former smokers</td>
<td>Per 100 g/day</td>
<td>0.97 (0.91–1.05)</td>
<td>25%</td>
<td>4</td>
<td>3,771</td>
</tr>
<tr>
<td>Never smokers</td>
<td>Per 100 g/day</td>
<td>1.00 (0.91–1.10)</td>
<td>0%</td>
<td>5</td>
<td>680</td>
</tr>
</tbody>
</table>

All studies included in the dose-response analysis were adjusted for age, sex and smoking status. Most studies (18 out of 19 studies) also adjusted for intensity and duration of smoking and other smoking variables.
Three studies were not included in any of the CUP analyses; two did not report confidence intervals [58, 59] and one did not report sufficient data [60].

The CUP findings are similar to those from the 2005 SLR, which showed a significant inverse association per 80 grams of vegetables consumed per day (RR = 0.95 (95% CI 0.92–0.98)) for 10 studies. The CUP update includes more than double the number of studies and over 5,000 more cases of lung cancer. No analysis by smoking status was possible for the 2005 SLR.

**Published pooled analyses and meta-analyses**

One published pooled analysis of cohort studies on vegetables and lung cancer risk was identified in the CUP Lung SLR 2015. No significant associations were observed in the pooled analysis when comparing the highest with the lowest vegetable consumers in current, former or never smokers. When the studies identified by the CUP 2015 (but not in the pooled analysis) were combined with the results of the pooled analysis, a significant inverse association was observed overall and in current smokers. Results from the CUP and the published pooled-analysis are presented in Table 5.

**Table 5: Summary of CUP 2015 meta-analysis and published pooled analysis – vegetables**

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Increment/Contrast</th>
<th>RR (95% CI)</th>
<th>I² or P-value</th>
<th>No. Studies</th>
<th>No. Cases</th>
<th>Sub-group</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015 CUP</td>
<td>Per 100 g/day</td>
<td>0.94 (0.89–0.98)</td>
<td>48%</td>
<td>20</td>
<td>12,563</td>
<td></td>
</tr>
<tr>
<td>Pooling Project of cohort studies [61]</td>
<td>Q5 vs. Q1</td>
<td>0.88 (0.78–1.00)</td>
<td>0.76</td>
<td>7</td>
<td>3,206</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q4 vs. Q1</td>
<td>0.86 (0.74–1.00)</td>
<td>0.85</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.97 (0.76–1.24)</td>
<td>0.30</td>
<td>5</td>
<td>981</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.90 (0.58–1.40)</td>
<td>0.35</td>
<td></td>
<td>259</td>
<td></td>
</tr>
<tr>
<td>CUP additional analysis: pooled analyses of Pooling Project of cohort studies [61] combined with all studies from the CUP</td>
<td>Highest vs. lowest</td>
<td>0.93 (0.88–0.98)</td>
<td>0%</td>
<td>24*</td>
<td>18,927</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.88 (0.80–0.97)</td>
<td>32%</td>
<td>10</td>
<td>8,435</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.98 (0.83–1.16)</td>
<td>55%</td>
<td>8</td>
<td>4,752</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.96 (0.76–1.20)</td>
<td>0%</td>
<td>9</td>
<td>939</td>
<td></td>
</tr>
</tbody>
</table>

*Three overlapping studies [62, 63] in CUP and pooled analysis.
Other vegetable exposures

The CUP Lung SLR 2015 conducted stratified dose-response meta-analyses for green leafy vegetables by smoking status. A significant inverse association was observed in former smokers, and no significant association was observed in current and never smokers (see Table 6 and CUP Lung SLR 2015 Figure 33).

Table 6: Summary of CUP 2015 meta-analysis – green leafy vegetables

<table>
<thead>
<tr>
<th>Analysis</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>2015 CUP</td>
<td>Per 50 g/day</td>
<td>0.89 (0.79–1.00)</td>
<td>50%</td>
<td>8</td>
<td>5,732</td>
</tr>
<tr>
<td>Current smokers</td>
<td>Per 50 g/day</td>
<td>0.83 (0.66–1.06)</td>
<td>44%</td>
<td>4</td>
<td>1,388</td>
</tr>
<tr>
<td>Former smokers</td>
<td>Per 50 g/day</td>
<td>0.63 (0.41–0.95)</td>
<td>28%</td>
<td>3</td>
<td>425</td>
</tr>
<tr>
<td>Never smokers</td>
<td>Per 50 g/day</td>
<td>0.96 (0.76–1.22)</td>
<td>0%</td>
<td>4</td>
<td>591</td>
</tr>
</tbody>
</table>

Mechanisms

Non-starchy vegetables provide many potentially cancer-preventive substances, including several nutrients (such as pro-vitamin A carotenoids and vitamin C) and dietary fibre, as well as phytochemicals (such as glucosinolates, dithiolthiones, indoles, chlorophyll, flavonoids, allylsulphides and phytoestrogens). Phytochemicals might influence cancer risk through multiple mechanisms, including antioxidant activity, modulation of detoxification enzymes, stimulation of the immune system, antiproliferative activity, ligand-dependent signalling through retinoid receptors and/or modulation of steroid hormone concentration and hormone metabolism. Non-starchy vegetables are also a source of folate, which plays an important role in synthesis and methylation of DNA. Abnormal DNA methylation has been linked to aberrant gene expression and also to cancers at several sites and may be particularly important in rapidly dividing tissues. It is difficult to unravel the relative importance of each constituent and likely that a protective effect may result from a combination of influences on several pathways involved in carcinogenesis [1].

Update: As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see Exposures: Wholegrains, vegetables and fruit (Appendix – Mechanisms) for the updated mechanisms summary.
CUP Panel’s conclusion:

The evidence for consumption of vegetables was limited but generally consistent. The dose-response meta-analysis showed a significant decreased risk of lung cancer, however, moderate heterogeneity was observed and there was also evidence of small study bias. Decreased risk was observed for former and current smokers, which was significant for current smokers. There was evidence of a non-linear dose-response of lung cancer and vegetable intake but only for intakes up to 300–400 grams per day. Although studies adjusted for smoking, there is the potential for residual confounding due to smoking. There is evidence for plausible mechanisms operating in humans. The CUP Panel concluded the following:

The evidence suggesting that higher consumption of vegetables decreases the risk of lung cancer in current and former smokers is limited.

7.4 Fruits

(Also see CUP Lung SLR 2015: Sections 2.2.2 and 2.2.2.1)

The CUP identified six new or updated studies (11 publications) [51, 53-57, 64-68], giving a total of 30 studies (44 publications) reviewing the evidence for fruits and lung cancer (see CUP Lung SLR 2015 Tables 33 and 34 for a full list of references). Of 17 studies reporting on lung cancer incidence, 15 reported inverse associations, six of which were significant, and two studies reported non-significant positive associations when comparing the highest and lowest categories of intake. All eight studies reporting on lung cancer mortality showed inverse associations, two of which were significant when comparing the highest and lowest categories of intake (see CUP Lung SLR 2015 Figure 37). Twenty-three of the 30 studies were included in the dose-response meta-analysis (n = 14,506 cases), which showed a statistically significant eight per cent decreased risk per 100 grams of fruit per day (RR 0.92 (95% CI 0.88–0.95); see CUP Lung SLR 2015 Figure 39). High heterogeneity (I² = 57%) was observed that appears to be explained by the size of the effect. The overall association remained statistically significant in influence analysis.

There was evidence of a non-linear association (p < 0.01). Non-linear analysis showed that risk of lung cancer decreased for intakes up to 200–300 grams per day, with no further decrease for higher intake levels (CUP Lung SLR 2015 Figure 46 and Table 35). There was evidence of small study bias with Egger’s test (p < 0.01). The funnel plot shows that the smaller studies identified reported stronger inverse associations than the average and that no small studies reported positive associations (see CUP Lung SLR 2015 Figure 40).

When stratified by smoking status, the dose-response meta-analysis showed a nine per cent decreased risk per 100 grams of fruit per day in current smokers (RR = 0.91 (95% CI 0.85–0.98). No significant associations were observed for former or never smokers (see Table 7 and CUP Lung SLR 2015 Figure 44).
Table 7: Summary of CUP 2015 stratified dose-response meta-analysis – fruits

<table>
<thead>
<tr>
<th>Analysis</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>Current smokers</td>
<td>Per 100 g/day</td>
<td>0.91 (0.85–0.98)</td>
<td>57%</td>
<td>9</td>
<td>7,141</td>
</tr>
<tr>
<td>Former smokers</td>
<td>Per 100 g/day</td>
<td>0.97 (0.92–1.02)</td>
<td>0%</td>
<td>5</td>
<td>3,828</td>
</tr>
<tr>
<td>Never smokers</td>
<td>Per 100 g/day</td>
<td>1.03 (0.97–1.09)</td>
<td>0%</td>
<td>8</td>
<td>1,260</td>
</tr>
</tbody>
</table>

All studies included in the dose-response analysis were adjusted for age, sex and smoking status. Most studies (21) adjusted for intensity, duration of smoking and other smoking variables in addition to smoking status. When the analysis was restricted to these studies, the overall association remained the same.

