



Diet, nutrition, physical activity and **oesophageal cancer**

2016

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WORLD CANCER RESEARCH FUND INTERNATIONAL

OUR VISION

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

OUR MISSION

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

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

OUR NETWORK

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

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



OUR CONTINUOUS UPDATE PROJECT (CUP)

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

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

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

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

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

This CUP report on oesophageal cancer updates the oesophageal cancer section of the Second Expert Report (Section 7.3) and is based on the findings of the CUP Oesophageal Cancer Systematic Literature Review (SLR) and the CUP Expert Panel discussion in June 2015.

For further details please see the full CUP Oesophageal SLR 2015

(wcrf.org/oesophageal-cancer-slr-2015).

HOW TO CITE THIS REPORT

World Cancer Research Fund International/American Institute for Cancer Research. Continuous Update Project Report: Diet, Nutrition, Physical Activity and Oesophageal Cancer. 2016. Available at: wcrf.org/oesophageal-cancer-2016.

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

[1] World Cancer Research Fund/American Institute for Cancer Research, *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*. wcrf.org/int/research-we-fund/continuous-update-project-cup/second-expert-report. 2007.

EXECUTIVE SUMMARY

Background and context

Oesophageal cancer is the eighth most common cancer worldwide. Around 456,000 new cases were recorded globally in 2012, accounting for three per cent of all new cases of cancer. It is the sixth most common cause of death from cancer [2].

Men are twice as likely as women to develop oesophageal cancer. About 80 per cent of cases occur in less developed countries [2]. The highest incidences of this cancer are in Asia and Africa, and the lowest incidences are in North America and Europe.

Significant symptoms often only appear at an advanced stage, which contributes to a poor prognosis. For example, in the United States the five-year survival rate of oesophageal cancer is about 20 per cent and in Europe it is about 10 per cent. However, these survival rates are far worse in less developed countries where oesophageal cancer is typically detected at a more advanced stage.

Oesophageal cancer is classified into two main types: squamous cell carcinoma, which occurs in the upper part of the oesophagus, and adenocarcinoma, which develops at the junction of the oesophagus and stomach. Globally, squamous cell carcinoma is the most common type and accounts for 88 per cent of cases; however, the proportion of adenocarcinomas is increasing dramatically in affluent nations.

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 oesophageal cancer. This includes new studies as well as those included in our 2007 Second Expert Report, *Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective* [1].

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

1. Smoking:

- ◆ Smoking is a cause of both types of oesophageal cancer. Squamous cell carcinoma is more strongly associated with smoking than adenocarcinoma.

2. Infection:

- ◆ Between 12 and 39 per cent of oesophageal squamous cell carcinomas worldwide are associated with human papilloma virus (HPV) infection.

3. Other diseases:

- ◆ Risk of adenocarcinoma of the oesophagus is increased by gastro-oesophageal reflux disease, a common condition in which stomach acid damages the lining of the lower part of the oesophagus. This type of oesophageal cancer is also increased by a rare condition, oesophageal achalasia (where the valve at the end of the oesophagus fails to open and food gets stuck).

How the research was conducted

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

More research has been conducted in this area since our 2007 Second Expert Report [1]. In total, this new report analysed 46 studies from around the world, comprising 15 million adults and nearly 31,000 cases of oesophageal 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 the findings can be found in the Evidence and judgements section of this report.

Findings

Strong evidence

- ◆ **There is strong evidence that being overweight or obese increases the risk of adenocarcinoma of the oesophagus. Being overweight or obese was assessed by body mass index (BMI), waist circumference and waist-hip ratio.**
- ◆ **There is strong evidence that consuming alcoholic drinks increases the risk of oesophageal squamous cell carcinoma.**
- ◆ **There is strong evidence that regularly consuming mate, as drunk in the traditional style in South America, increases the risk of oesophageal squamous cell carcinoma.**

Limited evidence

- ◆ **There is some evidence that suggests consuming vegetables decreases the risk of oesophageal cancer.**
- ◆ **There is some evidence that suggests consuming fruit decreases the risk of oesophageal squamous cell carcinoma.**
- ◆ **There is some evidence that suggests that being physically active decreases the risk of oesophageal cancer.**
- ◆ **There is some evidence that suggests consuming processed meat increases the risk of oesophageal squamous cell carcinoma.**

Recommendations

Our Cancer Prevention Recommendations – for preventing cancer in general – include maintaining a healthy weight, being physically active, eating a healthy diet and limiting alcohol consumption (if consumed at all). The Cancer Prevention Recommendations are listed on the inside back cover of this report, with full details available at wcrf.org/recommendations.

References

- [1] World Cancer Research Fund/American Institute for Cancer Research, *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*. Available from wcrf.org/int/research-we-fund/continuous-update-project-cup/second-expert-report. 2007.
- [2] Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. 2015. Available from <http://globocan.iarc.fr>

2016	DIET, NUTRITION, PHYSICAL ACTIVITY AND OESOPHAGEAL ADENOCARCINOMA		
		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	Convincing		Body fatness ¹
	Probable		
LIMITED EVIDENCE	Limited – suggestive	Vegetables Physical activity ²	
	Limited – no conclusion	Dietary fibre, fruit, red meat, processed meat, total meat, poultry, fish, coffee, high-temperature drinks, mate, alcohol, pyridoxine, vitamin C, vitamin E, folate, beta-carotene, adult attained height, patterns of diet, cereals (grains) and their products, starchy roots, tubers and plantains, pulses (legumes), soya and soya products, herbs spices and condiments, milk and dairy products, total fat, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, sugary foods and drinks, salt, salting, fermenting, pickling, smoked and cured foods, nitrates and nitrites, frying, grilling (broiling) and barbecuing (charbroiling), protein, vitamin A, retinol, thiamin, riboflavin, calcium, iron, zinc, pro-vitamin A carotenoids, beta-cryptoxanthin and energy intake	
STRONG EVIDENCE	Substantial effect on risk unlikely		

1 Body fatness is marked by body mass index (BMI), waist circumference and waist-hip ratio.
2 Adenocarcinoma and squamous cell carcinoma combined.

For an explanation of oesophageal cancer subtypes (adenocarcinoma and squamous cell carcinoma), see Section 2 on page 9 and the **Glossary** on page 46.

2016	DIET, NUTRITION, PHYSICAL ACTIVITY AND OESOPHAGEAL SQUAMOUS CELL CARCINOMA		
		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	Convincing		Alcoholic drinks
	Probable		Mate ¹
LIMITED EVIDENCE	Limited – suggestive	Vegetables Fruit Physical activity ²	Processed meat
	Limited – no conclusion	Dietary fibre, red meat, total meat, poultry, fish, coffee, high-temperature drinks, pyridoxine, vitamin C, vitamin E, folate, beta-carotene, body fatness, adult attained height, patterns of diet, cereals (grains) and their products, starchy roots, tubers and plantains, pulses (legumes), soya and soya products, herbs spices and condiments, milk and dairy products, total fat, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, sugary foods and drinks, salt, salting, fermenting, pickling, smoked and cured foods, nitrates and nitrites, frying, grilling (broiling) and barbecuing (charbroiling), protein, vitamin A, retinol, thiamin, riboflavin, calcium, iron, zinc, pro-vitamin A carotenoids, beta-cryptoxanthin and energy intake	
STRONG EVIDENCE	Substantial effect on risk unlikely		

1 As drunk traditionally in parts of South America, scalding hot through a metal straw.
2 Adenocarcinoma and squamous cell carcinoma combined.

For an explanation of oesophageal cancer subtypes (adenocarcinoma and squamous cell carcinoma), see Section 2 on page 9 and the **Glossary** on page 46.

1. Summary of Panel judgements

Oesophageal cancer is divided into two main subtypes. Adenocarcinoma arises from the glandular cells present in the lower oesophagus and squamous cell carcinoma arises from the epithelial cells that line the oesophagus.

Overall, the Panel notes the strength of the evidence that body fatness is a cause of oesophageal adenocarcinoma and consumption of alcoholic drinks and mate (as consumed scalding hot in South America) are causes of oesophageal squamous cell carcinoma.

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

- ◆ **Body fatness:** Greater body fatness (marked by BMI, waist circumference and waist-hip ratio) is a convincing cause of oesophageal adenocarcinoma.
- ◆ **Alcoholic drinks:** Consumption of alcoholic drinks is a convincing cause of oesophageal squamous cell carcinoma.
- ◆ **Mate:** Regular consumption of mate, as drunk in the traditional style in South America, probably causes oesophageal squamous cell carcinoma.
- ◆ **Fruit:** The evidence suggesting that consumption of fruit decreases the risk of oesophageal squamous cell carcinoma is limited.
- ◆ **Vegetables:** The evidence suggesting that consumption of vegetables decreases the risk of oesophageal adenocarcinoma and oesophageal squamous cell carcinoma is limited.
- ◆ **Processed meat:** The evidence suggesting that consumption of processed meat increases the risk of oesophageal squamous cell carcinoma is limited.
- ◆ **Physical activity:** The evidence suggesting that physical activity decreases the risk of oesophageal 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 55.

The Panel judgements for oesophageal adenocarcinoma and oesophageal squamous cell carcinoma are shown in the matrices on pages 6 and 7.

2. Trends, incidence and survival

The oesophagus is the muscular tube through which food passes from the pharynx to the stomach. The oesophagus is lined over most of its length by squamous epithelial cells, where squamous cell carcinomas arise. The portion just above the gastric junction (where the oesophagus meets the stomach) is lined by columnar epithelial cells, from which adenocarcinomas arise.

Oesophageal cancer is the eighth most common cancer worldwide, with an estimated 456,000 new cases in 2012, accounting for about 3.2 per cent of all cancers. It is the sixth most common cause of death from cancer, with an estimated 400,000 deaths (4.9 per cent of the total) [2, 3]. These figures include both adenocarcinoma and squamous cell carcinoma. About 80 per cent of the cases worldwide occur in less developed regions, where the age-standardised rate is almost double that of more developed regions. Oesophageal cancer incidence rates worldwide in men are twice as high as those in women [2].

The two major histologic types of oesophageal cancer, squamous cell carcinoma and adenocarcinoma, differ substantially in their underlying patterns of incidence and key aetiological factors. Both have a high mortality rate. Globally, squamous cell carcinomas account for 88 per cent of oesophageal cancer cases [4], although the incidence of oesophageal adenocarcinoma has increased sharply, and that of squamous carcinoma has declined over the past few decades [5]. In the United States, there has been a 30 per cent drop in the incidence of squamous cell carcinoma between 1973 and 2002 but a four-fold increase in the incidence of adenocarcinoma over the same period [6]. Adenocarcinoma of the oesophagus shows similarities in its histological and morphological characteristics with adenocarcinoma of the gastric cardia [7].

Survival rates are poor mainly because cancer of the oesophagus is usually diagnosed at a late stage [5]. Oesophageal cancer mortality closely follows the geographical patterns for incidence, with the highest mortality rates occurring in Eastern Asia and Southern Africa in men and in Eastern and Southern Africa in women [2]. In the United States, the five-year survival rate is 20 per cent [8] compared with 10 per cent in Europe [9]. For further information, see the **Box** overleaf.

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.

