

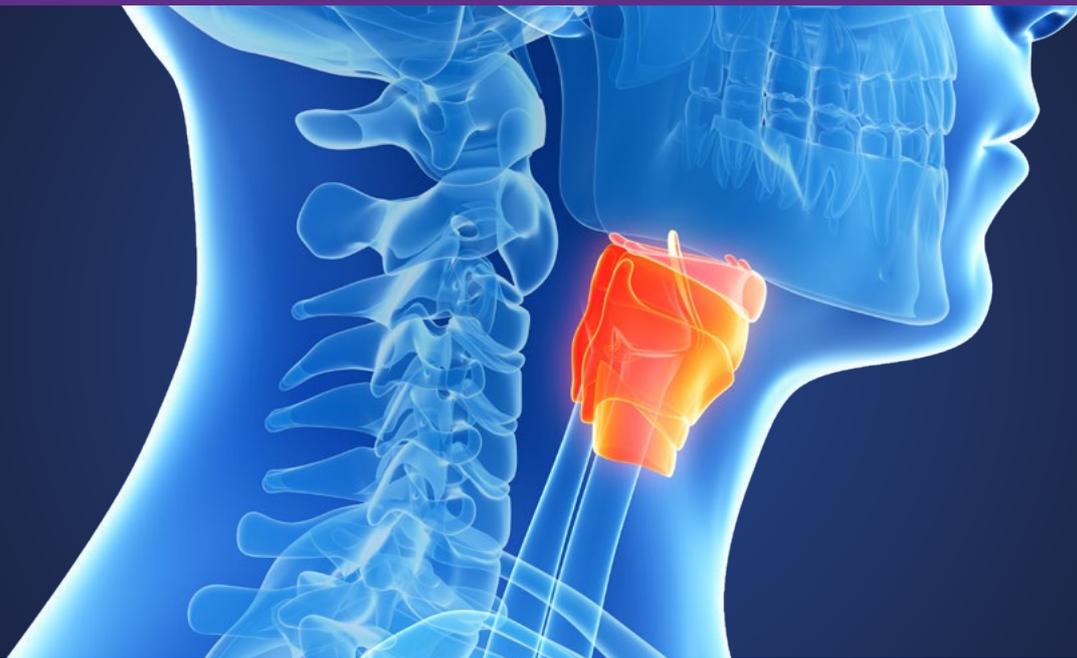
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American  
Institute for  
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Research

CUP Continuous  
Update  
Project

Analysing research on cancer  
prevention and survival



# Diet, nutrition, physical activity and **cancers of the mouth, pharynx and larynx**

2018

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# WORLD CANCER RESEARCH FUND NETWORK

## OUR VISION

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

## OUR MISSION

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

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

## OUR NETWORK

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

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

## OUR CONTINUOUS UPDATE PROJECT (CUP)

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

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

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

The launch of the WCRF Network's Third Expert Report, *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*, in 2018 brings together the very latest research from the CUP's review of the accumulated evidence on cancer prevention and survival related to diet, nutrition and physical activity. [Diet, nutrition, physical activity and cancers of the mouth, pharynx and larynx](#) is one of many parts that make up the CUP Third Expert Report: for a full list of contents, see [dietandcancerreport.org](http://dietandcancerreport.org).

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

## HOW TO CITE THIS REPORT

This part: World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. [Diet, nutrition, physical activity and cancers of the mouth, pharynx and larynx](#). Available at [dietandcancerreport.org](http://dietandcancerreport.org)

The whole report: World Cancer Research Fund/American Institute for Cancer Research. *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*. Continuous Update Project Expert Report 2018. Available at [dietandcancerreport.org](http://dietandcancerreport.org)

## KEY

References to other parts of the Third Expert Report are highlighted in [purple](#).

## EXECUTIVE SUMMARY

### Background and context

In this report, the term head and neck cancer includes cancers of the mouth, larynx (voice box), nasal cavity and pharynx (throat). The mouth includes the lips, tongue, inside lining of the cheeks, floor of the mouth, gums, palate and salivary glands. Most of the studies identified in this report did not include cancer of the lips or salivary glands. The pharynx (or throat) is the muscular cavity leading from the nose and mouth to the larynx, a muscular structure at the upper area of the windpipe, which includes the vocal cords. Cancer of the nasopharynx (the area that connects the back of the nose to the back of the throat) is not included in this report but is reviewed separately (see [dietandcancerreport.org](http://dietandcancerreport.org)).

Taken together, cancers of the mouth (including cancers of the lips and salivary glands), pharynx and larynx are the seventh most frequent type of cancer worldwide. Globally, in 2012, an estimated 600,000 new cases were diagnosed, accounting for 4.2 per cent of all new cancer cases [2].

Cancers of the mouth, pharynx and larynx are approximately three times more common in men than in women, which may in part be related to higher rates of smoking in men. Risk increases with age. The highest rates of these cancers are found in South-Central Asia, with Bangladesh, India, Pakistan and Sri Lanka contributing more than a quarter of cases in 2012 [2].

Globally, 4 per cent of all cancer deaths were attributed to these cancers, and they are the seventh most common cause of death from cancer [2]. In the USA, the overall five-year survival rates for mouth and pharyngeal cancer are about 64 per cent, although this figure rises to about 83 per cent for cancers that are diagnosed at an early stage [3]. Many survivors of cancers of the mouth, pharynx and larynx are left with long-term complications of therapy, related to breathing and food consumption, that require specialised care.

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 cancers of the mouth, pharynx and larynx. 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 cancers of the mouth, pharynx and larynx include:

### **1. Smoking, chewing tobacco and snuff**

- Smoking (or use of smokeless tobacco, sometimes called “chewing tobacco” or “snuff”) is a cause of cancers of the mouth, pharynx and larynx. Chewing betel quid (nuts wrapped in a betel leaf coated with calcium hydroxide), with or without added tobacco, is also a risk factor for cancers of the mouth and pharynx. It is estimated that as much as 90 per cent of mouth cancers worldwide are attributable to tobacco use, alcohol consumption or a combination of both.

### **2. Infection**

- Oral infection with high-risk human papilloma viruses (HPV) is a risk factor for mouth cancer. It is estimated that 72 per cent of oropharyngeal cancer is linked to high-risk HPV infection.

### **3. Environmental exposures**

- Exposure to asbestos increases the risk of laryngeal cancer.

## **How the research was conducted**

The global scientific research on diet, weight, physical activity and the risk of cancers of the mouth, pharynx and larynx 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 25 studies from around the world, with more than 9 million participants and nearly 8,000 cases of cancers of the mouth, pharynx and larynx.

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 **Section 7, Evidence and Judgements** section of this report.

## Findings

### There is strong evidence that:

- **consuming alcoholic drinks increases the risk of cancers of the mouth, pharynx and larynx.**
- **being overweight or obese increases the risk of cancers of the mouth, pharynx and larynx.**

### There is some evidence that:

- **consuming non-starchy vegetables might decrease the risk of cancers of the mouth, pharynx and larynx.**
- **choosing healthy dietary patterns might decrease the risk of cancers of the mouth, pharynx and larynx.**
- **consuming coffee might decrease the risk of cancers of the mouth, pharynx and larynx.**
- **consuming mate might increase the risk of cancers of the mouth, pharynx and larynx.**

## Recommendations

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

### References

- [1] World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*. Washington DC: AICR, 2007. Available from [wcrf.org/about-the-report](http://wcrf.org/about-the-report)
- [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>
- [3] NIH Cancer Stat Facts: Oral Cavity and Pharynx Cancer. Available from <http://seer.cancer.gov/statfacts/html/oralcav.html>

2018	DIET, NUTRITION, PHYSICAL ACTIVITY AND CANCERS OF THE MOUTH, PHARYNX AND LARYNX		
		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	Convincing		Alcoholic drinks
	Probable		Body fatness <sup>1</sup>
LIMITED EVIDENCE	Limited – suggestive	Non-starchy vegetables Healthy dietary patterns <sup>2</sup> Coffee	Mate <sup>3</sup>
	Limited – no conclusion	Cereals (grains) and their products; starchy roots, tubers, and plantains; fruits; pulses (legumes); dietary fibre; total meat; red meat; processed meat; poultry; fish; eggs; dairy products; total fat; animal fats; plant oils; tea; soft drinks; fruit juices; frying, grilling (broiling) and barbecuing (charbroiling); cooked food-acrylamide; protein; vitamin A; thiamin; riboflavin; niacin; vitamin C, iron, selenium; energy intake, carotenoids; retinol; folate; vitamin D; vitamin E; calcium; other patterns of diet (not related to healthy dietary indices); physical activity; height	
STRONG EVIDENCE	Substantial effect on risk unlikely		

- 1 Body fatness marked by body mass index (BMI), waist circumference and waist-hip ratio.
- 2 Judgements relate to healthy dietary patterns as marked by greater healthy dietary indices. These indices produce an integrated score to assess adherence to healthy eating or lifestyle recommendations or patterns. They are characterised by factors such as healthy weight management, engagement in physical activity, limiting intake of foods and drinks that promote weight gain, limiting intake of red and processed meat, limiting intake of alcoholic drinks, higher intake of plant foods, and breastfeeding (in women).
- 3 Mate, an infusion prepared from dried leaves of *Ilex paraguariensis*, is drunk traditionally in parts of South America, through a metal straw.