Three studies were not included in any of the CUP analyses, two due to not reporting confidence intervals [58, 59] and one due to not reporting sufficient data [60].

The CUP findings are similar to those from the 2005 SLR, which showed a significant inverse association per 80 grams of fruit consumed per day (RR = 0.94 (95% CI 0.90–0.97)) for 14 studies. The CUP update includes nine more studies and almost double the number of cases.

Published pooled analyses and meta-analyses

One published pooled analysis of cohort studies on fruit and lung cancer was identified in the CUP Lung SLR 2015 [61]. The pooled analysis reported inverse associations when comparing the highest with the lowest fruit consumers, which was significant in current smokers. When the studies identified by the CUP 2015 (but not in the pooled analysis) were combined with the results of the pooled analysis, inverse associations were observed which were significant for current and former smokers. Results from the CUP and the published meta-analyses are presented in Table 8.
### Table 8: Summary of CUP 2015 meta-analysis and published pooled analysis – fruit

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Increment/Contrast</th>
<th>RR (95% CI)</th>
<th>I² or P- Value</th>
<th>No. Studies</th>
<th>No. Cases</th>
<th>Sub-group</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015 CUP</td>
<td>Per 100 g/day</td>
<td>0.92 (0.88–0.95)</td>
<td>57%</td>
<td>23</td>
<td>14,506</td>
<td></td>
</tr>
<tr>
<td>Pooling Project of cohort studies [61]</td>
<td>Q5 vs. Q1</td>
<td>0.77 (0.67–0.87)</td>
<td>0.56</td>
<td>7</td>
<td>3,206</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q4 vs. Q1</td>
<td>0.82 (0.68–0.99)</td>
<td>0.13</td>
<td>5</td>
<td>1,915</td>
<td>Current smokers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.85 (0.69–1.05)</td>
<td>0.49</td>
<td>5</td>
<td>981</td>
<td>Former smokers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.59 (0.34–1.04)</td>
<td>0.09</td>
<td>5</td>
<td>259</td>
<td>Never smokers</td>
</tr>
<tr>
<td>CUP additional analysis: pooled analyses of Pooling Project of cohort studies [61] combined with all studies from the CUP</td>
<td>Highest vs. lowest quantile</td>
<td>0.81 (0.75–0.87)</td>
<td>23%</td>
<td>28*</td>
<td>14,783</td>
<td>Current smokers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.83 (0.75–0.92)</td>
<td>16%</td>
<td>13</td>
<td>6,280</td>
<td>Former smokers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.89 (0.81–0.99)</td>
<td>0%</td>
<td>9</td>
<td>3,790</td>
<td>Former smokers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.91 (0.71–1.17)</td>
<td>33%</td>
<td>12</td>
<td>2,184</td>
<td>Never smokers</td>
</tr>
</tbody>
</table>

*Three overlapping studies [62, 63] in CUP and pooled analysis.

### Mechanisms

Fruit is a source of nutrients, such as vitamin C and a diverse array of phytochemicals, such as carotenoids, phenols and flavonoids. In addition, flavonoids found in fruit modular cytochrome P450 enzyme systems are involved in the metabolism of carcinogens [69]. It is difficult to unravel the relative importance of each constituent, and it is likely that any protective effect may result from a combination of influences on several pathways involved in lung carcinogenesis.

Update: As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see Exposures: Wholegrains, vegetables and fruit (Appendix – Mechanisms) for the updated mechanisms summary.

### CUP Panel’s conclusion:

Overall the evidence was reasonably consistent. The dose-response meta-analysis showed a significant decreased risk of lung cancer although high heterogeneity was observed. Non-linear analysis showed that risk of lung cancer decreased for intakes up to 200–300 grams per day with no further decreased risk beyond that amount.
Decreased risk was observed for former and current smokers, which was significant for current smokers. Although studies adjusted for smoking, there is the potential for residual confounding due to smoking. There is evidence for plausible mechanisms operating in humans. The CUP Panel concluded the following:

The evidence suggesting that greater consumption of fruit decreases the risk of lung cancer in current and former smokers is limited.

### 7.5 Foods containing carotenoids

*(Also see CUP Lung SLR 2015: Sections 5.5.2.5 and 5.5.2.1)*

The CUP identified one new study [53], giving a total of nine studies (10 publications) reviewing the evidence for dietary total carotenoids and lung cancer (see CUP Lung SLR 2015 Tables 173 and 174 for a full list of references). All five studies reporting on lung cancer incidence showed inverse associations, one of which was significant when comparing the highest and lowest categories of intake. Of two studies reporting on lung cancer mortality, one reported a non-significant inverse association and one reported a significant inverse association in men and a non-significant inverse association in women when comparing the highest and lowest categories of intake (see CUP Lung SLR 2015 Figure 191).

Seven of the nine studies were included in the dose-response meta-analysis \( n = 4,491 \) cases), which showed a two per cent decreased risk per 1,000 micrograms of dietary total carotenoids per day \( (RR = 0.98 \ (95\% \ CI \ 0.97–0.99); \text{see CUP Lung SLR} \ 2015 \ Figure \ 192) \). There was evidence of moderate heterogeneity \( (I^2 = 37\%, \text{p}_{\text{heterogeneity}} = 0.16) \).

There were not enough studies to do stratified analysis by smoking status. In one study [53], an inverse association was observed among heavy smokers only, and not in non-smokers or light smokers. Two other studies [70, 71] reported no inverse association in either current smokers (light or heavy) or non-smokers. Two studies on smokers or populations exposed to asbestos [72, 73] did not report significant associations.

Results were not significant when stratified by men \( (RR = 0.98 \ (95\% \ CI \ 0.96–1.00)) \) or women \( (RR = 0.99 \ (95\% \ CI \ 0.98–1.00)) \) respectively; see CUP Lung SLR 2015 Figure 194).

All studies adjusted for at least smoking status, all except for one [70] adjusted for intensity, duration of smoking and other smoking variables.

The 2005 SLR also found a significant inverse association but included only two studies in the dose-response meta-analysis. The CUP update includes more studies and cases.

### Published pooled analyses and meta-analyses

No pooled analyses were identified. One published meta-analysis of cohort studies on total carotenoids intake and lung cancer risk was identified in the CUP Lung SLR 2015 [74]. A significant inverse association was reported per 1,000 µg per day \( (RR = 0.98 \ (95\% \ CI \ 0.97–0.99), \ I^2 = 0\% \).
Serum total carotenoids

The CUP identified one new study [75], giving a total of five studies (seven publications) reviewing the evidence for serum total carotenoids and lung cancer (see CUP Lung SLR 2015 Tables 178 and 179 for a full list of references). Two studies reporting on lung cancer incidence showed non-significant inverse associations when comparing the highest and lowest levels. Of three studies reporting on lung cancer mortality, two reported inverse associations, one of which was significant, and one reported a non-significant positive association when comparing the highest and lowest levels (see CUP Lung SLR 2015 Figure 195).

There were not enough data to do stratified analysis by smoking status.

No analysis was conducted in the 2005 SLR.

Published pooled analyses and meta-analyses

No pooled analyses were identified. One published meta-analysis of cohort studies on serum total carotenoids and lung cancer risk was identified in the CUP Lung SLR 2015 [74]. A significant inverse association was reported per 0.75 µmol/L (RR = 0.64 (95% CI 0.46–0.88), I² = 0%).

Mechanisms

Several of the carotenoids are retinol (vitamin A) precursors and other metabolites may interact with various members of the steroid receptor superfamily. The pro-vitamin A carotenoids may be converted to retinol where they function in cellular differentiation, immunomodulation and activation of carcinogen-metabolising enzymes [76, 77]. Carotenoids at physiological concentrations may also protect cells and tissues from certain types of oxidant stress and the production of free radicals that may cause DNA damage.

Update: As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see Exposures: Wholegrains, vegetables and fruit (Appendix – Mechanisms) for the updated mechanisms summary.

CUP Panel’s conclusion:

The evidence for consumption of foods containing carotenoids was limited but generally consistent. The dose-response meta-analysis of dietary total carotenoid intake showed a significant decreased risk of lung cancer per 1,000 micrograms per day. No analysis was possible by smoking status. Smoking may affect serum carotenoid levels. Residual confounding could not be excluded. There is evidence for plausible mechanisms operating in humans. The CUP Panel concluded the following:

The evidence suggesting that foods containing carotenoids decrease the risk of lung cancer is limited.
7.6 Foods containing beta-carotene

(Also see CUP Lung SLR 2015: Sections 5.5.1.2.1 and 5.5.1.2.3)

Dietary beta-carotene

The CUP identified one new study [39], giving a total of 15 studies (19 publications) assessing dietary beta-carotene and lung cancer (see CUP Lung SLR 2015 Tables 134 and 135 for a full list of references). Of 12 studies reporting on lung cancer incidence, seven reported inverse associations, two of which were significant. Three reported non-significant positive associations. One study reported no association and one study showed a non-significant inverse association in women and a non-significant positive association in men when comparing the highest and lowest categories of intake. Both studies reporting on dietary beta-carotene and lung cancer mortality showed non-significant inverse associations when comparing the highest and lowest categories of intake (see CUP Lung SLR Figure 159).