The information on cancer survival shown here 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

There are two main forms of cancer of the oesophagus. Adenocarcinomas arise from the columnar glandular cells that line the lower end of the oesophagus, and squamous cell carcinomas arise from the squamous epithelial lining. The epithelial cells lining the oesophagus are exposed directly to carcinogens in food. Repeated exposure, to burns from very high-temperature drinks or irritation from the direct action of alcohol, for instance, may cause inflammation. The role of irritation and inflammation in the development of oesophageal cancer is supported by the finding that gastro-oesophageal reflux (where stomach acid flows upwards to the oesophagus) increases the risk of adenocarcinomas as much as five-fold [10].

Barrett's oesophagus, a probable intermediate stage between gastro-oesophageal reflux disease and oesophageal adenocarcinoma [11], is an acquired condition in which squamous cells are replaced by columnar epithelial cells; autopsy studies suggest that it usually remains undiagnosed [12]. The increasing use of endoscopy to investigate abdominal symptoms has resulted in the earlier detection of a small proportion of adenocarcinomas in people with Barrett's oesophagus.

In a condition called oesophageal achalasia, the lower oesophageal sphincter fails to relax and swallowed food is retained in the oesophagus. It is associated with a 16–28 per cent increase in the risk of squamous cell carcinomas [13, 14], which may be due to chronic irritation of the lining of the oesophagus or increased contact with food-borne carcinogens. In addition, Tylosis A, a late-onset, inherited familial disease characterised by thickening of the skin of the palms and soles (hyperkeratosis), is associated with a 25 per cent lifetime incidence of squamous cell cancer of the oesophagus. Plummer Vinson syndrome is a rare condition associated with iron deficiency in which growths of tissue block part of the oesophagus, making swallowing difficult. Plummer Vinson syndrome is associated with an increased risk of oesophageal squamous cell carcinoma [15]. *Helicobacter pylori* infection, an established risk factor for non-cardia stomach cancer, is associated with a 41–43 per cent decreased risk of oesophageal adenocarcinoma [16, 17].

4. Other established causes

Other diseases

Gastro-oesophageal reflux disease, oesophageal achalasia and Barrett's oesophagus increase the risk of, and thus can be seen as a cause of, oesophageal adenocarcinoma [11]. Tylosis A and Plummer Vinson syndrome have been linked to an increased risk of oesophageal squamous cell carcinoma [15].

Tobacco use

Smoking is a cause of oesophageal squamous cell carcinoma and oesophageal adenocarcinoma. Tobacco use is associated with a 70 per cent increased risk of oesophageal adenocarcinoma compared with non-use and a 180 per cent increased risk of oesophageal squamous cell carcinoma [18]. About two thirds of oesophageal cancers in the United Kingdom are attributed to tobacco smoking [19]. Chewing betel quid (on its own and also with tobacco quid) is also a cause of oesophageal cancer [20].

Infectious agents

Between 12 and 39 per cent of squamous cell carcinomas worldwide are estimated to be attributable to human papilloma virus (HPV) infection [21]. It may also play a role in the divergent geographical distribution of this cancer [22].

5. Interpretation of the evidence

5.1 General

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

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

5.2 Specific

Considerations specific to oesophageal cancer include:

Classification

Squamous cell carcinomas have different geographical and time trends from adenocarcinomas and follow a different disease path. The oesophageal-gastric junction and gastric cardia are also lined with columnar epithelial cells. Different approaches or definitions in different studies are potential sources of heterogeneity.

Confounding

Tobacco smoking is a potential confounder. Most studies included in this report adjusted for smoking.

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, cohort and nested case-control studies. Due to their methodological limitations, case-control studies were not analysed in the CUP Oesophageal SLR 2015 apart from those for mate, for which strong mechanistic evidence was used as an upgrading factor.

Where possible for this update, meta-analyses for incidence and mortality were conducted separately. However, analyses combining studies on oesophageal cancer incidence and mortality were also conducted to explore heterogeneity in the results. Separate meta-analyses were also conducted by oesophageal sub-type, smoking status, sex and geographical location, where possible.

Studies reporting mean difference as a measure of association were not included in the CUP Oesophageal 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 applied when the data suggested that the dose-response curve was non-linear and when detecting a threshold of exposure might be of interest. Details on the non-linear meta-analyses can be found in the CUP Oesophageal SLR 2015.

For this report, each subtype (adenocarcinoma and squamous cell carcinoma) was reviewed separately where possible. If there was inconsistency in direction of effect, then the overall risk estimates for oesophageal cancer (both types combined) were not considered. Where evidence was insufficient for sub-type analysis but there was no indication of inconsistency in direction of effect, conclusions were drawn for oesophageal cancer (both types combined) and applied both to adenocarcinoma and squamous cell carcinoma (this applies to physical activity in this report). If there was evidence for inconsistency in direction of effect, then conclusions for oesophageal cancer (both types combined) were not drawn. The meta-analyses for oesophageal cancer include any type of oesophageal cancer. Evidence on upper aerodigestive tract cancers and/or combined cancers of the oesophagus and stomach was reviewed separately.

The CUP Oesophageal SLR 2015 included studies published up to 28 February 2014. For more information on methodology, see the full CUP Oesophageal SLR 2015 at wcrf.org/oesophageal-cancer-slr-2015.

6.1 Mechanistic evidence

Where relevant, mechanistic reviews previously conducted for the Second Expert Report [1] are included in this report (more details can be found in chapters 2 and 4 of the Second Expert Report). These reviews have been updated, where possible, by the CUP Panel but will be updated in the future as part of a systematic literature review for the CUP of the mechanistic evidence. A brief summary is given of plausible mechanisms linking oesophageal adenocarcinoma with body fatness and vegetables; linking oesophageal squamous cell carcinoma with alcoholic drinks, mate, processed meat and vegetables; and linking oesophageal cancer with physical activity. Where an exposure presented in this report was previously judged as ‘limited – no conclusion’ or was not discussed for the Second Expert Report, there was no formal review of the mechanisms, although plausible mechanisms identified by CUP Panel members and published reviews are included in this report for physical activity.

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

7. Evidence and judgements

The following sections summarise the evidence identified in the CUP Oesophageal 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 plausible mechanisms for each exposure.

For information on the criteria for grading the epidemiological evidence, see the **Appendix** on page 55 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 Oesophageal SLR 2015.

7.1 Vegetables

(Also see *CUP Oesophageal SLR 2015: Sections 2.2.1 and 2.2.1.4*)

7.1.1 Oesophageal adenocarcinoma

The CUP identified three new studies [23-25], giving a total of three studies (four publications) reviewing the evidence for vegetables and oesophageal adenocarcinoma (for a full list of references, see CUP Oesophageal SLR 2015 Tables 7 and 8).

All three studies reporting on oesophageal adenocarcinoma incidence showed non-significant inverse associations when comparing the highest and the lowest categories (see CUP Oesophageal SLR 2015 Figure 2).



All three studies were included in the dose-response meta-analysis for oesophageal adenocarcinoma ($n = 415$ cases), which showed a statistically significant 11 per cent decreased risk per 100 grams of vegetables per day (RR = 0.89 (95% CI 0.80–0.99); see CUP Oesophageal SLR 2015 Figure 6). No heterogeneity was observed ($I^2 = 0\%$).

One study [23] reported results by smoking status. For oesophageal adenocarcinoma there was a statistically significant decreased risk in smokers (RR = 0.85 (95% CI 0.75–0.97)) but not in former smokers (RR = 1.02 (95% CI 0.93–1.11)) or never smokers (RR = 0.97 (95% CI 0.84–1.13)) per 25 grams per day.

No analysis by cancer subtype was conducted in the 2005 SLR.

Published pooled analyses and meta-analyses

One meta-analysis of cohort and case-control studies [26] on vegetable intake and oesophageal adenocarcinoma was identified in the CUP Oesophageal SLR 2015. The published meta-analysis reported a significant nine per cent decreased risk per 100 grams per day. Results from the CUP and the published meta-analysis are presented in **Table 1**.

Table 1: Summary of CUP 2015 meta-analysis and published meta-analysis of oesophageal adenocarcinoma – vegetables

ANALYSIS	INCREMENT/ CONTRAST	RR (95% CI)	I^2	NO. STUDIES	NO. CASES
CUP Oesophageal Cancer SLR 2015 adenocarcinoma	Per 100g/day	0.89 (0.80–0.99)	0%	3	415
Li, 2014 [26] Per 100g/day	Per 100g/day (6 studies)	0.91 (0.83–0.99)	23%	9 (3 cohort ¹ 6 case- control)	1,572
	Highest vs. lowest (cohort)	0.76 (0.54–1.05)	0%	3 cohorts ¹	

¹All cohorts were included in the CUP analysis.

Other vegetable exposures

The CUP Oesophageal SLR 2015 conducted a dose-response meta-analysis on green leafy vegetables and oesophageal adenocarcinoma, which showed a statistically significant 15 per cent decreased risk per 50 grams per day (RR = 0.85 (95% CI 0.74–0.96); see CUP Oesophageal SLR 2015 Figure 13).

7.1.2 Oesophageal squamous cell carcinoma

The CUP identified three new studies [23, 24, 27], giving a total of four studies (six publications) reviewing the evidence for vegetables and oesophageal squamous cell carcinoma (for a full list of references, see CUP Oesophageal SLR 2015 Tables 7 and 8).

All studies were included in the highest versus lowest analysis. Of four studies reporting on oesophageal squamous cell carcinoma, three showed non-significant inverse associations and one showed a non-significant positive association. One study reporting on total oesophageal cancer showed a non-significant inverse association.

All four studies were included in the dose-response meta-analysis for oesophageal squamous cell carcinoma ($n = 2,273$ cases), which showed no significant association per 100 grams of vegetables consumed per day (RR 0.91 (95% CI 0.81–1.03); see CUP Oesophageal SLR 2015 Figure 6). Moderate heterogeneity was observed ($I^2 = 31\%$).

For oesophageal squamous cell carcinoma, one study reported the results by smoking status [23]. There was a significantly lower risk in smokers (RR = 0.90 (95% CI 0.81–0.99)) but not former smokers (RR = 0.96 (95% CI 0.83–1.11)) or never smokers (RR = 1.08 (95% CI 0.98–1.19)) per 25 grams per day.

No analysis by subtype was conducted in the 2005 SLR.

Published pooled analyses and meta-analyses

One meta-analysis of cohort and case-control studies [28] on vegetable intake and oesophageal squamous cell carcinoma was identified in the CUP Oesophageal SLR 2015. The published meta-analysis reported a significant 16 per cent decreased risk per 100 grams per day. No significant association was observed when reviewing the cohort studies only. The meta-analysis reported no significant association when comparing the highest and lowest categories of consumption (cohort studies only). Results from the CUP and the published meta-analysis are presented in **Table 2**.

Table 2: Summary of CUP 2015 meta-analysis and published meta-analysis of oesophageal squamous cell carcinoma – vegetables

ANALYSIS	INCREMENT/ CONTRAST	RR (95% CI)	I ²	NO. STUDIES	NO. CASES
CUP Oesophageal Cancer SLR 2015 Squamous cell carcinoma	Per 100g/day	0.91 (0.81–1.03)	49%	4	2,273
Liu, 2013 [28]	Per 100g/day	0.84 (0.78–0.92)	82%	15 (4 cohort ¹ , 11 case- control)	6,509
		0.92 (0.84–1.01)	61%	4 cohort ¹	2,278
	Highest vs. lowest	0.80 (0.60–1.06)	36%	5 cohort ²	2,379

¹ All cohorts were included in the CUP analysis.