# 1. Summary of Panel judgements

Overall, the Panel notes the strength of the evidence that consumption of alcoholic drinks and greater body fatness are causes of cancers of the mouth, pharynx and larynx.

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

## **Convincing evidence**

**Alcoholic drinks:** Consumption of alcoholic drinks is a convincing cause of cancers of the mouth, pharynx and larynx.

## **Probable evidence**

**Body fatness:** Greater body fatness (marked by BMI, waist circumference and waist-hip ratio) is probably a cause of cancers of the mouth, pharynx and larynx.

## **Limited – suggestive evidence**

**Non-starchy vegetables:** The evidence suggesting that greater consumption of non-starchy vegetables decreases the risk of cancers of the mouth, pharynx and larynx is limited.

**Healthy dietary patterns:** The evidence suggesting that healthy dietary patterns (marked by greater healthy dietary index scores) decrease the risk of cancers of the mouth, pharynx and larynx is limited.

**Coffee:** The evidence suggesting that greater consumption of coffee decreases the risk of cancers of the mouth, pharynx and larynx is limited.

**Mate:** The evidence suggesting that greater consumption of mate, as consumed in South America, increases the risk of cancers of the mouth, pharynx and larynx 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 62. The Panel judgements for cancers of the mouth, pharynx and larynx are shown in the matrix on **page 8**.

## 2. Trends, incidence and survival

There are several different tissues and organs in and around the mouth, pharynx and larynx. The oral cavity includes the lips, the tongue, the inside lining of the cheeks (buccal mucosa), the floor of the mouth, the gums (gingiva), the palate and the salivary glands. The pharynx (or throat) is the muscular cavity leading from the nose and mouth to the larynx, which includes the vocal cords. Cancer of the lips and salivary glands and nasopharyngeal cancer are not included in this report. Nasopharyngeal cancer is reviewed separately (see [dietandcancerreport.org](http://dietandcancerreport.org)). In this report, the term head and neck cancer includes cancers of the mouth, larynx, nasal cavity, salivary glands and pharynx and the term upper aerodigestive tract cancer includes head and neck cancer and oesophageal cancer.

### Incidence and mortality

Taken together, cancers of the mouth, pharynx and larynx are the seventh most frequent types of cancer worldwide. In 2012, some 300,373 new cases of cancers of the lips and oral cavity, 142,387 new cases of pharyngeal cancer (excluding nasopharyngeal cancer) and 156,877 cases of cancer of the larynx were diagnosed worldwide. These figures represent 2.1 per cent, 1.0 per cent and 1.1 per cent, respectively, of the total number of cancer cases diagnosed per year (excluding non-melanoma skin cancers) [2]. Cancers of the lips and oral cavity, pharynx and larynx are about three times more common in men than in women [2], which may in part be related to smoking patterns. Risk increases with age [4].

Cancers of the mouth, pharynx and larynx are more prevalent in regions characterised by lower indices of development or income (about 65 per cent of new cases in 2012) than in regions characterised by higher indices of development or income. Age-standardised incidence rates range from 2.6 per 100,000 in Western Africa to 12.6 in Western Europe and 13.6 in South-Central Asia. Over a quarter of all cases are found in Bangladesh, India, Pakistan and Sri Lanka [2].

The trends in the incidence rates of these cancers vary according to geographical location and age group. Mouth cancer incidence rates have followed the changing prevalence in patterns of tobacco consumption, and international variations in these cancer rates and trends largely reflect differences in the stage and degree of the tobacco epidemic. In general, smoking-related cancers of the mouth have been declining in men and increasing or stable among women in countries characterised by higher indices of development or income where tobacco use peaked some time ago, but are increasing in many countries with tobacco epidemics that are more recently established and are currently peaking [5, 6]. In contrast, in a number of countries characterised by higher indices of development or income where tobacco use has declined, rates of oropharyngeal cancer have increased, which it has been suggested is linked to human papillomavirus (HPV) infection, particularly in younger birth cohorts [5, 6]. In the United States, rates for new laryngeal cancer cases have been falling on average 2.4 per cent each year over the last 10 years.

Globally, 4 per cent of all cancer deaths were attributed to these cancers and they are the seventh most common cause of death from cancer [2]. Mouth, pharyngeal and laryngeal cancer mortality closely follows the geographical patterns for incidence.

### Survival

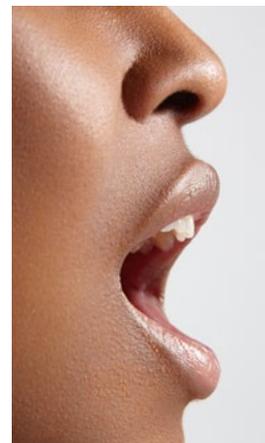
More than 60 per cent of patients do not seek medical advice until the disease is at an advanced stage; in these cases, long-term survival rates are poor, especially if the cancer site is inaccessible [4]. Five-year survival rates<sup>1</sup> for oral cavity and pharyngeal cancer combined are about 64 per cent in the United States, rising to about 83 per cent for cancers that are diagnosed at an early stage [3]. In the United Kingdom, five-year survival rates are between 54 and 66 per cent for oral, oropharyngeal and laryngeal cancers and are much lower for hypo-pharyngeal cancers at about 27 per cent in men and 30 per cent in women [7]. Many survivors of cancers of the mouth, pharynx and larynx are left with long-term complications of therapy related to breathing and food consumption that require specialised care.

For further information, see **Box 1**.

#### 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 applies mainly to 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 together with well-established treatment facilities. Survival is often a function of the stage at which a cancer is detected, diagnosed and treated.**



<sup>1</sup>The prevalence of oral cavity and pharyngeal cancer combined is defined as the number of persons in a defined population who were diagnosed five years before and who are still alive at the end of a given year.

### 3. Pathogenesis

Over 90 per cent of oral cavity, pharyngeal and laryngeal cancers are squamous cell carcinomas [8].

Cancers of the mouth, pharynx and larynx, like other cancer types, are the result of genetic alterations that lead to small, localised lesions in the mucosal membranes (very thin membranes that cover the gastrointestinal tract from the mouth to the anus) that grow in an abnormal way (dysplasia). These lesions may then progress to carcinoma in situ and/or become invasive cancers.

Exposure to carcinogens can be prolonged and consistent. The mouth and pharynx are directly exposed both to inhaled carcinogens and through eating and drinking. Chronic damage and inflammation caused by stomach acid due to reflux are also implicated. Recent studies have reported that laryngopharyngeal reflux (where stomach acid flows upwards to the larynx and/or pharynx) is associated with laryngeal cancers [9, 10].

Cancers of the mouth, pharynx and larynx frequently show multiple, independent, malignant foci (location of tumour cells can only be identified microscopically) – with second primary cancers occurring relatively frequently. This phenomenon (referred to as “field cancerisation”) occurs when an entire region of tissue is repeatedly exposed to carcinogens.

### 4. Other established causes

#### Tobacco use

Tobacco use (including smokeless tobacco, sometimes called “chewing tobacco” or “snuff”) [11] is a well-established risk factor for cancers of the mouth, pharynx and larynx, with risk increasing with the duration and amount of use [12]. It is also thought to interact with alcohol consumption to increase cancer risk [13, 14]. Betel quid use [15, 16], which is most common in India and Southeast Asia, is also a risk factor of oral cavity cancer and pharyngeal cancer [17]. Smoking is estimated to account for about 71 per cent of deaths from oral cavity cancer (including pharynx) in high-income countries and 37 per cent of deaths in low-income and middle-income countries [18].

#### Infection

There is sufficient evidence in humans that human papilloma virus (HPV) 16 causes cancer of the oral cavity and limited evidence that it causes cancer of the larynx. A positive association has also been observed between infection with HPV 18 and cancers of the oral cavity and larynx [19]. The reported prevalence of HPV in these cancers is variable [20].

Reports show an increase in the proportion of HPV-related oropharyngeal cancer over time, from 41 per cent before 2000 to 64 per cent between 2000 and 2004, and 72 per cent between 2005 and 2009 [19, 21]. The prevalence of oral HPV infection may also play a role in the divergent geographical distribution of these cancers. HPV vaccines

are available for the prevention of cervical cancer and are effective for the prevention of initial oral infection with high-risk HPV types that can cause oropharyngeal cancers, but additional studies are necessary to define the impact on cancer risk.

### **Environmental exposures**

There is some evidence that exposure to asbestos is associated with an increased risk of laryngeal cancer [22].

## **5. Interpretation of the evidence**

### **5.1 General**

For general considerations that may affect interpretation of the evidence please see [Judging the evidence](#).

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

### **5.2 Specific**

Considerations specific to mouth, pharynx and larynx cancer include the following:

#### **Confounding**

Tobacco smoking is a potential confounder. The vast majority of studies included in this report adjusted for smoking.