Thirteen studies were included in the dose-response meta-analysis (n = 7,560 cases), which showed no significant association (RR 0.99 (95% CI 0.98–1.00) per 700 μg per day) (CUP Lung SLR 2015 Figure 160). Low heterogeneity was observed (I² = 5%).

When stratified by smoking status, no significant associations were observed in current, former or never smokers (see CUP Lung SLR 2015 Figure 162).

One study [78] was not included in any of the CUP analyses because it reported insufficient data.

All studies adjusted for intensity, duration of smoking and other smoking variables in addition to smoking status, except one study [70] that was adjusted only for smoking status.

The CUP findings, like the 2005 SLR, showed no significant association.

Published pooled analyses and meta-analyses

Results from one published pooled analysis [79] and one published meta-analysis [74] were identified in the CUP Lung SLR 2015. The pooled analysis reported no significant association (see Table 9). The meta-analysis reported no significant associations for both the continuous and the highest versus lowest analyses (RR 0.99 (95% CI 0.98–1.00) and RR 0.92 (95% CI 0.83–1.01)). Results from the CUP meta-analysis and published pooled analysis are presented in Table 9.
Table 9: Summary of CUP 2015 meta-analysis and published pooled analysis – foods containing beta-carotene

<table>
<thead>
<tr>
<th>Study</th>
<th>Increment/Contrast</th>
<th>RR (95% CI)</th>
<th>I²</th>
<th>No. Studies</th>
<th>No. Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>CUP Lung SLR 2015</td>
<td>700 μg/day</td>
<td>0.99 (0.98–1.00)</td>
<td>5%</td>
<td>13</td>
<td>7,560</td>
</tr>
<tr>
<td>Männistö 2004 [79]</td>
<td>Q5 vs. Q1</td>
<td>0.98 (0.87–1.11)</td>
<td>-</td>
<td>7</td>
<td>3,155</td>
</tr>
</tbody>
</table>

Serum beta-carotene

The CUP identified two new studies, giving a total of 17 studies (20 publications) assessing serum beta-carotene and lung cancer (see CUP Lung SLR 2015 Tables 141 and 142 for a full list of references). Of nine studies reporting on lung cancer incidence, five reported an inverse association, three of which were significant. Two studies reported positive associations, one of which was significant. One study reported inconsistent results by smoking status and one study showed a significant inverse association in men and non-significant positive association in women when comparing the highest and lowest levels. Of the five studies reporting on lung cancer mortality, three reported non-significant inverse associations, one reported a non-significant positive association and one reported inverse associations in men and women, significant in men only when comparing the highest and lowest levels (see CUP Lung SLR 2015 Figure 166).

Thirteen studies were included in the dose-response meta-analysis (n = 2,958 cases), which showed a significant eight per cent decreased risk per 10 micrograms per 100 millilitres (RR 0.92 (95% CI 0.87–0.97)) (see CUP Lung SLR 2015 Figure 167). Moderate heterogeneity was observed (I² = 40%, p heterogeneity = 0.10). There were not enough data to stratify by smoking status.

Two studies [80, 81] were not included in any of the CUP analyses because they reported insufficient data.

All studies adjusted for intensity, duration of smoking and other smoking variables in addition to smoking status.

The findings from the CUP Lung Cancer SLR 2015 are stronger than those reported in the 2005 SLR, which included five studies and reported a non-significant inverse association (RR 0.97 (95% CI 0.93–1.02)).

Published pooled analyses and meta-analyses

No pooled analyses were identified. One published meta-analysis of cohort studies on serum beta-carotene and lung cancer risk was identified in the CUP Lung SLR 2015 [74]. No significant association was reported per 0.1 μmol/L (RR 0.95 (95% CI 0.87–1.03), I² = 72%).
Mechanisms

Many of the carotenoids, including beta-carotene, are pro-vitamin A carotenoids and on central cleavage form two molecules of vitamin A (retinol). Retinol has known functions in cellular differentiation, immune-modulation and activation of carcinogen-metabolising enzymes [76, 77]. Beta-carotene may also participate in host responses to oxidant stress and is hypothesised to protect the host from free radicals that cause DNA damage and the carcinogenic cascade [1].

Update: As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see Exposures: Wholegrains, vegetables and fruit (Appendix – Mechanisms) for the updated mechanisms summary.

CUP Panel’s conclusion:

The evidence for consumption of foods containing beta-carotene was limited but generally consistent. The dose-response meta-analysis of dietary beta-carotene intake showed no significant association, and no significant associations were observed in current, former or never smokers in analyses stratified by smoking status. The analysis of serum beta-carotene showed a significant eight per cent decreased risk of lung cancer per 10 micrograms per 100 millilitres. However, because smoking lowers serum beta-carotene levels, residual confounding cannot be excluded. There is evidence for plausible mechanisms operating in humans. The CUP Panel concluded the following:

The evidence suggesting that foods containing beta-carotene decreases the risk of lung cancer is limited.

7.7 Foods containing vitamin C

(Also see CUP Lung SLR 2015: Section 5.5.9)

The CUP identified two new studies [39, 53], giving a total of 13 studies (17 publications) reviewing the evidence for foods containing vitamin C and lung cancer (see CUP Lung SLR 2015 Tables 191 and 192 for a full list of references). Of nine studies reporting on lung cancer incidence, six showed inverse associations, three of which were significant. Three studies reported inconsistent results by treatment arm, smoking status or sex when comparing the highest and lowest categories of intake. Three studies reported on lung cancer mortality. Two studies showed inverse associations, one of which was significant. One study reported inverse associations, significant for men only when comparing the highest and lowest categories of intake (see CUP Lung SLR 2015 Figure 206).

Ten of the 13 studies were included in the dose-response meta-analysis (n = 4,379 cases), which showed an eight per cent decreased risk per 40 milligrams per day of vitamin C (RR 0.92 (95% CI 0.88–0.96)) (CUP Lung SLR 2015 Figure 207). There was evidence of high heterogeneity ($I^2 = 66\%$, $p_{\text{heterogeneity}} < 0.01$) that was partially explained in stratified analysis in which the significant inverse association was observed in current
smokers but not in former or never smokers (see CUP Lung SLR 2015 Figure 209). There was evidence of non-linear dose-response ($p < 0.01$). There was a decreasing risk of lung cancer for increasing vitamin C intakes up to approximately 100 milligrams per day, but little additional risk decrease at higher intakes (see CUP Lung SLR 2015 Figure 213 and Table 193).

After stratification by smoking status, the results remained significant in current smokers (13 per cent decreased risk per 40 milligrams per day), but there was no significant association in former or never smokers (see Table 10 and CUP Lung SLR 2015 Figure 209).

### Table 10: Summary of CUP 2015 stratified dose-response meta-analysis – foods containing vitamin C

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Increment</th>
<th>RR (95% CI)</th>
<th>$I^2$</th>
<th>No. Studies</th>
<th>No. Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smokers</td>
<td>Per 40 mg/day</td>
<td>0.87 (0.79–0.96)</td>
<td>62%</td>
<td>4</td>
<td>1,664</td>
</tr>
<tr>
<td>Former smokers</td>
<td>Per 40 mg/day</td>
<td>0.96 (0.87–1.05)</td>
<td>0%</td>
<td>3</td>
<td>582</td>
</tr>
<tr>
<td>Never smokers</td>
<td>Per 40 mg/day</td>
<td>0.93 (0.79–1.08)</td>
<td>0%</td>
<td>3</td>
<td>225</td>
</tr>
</tbody>
</table>

One study [59] was not included in any of the CUP analyses because it reported insufficient data.

All studies adjusted for intensity, duration of smoking and other smoking variables in addition to smoking status.

The 2005 SLR did not find a significant association and included only two studies in the dose-response meta-analysis. The CUP update includes more studies and cases.

### Published pooled analyses and meta-analyses

Results from one published pooled analysis and one published meta-analysis on dietary vitamin C and lung cancer risk were identified in the CUP Lung SLR 2015. The pooled analysis reported non-significant inverse associations for current, former and never smokers. The meta-analysis reported inverse associations for both current and former smokers, significant in current smokers. A non-significant positive association was observed for never smokers. Results from the CUP Lung SLR 2015 and the published pooled analysis are presented in Table 11.
### Table 11: Summary of CUP 2015 meta-analysis and published pooled-analysis – foods containing vitamin C

<table>
<thead>
<tr>
<th>Study</th>
<th>Increment/Contrast</th>
<th>RR (95% CI)</th>
<th>I²</th>
<th>No. Studies</th>
<th>No. Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>CUP Lung SLR 2015 (smokers)</td>
<td>Per 40 mg/day</td>
<td>0.87 (0.79–0.96)</td>
<td>62%</td>
<td>4</td>
<td>1,664</td>
</tr>
<tr>
<td>Pooling Project (smokers) [82]</td>
<td>Highest vs. lowest</td>
<td>0.85 (0.70–1.02)</td>
<td></td>
<td>8*</td>
<td>1,915</td>
</tr>
</tbody>
</table>

*Three studies were included in both the CUP highest vs. lowest analysis and Pooling Project [63, 71, 83].