² One cohort [29] was identified in the CUP but not included in the dose-response analysis.

Other vegetable exposures

The CUP Oesophageal SLR 2015 conducted a dose-response meta-analysis on green leafy vegetables and oesophageal squamous cell carcinoma. No significant association was observed for oesophageal squamous cell carcinoma (RR = 0.89 (95% CI 0.75–1.06); see CUP Oesophageal SLR Figure 13).

Mechanisms

*Note: This is adapted from section 4.2 of the Second Expert Report. An updated review of mechanisms for this exposure will form part of a larger review of mechanisms (see **Section 6.1** in this report).*

Non-starchy vegetables contain several potentially cancer-preventive substances, including antioxidant nutrients (such as carotenoids and vitamin C), dietary fibre and other phytochemicals (such as glucosinolates, dithiolthiones, indoles, chlorophyll, flavonoids, allylsulphides and phytoestrogens). Phytochemicals might influence cancer risk through antioxidant activity, modulation of detoxification enzymes, stimulation of the immune system or antiproliferative activities. 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 [1]. Vitamin C can inhibit intragastric nitrosation – a process that may promote the development of both oesophageal adenocarcinoma and oesophageal squamous cell carcinoma [30, 31]. It is difficult to unravel the relative importance of each constituent and likely that any protective effect may result from a combination of influences on several pathways involved in carcinogenesis.

CUP Panel's conclusions:

For oesophageal adenocarcinoma, the evidence for consumption of vegetables was limited but generally consistent. The dose-response meta-analysis showed a significantly decreased risk with greater vegetable consumption; however, this included only three studies with 415 cases. Although studies adjusted for smoking, there is the potential for residual confounding due to smoking. The CUP Panel concluded:

The evidence suggesting that greater consumption of vegetables decreases the risk of oesophageal adenocarcinoma is limited.

For oesophageal squamous cell carcinoma, the evidence for consumption of vegetables was limited but generally consistent. The dose-response meta-analysis showed no significant association between oesophageal squamous cell carcinoma risk and vegetable consumption; this included only four studies with moderate heterogeneity. Although most studies adjusted for smoking, there is the potential for residual confounding due to smoking. The CUP Panel concluded:

The evidence suggesting that greater consumption of vegetables decreases the risk of oesophageal squamous cell carcinoma is limited.

7.2 Fruit

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

Oesophageal squamous cell carcinoma

The CUP identified three new studies [23, 24, 27], giving a total of four studies (six publications) reviewing the evidence for fruit and oesophageal squamous cell carcinoma (for a full list of references, see CUP Oesophageal SLR 2015 Tables 16 and 17 for a full list of references).

All four studies reporting on oesophageal squamous cell carcinoma showed inverse associations, one of which was significant when comparing the highest and the lowest categories of consumption (see CUP Oesophageal SLR 2015 Figure 16).

Three of the four studies were included in the dose-response meta-analysis for oesophageal squamous cell carcinoma ($n = 320$ cases), which showed a 16 per cent decreased risk per 100 grams of fruit per day (RR 0.84 (95% CI 0.75–0.94); see CUP Oesophageal SLR 2015, Figure 19). No heterogeneity was observed ($I^2 = 0\%$).

One study [23] stratified analyses for oesophageal squamous cell carcinoma by smoking status and observed no significant associations.

One study was excluded from CUP analyses because it did not report sufficient data [32].

No analysis by subtype was conducted in the 2005 SLR.



Published pooled analyses and meta-analyses

The CUP Oesophageal SLR 2015 identified results from one meta-analysis on cohort and case-control studies [28] on fruit consumption and oesophageal squamous cell carcinoma. The published meta-analysis reported a 39 per cent decreased risk for oesophageal squamous cell carcinoma per 100 grams per day. The result remained significant when only cohort studies were analysed. The meta-analysis reported a significant decreased risk when comparing the highest versus the lowest categories of consumption. Results from the published meta-analysis are presented in **Table 3**.

Table 3: Summary of CUP 2015 meta-analyses and published meta-analyses of oesophageal squamous cell carcinoma – fruit

ANALYSIS	INCREMENT/ CONTRAST	RR (95% CI)	I ²	NO. STUDIES	NO. CASES
CUP Oesophageal Cancer SLR 2015 squamous cell carcinoma	Per 100g/day	0.84 (0.75–0.94)	0%	3	320
Liu, 2013 [28]	Per 100g/day	0.61 (0.52–0.72)	90%	18 studies (4 cohort, 14 case- control)	6,927
		0.87 (0.82–0.91)	0%	4 cohort	2,278
	Highest vs. lowest	0.68 (0.55–0.86)	25%	5 cohort ¹	2,379

¹ One cohort [29] was identified in the CUP but not included in the dose-response analysis.

Other fruit exposures

The CUP Oesophageal SLR 2015 included three studies on citrus fruit. The dose-response meta-analysis showed no significant association for oesophageal squamous cell carcinoma (RR = 0.87 (95% CI 0.69–1.08); see CUP Oesophageal SLR Figure 26 and Section 2.2.2.1 of the CUP Oesophageal SLR 2015 for further information).

Mechanisms

*Note: This is adapted from section 4.2 of the Second Expert Report. An updated review of mechanisms for this exposure will form part of a larger review of mechanisms (see **Section 6.1** in this report).*

Fruit, in particular citrus fruit, is a source of vitamin C and other antioxidants, such as phenols and flavonoids, as well as other potentially bioactive phytochemicals. Vitamin C traps free radicals and reactive oxygen molecules, protecting against oxidative damage.

It also regenerates other antioxidant vitamins such as vitamin E [33]. Vitamin C also inhibits the formation of carcinogens and protects DNA from mutagenic attack [34]. Beta-carotene and other carotenoid antioxidants are also found in fruit. Some fruit contains high levels of flavonoids, including apples (quercetin) and grapefruit (naringin). Flavonoids have antioxidant effects and can also inhibit carcinogen-activating enzymes. Flavonoids can also alter the metabolism of other dietary agents. For instance, quercetin directly inhibits expression of CYP1A1 (a cytochrome P450 enzyme that helps to metabolise toxins), resulting in decreased DNA damage [35]. The phytochemical antioxidants contained in fruit may reduce free-radical damage generated by inflammation.

Oesophageal adenocarcinoma

For oesophageal adenocarcinoma, no significant association was observed for three studies (RR 1.03 (95% CI 0.95–1.11), $I^2 = 0\%$; see CUP Oesophageal SLR 2015 Figure 19).

CUP Panel's conclusion:

For oesophageal squamous cell carcinoma, the evidence for consumption of fruit was limited but generally consistent. The dose-response meta-analysis showed a significant decreased risk of squamous cell carcinoma with higher consumption of fruit; however, this included only three studies with 320 cases. Although studies adjusted for smoking, there is the potential for residual confounding due to smoking.

For oesophageal adenocarcinoma, the evidence for an association was considered to be limited, and no conclusion was possible.

The CUP Panel concluded:

The evidence suggesting that greater consumption of fruit decreases the risk of oesophageal squamous cell carcinoma is limited.

7.3 Processed Meat

(Also see CUP Oesophageal SLR 2015: Section 2.5.1.2)

Oesophageal squamous cell carcinoma

The CUP identified two new studies [36, 37], giving a total of two studies (two publications) reviewing the evidence for processed meat and squamous cell carcinoma (for a full list of references, see CUP Oesophageal SLR 2015 Tables 25 and 26 for a full list of references).

Both studies reported on oesophageal squamous cell carcinoma. One showed a significant positive association in men and a non-significant inverse association in women; the other showed a non-significant positive association when comparing the highest and the lowest categories of intake in men and women combined (see CUP Oesophageal SLR 2015 Figure 29).

Both studies were included in the dose-response meta-analysis for oesophageal squamous cell carcinoma ($n = 322$ cases), which showed a borderline significant association (RR 1.34 (95% CI 1.00–1.81) per 50 grams of processed meat per day; see CUP Oesophageal SLR 2015, Figure 33). No heterogeneity was observed ($I^2 = 0\%$). It was not possible to conduct stratified analyses by smoking.

No analysis by subtype was conducted in the 2005 SLR.

Published pooled analyses and meta-analyses

Results from three meta-analyses [38-40] on processed meat and oesophageal squamous cell carcinoma were identified by the CUP Oesophageal SLR 2015. All published meta-analyses reported positive associations, one of which was statistically significant, when comparing the highest and lowest categories of intake, consistent with the CUP Oesophageal SLR 2015. The CUP analyses included only cohort studies. Results from the published meta-analyses are presented in **Table 4**.

Table 4: Summary of CUP 2015 meta-analysis and published meta-analyses of oesophageal squamous cell carcinoma – processed meat

ANALYSIS	INCREMENT/ CONTRAST	RR (95% CI)	I^2	NO. STUDIES	NO. CASES
CUP Oesophageal Cancer SLR 2015 squamous cell carcinoma	Per 50g/day	1.34 (1.00–1.81)	0%	2	322
Zhu, 2014 [38]	Highest vs. lowest	1.34 (0.62–2.92)	69%	2 ¹	1,737
Qu, 2013 [39]	Highest vs. lowest	1.41 (1.11–1.78)	0%	8 cohort ¹ and case- control	-
		1.28 (0.88–1.86)	0%	2 cohort ¹	322
	Per 50g/day	1.42 (0.98–2.05)	0%	2 cohort ¹	322

¹ All cohorts included in the CUP analysis.

Two meta-analyses [40, 41] were not included in the table as separate results for cohort studies were not reported.

Mechanisms

Note: This is adapted from section 4.3 of the Second Expert Report. An updated review of mechanisms for this exposure will form part of a larger review of mechanisms (see **Section 6.1** in this report).

Nitrates are added as preservatives to processed meats and may contribute to N-nitroso compound production and exposure. Several N-nitroso compounds are known mutagens and carcinogens [42]. Many processed meats also contain high levels of salt and nitrite, which may be involved in carcinogenesis, due to reactions during the curing process or in the body. A further potential mechanism linking processed meat intake to oesophageal squamous cell carcinoma includes haem iron, which is found in red meat that is processed or otherwise [43]. Haem iron contributes to endogenous formation of N-nitroso compounds and causes oxidative stress and DNA damage. Some processed meats are also cooked at high temperatures, resulting in the production of heterocyclic amines and polycyclic aromatic hydrocarbons, which are known carcinogens. There is some evidence that DiMeIQx and MeIQx, compounds formed during cooking or processing of meat, specifically increase the risk of oesophageal squamous cell carcinoma [37].

Oesophageal adenocarcinoma

For oesophageal adenocarcinoma, no significant association was observed for three studies (RR 1.19 (95% CI 0.85–1.68), $I^2 = 63%$; see CUP Oesophageal SLR 2015 Figure 33).

CUP Panel's conclusion:

For oesophageal squamous cell carcinoma, the evidence for processed meat was generally consistent and the dose-response relationship showed a borderline significant increased risk. There is evidence of plausible mechanisms operating in humans.