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

The relationship between smoking and body composition presents particular problems in the interpretation of observational data in relation to cancers of the mouth, pharynx and larynx. Smokers tend to have lower body mass index (BMI) than non-smokers (except for very heavy smokers), and so lower BMI may appear to be associated with increased risk (and conversely higher BMI with decreased risk) of smoking-related cancers because



of confounding by smoking. Imprecision in the ascertainment of exposure to smoking makes residual confounding a likely consequence. Furthermore, despite the tendency toward lower BMI among smokers, they also tend to have greater waist circumference. These anthropometric measures are valuable markers of body composition in observational epidemiology but are not able to precisely characterise the proportions of lean and fat tissue, nor the distribution of body fat. The metabolic consequences of greater body fatness (which are responsible for associations between body composition and cancer risk) may be more pronounced in relation to visceral adiposity, which is not marked by BMI. Furthermore, low BMI may reflect predominant loss of lean rather than fat mass, and this may be a consequence or pre-existing disease or a marker of disease severity. In the case of cancers of the mouth, pharynx and larynx, there was sufficient evidence from never smokers to identify an association, not confounded by smoking, between higher BMI and greater risk of these cancers. This relationship was attenuated or reversed among current and former smokers, emphasising the possible impact of confounding by smoking status.

### **Changing natural history**

The characteristics of people who develop cancers of the mouth, pharynx and larynx are changing. Increasingly, a large cohort of younger people who are infected with high-risk HPV 16 or 18, and who are non-smokers and not heavy drinkers, are now developing these cancers. As far as possible, the conclusions in this report take account of this changing natural history. However, most published epidemiological studies reviewing diet, nutrition, physical activity and body fatness and cancers of the mouth, pharynx and larynx have not included data on HPV infection.

### **Study type**

There is limited information from cohort studies reporting on cancers of the mouth, pharynx and larynx. Additional information from pooled case-control analyses is available but due to the methodological issues related to case-control studies is not considered reliable. Therefore, although results from pooled case-control analyses are included in this report they did not strongly influence the Panel's conclusions.

## 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 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 were made to the methodology. The updated literature search was restricted to Medline and included only randomised controlled trials, cohort and nested case-control studies. Owing to their methodological limitations, case-control studies were not analysed in the CUP Mouth, Pharynx and Larynx SLR 2016, apart from those for mate, for which strong mechanistic evidence was used as an upgrading factor.

Dose-response meta-analyses were only possible for alcohol (as ethanol) and where possible are presented by mouth, pharynx and larynx cancer subtype, and by sex. Although it was not possible to do stratified analysis by smoking status, information on never, former and current smokers from individual studies and from pooled and published meta-analyses was included as appropriate. The pooled analyses included INHANCE, a pooled analysis of case-control studies [23].

Studies reporting mean difference as a measure of association were not included in the CUP Mouth, Pharynx and Larynx SLR 2016, 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 is applied when the data suggests that the dose-response curve is non-linear and when a threshold or plateau of effect is detected that might be of interest. The protocol method states that exploratory nonlinear dose-response meta-analyses are conducted only when there are five or more studies with three or more categories of exposure. Owing to lack of sufficient data, this was not possible for the CUP Mouth, Pharynx and Larynx SLR 2016.

For this report, where possible, cancers of the mouth (oral cavity), pharynx (pharynx, oropharynx, hypopharynx), larynx, head and neck, and upper aerodigestive tract were reviewed separately.

The CUP Mouth, Pharynx and Larynx SLR 2016 included studies published up to 30 April 2015 (and one published pooled analysis of cohort studies that was published online after the date of the literature search).

For more information on methodology, see the full CUP Mouth, Pharynx and Larynx SLR 2016 at [wcrf.org/mouth-pharynx-larynx-cancer-slr](http://wcrf.org/mouth-pharynx-larynx-cancer-slr).

## 6.1 Mechanistic evidence

The mechanisms included in this report were produced by the International Agency for Research on Cancer and reviewed by CUP Panel members. A brief summary is given of possible mechanisms for non-starchy vegetables, healthy dietary patterns, mate, coffee, alcoholic drinks and body fatness.

## 7. Evidence and judgements

The following sections summarise the evidence identified in the CUP Mouth, Pharynx and Larynx SLR 2016 and provide a comparison with the findings from the Second Expert Report [1], where possible. They also include a brief description of plausible mechanisms for each exposure and the Panel's conclusions.

For information on the criteria for grading the epidemiological evidence, see the **Appendix** on page 62 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 Mouth, Pharynx and Larynx SLR 2016.

### 7.1 Non-starchy vegetables

*(Also see CUP Mouth, Pharynx and Larynx SLR 2016: Section 2.2.1)*

The CUP identified three new studies (four publications) [24–27], giving a total of three studies (four publications) reviewing the evidence for non-starchy vegetable intake and cancers of the mouth, pharynx and larynx (for more details, see CUP Mouth, Pharynx and Larynx SLR 2016 Table 3).

All studies reporting on cancers of the mouth, pharynx and larynx incidence reported inverse associations when comparing the highest and the lowest categories of non-starchy vegetable intake, the majority of which were non-significant (see CUP Mouth, Pharynx and Larynx SLR 2016 Figure 3).

All the studies reported continuous risk estimates in men and women combined, the results of which are summarised in **Table 1** (for more details, see CUP Mouth, Pharynx and Larynx SLR 2016, Table 3). All studies reported inverse associations, which were statistically significant for two cancer types in one study [25]. All studies adjusted for smoking.

**Table 1: Summary of cohort studies – non-starchy vegetables. Dose-response analyses from individual studies identified in the CUP**

Cancer type	Study	Increment	No. Cases	RR (95% CI)
<b>Oral cavity</b>	Netherlands Cohort Study [24]	Per 25 g/day	131	0.95 (0.89–1.02)
	NIH-AARP [25]	Per serving/ 1,000 kcal	319	0.84 (0.73–0.95)
<b>Oro- and hypo-pharyngeal combined</b>	Netherlands Cohort Study [24]	Per 25 g/day	88	0.94 (0.85–1.04)
	NIH-AARP [25]	Per serving/ 1,000 kcal	142	0.90 (0.74–1.09)
<b>Laryngeal</b>	Netherlands Cohort Study [24]	Per 25 g/day	193	0.98 (0.92–1.04)
	NIH-AARP [25]	Per serving/ 1,000 kcal	279	0.91 (0.79–1.05)
<b>Head and neck</b>	Netherlands Cohort Study [24]	Per 25 g/day	415	0.96 (0.92–1.01)
	NIH-AARP [25]	Per serving/ 1,000 kcal	787	0.89 (0.82–0.97)
<b>Upper aerodigestive tract</b>	European Prospective Investigation into Cancer and Nutrition [27]	Per 40 g/day	352	0.89 (0.78–1.02)

Note: All studies in men and women.



For head and neck cancer, one study [25] reported a significant inverse association in former smokers (RR 0.83 (95% CI 0.73–0.94) per serving per 1,000 kilocalories). No significant association was reported for current smokers or never smokers. A significant inverse association was reported in participants who did not drink alcohol (RR 0.84 (95% CI 0.72–0.98)); no significant association was observed in those who did drink alcohol.

The 2005 SLR found a significant inverse association (RR 0.72 (95% CI 0.63–0.82) per 50 grams per day) but included only four case-control studies in the dose-response meta-analysis. No cohort studies were identified. The CUP update includes cohort studies only.

### Published pooled analyses and meta-analyses

One published pooled analysis [23] of 22 case-control studies was identified in the CUP Mouth, Pharynx and Larynx SLR 2016. Significant inverse associations with vegetable intake were reported across the various cancers (head and neck, oral, oropharyngeal, pharyngeal and laryngeal separately). The pooled analysis, although in case-control studies, was able to conduct analyses stratified by smoking and alcohol, and non-significant results were found for never smokers and light drinkers [23] (see **Table 2**).

**Table 2: Summary of published pooled analysis of head and neck cancer, case-control studies – vegetables (excluding potatoes)**

Analysis	Contrast	RR (95% CI)	P trend	No. studies	No. cases
<b>Chuang, 2012 [23]</b>	Highest vs. lowest				
	All	0.66 (0.49–0.90)	0.01	22	12,968
	Never smokers and light drinkers ( $\leq 3$ drinks a day)	0.85 (0.60–1.19)	0.15		1,015

## Mechanisms

Vegetables comprise a diverse food group and their consumption provides exposure to a wide array of nutrients and phytochemicals. There is a substantial body of evidence demonstrating potential anti-tumorigenic effects of many agents found in vegetables including carotenoids; vitamins A, C, and E; selenium; phenolic acids; flavonoids; glucosinolates; among others, in a range of different tissue types. However, experimental models of *de novo* carcinogenesis of the oral, oropharyngeal, pharyngeal and laryngeal mucosa are limited, and thus the number of studies of the effects of vegetables, vegetable extracts or specific phytochemicals on these tissues remains modest. This approach is complemented by studies of tumorigenesis using transplantable models employing human squamous cell carcinoma cells in immune-deficient mice. In parallel, *in vitro* studies examine how specific substances affect various aspects of carcinogenesis and cancer cell growth [28]. Randomised controlled studies in humans of vegetable intake or components from vegetables are few, limited in size and often focus upon biomarkers or premalignant oral conditions, such as leukoplakia [29]. It is likely that the epidemiological relationships between vegetables and reduced risk of cancers of the mouth, pharynx and larynx are mediated by multiple components mediated by a range of mechanisms [30]. Future studies focusing upon how diets rich in vegetables or specific vegetables and their unique phytochemicals may affect cancers of the mouth, pharynx and larynx are necessary.