No studies on serum vitamin C were identified.

### Mechanisms

It is biologically plausible that vitamin C could protect against cancer, but a clear mechanism has not been established in humans. Vitamin C traps free radicals and reactive oxygen molecules, protecting against lipid peroxidation, reducing nitrates and stimulating the immune system [84, 85]. Moreover, it helps to regenerate vitamin E, another antioxidant vitamin [86]. Vitamin C has also been shown to inhibit formation of carcinogens and protect DNA from mutagenic attack in experimental in vitro models [87].

*Update: As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see Exposures: Wholegrains, vegetables and fruit (Appendix – Mechanisms) for the updated mechanisms summary.*

### CUP Panel’s conclusion:

The evidence for consumption of foods containing vitamin C was limited but generally consistent. The dose-response meta-analysis showed a significant decreased risk of lung cancer risk in smokers. Although studies adjusted for smoking and for intensity and duration of smoking, there is the potential for residual confounding due to smoking. There is evidence for plausible mechanisms operating in humans. The CUP Panel concluded the following:

*The evidence suggesting that higher consumption of foods containing vitamin C decreases the risk of lung cancer in current smokers is limited.*
7.8 Foods containing isoflavones

(Also see CUP Lung SLR 2015: Section 5.8)

The CUP identified four new studies (five publications) [88–92] reviewing the evidence for foods containing isoflavones and lung cancer (see CUP Lung SLR 2015 Tables 219 and 220 for a full list of references). Of the four studies reporting on lung cancer incidence, three reported non-significant inverse associations and one reported a non-significant inverse association in never smokers, as well as a non-significant positive association in current and former smokers combined, when comparing the highest and lowest categories of intake (see CUP Lung SLR 2015 Figure 232).

Most studies did not have the information needed for dose response meta-analysis; therefore, only highest versus lowest analysis was performed. All four studies were included in an analysis comparing the highest and lowest consumers of foods containing isoflavones (n = 2,919 cases), which showed a significant decreased risk (RR 0.88 (95% CI 0.79–0.99)) (CUP Lung SLR 2015 Figure 232). There was no evidence of heterogeneity (I² = 0%).

When the results were stratified by smoking status, they remained significant in never smokers (34 per cent decreased risk when comparing the highest with the lowest consumers). There was no significant association in current or former smokers (see Table 12 and CUP Lung SLR 2015 Figure 233).

Table 12: Summary of CUP 2015 stratified highest vs. lowest analysis – foods containing isoflavones

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Contrast</th>
<th>RR  (95% CI)</th>
<th>I²</th>
<th>No. Studies</th>
<th>No. Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>CUP 2015</td>
<td>Highest vs. lowest</td>
<td>0.88 (0.79–0.99)</td>
<td>0%</td>
<td>4</td>
<td>2,919</td>
</tr>
<tr>
<td>CUP 2015 current and former smokers</td>
<td>Highest vs. lowest</td>
<td>1.02 (0.84–1.25)</td>
<td>0%</td>
<td>2</td>
<td>1,054</td>
</tr>
<tr>
<td>CUP 2015 never smokers</td>
<td>Highest vs. lowest</td>
<td>0.66 (0.51–0.84)</td>
<td>0%</td>
<td>3</td>
<td>714</td>
</tr>
</tbody>
</table>

All studies included in the analysis were adjusted for smoking status.

No studies were identified in the 2005 SLR.

Published pooled analyses and meta-analyses

Results from two published meta-analyses [89, 93] on dietary isoflavone consumption and lung cancer risk were identified in the CUP Lung SLR 2015. Both analyses reported inverse associations, which were significant when comparing the highest with the lowest levels of intake (RR 0.63 (95% CI 0.45–0.90) [89] and RR 0.80 (95% CI 0.71–0.89) [93]).
Mechanisms

Isoflavones are antioxidants and have been shown to inhibit expression of CYP1A1 (a cytochrome P450 enzyme that helps to metabolise toxins), resulting in decreased formation of reactive carcinogen metabolites that form DNA adducts [94]. Elevated CYP1A1 activity has been associated with increased risk of lung cancer, primarily in smokers [69]. The evidence for interactions between CYP1A1 and flavonoids is supported by the observation that protective associations of flavonoids are associated with specific CYP1A1 genotypes [69, 95]. Isoflavones have diverse effects on cancer cells that may be relevant to lung cancer, but a precise mechanism of action in lung cancer has not been defined.

Update: As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see Exposures: Wholegrains, vegetables and fruit (Appendix – Mechanisms) for the updated mechanisms summary.

CUP Panel’s conclusion:

The evidence for consumption of foods containing isoflavones was limited but generally consistent. The highest versus lowest analysis showed a significant decreased risk of lung cancer. A significant inverse association was also observed in never smokers. There is evidence for plausible mechanisms operating in humans. The CUP Panel concluded the following:

The evidence suggesting that higher consumption of foods containing isoflavones decreases the risk of lung cancer in individuals who have never smoked is limited.

7.9 Red meat

(Also see CUP Lung SLR 2015: Section 2.5.1.3)

The CUP identified six new studies, giving a total of seven studies (eight publications) [52, 54, 96-100] reviewing the evidence for red meat and lung cancer (see CUP Lung SLR 2015 Tables 67 and 68 for a full list of references). Of five studies reporting on lung cancer incidence, one reported a significant positive association, two reported non-significant positive associations and one reported a non-significant inverse association. One study reported a significant positive association for men and a non-significant positive association for women, when comparing the highest and lowest categories of intake. One study, on lung cancer mortality, reported a borderline significant positive association when comparing the highest and lowest categories of intake (see CUP Lung SLR 2015 Figure 79).
All seven studies were included in a dose-response meta-analysis (n = 9,765 cases), which showed a 22 per cent increased risk per 100 grams per day of red meat (RR 1.22 (95% CI 1.02–1.46)) (CUP Lung SLR 2015 Figure 80). High heterogeneity was observed ($I^2 = 66\%$, $\chi^2$ heterogeneity < 0.01) for all studies combined. Visual inspection of the forest plot suggests it is explained by two studies that reported stronger associations than the average: one study in high-risk people participating in a screening for lung cancer [64] and the follow-up of the 1987 National Health Interview Survey with lung cancer mortality as an endpoint [101]. Both studies were adjusted for smoking duration and intensity (see CUP Lung SLR 2015 Figure 80).

When stratified by gender, the results for men showed a 14 per cent increased risk (RR 1.14 (95% CI 1.05–1.24)) and the results for women showed no significant association (RR 1.08 (95% CI 0.90–1.29); see CUP Lung SLR 2015 Figure 82). Four studies reported data stratified by smoking status. Two [97, 101] reported no significant associations, one [99] reported a significant positive association in men who had quit more than 10 years previously and one [64] reported significant positive associations in current and former smokers when comparing the highest with the lowest consumers.

All studies adjusted for intensity and duration, as well as smoking status, except one study [96], which adjusted for smoking in two categories (yes and no).

There was no meta-analysis of cohort studies conducted for the 2005 SLR. The 2005 SLR finding of ‘limited – suggestive increases risk’ was based on case-control studies.

**Published pooled analyses and meta-analyses**

Results from two published meta-analyses on red meat and lung cancer were identified in the CUP Lung SLR 2015. Both meta-analyses reported significant increased risk, consistent with the CUP Lung SLR 2015. Results from the published meta-analyses are presented in Table 13.

**Table 13: Summary of CUP 2015 meta-analysis and published meta-analyses – red meat**

<table>
<thead>
<tr>
<th>Study</th>
<th>Increment/Contrast</th>
<th>RR (95% CI)</th>
<th>$I^2$</th>
<th>No. Studies</th>
<th>No. Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>CUP Lung SLR 2015</td>
<td>Per 100 g/day</td>
<td>1.22 (1.02–1.46)</td>
<td>66%</td>
<td>7</td>
<td>9,765</td>
</tr>
<tr>
<td>Xue (2014) [102]</td>
<td>Per 120 g/day</td>
<td>1.21 (1.14–1.28)</td>
<td>-</td>
<td>6</td>
<td>7,070</td>
</tr>
<tr>
<td>Yang (2012b) [103]</td>
<td>Highest vs. lowest</td>
<td>1.20 (1.10–1.30)</td>
<td>0%</td>
<td>5</td>
<td>9,174</td>
</tr>
</tbody>
</table>
Mechanisms

Red meat contains haem iron, which has been proposed to lead to the production of free radicals. When cooked at high temperatures, red meat can also contain heterocyclic amines and polycyclic aromatic hydrocarbons [1]. However, a specific mechanism linking red meat to lung cancer risk has not been clearly identified.

Update: As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see Exposures: Meat, fish and dairy products (Appendix – Mechanisms) for the updated mechanisms summary.