For oesophageal adenocarcinoma, the evidence for an association was considered to be limited, and no conclusion was possible.

The CUP Panel concluded:

The evidence suggesting that greater consumption of processed meat increases the risk of oesophageal squamous cell carcinoma is limited.

7.4 Mate

(Also see CUP Oesophageal SLR 2015: Section 3.6.3)

Mate, an aqueous infusion prepared from dried leaves of *Ilex paraguariensis*, is usually drunk scalding hot following repeated addition of almost boiling water to the infusion [44]. Mate is consumed mainly in South America, specifically Argentina, Bolivia, Brazil, Chile, Ecuador, Paraguay and Uruguay. These countries correspond to areas of higher incidence of oesophageal squamous cell carcinoma within South America [45]. Hot mate consumption is graded by the International Agency for Research on Cancer (IARC) as probably carcinogenic to humans [44].

Oesophageal squamous cell carcinoma

No cohort studies were identified in the CUP. A meta-analysis of five case-control studies in the 2005 SLR showed a significant positive association (RR = 1.16 (95% CI 1.07–1.25)) per cup per day. Four of these studies reported on oesophageal squamous cell carcinoma and the fifth did not specify cancer type.

No analysis by subtype was conducted in the 2005 SLR.

Published pooled analyses and meta-analyses

One published pooled analysis of two case-control studies [46] and one published meta-analysis of case-control studies [47] on mate and oesophageal squamous cell carcinoma risk were identified in the CUP Oesophageal SLR 2015. Both published pooled and meta-analyses reported positive associations for highest levels of consumption compared with lowest. Results from the published pooled and meta-analyses are presented in **Table 5**.

Table 5: Summary of pooled analysis and published meta-analysis of oesophageal squamous cell carcinoma – mate

ANALYSIS	CONTRAST	RR (95% CI)	I ²	NO. STUDIES	NO. CASES	COMMENTS
Lubin, 2014 [46]	Ever vs. never	1.60 (1.2–2.2)	-	2 case-control	1,391	Adjusted for smoking, alcohol consumption, age, sex, sex by education, and for Uruguay income and urban/rural residence. Odds ratios increased linearly with cumulative mate consumption.
	Warm vs. never	1.20 (0.8–1.7)			168	
	Hot vs. never	1.61 (1.2–2.2)			929	
	Very hot vs. never	2.15 (1.5–3.1)			213	
Andrici, 2013 [47]	Ever vs. never	2.57 (1.66–3.98)	65%	9 case-control ¹	1,565	

¹ Includes the studies used in the published pooled analysis [46]

Mechanisms

*Note: This is adapted from section 4.7 of the Second Expert Report. An updated review of mechanisms for this exposure will form part of a larger review of mechanisms (see **Section 6.1** in this report).*

Mate is typically drunk scalding hot through a metal straw. This produces heat damage in the mouth, pharynx, larynx and oesophagus. Repeated damage of this nature can lead to cancer. Chemical carcinogenesis from constituents of mate has also been postulated [48, 49]. Non-thermal factors may be involved, such as benzo[a]pyrene, which has been classified as a human carcinogen by IARC [50, 51] and is present in both the dry leaves of mate and in infusions made from them [52].

Oesophageal adenocarcinoma

No study reported on oesophageal adenocarcinoma.

CUP Panel's conclusion:

For squamous cell carcinoma, the evidence from case-control studies reviewed for the Second Expert Report is consistent and a dose-response relationship is apparent. There is robust evidence for plausible mechanisms. This was consistent with findings from recent published pooled and meta-analyses.

For oesophageal adenocarcinoma, the evidence for an association was considered to be limited, and no conclusion was possible. The CUP Panel concluded:

Regular consumption of mate, as drunk scalding hot in the traditional style in South America, is probably a cause of oesophageal squamous cell carcinoma.

We are aware that in May 2016, after the systematic literature reviews on which this Report is based were completed and the evidence judged by the CUP Panel, the International Agency for Research on Cancer (IARC) published a report on the carcinogenicity of coffee, mate and very hot beverages. They concluded that drinking coffee or mate that was not very hot was unclassifiable in terms of its carcinogenicity in humans, but that drinking very hot (greater than 65 degrees centigrade) beverages, including mate, was probably carcinogenic in humans. Epidemiological studies of oesophageal cancer and drinking mate were an important basis for their conclusion. The IARC report is consistent with the conclusions in this Report.*

**Loomis D, Guyton KZ, Grosse Y, et al. Carcinogenicity of drinking coffee, mate, and very hot beverages. Lancet Oncol 2016; 17: 877-8.*

7.5 Alcoholic drinks

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

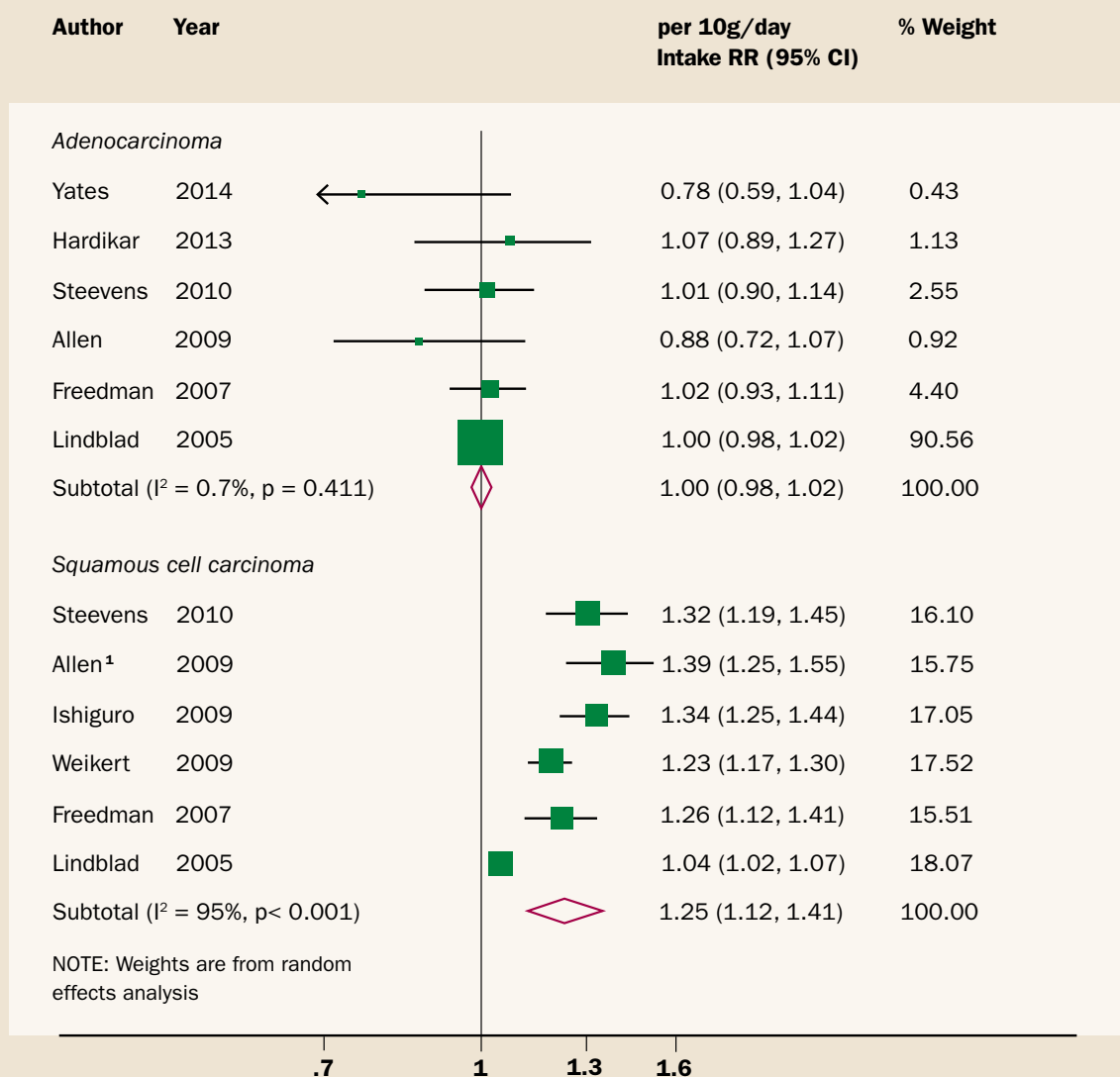
Oesophageal squamous cell carcinoma

The CUP identified six new studies [53-58], giving a total of eight studies (nine publications) (for a full list of references, see CUP Oesophageal SLR 2015 Tables 40 and 41). Seven studies reported on oesophageal squamous cell carcinoma incidence; six showed positive associations, five of which were significant, and one showed a non-significant inverse association when comparing the highest and the lowest categories of intake (see CUP Oesophageal SLR 2015 Figure 45).



Six of the eight studies were included in the dose-response meta-analysis which showed a statistically significant 25 per cent increased risk per 10 grams of alcohol per day (RR 1.25 (95% CI 1.12–1.41); see **Figure 1**, CUP Oesophageal SLR 2015 Figure 51). High heterogeneity was observed ($I^2 = 95\%$). Inspection of the forest plot indicated that a substantial part of the heterogeneity in the analysis was due to one study [59]. After exclusion of this study, which analysed a computerised database of patient records rather than dietary intake questionnaires, the heterogeneity was reduced ($I^2 = 39\%$). There was evidence of small study bias with Egger’s test ($p = 0.009$). Inspection of the funnel plot identified the same study [59] as an outlier (see CUP Oesophageal SLR Figure 52), when this study was removed there was no evidence of small study bias ($p = 0.29$).