## CUP Panel's conclusion:

The evidence from cohort studies suggesting increased consumption of non-starchy vegetables decreases the risk of cancers of the mouth, pharynx and larynx was limited but generally consistent. Although all the studies identified in the CUP adjusted for smoking, in the one study that did stratify by smoking status, no significant association was observed in never smokers, suggesting there is potential for residual confounding due to smoking. Overall, findings from the studies identified in the CUP are generally consistent with a published pooled analysis of case-control studies, which found significant associations overall and no significant association for never smokers and light drinkers. There is evidence of plausible mechanisms in humans. The CUP Panel concluded the following:

**The evidence suggesting that greater consumption of non-starchy vegetables decreases the risk of cancers of the mouth, pharynx and larynx is limited.**

## 7.2 Healthy dietary patterns

(Also see *CUP Mouth, Pharynx and Larynx SLR 2016: Section 1*)

This section covers healthy dietary patterns as described by specific healthy dietary indices. These include the American Cancer Society (ACS) Cancer Prevention Guidelines score [31], the Healthy Eating Index-2005 (HEI-2005) [32], the alternate Mediterranean (aMED) score [33] and the WCRF/AICR score [34] (for details, see the **Glossary**).

The CUP identified two new studies (three publications) [34–36], giving a total of two studies (three publications) reviewing healthy diet indices and cancers of the mouth, pharynx and larynx. A summary of results from the categorical analyses is presented in **Table 3** (for more details, see *CUP Mouth, Pharynx and Larynx SLR 2016, Table 2*). All the studies adjusted for smoking.

Significant inverse associations were reported for continuous analyses conducted for the Healthy Eating Index-2005 and head and neck and laryngeal cancers, and the WCRF/AICR score and upper aerodigestive tract cancer (for more details, see *CUP Mouth, Pharynx and Larynx SLR 2016, Table 2*).



**Table 3: Summary of categorical analyses from studies reporting on healthy dietary indices and cancers of the mouth, pharynx and larynx**

Diet index/ Cancer type	Study	Contrast	No. Cases	RR (95% CI)	P trend
<b>American Cancer Society Guidelines score</b>					
<b>Oral cavity</b>	NIH-AARP [35]	Quintile 5 vs. Quintile 1	862 M, 292 W	0.79 (0.64–0.97) 0.71 (0.48–1.06)	0.06 0.03
<b>Laryngeal</b>			620	0.82 (0.64–1.05)	0.06
<b>Healthy Eating Index-2005</b>					
<b>Oral cavity</b>	NIH-AARP [36]	Quintile 5 vs. Quintile 1	572 M, 208 W	0.84 (0.63–1.14) 0.58 (0.36–0.96)	0.25 0.004
<b>Orohyppo- pharyngeal</b>			263 M, 74 W	0.64 (0.41–1.01) 0.42 (0.17–1.08)	0.008 0.054
<b>Laryngeal</b>			526 M, 96 W	0.70 (0.51–0.96) 0.40 (0.17–0.93)	0.098 0.0007
<b>Head and neck</b>		Quintile 5 vs. Quintile 1	1,466 M, 402 W	0.74 (0.61–0.89) 0.48 (0.33–0.70)	0.0008 <0.0001
<b>aMED (Mediterranean) score</b>					
<b>Oral</b>	NIH-AARP [36]	7-9 vs. 0-2	572 M, 208 W	0.95 (0.66–1.37) 0.47 (0.24–0.93)	0.31 <0.0001
<b>Orohyppo- pharyngeal</b>			7-9 vs. 0-2 5-6 vs. 0-2	263 M, 74 W	0.91 (0.54–1.52) 0.68 (0.35–1.32)
<b>Laryngeal</b>		7-9 vs. 0-2	526 M, 96 W	0.68 (0.45–1.03) 0.59 (0.18–2.01)	0.059 0.075
<b>Head and neck</b>		7-9 vs. 0-2	1,466 M, 402 W	0.80 (0.64–1.01) 0.42 (0.24–0.74)	0.002 <0.0001
<b>WCRF/AICR score</b>					
<b>Upper aerodigestive tract</b>	European Prospective Investigation into Cancer and Nutrition [34]	Quintile 5 vs. Quintile 1	602	0.69 (0.50–0.95)	<0.0001

One study examined the associations between the HEI-2005 and the aMED (Mediterranean) score and head and neck cancer by smoking status [36]. It is unclear whether the apparent lack of association in never smokers and significant associations observed only in smokers was due to residual confounding or a specific effect.

A summary of results from the categorical analyses is presented in **Table 4**.

**Table 4: NIH-AARP dose-response analysis results by dietary index and head and neck cancer stratified by smoking**

	Per increment of 10-score of the HEI-2005		Per increment of 1-score of the aMED score	
	Men	Women	Men	Women
<b>Never smokers</b>	1.00 (0.87–1.15)	0.80 (0.62–1.04)	1.00 (0.91–1.10)	0.91 (0.76–1.09)
<b>Former smokers</b>	0.91 (0.84–0.99)	0.79 (0.65–0.97)	0.93 (0.89–0.99)	0.75 (0.65–0.86)
<b>Current smokers</b>	0.87 (0.78–0.98)	0.74 (0.62–0.88)	0.91 (0.84–0.99)	0.87 (0.77–0.98)

No cohort studies were identified and no judgement was made for healthy dietary patterns in the Second Expert Report. The CUP included two new cohort studies.

### Published pooled analyses and meta-analyses

No pooled or published meta-analyses reviewing healthy diet indices were identified in the CUP Mouth, Pharynx and Larynx SLR 2016.

### Mechanisms

Healthy dietary patterns characterised by higher consumption of vegetables and fruits and reflecting lower consumption of alcohol, red and processed meats, have been linked to decreased risk of mouth, pharynx and larynx cancers [37]. It is likely that multiple individual components of healthy dietary patterns contribute to a potential protective effect on the development of cancers of the mouth, pharynx and larynx, with either additive or interactive effects on pathways involved in oral carcinogenesis. Further development of statistical and bioinformatics approaches to examining dietary patterns in prospective cohort studies and oral cancer risk, particularly in those at higher risk due to smoking and infections, will provide greater insight into key relationships. There are currently no human clinical intervention trials evaluating healthy dietary patterns and the risk of cancers of the mouth, pharynx and larynx.

### CUP Panel's conclusion:

The evidence is generally consistent, and all studies showed a decreased risk of cancers of the mouth, pharynx and larynx with higher healthy dietary index scores, although not all were statistically significant. However, due to the limited number of studies for each cancer type, no meta-analyses could be conducted. Although all the studies adjusted for smoking, in one study that stratified by smoking status, no significant decreased risk of head and neck cancer was observed in never smokers, suggesting potential for residual confounding due to smoking. There is evidence of plausible mechanisms in humans. The CUP Panel concluded the following:

**The evidence suggesting that healthy dietary patterns (marked by greater healthy dietary index scores) decrease the risk of cancers of the mouth, pharynx and larynx is limited.**

### 7.3 Mate

(Also see *CUP Mouth, Pharynx and Larynx SLR 2016: Section 3.6.3*)

Mate, an aqueous infusion prepared from dried leaves of *Ilex paraguariensis*, is traditionally drunk scalding hot following repeated addition of almost boiling water to the infusion. Mate is consumed mainly in South America, specifically Argentina, Bolivia, Brazil, Chile, Ecuador, Paraguay and Uruguay. Hot mate consumption is graded by the International Agency for Research on Cancer (IARC) as probably carcinogenic to humans [38].

No cohort studies were identified in the CUP. Two new case-control studies were identified [39, 40], giving a total of five case-control studies (five publications) reviewing mate consumption and cancers of the mouth, pharynx and larynx, which are summarised in **Table 5** (for details, see *CUP Mouth, Pharynx and Larynx SLR 2016 Table 5*). Nearly all studies reported positive associations for categorical analyses, many of which were statistically significant. In studies that compared very hot, hot, warm or cold mate with never drinkers, there was no clear association with the temperature at which mate was consumed [39, 40]. All studies adjusted for smoking.

**Table 5: Summary of case-control studies – mate**

Cancer type	Study	Contrast	No. Cases, Controls	OR (95% CI)	P trend
<b>Oral cavity</b>	Deneo-Pellegrini, 2013, M [39]	Ever vs. never drinkers	696 cases, 696 controls	1.05 (0.70–1.55)	-
		Hot or very hot vs. never		1.11 (0.74–1.66)	0.37
	Franco, 1989 [41]	30 cups/month vs. <1 cup/month	232 cases, 464 controls	1.6 (0.8–3.3)	-
<b>Oral cavity and pharyngeal combined</b>	De Stefani 1988, M [42]	>2 L/day vs. <1 L/day	108 cases, 286 controls	5.2 (2.1–13.1)	-
<b>Mouth</b>	Pintos, 1994 [43]	>3 gourds/day vs. never	169 cases, 338 controls	2.82 (1.2–6.6)	0.038
<b>Oral cavity and oropharyngeal combined</b>	Szymanska, 2010 [40]	Ever vs. never	628 cases, 1,026 controls	1.48 (1.05–2.08)	-
		Hot or very hot vs. never		1.15 (0.79–1.66)	0.72
<b>Hypo-pharyngeal and laryngeal combined</b>	Szymanska, 2010 [40]	Ever vs. never drinkers	410 cases, 1,026 controls	1.51 (1.05–2.18)	-
		Hot or very hot vs. never		1.28 (0.87–1.9)	0.72
<b>Upper aerodigestive tract</b>	Szymanska, 2010 [40]	Ever vs. never drinkers	37 cases,* 1,026 controls	2.29 (0.58–9.07)	0.12
		Hot or very hot vs. never		2.50 (0.93–6.74)	0.095

\* Never drinkers, never smokers

Six case-control studies were identified in the 2005 SLR, all reported increased risk from drinking mate, and results were significant in four analyses. The CUP update included two new case-control studies.