CUP Panel’s conclusion:

The evidence for consumption of red meat was limited but generally consistent. The dose-response meta-analysis showed a significant increased risk of lung cancer per 100 grams per day. There was evidence of high heterogeneity. No analysis by smoking status was possible, and although studies adjusted for smoking, there is the potential for residual confounding due to smoking. There is evidence for plausible mechanisms operating in humans. The CUP Panel concluded the following:

The evidence suggesting that consumption of red meat increases the risk of lung cancer is limited.

7.10 Processed meat

(Also see CUP Lung SLR 2015: Section 2.5.1.2)

The CUP identified six new or updated studies (eight publications) [64, 66, 96-100, 104] giving a total of nine studies (11 publications) reviewing the evidence for processed meat and lung cancer (see CUP Lung SLR 2015 Tables 59 and 60 for a full list of references). Of four studies reporting on lung cancer incidence, one reported a non-significant positive association, one reported a non-significant inverse association and two reported inconsistent results for men and women when comparing the highest and lowest categories of intake. Three studies reported on lung cancer mortality: one reported a non-significant inverse association, and two reported inconsistent results for men and women when comparing the highest and lowest categories of intake (see CUP Lung SLR 2015 Figure 71).

Seven of the nine studies were included in the dose-response meta-analysis \( (n = 10,292 \text{ cases}) \), which showed a 14 per cent increased risk per 50 grams per day of processed meat \( (RR = 1.14 \text{ (95% CI 1.05–1.24)}) \); see CUP Lung SLR 2015 Figure 72). No heterogeneity was observed \( (I^2 = 0\%) \). When one study that did not adjust for smoking (Iso, 2007) was removed, the results remained similar \( (RR = 1.16 \text{ (95% CI 1.07–1.27)}) \); see CUP Lung SLR 2015 Figure 73). The observed overall significant positive association was influenced by one large study [99], which contributed 58 per cent of the weight in the analysis; the summary RR was 1.07 \( (95\% \text{ CI} = 0.94–1.22) \) when this study was omitted. There was an indication of small study bias with Egger’s test \( (p = 0.04) \); see CUP...
Lung SLR 2015 Figure 74), appearing to be due to an absence of small studies showing positive association. There was evidence of a non-linear relationship (p < 0.01) with a steeper increase of the curve at lower intake level followed by a plateau (see CUP Lung SLR 2015 Figure 77 and Table 61).

When the results were stratified by outcome, they remained significant for incidence (RR 1.17 (95% CI 1.07–1.27) per 50 grams per day) but showed no significant association for mortality (RR = 0.79 (95% CI 0.56–1.12); see CUP Lung SLR Figure 76). The results for men and women showed no significant associations per 50 grams per day (RR = 1.01 (95% CI 0.73–1.41) and RR = 1.04 (95% CI 0.81–1.35), respectively; see CUP Lung SLR 2015 Figure 75). No analysis by smoking status was possible. Three studies did report data stratified by smoking status. Two [97, 101] reported no significant associations, and one [99] showed significant positive associations in male former (< 10 years) and current smokers when comparing the 90th and the 10th percentiles (RR = 1.31 (95% CI 1.11–1.55) and RR = 1.18 (95% CI 1.04–1.33), respectively).

All studies were adjusted for duration of smoking, intensity or time since quitting, as well as smoking status, apart from two studies: one study on mortality reported a non-significant inverse association [104], and one study adjusted only for smoking status and reported a non-significant positive association [96].

The CUP findings strengthen the results from the 2005 SLR, which showed a non-significant positive association and included only two studies (RR = 1.03 (0.92–1.16). The CUP update includes five more studies and many more cases of lung cancer.

**Published pooled analyses and meta-analyses**

No published pooled analysis was identified. Results from two published meta-analyses on processed meat and lung cancer were identified in the CUP Lung SLR 2015. Both meta-analyses reported non-significant positive associations. Results from the published meta-analyses are presented in Table 14.

**Table 14: Summary of CUP 2015 meta-analysis and published meta-analyses – processed meat**

<table>
<thead>
<tr>
<th>Study</th>
<th>Increment/Contrast</th>
<th>RR (95% CI)</th>
<th>I²</th>
<th>No. Studies</th>
<th>No. Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>CUP Lung SLR 2015</td>
<td>Per 50 g/day</td>
<td>1.14 (1.05–1.24)</td>
<td>0%</td>
<td>7</td>
<td>10,292</td>
</tr>
<tr>
<td>Xue (2014) [102]</td>
<td>Per 50 g/day</td>
<td>1.09 (0.99–1.19)</td>
<td>-</td>
<td>5</td>
<td>7,070</td>
</tr>
<tr>
<td>Yang (2012b) [103]</td>
<td>Highest vs. lowest</td>
<td>1.05 (0.92–1.19)</td>
<td>49%</td>
<td>4</td>
<td>9,174</td>
</tr>
</tbody>
</table>
Mechanisms

*N*-nitroso compounds are suspected mutagens and carcinogens that are found in processed meats and produced in the stomach from nitrates, including those used to preserve meats [105]. When cooked at high temperatures, meats can also contain heterocyclic amines and polycyclic aromatic hydrocarbons. Haem promotes the formation of *N*-nitroso compounds and also contains iron, which is hypothesised to increase production of free radicals [1]. However, no direct mechanism linking these processes to lung cancer has been identified.

*Update:* As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see *Exposures: Meat, fish and dairy products* (Appendix – Mechanisms) for the updated mechanisms summary.

**CUP Panel’s conclusion:**

The evidence for consumption of processed meat was limited but generally consistent. The dose-response meta-analysis showed a significant increased risk of lung cancer per 50 grams per day. No analysis by smoking status was possible and although the studies adjusted for smoking, there is the potential for residual confounding due to smoking. There is evidence for plausible mechanisms operating in humans. The CUP Panel concluded the following:

> The evidence suggesting that consumption of processed meat increases the risk of lung cancer is limited.

7.11 Foods containing retinol

*(Also see CUP Lung SLR 2015: Section 5.5.1.1)*

**Dietary retinol**

The CUP identified one new study [53], giving a total of seven studies. The new study reported no significant association (RR 0.85 (95% CI 0.62–1.16)) when comparing the highest with the lowest categories of intake. The 2005 SLR identified nine studies and showed no significant association between dietary retinol consumption and lung cancer risk in a meta-analysis of three of these studies (RR 1.00 (95% CI 1.00–1.00) per 100 International units per day). No new meta-analysis was conducted.

**Serum retinol**

The CUP identified two new or updated cohort studies giving a total of 15 studies (20 publications) assessing serum retinol and lung cancer (see CUP Lung SLR 2015 Tables 128 and 129 for a full list of references). Of nine studies reporting on lung cancer incidence, seven reported inverse associations, one of which was significant. Two studies reported inconsistent findings in men and women when comparing the highest and lowest levels. Of two studies reporting on lung cancer mortality, one reported a non-
significant inverse association, and the other reported inconsistent findings in men by age group (≤ 60 or > 60 years) when comparing the highest and lowest levels (see CUP Lung SLR 2015 Figure 153).

Eight studies were included in the dose-response meta-analysis (n = 2,855 cases), which showed a three per cent decreased risk per 10 micrograms per 100 millilitres (RR 0.97 (95% CI 0.95–0.98)) (CUP Lung SLR 2015 Figure 154). No heterogeneity was observed (I² = 0%). There was evidence of non-linearity (p < 0.01 (see CUP Lung SLR 2015 Figure 157 and Table 130). The curve is suggestive of a decreased risk of lung cancer with higher blood retinol levels but may start to plateau after 90 μg/100 ml. No significant association was observed in the Multiethnic cohort [75], where the retinol blood levels were higher than in the other studies.

Three studies [106-108] were not included in any of the CUP analyses because they reported insufficient data.

All studies adjusted for intensity, duration of smoking and other smoking variables, in addition to smoking status, except one study [109] which was adjusted only for smoking status.

The CUP findings, like the 2005 SLR, show an inverse association, but the results in the CUP are significant. The CUP update includes twice the number of studies and 805 more cases of lung cancer.

**Published pooled analyses and meta-analyses**

No pooled analyses or meta-analyses were identified in the CUP Lung SLR 2015.

**Mechanisms**

The diverse and complex mechanisms whereby retinoids may have an impact on lung carcinogenesis are not completely understood. Retinol and its metabolites are known to bind to a family of receptors involved in differentiation, membrane structure and function, and immunological effects associated with carcinogenesis [110].

_update:_ As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see Exposures: Other dietary exposures (Appendix – Mechanisms) for the updated mechanisms summary.