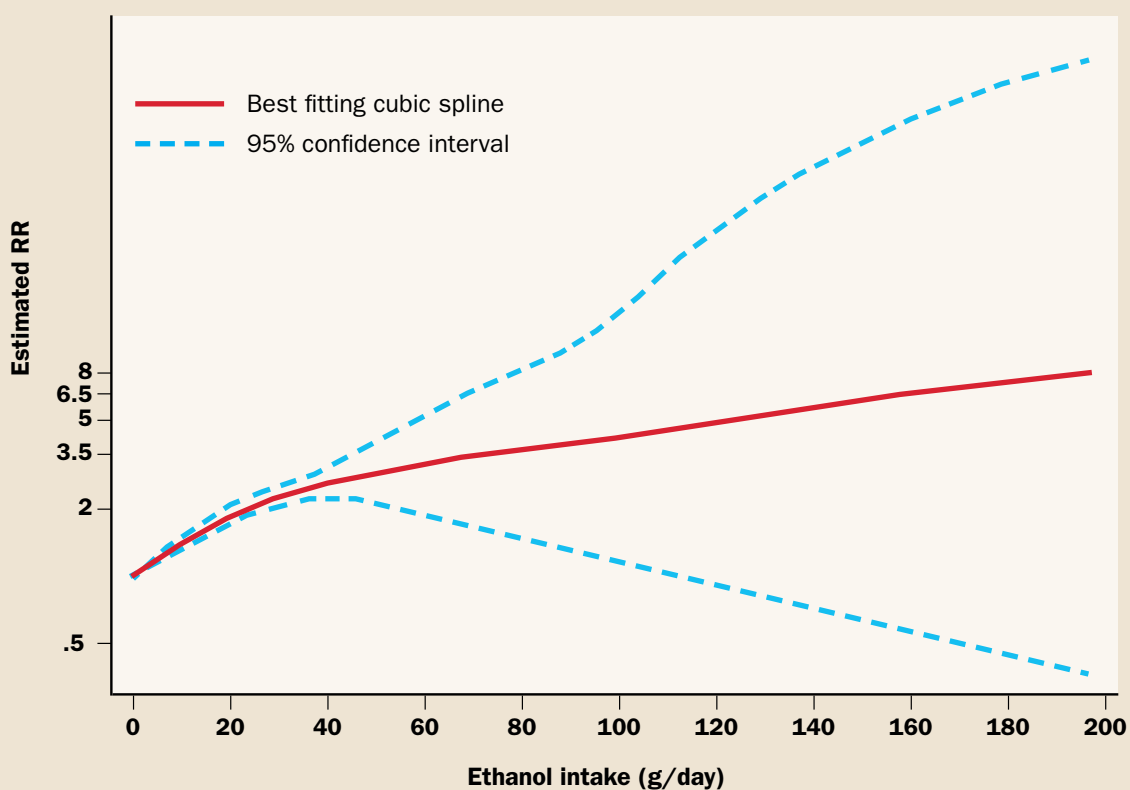
Figure 1: Dose-response meta-analysis of alcohol (as ethanol) and oesophageal adenocarcinoma and squamous cell carcinoma, per 10g per day



¹RR estimates of ‘non adenocarcinoma oesophageal cancers’ were included in the analysis of oesophageal squamous cell carcinoma.

A non-linear dose-response analysis conducted on the studies on oesophageal squamous cell carcinoma combined with Asian studies on oesophageal cancer incidence suggested evidence of non-linearity ($p = 0.04$). The Asian studies were included in this analysis as cancers in Asia are mostly squamous cell carcinomas. There was evidence of a steeper increase in risk for lower intakes; however, no threshold was detected. Most of the observations in the analysis were for intakes below 80g/day (see **Figure 2** (CUP Oesophageal SLR 2015 Figure 57 and Table 43)).

Figure 2: Non-linear dose-response association of alcohol (as ethanol) and oesophageal squamous cell carcinoma combined with Asian studies of oesophageal cancer



Dose-response meta-analyses for oesophageal squamous cell carcinoma by geographical location showed statistically significant increased risks in Asia (RR = 1.34 (95% CI 1.19–1.51), $I^2 = 86\%$), Europe (RR = 1.23 (95% CI 1.07–1.42), $I^2 = 96\%$) and North America (RR = 1.28 (95% CI 1.16–1.41), single study); see CUP Oesophageal SLR 2015 Figure 55).

Other alcohol exposures

Dose-response meta-analyses for oesophageal squamous cell carcinoma stratified by type of alcohol were not possible due to lack of data, so highest versus lowest consumption stratified analyses were conducted. Significant increased risk was observed for beer and spirits, but not wine. When the studies reporting on spirits and squamous cell carcinoma were combined with the Asian studies, a significant increased risk was observed (see **Table 6** and CUP Oesophageal SLR 2015 Figures 60, 63 and 66).

Table 6: Summary of CUP 2015 highest vs. lowest meta-analyses of oesophageal squamous cell carcinoma – alcohol

ANALYSIS	CONTRAST	RR (95% CI)	I ²	NO. STUDIES	NO. CASES
Beer	Highest vs. lowest	2.56 (1.18–5.57)	44%	2	
Wine	Highest vs. lowest	0.81 (0.09–7.01)	68%	2	
Spirits	Highest vs. lowest	2.77 (0.98–7.84)	73%	2	
Spirits¹	Highest vs. lowest	3.41 (2.16–5.38)	42%	4	

¹ Squamous cell carcinoma and Asian studies

No analysis by subtype was conducted in the 2005 SLR.

Published pooled analyses and meta-analyses

Results from one pooled analysis of cohort and case-control studies [60] have been published on alcoholic drinks and oesophageal squamous cell carcinoma risk. The pooled analysis reported a significant increased risk when comparing the highest and lowest levels of alcohol intake (see **Table 7**). Two published meta-analyses of cohort studies [61, 62] have reported on alcohol intake and oesophageal squamous cell carcinoma risk. Both meta-analyses reported increased risk, although only one was significant (RR = 1.34 (95% CI 0.96–1.87) and RR = 3.51 (95% CI 3.09–4.00), respectively). Results from the CUP and the published pooled analysis are presented in **Table 7**.

Table 7: Summary of CUP 2015 meta-analysis and published pooled analysis of oesophageal squamous cell carcinoma – alcohol

ANALYSIS	INCREMENT/ CONTRAST	RR (95% CI)	I ² /P TREND	NO. STUDIES	NO. CASES	COMMENTS
CUP Oesophageal SLR 2015 squamous cell carcinoma	Per 10g/day	1.25 (1.12–1.41)	95%	6	-	
Freedman, 2011¹ (BEACON Consortium)	≥7 drinks/day vs. none	9.62 (4.26– 21.71)	<0.0001	5 case- control, 2 cohort	1,016	Adjusted for sex, age, body mass index, education, pack-years of smoking and, where available, for gastro-oesophageal reflux

¹ The Kaiser-Permanente Multiphasic Health check-up and NIH-AARP Diet and Health studies are included in the CUP analyses.



Mechanisms

*Note: This is adapted from section 4.8 of the Second Expert Report. An updated review of mechanisms for this exposure will form part of a larger review of mechanisms (see **Section 6.1** in this report).*

Metabolites of alcohol, such as acetaldehyde, are carcinogenic [63]. Additionally, the effects of alcohol may be mediated through the production of prostaglandins, lipid peroxidation and the generation of free-radical oxygen species. Alcohol also acts as a solvent, enhancing penetration of carcinogens into cells. Alcohol has been demonstrated to alter retinoid status in rodent studies and, as a result, cellular growth, cellular differentiation and apoptosis are adversely altered [64].

The risk of cancer for alcohol drinkers may be modulated by genetic factors, such as variants in genes for alcohol metabolism, folate and methionine metabolism and DNA repair [65, 66]. Acetaldehyde, a toxic metabolite of alcohol that damages DNA, is considered a major cause of the observed carcinogenic effect on the upper aerodigestive tract. Ingested ethanol is oxidised by the enzymes alcohol dehydrogenase (ADH), cytochrome P-450 2E1 (CYP2E1) and catalase to form acetaldehyde, which is subsequently oxidised by aldehyde dehydrogenase 2 (ALDH2) to produce acetate, which is non-toxic. Polymorphisms of the genes that encode enzymes for ethanol metabolism affect ethanol and acetaldehyde oxidizing capacity and are responsible for the limited action of the

enzyme that converts acetaldehyde to acetate [67]. Risk of cancers of the upper aerodigestive tract associated with alcohol is highest in East Asia, where 28–45 per cent of the population has a variation of the gene ALDH2 [68, 69].

Heavy consumers of alcohol may have diets deficient in essential nutrients, making tissue susceptible to carcinogenesis. In addition, alcohol acts as a synergistic carcinogen with tobacco. Smoking is an important confounder and potential effect modifier; tobacco may induce specific mutations in DNA that are less efficiently repaired in the presence of alcohol.

Oesophageal adenocarcinoma

For oesophageal adenocarcinoma, no significant association was observed (RR = 1.00 (95% CI 0.98–1.02), $I^2 = 1\%$; see **Figure 1** (CUP Oesophageal SLR 2015 Figure 51)).

CUP Panel's conclusion:

For oesophageal squamous cell carcinoma, the evidence was generally consistent and the dose response meta-analysis showed a significant increased risk with increasing alcohol consumption. There was evidence of high heterogeneity, but this appeared to be due to the size of the effect. There was a suggestion of non-linearity with a steeper increase in risk for lower intakes. No threshold was detected. All studies adjusted for smoking. The findings were consistent with one pooled analysis and two published meta-analyses. There is robust evidence for mechanisms operating in humans.

For oesophageal adenocarcinoma, the evidence for an association was considered to be limited, and no conclusion was possible.

The CUP Panel concluded:

Consumption of alcoholic drinks is a convincing cause of oesophageal squamous cell carcinoma.

7.6 Physical Activity

(Also see CUP Oesophageal SLR 2015: Sections 6.1, 6.1.1.1, 6.1.1.2, 6.1.1.4 and 6.1.3)

Oesophageal cancer

The Panel reviewed the evidence by oesophageal cancer subtype and concluded the evidence was consistent for oesophageal adenocarcinoma and oesophageal squamous cell carcinoma, as well as for oesophageal cancer where a subtype was unspecified.

The CUP identified four new cohort studies, giving a total of five studies (seven publications) [70-74] assessing physical activity and oesophageal cancer.

A variety of measures were used to collect the data, so dose-response meta-analyses were not possible. In an analysis comparing the highest with the lowest level of recreational physical activity, no significant association was observed (RR = 0.85 (95% CI 0.72–1.01); see CUP Oesophageal SLR 2015 Figure 69).

The evidence for total physical activity, occupational physical activity, recreational physical activity, walking and vigorous physical activity is presented in **Table 8** (for a full list of references, see CUP Oesophageal SLR 2015 Tables 64, 65, 68 and 69).

Table 8: Summary of studies of physical activity and oesophageal cancer

ANALYSIS	STUDY	CANCER TYPE	RR (95% CI)	CONTRAST
Physical activity index	Huerta, 2010 [70]	Adenocarcinoma ¹	0.98 (0.48–2.01)	Active vs. inactive
Occupational physical activity	Cook, 2013 [71]	Adenocarcinoma ¹	0.60 (0.34–1.07)	Heavy work vs. all day sitting
		Squamous cell carcinoma ¹	0.73 (0.27–2.01)	
	Huerta, 2010 [70]	Adenocarcinoma ¹	0.95 (0.41–2.20)	Manual work vs. sedentary occupation
Recreational physical activity	Cook, 2013 [71]	Adenocarcinoma ¹	0.98 (0.69–1.39)	Typical moderate-vigorous activity in last 10 years: >7 hours/week vs. never
		Squamous cell carcinoma ¹	0.88 (0.49–1.58)	
	Huerta, 2010 [70]	Adenocarcinoma ¹	0.63 (0.32–1.22)	Recreational and household activity: Very high vs. low
	Yun, 2008 [72]	Oesophageal ¹	0.84 (0.66–1.06)	Vigorous, sweat-producing activity: Moderate-high vs. low
	Suzuki ² , 2007 [73]	Oesophageal ³	0.81 (0.50–1.31)	Sports: >3 vs. <1 hours/week
Vigorous physical activity	Cook, 2013 [71]	Squamous cell carcinoma ¹	0.84 (0.47–1.52)	Strenuous physical activity during last 12 months: >5 times/week vs. never
		Adenocarcinoma ¹	0.74 (0.49–1.12)	
	Huerta, 2010 [70]	Adenocarcinoma ¹	0.72 (0.36–1.42)	Vigorous physical activity: >2 hours/week vs. none
	Leitzmann, 2009 [74]	Squamous cell carcinoma ¹	1.05 (0.64–1.74)	Physical activity lasting ≥20 minutes and caused increase in breathing, heart rate or sweating: ≥5 vs. 0 times/week
		Adenocarcinoma ¹	0.75 (0.53–1.06)	
	Yun, 2008 [72]	Oesophageal ¹	0.84 (0.66–1.06)	Vigorous, sweat-producing leisure time physical activity: Moderate-high vs. low
Walking	Huerta, 2010 [70]	Adenocarcinoma ¹	0.73 (0.32–1.67)	Tertile 3 vs. never
	Suzuki ² , 2007 [73]	Oesophageal ³	Men: 0.97 (0.63–1.50)	>1 vs. <0.5 hours/day
			Women: 0.57 (0.23–1.4)	

¹ Incidence. ² Not adjusted for smoking. ³ Mortality.