## Published pooled analyses and meta-analyses

No pooled or published meta-analysis was identified on mate and cancers of the mouth, pharynx and larynx.

The Panel is aware that in May 2016, after the systematic literature reviews on which this Report is based were completed, the International Agency for Research on Cancer (IARC) published a paper 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 [44]. The conclusions for mate and the drinking temperature of other beverages were largely based on evidence related to oesophageal cancer risk and do not specifically mention cancers of the mouth, pharynx and larynx.

## Mechanisms

Mate is an infusion made from dried leaves of the plant *Ilex paraguariensis*. Habitually drunk in South America, mate can be drunk hot or cold. Any carcinogenic effects of mate are believed to be due to its consumption at very hot temperatures (over 70°C), which can cause chronic mucosal injury that can promote tumorigenesis. Repeated thermal injury has been shown to promote upper oesophageal carcinogenesis in rodent studies, supporting this proposed mechanism [44, 45].

### CUP Panel's conclusion:

The evidence from case-control studies consistently suggests an increased risk of cancers of the mouth, pharynx and larynx with consumption of mate. However, the evidence from the individual studies relating to temperature was not conclusive, and the associations with quantity of mate tended to be non-significant. There is evidence for plausible mechanisms. The CUP Panel concluded the following:

**The evidence suggesting that greater consumption of mate, as consumed in South America, increases the risk of cancers of the mouth, pharynx and larynx is limited.**

## 7.4 Coffee

(Also see CUP Mouth, Pharynx and Larynx SLR 2016: Section 3.6.1)

The CUP identified four new studies (four publications) [46–49], giving a total of six studies (six publications) reviewing coffee consumption and risk of cancers of the mouth, pharynx and larynx. A summary of results is presented in **Table 6**. All studies adjusted for smoking.

**Table 6: Summary of cohort studies – coffee. Dose-response analyses from individual studies identified in the CUP**

Cancer type	Study	Contrast/ Increment	No. Cases	RR (95% CI)	P trend
<b>Oral cavity</b>	NIH-AARP [46]	>3 vs. <1 cups/day	392	0.85 (0.62–1.16)*	0.14
<b>Oral cavity and pharyngeal combined</b>	Cancer Prevention Study II (mortality) [47]	>4 cups/day vs. no coffee/tea	299	0.58 (0.37–0.92)*	0.01
	Miyagi Cohort Study [48]	≥1 cup/day vs. never	48	0.35 (0.16–0.77)*	0.009
	Norwegian cohort [50]	≥7 cups/day vs. ≤2 cups/day ≥5 cups/day vs. <5 cups/day	33 M, 12 W	M: 0.5 W: 0.7	-
<b>Pharyngeal</b>	NIH-AARP [46]	>3 vs. <1 cups/day	177	1.23 (0.75–2.01)*	0.34
<b>Laryngeal</b>	NIH-AARP [46]	>3 vs. <1 cups/day	306	1.01 (0.71–1.44)*	0.95
<b>Head and neck</b>	Prostate, Lung, Colorectal, Ovarian cancer screening trial [49]	Per 1 cup/day	145	0.99 (0.91–1.09)*	
<b>Upper aerodigestive tract</b>	Miyagi Cohort Study [48]	≥1 cup/day vs. never	157	0.51 (0.33–0.77)*	0.002
	Hawaiian Prospective UADT Study M [51]	≥5 cups/week vs. ≤1 cup/week	92	1.44 (0.63–3.32)	0.441

\* Hazard ratios



One study [47] investigated oral and pharyngeal cancer mortality combined. In this study, inverse associations were noted across the smoking status groups; these were statistically significant for never smokers (HR 0.36 (95% CI 0.23–0.58)) and current smokers (HR 0.64 (95% CI 0.50–0.81)) but not former smokers. Significant inverse associations were observed across the strata of alcohol use (non-drinkers: HR 0.70 (95% CI 0.54–0.92), light drinkers: HR 0.45 (95% CI 0.33–0.61), moderate or heavy drinkers: HR 0.56 (95% CI 0.42–0.75)).

One study [48] reported higher coffee consumption was associated with significantly lower risk of upper aerodigestive tract cancers in current alcohol drinkers (HR 0.49 (95% CI: 0.31–0.77)) and in current smokers (HR 0.49 (95% CI 0.30–0.79)).

Most of the evidence available in the 2005 SLR came from case-control studies. In categorical analyses of ten case-control studies, two reported statistically significant inverse associations; the other eight studies reported non-significant associations. No meta-analysis was conducted. Two cohort studies on oral cavity and pharyngeal cancer combined and on upper aerodigestive tract cancer were identified in the 2005 SLR; no significant associations were observed.

### Published pooled analyses and meta-analyses

A published pooled analysis [52] of nine case-control studies reported significant inverse associations for coffee and oral cavity and pharyngeal cancers combined, oral cavity cancer, and oro- and hypo-pharyngeal cancers combined. No significant association was observed for laryngeal cancer (see **Table 7**).

**Table 7: Summary of published pooled analysis of cancers of the mouth, pharynx and larynx, case-control studies – coffee\***

Analysis		Increment	OR (95% CI)	No. Studies	No. Cases
<b>Galeone, 2010 [52]</b>	Oral cavity and pharyngeal combined	Per 1 cup/day	0.96 (0.94–0.98)	9	3,745
	Oral cavity		0.96 (0.92–0.99)		1,130
	Oro- and hypo-pharyngeal		0.95 (0.93–0.98)		2,023
	Laryngeal		0.99 (0.95–1.04)		1,178

\* Results shown are for caffeinated coffee.

The Panel is aware that in May 2016, after the systematic literature review on which this Report is based was completed, the IARC published a paper on the carcinogenicity of coffee, mate and very hot beverages. Based on evidence, largely related to oesophageal cancer risk, they concluded that drinking very hot (greater than 65 degrees centigrade) beverages was probably carcinogenic in humans [44]. Overall coffee drinking was evaluated as unclassifiable as to its carcinogenicity to humans.

## Mechanisms

The biological mechanisms specifically linking coffee consumption to reduced risk of cancers of the mouth, pharynx and larynx are unclear. Coffee drinking provides exposure to a range of biologically active compounds, many of which have been demonstrated to target pathways associated with carcinogenesis in a variety of tissues. For example, phenolic phytochemicals such as the antioxidants caffeic acid and chlorogenic acid have both been shown to inhibit DNA methylation in vitro [53, 54]. Coffee is also a source of natural diterpenes, such as cafestol and kahweol, which have been shown to induce apoptosis and to have anti-oxidative and anti-inflammatory effects [55, 56]. However, there is a paucity of experimental data on the effects of coffee and its constituent compounds specifically on cancers of the mouth, pharynx and larynx.

### CUP Panel's conclusion:

The evidence for consumption of coffee was too limited to produce meta-analyses for each of the cancers. There were some inconsistencies in the evidence, but the individual dose-response analyses in some newly identified cohort studies showed a significant decreased risk with increased coffee consumption. The inverse association was observed in never smokers in two newly identified studies and was significant in one of these. A published pooled analysis of case-control studies reported significant inverse associations for coffee and oral cavity and pharyngeal cancers combined, oral cavity cancer, and oro- and hypo-pharyngeal cancers combined. There is evidence of plausible mechanisms in humans. The CUP Panel concluded the following:

**The evidence suggesting that greater consumption of coffee decreases the risk of cancers of the mouth, pharynx and larynx is limited.**

## 7.5 Alcoholic drinks

*(Also see CUP Mouth, Pharynx and Larynx SLR 2016: Section 3.7)*

Dose-response meta-analyses in this section include studies reporting on incidence and/or mortality.

### Oral cavity cancer

The CUP identified ten new or updated studies (11 new publications) [57–67], giving a total of 12 studies (14 publications) reviewing total alcohol (as ethanol) and oral cancer (for a full list of references, see CUP Mouth, Pharynx and Larynx SLR 2016 Tables 8 and 9).