**CUP Panel’s conclusion:**

The evidence for consumption of foods containing retinol was limited but generally consistent. The dose-response meta-analysis showed a significant decreased risk of lung cancer per 10 micrograms per 100 millilitres for serum retinol. The non-linear analysis suggests a decreased risk of lung cancer at higher blood retinol levels. There is evidence for plausible mechanisms operating in humans. The CUP Panel concluded the following:

_The evidence suggesting that foods containing retinol decrease the risk of lung cancer is limited._
7.12 Alcoholic drinks

(Also see CUP Lung SLR 2015: Sections 5.4, 5.4.1, 5.4.2 and 5.4.3)

The CUP identified 18 new or updated cohort studies [65, 88, 111-126], giving a total of 45 studies (50 publications) assessing alcohol in the form of ethanol and lung cancer (see CUP Lung SLR 2015 Tables 104 and 105 for a full list of references). Of 24 studies reporting on incidence, 14 reported positive associations, two of which were significant. Three studies reported non-significant inverse associations and three reported no effect. Four studies reported inconsistent results for men and women when comparing the highest and lowest categories of intake. Of 12 studies reporting on mortality, seven reported positive associations, two of which were significant. Two reported non-significant inverse associations and one study reported no association. Three studies reported inconsistent results for men and women when comparing the highest and lowest categories of intake (see CUP Lung SLR 2015 Figure 120).

Twenty-six studies were included in the dose-response meta-analysis (n = 21,940 cases), which showed a three per cent increased risk per 10 grams of ethanol per day (RR 1.03 (95% CI 1.01–1.05); see CUP Lung SLR 2015 Figure 121. High heterogeneity was observed (I² = 67%, p < 0.001) for all studies combined. In meta-regression analysis, year of publication and adjustment for smoking significantly explained heterogeneity, but not geographic location, unit of intake (servings or g/day), sex, outcome or study size. In meta-regression models with both variables, lower RR estimates were found in more recent studies (p = 0.012 for those published after 2006 versus before 2002) and with more adjustment for smoking (p = 0.017 for more adjusted compared with unadjusted).

There was indication of small study bias with Egger’s test (p = 0.02) (see CUP Lung SLR 2015 Figure 123). The asymmetry suggests missing small studies on the left side of the plot. Non-linear analysis showed that no increased risk was evident at low levels and risk becoming significantly increased at approximately 40 grams per day of ethanol intake (p < 0.01; see CUP Lung SLR 2015 Figure 131 and Table 106). Non-linear analyses were performed for men and women; tests were significant for both (p < 0.01; see CUP Lung SLR 2015 Figures 132 and 133 and Tables 107 and 108).

When the results were stratified by smoking status, no significant associations were observed (see CUP Lung SLR 2015 Table 102).

Seven studies [50, 106, 127-131] were not included in any of the CUP analyses because they reported insufficient data.

Four studies did not adjust for smoking; five studies adjusted for smoking status only, 10 studies adjusted for smoking status and intensity (cigarettes per day, pack-years) smoked and 11 studies adjusted for smoking status, intensity and duration (years smoking and/or time since quitting). The studies included in the Pooling Project adjusted for smoking status, smoking duration for past and current smokers, and cigarettes smoked daily for current smokers.
The CUP findings are similar to those from the 2005 SLR, which showed a borderline positive association (RR = 1.02 (95% CI 1.00–1.05)) per 10 grams of ethanol per week, although the CUP meta-analysis reached statistical significance. The CUP update includes 17 more studies and many more cases of lung cancer.

**Published pooled analyses and meta-analyses**

Results from one published pooled analysis [132] and two published meta-analyses [133, 134] on alcohol and lung cancer were identified by the CUP Lung SLR 2015. In the pooled analysis no significant associations were observed in men or women when comparing the highest with the lowest alcohol consumers. Six of the seven cohorts from this pooled analysis were included in the CUP analysis. When the results from the CUP and the Pooling Project were stratified by smoking status, no significant associations were observed (see CUP Lung SLR 2015 Figure 127). Both meta-analyses reported no significant associations (RR 1.02 (95% CI 0.92–1.28) [133] and RR 1.27 (95% CI 0.85–1.91)) [134].

Results from the CUP Lung SLR 2015 and the published pooled analysis are presented in Table 15.

**Table 15: Summary of CUP 2015 meta-analysis and published pooled-analysis – ethanol**

<table>
<thead>
<tr>
<th>Study</th>
<th>Increment/Contrast</th>
<th>RR (95% CI)</th>
<th>I²</th>
<th>No. Studies</th>
<th>No. Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>CUP</td>
<td>Per 10 g/day</td>
<td>1.03 (1.01–1.05)</td>
<td>67%</td>
<td>26</td>
<td>21,940</td>
</tr>
<tr>
<td>CUP Lung SLR 2015 + pooled analysis</td>
<td>Per 10 g/day</td>
<td>1.03 (1.02–1.05)</td>
<td>67%</td>
<td>32</td>
<td>24,630</td>
</tr>
<tr>
<td>Pooled analysis of cohort studies [132]</td>
<td>≥ 30 g/day vs. none – men</td>
<td>1.21 (0.91–1.61)</td>
<td>-</td>
<td>7</td>
<td>3,137</td>
</tr>
<tr>
<td></td>
<td>≥ 30 g/day vs. none – women</td>
<td>1.16 (0.94–1.43)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Other alcohol exposures**

Dose-response meta-analyses were conducted for beer, wine and spirits, and lung cancer. No significant associations were observed for beer and spirits, although a significant inverse association was observed for wine and lung cancer. When the studies from the CUP analysis (but not those included in the pooled analysis) were combined with the results from the pooled analysis, a similar pattern emerged (see Table 16 and CUP Lung SLR 2015 Figures 138, 144, 145, 149 and 150).
Table 16: Summary of CUP dose-response meta-analyses – other alcohol exposures, as ethanol

<table>
<thead>
<tr>
<th>Analysis</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>CUP 2015 Beer</td>
<td>Per 10 g/day</td>
<td>1.04 (0.93–1.16)</td>
<td>64%</td>
<td>7</td>
<td>3,481</td>
</tr>
<tr>
<td>CUP 2015 Wine</td>
<td>Per 10 g/day</td>
<td>0.87 (0.76–0.98)</td>
<td>62%</td>
<td>5</td>
<td>2,701</td>
</tr>
<tr>
<td>CUP 2015 Spirits</td>
<td>Per 10 g/day</td>
<td>1.03 (0.98–1.10)</td>
<td>0%</td>
<td>6</td>
<td>2,920</td>
</tr>
</tbody>
</table>

Mechanisms

Reactive metabolites of alcohol such as acetaldehyde are carcinogenic. There is also an interaction with smoking: tobacco may induce specific mutations in DNA that are less efficiently repaired in the presence of alcohol. Alcohol may also function as a solvent, enhancing penetration of other carcinogenic molecules into mucosal cells [135]. In addition, the effects of alcohol may be mediated through the production of prostaglandins, lipid peroxidation and the generation of free radical oxygen species. Last, high consumers of alcohol may have diets low in essential nutrients, making tissues susceptible to carcinogenesis [1].

Update: As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see Exposures: Alcoholic drinks (Appendix – Mechanisms) for the updated mechanisms summary.

CUP Panel’s conclusion:

The evidence was generally consistent, and the dose response meta-analysis showed a significant increased risk per 10 grams of ethanol per day for lung cancer. There was evidence of high heterogeneity, explained by year of publication and adjustment for smoking. There was evidence of non-linearity: no increase was evident at low levels but it became significant at approximately 40 grams per day of ethanol. This pattern was similar in both men and women. It is not possible to exclude residual confounding by smoking. There is evidence for plausible mechanisms operating in humans. The CUP Panel concluded the following:

The evidence suggesting that consumption of alcoholic drinks increases the risk of lung cancer is limited.
7.13 Physical activity

(Also see CUP Lung SLR 2015: Sections 6.1, 6.1.1.1 and 6.1.1.2)

The CUP identified one new study (one publication) [136], giving a total of five studies (six publications) reviewing the evidence for total physical activity and lung cancer (see CUP Lung SLR 2015 Tables 225 and 226 for a full list of references).

All five studies were included in an analysis comparing the highest and lowest total physical activity levels ($n = 1,457$ cases), which showed no significant association ($RR = 0.90$ (95% CI 0.77–1.04)) (CUP Lung SLR 2015 Figure 234). There was evidence of moderate, but not significant heterogeneity ($I^2 = 40\%$, $p_{\text{heterogeneity}} = 0.10$). When one study [137] that carried 44 per cent of the weight was excluded from the analysis, no heterogeneity was observed and the association became significant (summary $RR = 0.85$ (95% CI 0.72–0.99)).

All studies adjusted for smoking status and intensity.

Published pooled and meta-analyses

One published pooled analysis [138] of cohort studies reporting on total physical activity and lung cancer was identified in the CUP Lung SLR 2015. It reported significant decreased risk of lung cancer in both men and women when comparing the highest with the lowest levels of physical activity (total and leisure time combined) ($RR = 0.78$ (95% CI 0.73–0.83) and $RR = 0.76$ (95% CI 0.69–0.84), respectively).