Physical activity was not discussed in relation to oesophageal cancer in the Second Expert Report due to a lack of evidence.

Published pooled analyses and meta-analyses

One published meta-analysis of cohort studies [75] on physical activity and oesophageal cancer was identified in the CUP Oesophageal SLR 2015. The meta-analysis reported a statistically significant 22 per cent decreased risk for any physical activity (RR = 0.78 (95% CI 0.66–0.92), $I^2 = 0\%$). The three cohort studies included in the published meta-analysis were included in the CUP review.

Mechanisms

*Note: In the future, a full review of mechanisms for this exposure will form part of a larger review of mechanisms (see **Section 6.1** in this report).*

Physical activity can modify the risk of cancer through several proposed mechanisms. Increased physical activity can decrease fat overall and in specific areas including subcutaneous, visceral and liver fat, reducing secretion of potentially carcinogenic adipocytokines. Physical activity improves insulin sensitivity and reduces fasting insulin and C-peptide levels [76].

Metabolic syndrome and insulin resistance have been associated with increased risk of cancer, including oesophageal adenocarcinoma [77-80]. This is thought to be mediated by adipokines and cytokines released by metabolically active visceral fat, which result in low-grade inflammation, chronic hyperinsulinemia and increased risk of insulin-like growth factor-mediated carcinogenesis [81]. Increasing physical activity may reduce inflammation, but only when accompanied by weight loss [82, 83].

Additionally, physical activity has been shown to have immunomodulatory effects, improving innate and acquired immune response, and promoting tumour surveillance [76, 84].

Studies have also shown that aerobic exercise can decrease oxidative stress and enhance DNA repair mechanisms, decreasing carcinogenesis [84]. Physically active individuals also tend to have higher sunlight exposure and consequently increased vitamin D, which may modify cell proliferation cascades [85].

CUP Panel's conclusion:

The evidence is generally consistent and all studies, whether reporting on oesophageal cancer (unspecified) or its subtypes, showed decreased risk of oesophageal cancer with higher levels of various measures of physical activity, although none was statistically significant. However, because different types of activity were measured and a variety of measures was used to collect the data, no meta-analyses could be conducted. Although studies adjusted for smoking, there was a lack of evidence showing decreased risk in never smokers, and therefore potential for residual confounding due to smoking. The CUP Panel concluded:

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

7.7 Body fatness

(Also see CUP Oesophageal SLR 2015: Sections 8.1.1, 8.2.1 and 8.2.3)

Oesophageal adenocarcinoma

The Panel interpreted body mass index (BMI), waist circumference and waist-hip ratio as measures of body fatness and its distribution. The Panel recognises that these anthropometric measures are imperfect and cannot distinguish between lean mass and body fat, or among visceral, subcutaneous abdominal, intra-muscular, hepatic and other areas of fat accumulation.

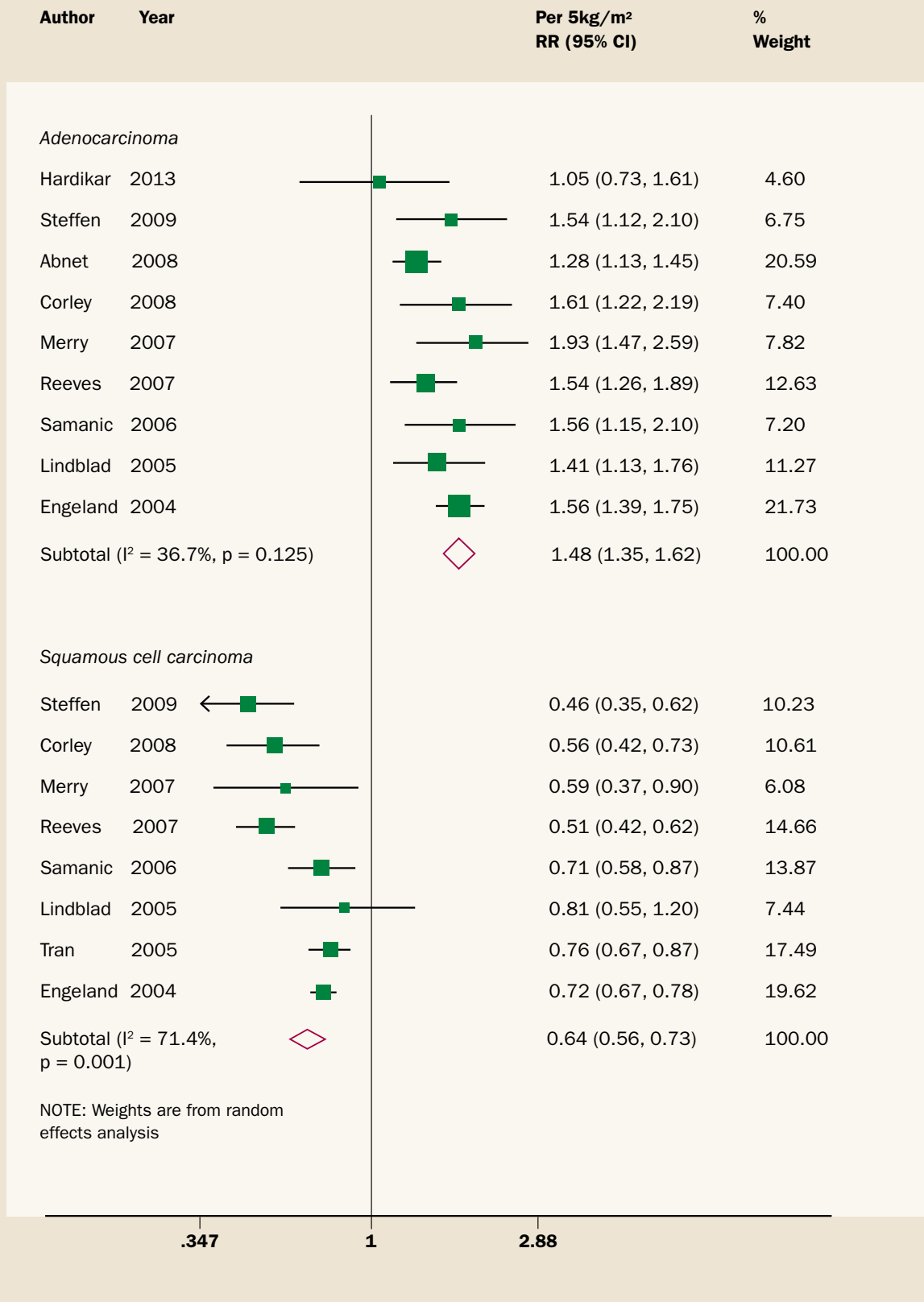
The CUP identified nine studies (10 publications) on body fatness, all of which reported on BMI; two studies were identified which additionally reported on waist circumference, and three on waist-hip ratio.

Body mass index

The CUP identified seven new or updated studies (eight publications) [86-92], giving a total of nine studies (10 publications; for a full list of references, see CUP Oesophageal SLR 2015 Tables 74 and 75). All nine studies (10 estimates) were on oesophageal adenocarcinoma incidence and reported a positive association, eight of which were significant (see CUP Oesophageal Cancer SLR 2015 Figure 71).

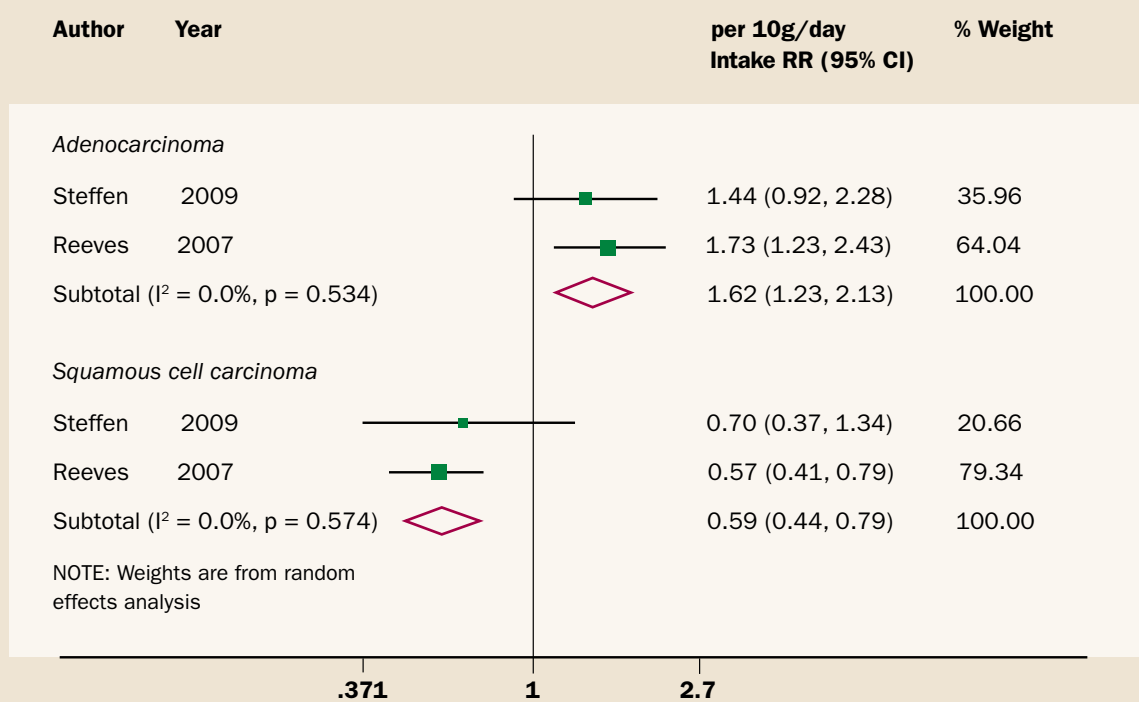
All nine studies were included in the dose-response meta-analysis ($n = 1,725$ cases), which showed a statistically significant 48 per cent increased risk of oesophageal adenocarcinoma per 5 kg/m² (RR = 1.48 (95% CI 1.35–1.62); see **Figure 3**, CUP Oesophageal SLR 2015 Figure 78). Moderate heterogeneity was observed ($I^2 = 37\%$).