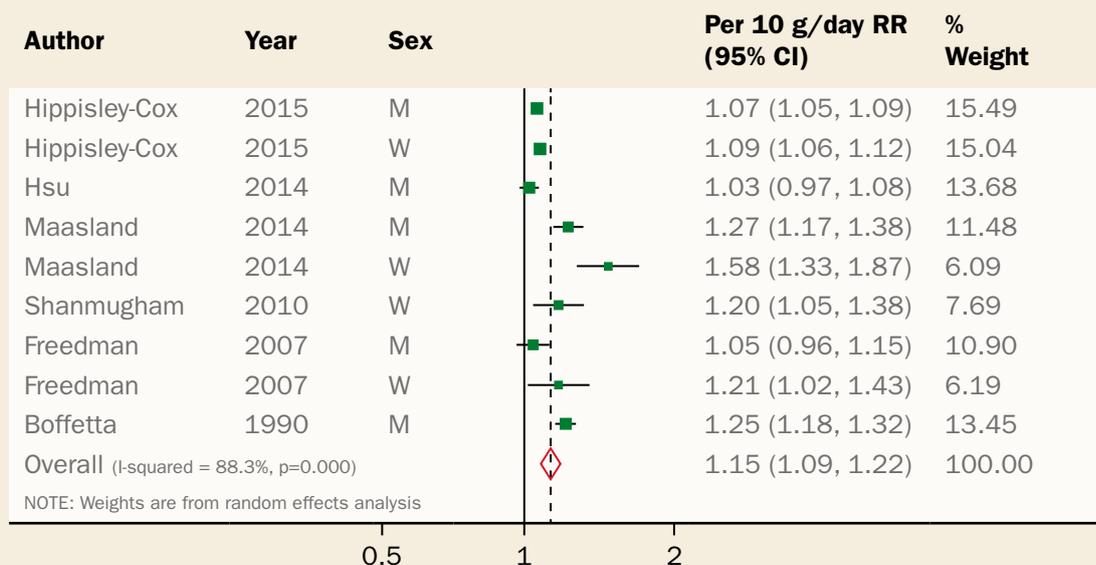


All ten studies reporting on oral cavity cancer incidence reported positive associations, six of which were significant, when comparing the highest and lowest levels of alcohol intake. Five studies did not adjust for smoking [63–66, 68]. Both studies reporting on oral cancer mortality reported significant increased risk when comparing the highest and lowest levels of alcohol intake. (See CUP Mouth, Pharynx and Larynx SLR 2016 Figure 7).

Six studies were included in the dose-response meta-analysis, which showed a statistically significant 15 per cent increased risk per 10 grams of alcohol per day (RR 1.15 (95% CI 1.09–1.22); see **Figure 1**; CUP Mouth, Pharynx and Larynx SLR 2016 Figure 8). High heterogeneity was observed ( $I^2 = 88\%$ ).

There was evidence of small study bias with Egger’s test ( $p = 0.04$ ; see CUP Mouth, Pharynx and Larynx SLR 2016 Figure 10). Visual inspection of the funnel plot showed three outliers [59, 60, 69]. All studies included in the dose-response analysis were adjusted for smoking.

**Figure 1. Dose-response meta-analysis of alcohol (as ethanol) and oral cavity cancer, per 10 grams per day**



When stratified by sex, significant positive associations were observed in both men and women (RR 1.13 (95% CI 1.04–1.22) and RR 1.24 (95% CI 1.07–1.45) respectively), although high heterogeneity persisted (see CUP Mouth, Pharynx and Larynx SLR 2016 Figure 9).

Interactions with smoking were investigated in four studies [60, 61, 64, 67], with positive associations tending to be seen in smokers. In one study [60], a significant positive association was seen in both never smokers (RR 4.16 (95% CI 1.82–9.52)) as well as in those who smoked (RR 3.54 (95% CI 1.66–7.52)).

One study [61] reported a significant increased risk of oral cancer in women with high levels of alcohol consumption ( $\geq 30$  g/day) and low folate status ( $< 350$   $\mu\text{g}/\text{day}$ ) when compared with non-drinkers with low folate intake (RR 3.36 (95% CI 1.57–7.20); p-interaction = 0.02). No significant association was observed when women with high alcohol and high folate intake were compared with non-drinkers with high folate intake.

### Published pooled analyses and meta-analyses

A pooled analysis of 15 case-control studies [70] reported positive associations, which were significant in men only when comparing consumption of 5–10 drinks per day to less than 1 drink per day and oral cavity cancer risk (see **Table 8**).

**Table 8: Summary of CUP 2016 meta-analysis and published pooled analysis of case-control studies, oral cavity cancer – alcohol**

Analysis	Increment/ Contrast	RR (95% CI)	I <sup>2</sup> /P trend	No. Studies	No. Cases
<b>CUP Mouth, Pharynx and Larynx SLR 2016</b>	Per 10 g/day	1.15 (1.09–1.22)	88%	6	5,617
<b>Lubin 2011 [70]</b>	5–10 drinks/ day vs. 0.01–0.9 drinks/day	M	<0.01	15	1,333
		W	<0.01		456

### Oral cavity and pharyngeal cancers combined

The CUP identified nine new studies (nine publications) [65, 66, 71–77], giving a total of ten studies (ten publications) reviewing total alcohol (as ethanol) and oral cavity and pharyngeal cancers combined (for a full list of references, see CUP Mouth, Pharynx and Larynx SLR 2016 Tables 12 and 13).

All five studies reporting on combined oral cavity and pharyngeal cancers incidence showed significant positive associations when comparing the highest and lowest categories of alcohol intake (two studies did not adjust for smoking [65, 66]). All three studies reporting on oral cavity and pharyngeal cancers mortality showed positive associations, two of which were significant, when comparing the highest and lowest categories of alcohol intake (see CUP Mouth, Pharynx and Larynx SLR 2016 Figure 12).

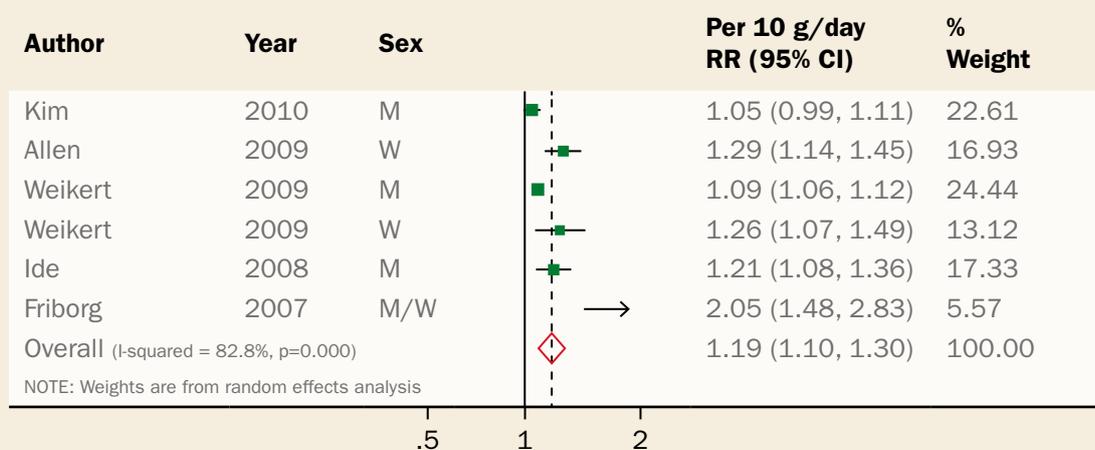
Five studies were included in the dose-response meta-analysis, which showed a statistically significant 19 per cent increased risk per 10 grams of alcohol per day (RR 1.19 (95% CI 1.10–1.30); see **Figure 2**, CUP Mouth, Pharynx and Larynx SLR 2016 Figure 13). High heterogeneity was observed ( $I^2 = 83\%$ ), mainly explained by a strong association reported in one study [75]. There was evidence of small study bias with Egger’s test ( $p = 0.04$ ). Visual inspection of the funnel plot showed asymmetry, with two studies [72, 75] reporting an association stronger than expected (see CUP Mouth,

Pharynx and Larynx SLR 2016 Figure 15). All the studies included in the dose-response analysis were adjusted for smoking.

Significant positive associations were observed when stratified by sex (RR 1.09 (95% CI 1.04–1.15) for men and RR 1.28 (95% CI 1.16–1.41) for women; see CUP Mouth, Pharynx and Larynx SLR 2016 Figure 14).

One study was not included in any of the CUP analyses owing to lack of required data [78].

**Figure 2. Dose-response meta-analysis of alcohol (as ethanol) and oral cavity and pharyngeal cancers combined, per 10 grams per day**



Several studies stratified by smoking status and alcohol consumption. In one study of cancer mortality in men [74], a significant increased risk was observed for those who were smokers and drinkers compared with never smokers and never drinkers (RR 3.3 (95% CI 1.1–9.6)). No significant association was observed for drinkers and never smokers compared with never smokers and never drinkers (RR 1.0 (95% CI 0.3–3.3)). In another study [75], compared with non-smokers and non-drinkers, significant increased risks of oral cavity and pharyngeal cancers combined were observed in people who drank more than seven drinks per week, in people with less than 39 years of smoking (RR 4.9 (95% CI 1.3–18.5)) and in those with more than 39 years of smoking (RR 18.4 (95% CI 7.5–14.5)).

## Published pooled analyses and meta-analyses

No published pooled analyses reporting on oral cavity and pharyngeal cancers combined were identified. Results from one meta-analysis of five cohorts [79] were identified in the CUP Mouth, Pharynx and Larynx SLR 2016. Significant positive associations were observed in both moderate and heavy drinkers. Results from the CUP meta-analysis and published meta-analysis are shown in **Table 9**.

**Table 9: Summary of CUP 2016 meta-analysis and published meta-analysis of cohort studies, oral cavity and pharyngeal cancers combined – alcohol**

Analysis	Increment/Contrast	RR (95% CI)	I <sup>2</sup>	No. Studies	No. Cases
<b>CUP Mouth, Pharynx and Larynx SLR 2016</b>	Per 10 g/day	1.19 (1.10–1.30)	83%	5	954
<b>Bagnardi, 2015 [79]</b>	Moderate drinkers (≤50 g/day) vs. non-drinkers	1.25 (1.02–1.53)	16%	5	993
	Heavy drinking (>50 g per day) vs. non-drinker	3.13 (1.59–6.19)	69%	3	

## Pharyngeal cancer

The CUP identified eight new or updated studies (eight new publications) [59, 60, 62–66, 71], giving a total of eight studies (nine publications) reviewing total alcohol (as ethanol) and pharyngeal cancer (for a full list of references, see CUP Mouth, Pharynx and Larynx SLR 2016 Table 15).