Other physical activity exposures

The CUP Lung SLR 2015 compared highest and lowest levels of occupational and recreational physical activity. No association was observed for occupational physical activity ($RR = 1.12$ (95% CI 0.99–1.28)), a significant inverse association was observed for recreational physical activity ($RR = 0.86$ (95% CI 0.81–0.92)), and no significant association was observed for never smokers (see Table 17 and Figures 235, 236 and 238 in the CUP Lung SLR 2015), a pattern suggestive of residual confounding by smoking. One published meta-analysis [139] reported significant inverse associations in men, women, heavy and light smokers (see CUP Lung SLR 2015 Table 233).
Table 17: Summary of CUP highest vs. lowest meta-analysis – other physical activity exposures

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Contrast</th>
<th>RR (95% CI)</th>
<th>$I^2$</th>
<th>No. Studies</th>
<th>No. Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Occupational physical activity</strong></td>
<td>Highest vs. lowest</td>
<td>1.12 (0.99–1.28)</td>
<td>0%</td>
<td>5</td>
<td>3,773</td>
</tr>
<tr>
<td></td>
<td>Highest vs. lowest</td>
<td>0.86 (0.81–0.92)</td>
<td>41%</td>
<td>18</td>
<td>17,655</td>
</tr>
<tr>
<td></td>
<td>Highest vs. lowest, current smokers</td>
<td>0.81 (0.71–0.91)</td>
<td>65%</td>
<td>6</td>
<td>6,596</td>
</tr>
<tr>
<td></td>
<td>Highest vs. lowest, former smokers</td>
<td>0.68 (0.51–0.90)</td>
<td>50%</td>
<td>3</td>
<td>3,647</td>
</tr>
<tr>
<td></td>
<td>Highest vs. lowest, never smokers</td>
<td>0.99 (0.76–1.31)</td>
<td>19%</td>
<td>3</td>
<td>894</td>
</tr>
</tbody>
</table>

**Mechanisms**

The association between physical activity and lung cancer is complex. Unlike many other cancers, lung cancer is not positively associated with BMI. The observed association between physical activity and lung cancer may be a reflection of reverse causation due to chronic lung disease, which is associated with lung cancer risk and limits physical activity. Residual confounding by smoking is also possible, perhaps explaining why leisure activity has an inverse association and occupational activity a positive association. There is evidence showing a lower risk of lung cancer with higher levels of physical activity. Sustained, moderate physical activity raises the metabolic rate and increases maximal oxygen uptake. In the long term, regular periods of such activity increase the body’s metabolic efficiency and capacity (the amount of work that it can perform), as well as reducing blood pressure and insulin resistance. The relationship between activity, BMI and lung cancer makes the evidence difficult to interpret. There is limited evidence suggesting that physical activity protects against lung cancer.

*Update: As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see Exposures: Physical activity (Appendix – Mechanisms) for the updated mechanisms summary.*
CUP Panel’s conclusion:

The evidence is inconsistent – a significant decreased risk was observed with higher levels of recreational physical activity but an increased risk (non-significant) was observed for occupational physical activity. Although studies in the occupational physical activity analysis adjusted for smoking status, BMI and other confounders, the potential for residual confounding remains. There is evidence for plausible mechanisms operating in humans. The CUP Panel concluded the following:

The evidence suggesting that higher levels of physical activity decrease the risk of lung cancer is limited.

7.14 Other

Other exposures were evaluated. However, data were either of too low quality or too inconsistent, or the number of studies too few to allow conclusions to be reached. This list of exposures judged as ‘limited – no conclusion’ is summarised in the matrix on page 8.

The evidence for foods containing selenium, foods containing quercetin, selenium supplements, total fat, butter, retinol supplements and low body fatness, previously judged as ‘limited – suggestive’ in the Second Expert Report [1], was less consistent, and the Panel could not draw any conclusions from the updated evidence.

Evidence for the following exposures previously judged as ‘limited – no conclusion’ in the Second Expert Report remained unchanged after updating the analyses with new data identified in the CUP Lung SLR 2015: pulses (legumes), poultry, fish, eggs, milk and dairy products, coffee, tea, folate, vitamin C supplements, multivitamin supplements, pro-vitamin A carotenoids, lycopene, patterns of diet, body fatness.

The following exposures, which were also previously too limited to draw conclusions in the Second Expert Report and not updated as part of the CUP Lung SLR 2015 owing to a lack of new evidence, remained ‘limited – no conclusion’: cereals (grains) and their products, starchy tubers; dietary fibre; animal fats; plant oils; soft drinks; preservation, processing, and preparation; carbohydrate; protein; vitamin A; thiamin; riboflavin; niacin; vitamin B6; vitamin E; calcium; copper; iron; zinc; energy intake.

In addition, evidence for the following new exposures, for which no judgement was made in the Second Expert Report, was too limited to draw any conclusions: citrus fruit; total meat; green tea; beta-cryptoxanthin, lutein and zeaxanthin; plasma hydroxyvitamin D; and height.
8. Comparison with the Second Expert Report

More exposures in this CUP update were analysed according to smoking status. Much of the new evidence was on foods containing retinol, beta-carotene, vitamin C and isoflavones, and on alcohol. The updated evidence on fruit and foods containing carotenoids was less strong than in the Second Expert Report [1]. The increase in the amount and quality of the evidence highlighted the need for further research, particularly in non-smokers.
9. Conclusions

The CUP Panel concluded the following:

**Convincing evidence**

Arsenic in drinking water: Consumption of arsenic in drinking water is a convincing cause of lung cancer.

Beta-carotene supplements: Consumption of high-dose beta-carotene supplements is a convincing cause of lung cancer in current and former smokers.

**Limited-suggestive evidence**

Vegetables: The evidence suggesting that consumption of vegetables decreases the risk of lung cancer in current and former smokers is limited.

Fruit: The evidence suggesting that consumption of fruit decreases the risk of lung cancer in current and former smokers is limited.

Foods containing carotenoids: The evidence suggesting that foods containing carotenoids decrease the risk of lung cancer is limited.

Foods containing beta-carotene: The evidence suggesting that foods containing beta-carotene decrease the risk of lung cancer is limited.

Foods containing retinol: The evidence suggesting that foods containing retinol decrease the risk of lung cancer is limited.

Foods containing vitamin C: The evidence suggesting that foods containing vitamin C decrease the risk of lung cancer in current smokers is limited.

Foods containing isoflavones: The evidence suggesting that foods containing isoflavones decrease the risk of lung cancer in individuals who have never smoked is limited.

Physical activity: The evidence suggesting that physical activity decreases the risk of lung cancer is limited.

Red meat: The evidence suggesting that consumption of red meat increases the risk of lung cancer is limited.

Processed meat: The evidence suggesting that consumption of processed meat increases the risk of lung cancer is limited.

Alcoholic drinks: The evidence suggesting that consumption of alcoholic drinks increases the risk of lung 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 on page 67.

The Cancer Prevention Recommendations were reviewed by the CUP Panel and published in 2018. Please see Recommendations and public health and policy implications for further details.

Each conclusion on the likely causal relationship between an exposure and the risk of cancer forms a part of the overall body of evidence that is considered during the process of making Cancer Prevention Recommendations. Any single conclusion does not represent a recommendation in its own right. The 2018 Cancer Prevention Recommendations are based on a synthesis of all these separate conclusions, as well as other relevant evidence.
Acknowledgements

Panel Members

CHAIR – Alan Jackson CBE MD FRCP FRCPATH FRCPCH FAfN
University of Southampton
Southampton, UK

DEPUTY CHAIR – Hilary Powers PhD RNutr
University of Sheffield
Sheffield, UK

Elisa Bandera MD PhD
Rutgers Cancer Institute of New Jersey
New Brunswick, NJ, USA

Steven Clinton MD PhD
The Ohio State University
Columbus, OH, USA

Edward Giovannucci MD ScD
Harvard School of Public Health
Boston, MA, USA

Stephen Hursting PhD MPH
University of North Carolina at Chapel Hill
Chapel Hill, NC, USA

Michael Leitzmann MD DrPH
Regensburg University
Regensburg, Germany

Anne McTiernan MD PhD
Fred Hutchinson Cancer Research Center
Seattle, WA, USA

Inger Thune MD PhD
Oslo University Hospital and University
of Tromsø
Oslo and Tromsø, Norway

Ricardo Uauy MD PhD
Instituto de Nutrición y Tecnología
de los Alimentos
Santiago, Chile

Observers

Elio Riboli MD ScM MPH
Imperial College London
London, UK

Isabelle Romieu MD MPH ScD
International Agency for Research
on Cancer
Lyon, France

Research Team

Teresa Norat PhD
Principal Investigator
Imperial College London
London, UK

Doris Chan MSc
Research Associate
Imperial College London
London, UK

Snieguole Vingeliene MSc
Research Associate
Imperial College London
London, UK

Dagfinn Aune MSc
Research Associate
Imperial College London
London, UK
Leila Abar MSc
Research Associate
Imperial College London
London, UK

Ana Rita Vieira MSc
Research Associate
Imperial College London
London, UK

Deborah Navarro-Rosenblatt MSc
Research Associate
Imperial College London
London, UK

Darren Greenwood PhD
Statistical Adviser
Senior Lecturer in Biostatistics
University of Leeds
Leeds, UK