Figure 3: Dose-response meta-analysis of BMI and oesophageal cancer, per 5 kg/m²



Significant increased risk remained for oesophageal adenocarcinoma when stratified by sex (RR = 1.56 (95% CI 1.39–1.74) and RR = 1.48 (95% CI 1.29–1.71) for men and women respectively (see CUP Oesophageal SLR 2015 Figure 81)) and when stratified by geographical region (RR = 1.56 (95% CI 1.44–1.69) and RR = 1.32 (95% CI 1.10–1.57) for European and North America studies respectively; see CUP Oesophageal SLR 2015 Figure 84)). When stratified by smoking status, the significant increased risk remained for non-smokers. A meta-analysis of two studies showed a 62 per cent increased risk in non-smokers per 5kg/m² (RR = 1.62 (95% CI 1.23–2.13); see **Figure 4**, CUP Oesophageal SLR 2015 Figure 83). No heterogeneity was observed.

Figure 4: Dose-response meta-analysis of BMI and oesophageal cancer in non-smokers, per 5 kg/m²



The CUP findings are similar to the dose-response meta-analysis in the 2005 SLR, which also reported a significant increased risk of oesophageal adenocarcinoma (RR = 1.11 (95% CI 1.07–1.15) per 1 kg/m²). The CUP Oesophageal SLR 2015 included many more studies and cases of oesophageal adenocarcinoma than the 2005 SLR.

Published pooled analyses and meta-analyses

Results from two pooled [93, 94] and four meta-analyses [95-98] on BMI and oesophageal adenocarcinoma were identified by the CUP Oesophageal SLR 2015. Both published pooled analyses reported significant positive associations in continuous analyses, consistent with the CUP Oesophageal SLR 2015. All four published meta-analyses also reported significant positive associations in continuous and highest versus lowest analysis. When the studies identified in the CUP Oesophageal SLR 2015 (but not in the pooled analysis) were combined with the results of the pooled analysis of the Me-Can project (European cohorts), a statistically significant 51 per cent increased risk per 5 kg/m² was observed (see **Table 9**).



Table 9: Summary of CUP 2015 meta-analysis and published pooled analysis – BMI

ANALYSIS	INCREMENT	RR (95% CI)	I ²	NO. STUDIES	NO. CASES	FACTORS ADJUSTED FOR
CUP Oesophageal Cancer SLR 2015 adenocarcinoma	Per 5 kg/m ²	1.48 (1.35–1.62)	37%	9	1,725	
Me-Can [93]	Per 5 kg/m ²	1.78 (1.45–2.17)	-	7		Adjusted for sex, age at baseline, smoking status
BEACON Consortium [94]	Per 1 kg/m ²	1.09 (1.06–1.12)	76%	2 cohorts, 10 case-control	1,897	Adjusted for age, gender, pack-years of smoking, education, and other study-specific adjustment variables (e.g., study centre) where applicable
CUP additional analysis: Pooled analysis of Me-Can studies [93] combined with all studies from the CUP	Per 5 kg/m ²	1.51 (1.38–1.65)	43%	16 cohorts	1,839	

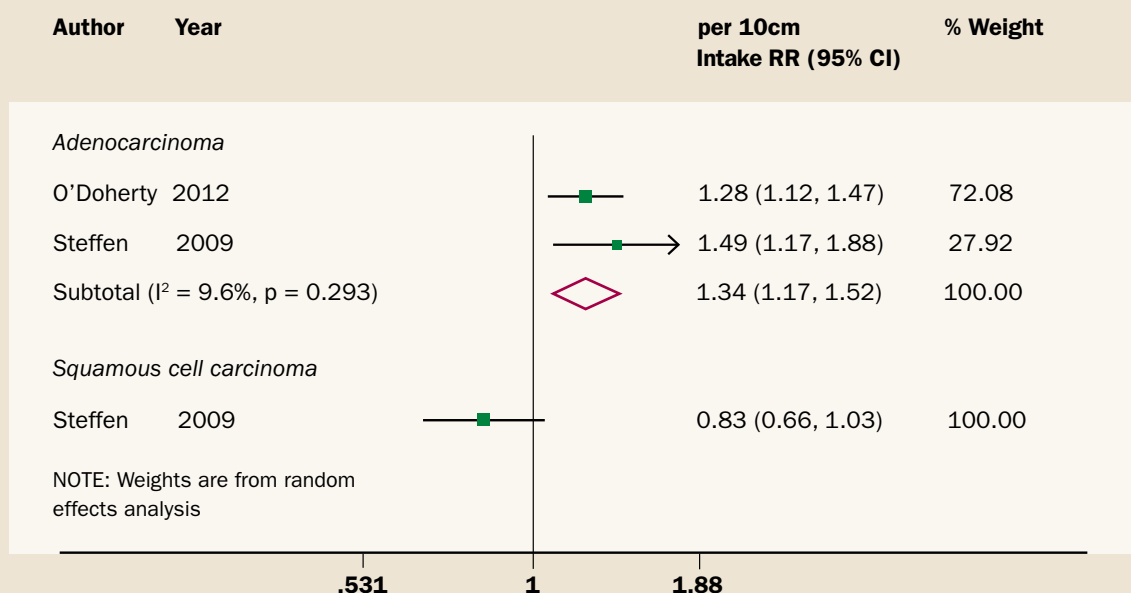
Note: The seven component cohorts in the Me-Can study [93] and the Kaiser Permanente Cohort in the BEACON Consortium [94] did not publish results previously. Sensitivity analysis was conducted by including the pooled results from the Me-Can study [93].

Waist circumference

The CUP identified two new studies (two publications) [87, 99], giving a total of two studies (two publications; for a full list of references, see CUP Oesophageal SLR 2015 Tables 86 and 87). Both studies (two estimates) reporting on oesophageal adenocarcinoma incidence reported significant positive associations (see CUP Oesophageal Cancer SLR 2015 Figure 101).

Both studies were included in the dose-response meta-analysis ($n = 335$ cases), which showed a statistically significant 34 per cent increased risk per 10 centimetres of waist circumference (RR = 1.34 (95% CI 1.17–1.52); see **Figure 5**, CUP Oesophageal SLR 2015 Figure 102). Low heterogeneity was observed ($I^2 = 10\%$).

Figure 5: Dose-response meta-analysis of waist circumference and oesophageal cancer, per 10 cm



One study [87] analysed data by smoking status and reported a non-significant positive association in non-smokers and a significant positive association in smokers.

Published pooled analyses and meta-analyses

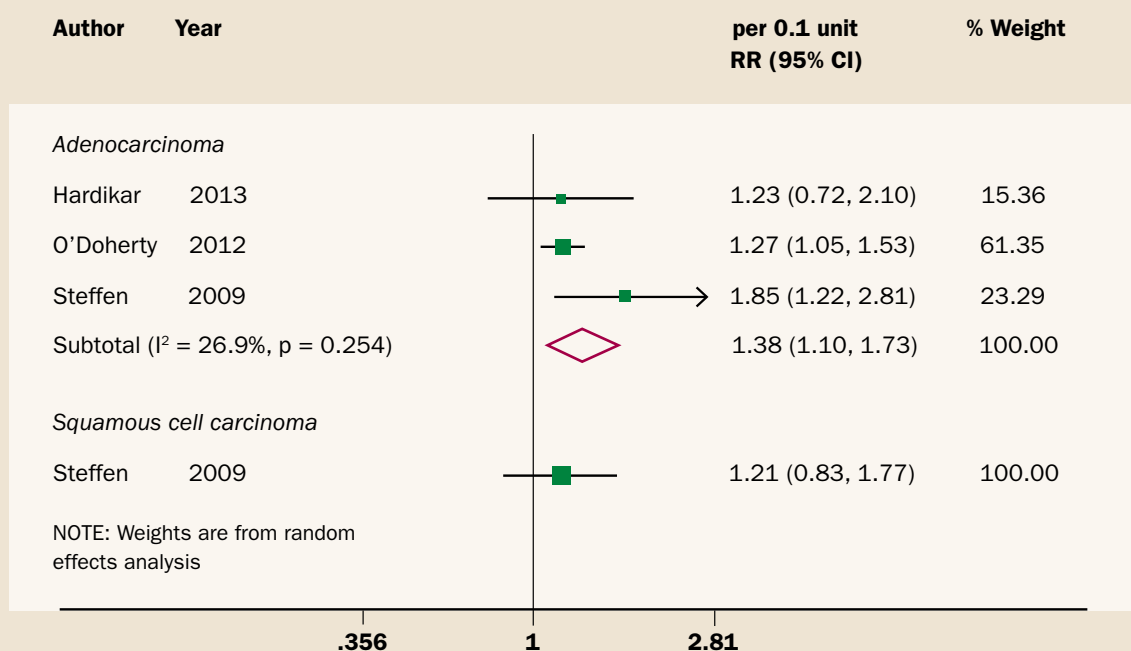
No published pooled analyses were identified. One published meta-analysis of cohort and case-control studies [100] reporting on central adiposity observed a significant increased risk of oesophageal adenocarcinoma when comparing the highest and the lowest levels of adiposity (RR = 2.51 (95% CI 1.56–4.04, $I^2 = 62\%$).

Waist-hip ratio

The CUP identified three new studies (three publications) [86, 87, 99], giving a total of three studies (three publications; for a full list of references, see CUP Oesophageal SLR 2015 Tables 91 and 92). All studies (three estimates) were on oesophageal adenocarcinoma incidence and reported positive associations, one of which was significant (see CUP Oesophageal Cancer SLR 2015 Figure 104).

All three studies were included in the dose-response meta-analysis ($n = 380$ cases), which showed a statistically significant 38 per cent increased risk per 0.1 unit (RR = 1.38 (95% CI 1.10–1.73); see **Figure 6**, CUP Oesophageal SLR 2015 Figure 105). Low heterogeneity was observed ($I^2 = 27\%$).

Figure 6: Dose-response meta-analysis of waist-hip ratio and oesophageal cancer, per 0.1 unit



Mechanisms

There is an established link between gastro-oesophageal reflux disease and oesophageal adenocarcinoma risk thought to be due to increased intra-abdominal pressure, causing reflux. In turn, risk for Barrett's oesophagus, known to be a precursor to oesophageal adenocarcinoma, increases [101]. However, while obesity increases intra-gastric pressure and the oesophageal pressure gradient, acid exposure in the oesophagus does not necessarily ensue [102]. Furthermore, obesity increases risk for oesophageal adenocarcinoma even in the absence of reflux [103]. Central obesity is strongly related to risk of developing Barrett's oesophagus, independent of BMI [103]. However, central obesity is associated with increased oesophageal adenocarcinoma risk even in persons without Barrett's oesophagus [103]. Therefore, additional mechanisms might be involved.

In obese individuals, there is increased secretion of inflammatory cytokines and leptin, and decreased adiponectin. Insulin resistance, hyperinsulinemia and hyperglycemia are also increased with obesity. Elevated leptin is associated with increased risk for Barrett's oesophagus, and laboratory evidence supports carcinogenic effects of leptin on oesophageal cells [103]. Adiponectin, which is produced in lower amounts with obesity, is inversely associated with risk for Barrett's oesophagus and erosive oesophagitis, and in cell lines has anti-cancer effects [103]. Insulin is mitogenic to oesophageal cells.

Though there are no cohort studies in the general population, in one study of 427 patients with Barrett's oesophagus, elevated leptin levels and greater calculated insulin resistance were associated with progression to oesophageal adenocarcinoma, while there was a non-significant reduction in risk with increasing adiponectin [79].