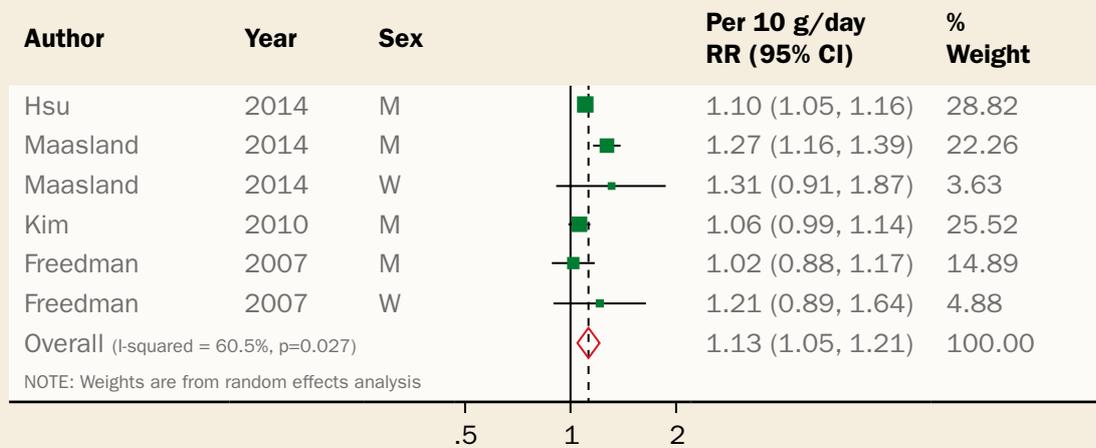
Six studies reported on incidence of pharyngeal cancer. Significant positive associations were observed in four of these studies when comparing the highest and lowest

categories of alcohol intake, two of which did not adjust for smoking [65, 66]. Of the two studies reporting non-significant associations, one did not adjust for smoking [64]. Two studies reported on pharyngeal cancer mortality, both of which reported positive associations when comparing the highest and lowest categories of alcohol intake, one of which was statistically significant [63] (see CUP Mouth, Pharynx and Larynx SLR 2016 Figure 16).

Four studies were included in the dose-response meta-analysis, which showed a statistically significant 13 per cent increased risk per 10 grams of alcohol per day (RR 1.13 (95% CI 1.05–1.21); see **Figure 3**, CUP Mouth, Pharynx and Larynx SLR 2016 Figure 17). High heterogeneity was observed (I<sup>2</sup> = 61%).



**Figure 3. Dose-response meta-analysis of alcohol (as ethanol) and pharyngeal cancer, per 10 grams per day**



When stratified by sex, positive associations were observed in both men and women, significant only in men (RR 1.11 (95% CI 1.03–1.21) and RR 1.25 (95% CI 0.99–1.58) respectively; see CUP Mouth, Pharynx and Larynx SLR 2016 Figure 18).

All the studies included in the dose-response analysis were adjusted for smoking.

Several studies stratified by smoking status and alcohol consumption. One study [60] reported a significant positive association for people who drank more than 15 grams per day and were smokers ( $\geq 20$  cigarettes per day), when compared with people who were both lighter drinkers (0–15 grams per day) and never smokers (RR 16.12 (95% CI 4.31–60.71),  $n = 31$  cases). A significant positive association was also observed for people who drank more than 15 grams per day and were never smokers, when compared with people who were both lighter drinkers (0–15 grams per day) and never smokers (RR 10.18 (95% CI 2.03–51.06),  $n = 3$  cases). No significant interaction was found between categories of alcohol consumption and cigarette smoking (P-interaction = 0.09). For another cohort [64], no significant association was reported between drinkers and tobacco chewers.

### Published pooled analyses and meta-analyses

One published pooled analysis of 15 case-control studies [70] was identified that reported significant positive associations in both men and women when comparing 5–10 drinks per day with less than one drink per day for both oropharyngeal and hypopharyngeal cancer. Results are shown in **Table 10**.

**Table 10: Summary of published pooled analysis of case-control studies, pharyngeal cancer – alcohol**

Analysis	Cancer types	Contrast	OR (95% CI)	P trend	No. Studies	No. Cases
Lubin 2011 [70]	Oropharyngeal cancer	5–10 drinks/day vs. 0.01–0.9 drinks/day			15	
		M	2.82 (1.8–4.3),	<0.01		1,528
	W	7.63 (2.8–21.0)	<0.01	404		
	Hypo-pharyngeal cancer	5–10 drinks/day vs. 0.01–0.9 drinks/day				
	M	7.03 (2.6–19.0),	<0.01	395		
	W	19.6 (1.8–217.0)	<0.01	77		

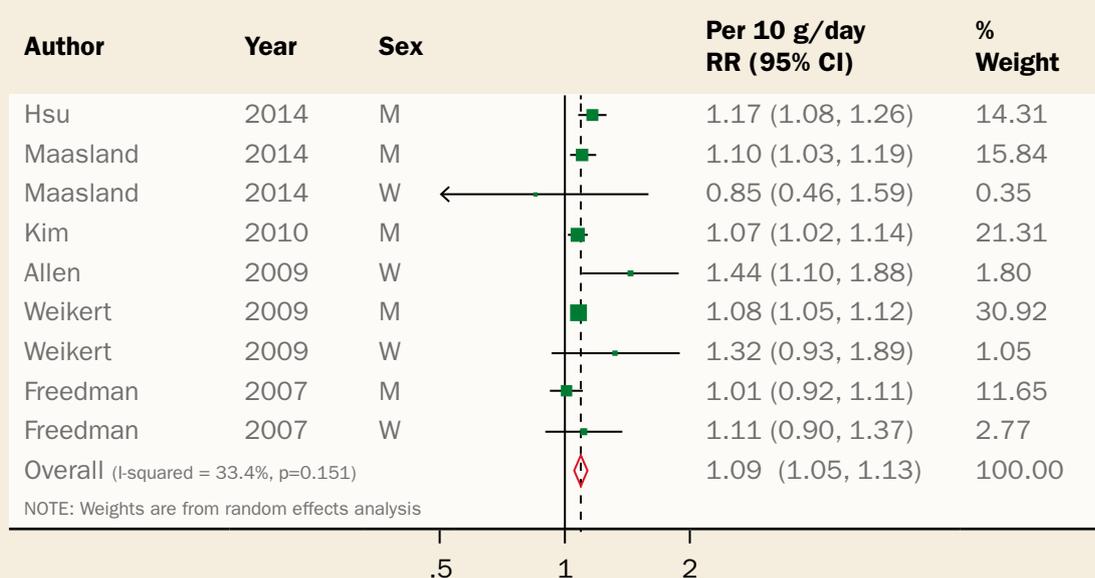
### Laryngeal cancer

The CUP identified 11 new studies (11 publications) [59, 60, 62, 63, 65, 66, 71–73, 76, 80], giving a total of 13 studies (13 publications) reviewing total alcohol (as ethanol) and laryngeal cancer (for a full list of references, see CUP Mouth, Pharynx and Larynx SLR 2016 Tables 18 and 19).

Nine studies reported on laryngeal cancer incidence, comparing the highest and lowest categories of alcohol intake. Eight studies reported positive associations, four of which were significant. One study reported inconsistent results for men and women. Four studies reporting on incidence did not adjust for smoking [65, 66, 68, 80]. Two studies reported on laryngeal cancer mortality; significant positive associations were reported in both studies when comparing the highest and lowest categories of alcohol intake (see CUP Mouth, Pharynx and Larynx SLR 2016 Figure 20).

Six studies were included in the dose-response meta-analysis, which showed a statistically significant 9 per cent increased risk per 10 grams of alcohol per day (RR 1.09 (95% CI 1.05–1.13); see **Figure 4** and CUP Mouth, Pharynx and Larynx SLR 2016 Figure 21). Moderate heterogeneity was observed ( $I^2 = 33\%$ ). All studies included in the dose-response analysis were adjusted for smoking.

**Figure 4. Dose-response meta-analysis of alcohol (as ethanol) and laryngeal cancer, per 10 grams per day**



When stratified by sex, significant positive associations were observed in both men and women (RR 1.09 (95% CI 1.05–1.12) and RR 1.22 (95% CI 1.03–1.45) respectively; see CUP Mouth, Pharynx and Larynx SLR 2016 Figure 22).

One study was not included in any of the CUP analyses owing to lack of required data [78]. Studies on alcoholism found that alcoholics had a significantly increased risk of laryngeal cancer compared with non-alcoholics [63, 65, 68].

One study [60] reported significant positive associations for people who drank (more than 15 g/day) and were smokers ( $\geq 20$  cigarettes per day) when compared with people who were lighter alcohol drinkers (0–15 g/day) and never smokers (RR 5.54 (95% CI 2.15–14.27)). No significant interaction was found between categories of alcohol consumption and cigarette smoking (P-interaction = 0.19).