Christophe Stevens
Database Manager
Imperial College London
London, UK

WCRF Executive

Marilyn Gentry
President
WCRF International

Kelly Browning
Executive Vice President
AICR

Kate Allen PhD
Executive Director
Science and Public Affairs
WCRF International

Deirdre McGinley-Gieser
Senior Vice President for Programs and Strategic Planning
AICR

Stephenie Lowe
Executive Director
International Financial Services
WCRF Network

Rachael Gormley
Executive Director
Network Operations
WCRF International

Nadia Ameyah
Director
Wereld Kanker Onderzoek Fonds

Secretariat

HEAD – Rachel Thompson PhD RNutr
Head of Research Interpretation
WCRF International

Susannah Brown MSc
Science Programme Manager (Research Evidence)
WCRF International

Stephanie Fay PhD
Science Programme Manager (Research Interpretation)
WCRF International

Susan Higginbotham PhD RD
Vice President of Research
AICR

Giota Mitrou PhD
Director of Research Funding and Science External Relations
WCRF International

Martin Wiseman FRCP FRCPath FAfN
Medical and Scientific Adviser
WCRF International
Abbreviations

AICR  American Institute for Cancer Research
BMI  Body mass index
CI  Confidence interval
CUP  Continuous Update Project
DNA  Deoxyribonucleic acid
IARC  International Agency for Research on Cancer
n  Number of cases
RR  Relative risk
SLR  Systematic literature review
WCRF  World Cancer Research Fund
Glossary

Adenocarcinoma
Cancer of glandular epithelial cells.

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

Antioxidant
A molecule that inhibits the oxidation of other molecules. Oxidation is a chemical reaction involving the loss of electrons, which can produce free radicals. In turn, these radicals can start chain reactions, which can cause damage or death to cells (see free radicals).

Antiproliferative
Of, or relating to, a substance used to prevent or delay the increase in cell numbers characteristic of tumours.

Bias
In epidemiology, consistent 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 selection bias).

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

Carcinogen
Any substance or agent capable of causing cancer.

Case-control study
An epidemiological study in which the participants are chosen on the basis of 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.

Chronic
A health condition or disease that is persistent or long lasting.

Cohort study
A study of a (usually large) group of people whose characteristics are recorded at recruitment (and sometimes also 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 a 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 may be expressed as 10 (95% CI 5–15). This means that the estimate of the relative risk was calculated as 10 and that there is a 95% 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 (adjusted) 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, which 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.

**DNA methylation**
A process by which methyl groups are added to DNA. DNA methylation is one of several epigenetic mechanisms that regulate gene expression.

**Dose-response**
A term derived from pharmacology that describes the degree to which an effect changes as the level of an exposure changes, for instance, intake of a drug or food.

**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.
Free radicals
An atom or group of atoms that has one or more unpaired electrons. A prominent feature of radicals is that they have high chemical reactivity, which explains their normal biological activities and how they inflict damage on cells. There are many types of radicals, but those of most importance in biological systems are derived from oxygen and known collectively as reactive oxygen species.

Genotoxic
Chemical agents that damage the genetic information within a cell, causing mutations, which may lead to cancer.

Genotype
Part of the genetic makeup of a cell (DNA sequence), and therefore of an organism or individual, which determines a specific characteristic (phenotype) of that cell, organism or individual.

Heterocyclic amines
Along with polycyclic aromatic hydrocarbons, chemicals formed when muscle meat, including beef, pork, fish or poultry, is cooked using high-temperature methods.

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 I² test.

High-income countries
As defined by the World Bank, countries with a gross national income per captia of more than US $12,732. This term is more precise than and used in preference to ‘economically developed countries’.

Immune response
The production of antibodies or specialised cells in response to foreign proteins or other substances.

Immunomodulation
Encompasses all therapeutic interventions aimed at modifying the immune response.

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, characterized by accumulation of white blood cells that produce several bioactive chemicals (cytokines), causing redness, pain, heat and swelling. Inflammation may be acute (such as in response to infection or injury) or chronic (as part of several conditions, including obesity).
**Less developed regions**
As defined by the IARC, all regions of Africa, Asia (excluding Japan), Latin America and the Caribbean, Melanesia, Micronesia and Polynesia.

**Lipid peroxidation**
The oxidative degradation of lipids. It is the process in which free radicals ‘steal’ electrons from the lipids in cell membranes, resulting in cell damage.

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

**Metastasis**
Also metastatic disease; the spread of a cancer or other disease from one organ or part of the body to another not directly neighbouring it.

**More developed regions**
As defined by the IARC, all regions of Europe plus northern America, Australia, New Zealand and Japan.

**Mutation**
A permanent change of the nucleotide sequence of the genome (an organism’s complete set of DNA).

**Nested case-control study**
A case-control study in which cases and controls are drawn from the population of a cohort study; often used for studies of prospectively collected information or biological samples.

**Non-small-cell lung cancer**
Non-small-cell lung cancer (NSCLC) is the most common type of lung cancer. It usually grows and spreads more slowly than small-cell lung cancer.

**Odds ratio**
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 relative risk.

**Oncogene**
A gene which in certain circumstances can transform a cell into a tumour cell.

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

**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 of what precisely is included vary between countries and studies.

**Prostaglandins**
A group of physiologically active lipid compounds having diverse hormone-like effects in animals.

**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. Sometimes, neither investigators nor subjects know to which intervention they have been randomised; this is called ‘double-blinding’.

**Relative risk (RR)**
The ratio of the rate of an outcome (e.g., disease (incidence) or death (mortality)) among people exposed to a factor, compared with the rate among the unexposed; usually used in cohort studies.

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

**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).

**Small-cell lung cancer**
Small-cell lung cancer (also known as ‘small-cell carcinoma’) is a highly malignant type of cancer that commonly arises within the lung.

**Squamous cell carcinoma**
Squamous cell carcinoma is a cancer of squamous cells, one kind of epithelial cell.

**Systematic literature review (SLR)**
A means of compiling and assessing published evidence that addresses a scientific question with a predefined protocol and transparent methods. May or may not include meta-analysis.

**Tumour-suppressor genes**
Normal genes that slow down cell division, repair DNA mistakes, or promote apoptosis or programmed cell death. When tumor suppressor gene function is impaired, cells can accumulate errors in DNA that can lead to cancer.
References


Appendix: Criteria for grading evidence for cancer prevention

See also Judging the evidence, section 8.

Adapted from Chapter 3 of the 2007 Second Expert Report. Listed here are 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.

These criteria were used in a modified form for breast cancer survivors (see CUP Breast cancer survivors report 2014).

CONVINCING (STRONG EVIDENCE)

Evidence strong enough to support a judgement of a convincing causal (or protective) relationship, which justifies making recommendations designed to reduce the risk of cancer. The evidence is 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.
- 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 (STRONG EVIDENCE)

Evidence strong enough to support a judgement of a probable causal (or protective) relationship, which generally justifies recommendations designed to reduce the risk of cancer.

All of 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

Evidence that is too limited to permit a probable or convincing causal judgement but is suggestive of a direction of effect. The evidence may be limited in amount or by methodological flaws but shows a generally consistent direction of effect. This judgement is broad and includes associations where the evidence falls only slightly below that required to infer a probably causal association through to those where the evidence is only marginally strong enough to identify a direction of effect. This judgement is very rarely sufficient to justify recommendations designed to reduce the risk of cancer; any exceptions to this 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 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 may be limited by the amount of evidence in terms of the number of studies available, by inconsistency of direction of effect, by methodological flaws (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 (dietandcancerreport.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- 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, from either human studies or relevant animal models, that typical human exposure levels lead to relevant cancer outcomes.

Factors that might misleadingly imply an absence of effect include imprecision of the exposure assessment, insufficient range of exposure in the study population and inadequate statistical power. Defects such as these and in 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 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 one 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 the following:

- 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 within the healthy range and avoid weight gain in adult life

Be physically active
Be physically active as part of everyday life – walk more and sit less

Eat a diet rich in wholegrains, vegetables, fruit and beans
Make wholegrains, vegetables, fruit, and pulses (legumes) such as beans and lentils a major part of your usual daily diet

Limit consumption of ‘fast foods’ and other processed foods high in fat, starches or sugars
Limiting these foods helps control calorie intake and maintain a healthy weight

Limit consumption of red and processed meat
Eat no more than moderate amounts of red meat, such as beef, pork and lamb. Eat little, if any, processed meat

Limit consumption of sugar sweetened drinks
Drink mostly water and unsweetened drinks

Limit alcohol consumption
For cancer prevention, it’s best not to drink alcohol

Do not use supplements for cancer prevention
Aim to meet nutritional needs through diet alone

For mothers: breastfeed your baby, if you can
Breastfeeding is good for both mother and baby

After a cancer diagnosis: follow our Recommendations, if you can
Check with your health professional what is right for you

Not smoking and avoiding other exposure to tobacco and excess sun are also important in reducing cancer risk.

Following these Recommendations is likely to reduce intakes of salt, saturated and trans fats, which together will help prevent other non-communicable diseases.