In a cohort of 397 patients with Barrett's oesophagus, inflammation-related elevated concentrations of C-reactive protein and interleukin-6 were associated with increased risk of progression to oesophageal adenocarcinoma [104]. In a meta-analysis of observational studies, use of aspirin, an anti-inflammatory drug, was associated with a reduction in risk of oesophageal adenocarcinoma and gastric cardia cancers [105].

Oesophageal squamous cell carcinoma

For oesophageal squamous cell carcinoma and BMI, a significant inverse association was observed (see **Figure 3**, CUP Oesophageal SLR 2015 Figure 78). This inverse association is driven by an increase in risk at the lower end of the BMI range, with no further significant decrease in risk as BMI rises beyond about 25 kg/m² (see CUP Oesophageal SLR Figure 94 and Table 78).

For oesophageal squamous cell carcinoma and waist circumference, no significant association was observed in one study (see **Figure 5**, CUP Oesophageal SLR 2015 Figure 102). For waist-hip ratio, no significant association was observed in one study (see **Figure 6**, CUP Oesophageal SLR 2015 Figure 105).

CUP Panel's conclusion:

For oesophageal adenocarcinoma, the epidemiology was generally consistent, with graded increase in risk with increasing body fatness that is attributable to increased adiposity, for which plausible mechanisms in humans exist. The dose-response meta-analysis showed a significant increased risk, and there was no evidence of non-linearity. Significant positive associations were shown in non-smokers, in men and women, and for Europe and North America. The CUP findings are supported by two published pooled analyses.

For oesophageal squamous cell carcinoma, there was an inverse association driven by an increase in risk at the lower end of the BMI range, but no further significant decrease in risk as BMI rises beyond about 25 kg/m². This association is unlikely to be driven by a protective effect of adiposity, for which no plausible mechanisms have been identified. As BMI cannot distinguish between lean and fat mass, the association of lower BMI with higher risk may relate to other aspects of body composition, for example, lower lean mass. Despite the significant inverse association between BMI and oesophageal squamous cell carcinoma, in view of the lack of identified mechanisms required to draw causality, the evidence was judged as limited – no conclusion.

The CUP Panel concluded:

Greater body fatness (marked by BMI, waist circumference and waist-hip ratio) is a convincing cause of oesophageal adenocarcinoma.

7.8 Other

Other exposures were evaluated, but data were either of too low quality or too inconsistent, or the number of studies too few to allow conclusions to be reached. The list of exposures judged as 'limited – no conclusion' is summarised in the matrices on pages 6 and 7.

The evidence for foods containing beta-carotene and foods containing vitamin C, previously judged as 'probable decreases risk'; foods containing dietary fibre, foods containing folate, foods containing pyridoxine and foods containing vitamin E, previously judged as 'limited – suggestive decrease risk'; and red meat and high-temperature drinks, previously judged as 'limited-suggestive increases risk' in the Second Expert Report was less consistent, and the Panel could not draw any conclusions on the updated evidence.

Evidence for the following exposures, previously judged as 'limited – no conclusion' in the Second Expert Report [1], remains unchanged after updating the analyses with new data identified in the CUP Oesophageal SLR 2015: cereals (grains) and their products; starchy roots, tubers, and plantains; pulses (legumes); soya and soya products; herbs, spices, and condiments; poultry; fish; eggs; milk and dairy products; total fat; saturated fatty acids; monounsaturated fatty acids; polyunsaturated fatty acids; sugary foods and

drinks; salt; salting; fermenting; pickling; smoked and cured foods; nitrates and nitrites; frying; grilling (broiling) and barbecuing (charbroiling); protein; vitamin A; retinol; thiamin; riboflavin; calcium; iron; zinc; pro-vitamin A carotenoids; beta-cryptoxanthin; Seventh-day Adventist diets; adult attained height; energy intake.

In addition, evidence for the following exposures, for which no judgement was made in the Second Expert Report, is too limited to draw any conclusions: total meat, coffee and patterns of diet.

8. Comparison with the Second Expert Report

New cancer subtype-specific evidence was included throughout this review of the evidence for oesophageal cancer that was not available in the Second Expert Report [1]. Much of the new evidence was on physical activity and oesophageal cancer, evidence that was not previously examined. The updated evidence on vegetables, fruit, beta-carotene and vitamin C was less strong than in the Second Expert Report. The increase in the amount and quality of the evidence enabled some exposure evidence to be reviewed by smoking status and has highlighted the need for further research, particularly in non-smokers.

9. Conclusions

The CUP Panel concluded:

- ◆ **Body fatness:** Greater body fatness (marked by BMI, waist circumference and waist-hip ratio) is a convincing cause of oesophageal adenocarcinoma.
- ◆ **Alcoholic drinks:** Consumption of alcoholic drinks is a convincing cause of oesophageal squamous cell carcinoma.
- ◆ **Mate:** Regular consumption of mate, as drunk in the traditional style in South America, probably causes oesophageal squamous cell carcinoma.
- ◆ **Fruit:** The evidence suggesting that consumption of fruit decreases the risk of oesophageal squamous cell carcinoma is limited.
- ◆ **Vegetables:** The evidence suggesting that consumption of vegetables decreases the risk of oesophageal adenocarcinoma and oesophageal squamous cell carcinoma is limited.
- ◆ **Processed meat:** The evidence suggesting that consumption of processed meat increases the risk of oesophageal squamous cell carcinoma is limited.
- ◆ **Physical activity:** The evidence suggesting that physical activity decreases the risk of oesophageal cancer is limited.

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

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



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Abbreviations

AICR	American Institute for Cancer Research
BMI	body mass index
CI	confidence interval
CUP	Continuous Update Project
DNA	deoxyribonucleic acid
HPV	human papilloma virus
IARC	International Agency for Research on Cancer
<i>n</i>	number of cases
RR	relative risk
SLR	systematic literature review
WCRF	World Cancer Research Fund

Glossary

Adenocarcinoma

Cancer of glandular epithelial cells.

Adipokines

Cytokines (cell signalling proteins) secreted by adipose tissue.

Adjustment

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

Anthropometric measures

Measures of body dimensions.

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 a tumour.

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 ($BMI = \text{kg}/\text{m}^2$). Provides an indirect measure of body fatness. Also known as Quetelet's Index.

Carcinogen

Any substance or agent capable of causing cancer.

Cardia stomach cancer

A subtype of stomach cancer that occurs in the cardia, near the gastro-oesophageal junction.

Case-control study

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

Chronic

A chronic condition is a human 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 later), followed up for a period of time during which outcomes of interest are noted. Differences in the frequency of outcomes (such as disease) within the cohort are calculated in relation to different levels of exposure to factors of interest – for example, smoking, alcohol consumption, diet and exercise. Differences in the likelihood of a particular outcome are presented as the relative risk, comparing one level of exposure to another.



Confidence interval (CI)

A measure of the uncertainty in an estimate, usually reported as 95% confidence interval (CI), which is the range of values within which there is a 95% 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.

Cytokines

Cell-signalling molecules that aid cell-to-cell communication in immune responses and stimulate the movement of cells toward sites of inflammation, infection and trauma.

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 (see Second Expert Report Box 3.2).

Endogenous

Substances and processes that originate from within an organism, tissue or cell.

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 have 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.

Heterogeneity

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

High-income countries

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

Hyperinsulinemia

A condition in which there are high concentrations of insulin circulating in the blood. It is characteristic of insulin resistance, prediabetes and early type 2 diabetes.

Immune response

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

Incidence rates

The number of new cases of a condition appearing during a specified period of time expressed relative to the size of the population; for example, 60 new cases of breast cancer per 100,000 women per year.

Inflammation

The immunologic response of tissues to injury or infection. Inflammation is characterised by accumulation of white blood cells that produce several bioactive chemicals (cytokines), causing redness, pain, heat and swelling.

Insulin-like growth factor (IGF)

Polypeptides with high sequence similarity to insulin. IGFs are part of a complex system that cells use to communicate with their physiologic environment.

Interleukin-6

A cytokine involved in inflammation and infection responses and also in the regulation of metabolic, regenerative and neural processes.

Less developed regions

As defined by 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.

Low-income countries

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

Meta-analysis

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

Mitogenic

A mitogen is a chemical substance that encourages a cell to divide, by triggering mitosis. Mitogens are usually proteins. Mitogenesis is the induction (triggering) of mitosis, typically by a mitogen.

More developed regions

As defined by 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-cardia stomach cancer

A subtype of stomach cancer that occurs in the lower portion of the stomach.

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.

Pathogenesis

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

Polymorphisms

Common variations (in more than 1 per cent of the population) in the DNA sequence of a gene.

Pooled analysis

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

Processed meat

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

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 usually 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, to 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% ($p < 0.05$) that a study result has occurred by chance is considered 'statistically significant' (see confidence interval).

Systematic literature review (SLR)

A means of compiling and assessing published evidence that addresses a scientific question with a predefined protocol and transparent methods.

Waist-hip ratio (WHR)

A measure of body shape indicating central (abdominal) fat distribution.



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Appendix – Criteria for grading evidence

(Adapted from Chapter 3 of the Second Expert Report [1])

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

CONVINCING (STRONG EVIDENCE)

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

All of the following are generally required:

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

PROBABLE (STRONG EVIDENCE)

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

All the following are generally required:

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

LIMITED – SUGGESTIVE

This judgement is for evidence that is too limited to permit a probable or convincing causal judgement, but is suggestive of a direction of effect. The evidence may have methodological flaws, or be limited in amount, but shows a generally consistent direction of effect. This judgement 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 incidence of cancer; any exceptions to this require special explicit justification.

All 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 might be limited by the amount of evidence in terms of the number of studies available, by inconsistency of direction of effect, by poor quality of studies (for example, lack of adjustment for known confounders) or by any combination of these factors.

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

There are also many exposures for which there is such limited evidence that no judgement is possible. In these cases, evidence is recorded in the full CUP SLRs on the World Cancer Research Fund International website (wcrf.org). However, such evidence is usually not included in the summaries.

SUBSTANTIAL EFFECT ON RISK UNLIKELY (STRONG EVIDENCE)

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

All of the following are generally required:

- ◆ Evidence from more than one study type.
- ◆ Evidence from at least two independent cohort studies.
- ◆ Summary estimate of effect close to 1.0 for comparison of high- 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, an insufficient range of exposure in the study population and inadequate statistical power. Defects in these and other study design attributes might lead to a false conclusion of no effect.

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

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

SPECIAL UPGRADING FACTORS

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

Factors may include 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 as low as you can within the healthy range.

Move more

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

Avoid high-calorie foods and sugary drinks

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

Enjoy more grains, veg, fruit and beans

Eat a wide variety of whole grains, vegetables, fruit and pulses such as beans.

Limit red meat and avoid processed meat

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

For cancer prevention, don't drink alcohol

For cancer prevention, it's best not to drink alcohol. If you do, limit alcoholic drinks and follow national guidelines.

Eat less salt, and avoid mouldy grains and cereals

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

For cancer prevention, don't rely on supplements

Eat a healthy diet rather than relying on supplements to protect against cancer.

If you can, breastfeed your baby

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

Cancer survivors should follow our Recommendations (where possible)

After cancer treatment, the best advice is to follow the Cancer Prevention Recommendations. Check with your health professional.



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