### Published pooled analyses and meta-analyses

One published pooled analysis of 15 case-control studies [70] and one published meta-analysis [79] of three cohort studies were identified in the CUP 2016 SLR. The pooled analysis reported a significant positive association in men when comparing those who consumed 5–10 drinks per day with those who consumed less than one drink per day (RR 1.89 (95% CI 1.10–3.10),  $n = 1,361$  cases). No significant association was observed in women. The meta-analysis reported no significant associations in light, moderate or heavy drinkers.

## Head and neck cancer

The CUP identified three new studies (three publications) [60, 62, 81], giving a total of three studies (three publications) reviewing total alcohol consumption and head and neck cancer. No meta-analysis was conducted. Significant positive associations were observed in all studies; two studies compared the highest and lowest categories of alcohol intake and one conducted a dose-response meta-analysis. All the studies adjusted for smoking (see CUP Mouth, Pharynx and Larynx SLR 2016 page 105).

In one study [60], in which 506 out of 550 cases were in smokers, a significant positive association was observed in people who drank alcohol ( $\geq 30$  grams of ethanol per day) and smoked ( $\geq 20$  cigarettes per day) compared with those who were both non-drinkers and never smokers (RR 8.28 (95% CI 3.98–17.22),  $n = 80$  cases; P-interaction = 0.03). In another study [81], in which 139 out of 175 cases were smokers, a significant positive association was observed in people who drank ( $\geq 2$  drinks per day) and smoked ( $\geq 20$  cigarettes per day; RR 11.07 (95% CI 5.07–24.14)) compared with those who were non-drinkers and never smokers. No association was observed in drinkers who did not smoke ( $n = 2$  cases) compared with non-drinkers who did not smoke.

## Published pooled analyses and meta-analyses

No pooled analyses or meta-analyses were identified in the CUP Mouth, Pharynx and Larynx SLR 2016.

## Upper aerodigestive tract cancer

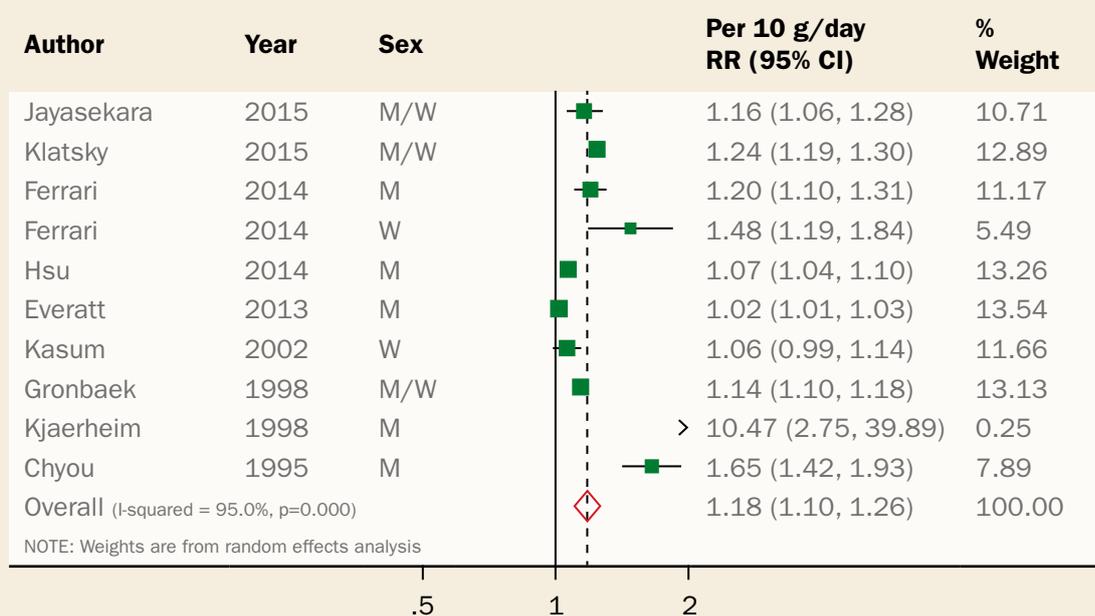
The CUP identified eight new or updated studies (nine publications) [51, 59, 73, 76, 82–86], giving a total of 10 studies (15 publications) reviewing total alcohol (as ethanol) and upper aerodigestive tract cancer (for a full list of references, see CUP Mouth, Pharynx and Larynx SLR 2016 Tables 23 and 24).

Nine studies reported on upper aerodigestive tract cancer incidence, comparing the highest and lowest categories of alcohol intake. All studies reported positive associations, seven of which were significant. One study [86] did not adjust for smoking. One study reported on upper aerodigestive tract cancer mortality and reported a significant positive association when comparing the highest and lowest categories of alcohol intake (see CUP Mouth, Pharynx and Larynx SLR 2016 Figure 25).

Nine studies were included in the dose-response meta-analysis, which showed a statistically significant 18 per cent increased risk per 10 grams of alcohol per day (RR 1.18 (95% CI 1.10–1.26); see **Figure 5** and CUP Mouth, Pharynx and Larynx SLR 2016 Figure 26). High heterogeneity was observed ( $I^2 = 95\%$ ). There was evidence of small study bias with Egger's test ( $p = 0.005$ ). Visual inspection of the funnel plot showed asymmetry, with one small study [87] reporting an association stronger than expected (see CUP Mouth, Pharynx and Larynx SLR 2016 Figure 28).

All studies included in the dose-response analysis were adjusted for age and smoking.

**Figure 5. Dose-response meta-analysis of alcohol (as ethanol) and upper aerodigestive tract cancer, per 10 grams per day**



When stratified by sex, positive associations were in both men and women (RR 1.17 (95% CI 1.08–1.27) and RR 1.19 (95% CI 0.95–1.49) respectively; see CUP Mouth, Pharynx and Larynx SLR 2016 Figure 27).

Three studies looked at interaction with smoking. One study in Taiwan [59] reported a significant increased risk for upper aerodigestive tract cancer in men who chewed betel quid and smoked but never drank alcohol (RR 8.88 (95% CI 6.08–12.98),  $n = 39$ ), and in men who chewed and smoked and also drank alcohol (RR 12.04 (95% CI 7.66–18.93),  $n = 33$ ), compared with men who never chewed, never smoked and never drank ( $n = 30$  cases). A study in Denmark [88] reported no significant interaction of alcohol and tobacco on the risk of upper aerodigestive tract cancers. A study of Hawaiian men [51] reported a significant increased risk estimate for upper aerodigestive tract cancer in men who drank more than 14 ounces per week and were non-smokers (RR 6.5 (95% CI 1.63–25.0),  $n = 6$ ) compared with those who did not drink or smoke ( $n = 3$  cases). For the same comparison, a stronger positive association was observed in men drinking more than 14 ounces per week who were also smokers of more than 20 cigarettes per day (RR 14.35,  $n = 28$  cases (95% CI not reported)).

### Published pooled analyses and meta-analyses

No published pooled analyses were identified. Results from meta-analysis of three cohorts [89] were identified, showing a significant positive association when comparing the highest versus the lowest intakes of alcohol. Results from the CUP meta-analysis and the published meta-analysis are shown in **Table 11**.

**Table 11: Summary of CUP 2016 meta-analysis and published meta-analysis of cohort studies, upper aerodigestive tract cancer – alcohol**

Analysis	Increment/Contrast	RR (95% CI)	I <sup>2</sup>	No. Studies	No. cases
<b>CUP Mouth, Pharynx and Larynx SLR 2016</b>	Per 10 g/day	1.18 (1.10–1.26)	95%	9	1,826
<b>Jayasekara, 2016 [89]</b>	Highest vs. lowest	2.83 (1.73–4.62)	0%	3	595

### Comparison with 2005 systematic literature review

The CUP findings for oral cancer, oral/pharyngeal cancer, pharyngeal cancer, laryngeal cancer, head and neck cancer, and upper aerodigestive tract cancer are similar to those from the 2005 SLR, which showed a significant positive association for cancers of the mouth, pharynx and larynx (RR 1.24 (95% CI 1.18–1.30) per one drink per week). The CUP update includes several more cohort studies and cases as well as more detailed stratified analyses.

### Other alcohol exposures

Dose-response meta-analyses were conducted for beer, wine and spirits and oral, pharyngeal, laryngeal cancer and head and neck cancers separately. The results are summarised in **Table 12** (see CUP Mouth, Pharynx and Larynx SLR 2016 Figures 29, 30 and 31). Significant positive associations were observed for beer and pharyngeal and head and neck cancer and for spirits and head and neck cancer. A weaker and generally inverse, though non-significant, association was observed for wine compared with the other alcohol exposures. All the studies adjusted for smoking, but residual confounding due to different patterns of smoking among drinkers of different types of alcoholic drink cannot be excluded.



**Table 12. Summary of CUP dose-response meta-analyses, per 10 grams per day – other alcohol exposures, by cancer type**

<b>Analysis</b>	<b>Cancer type</b>	<b>RR (95% CI)</b>	<b>I<sup>2</sup> (%)</b>	<b>No. studies</b>
<b>CUP 2016 Beer</b>	Oral cavity	1.14 (0.96–1.36)	74	2
	Pharyngeal	1.12 (1.02–1.24)	0	2
	Laryngeal	1.05 (0.98–1.13)	0	2
	Head and neck	1.09 (1.01–1.18)	49	2
<b>CUP 2016 Wine</b>	Oral cavity	0.90 (0.77–1.06)	18	2
	Pharyngeal	0.99 (0.83–1.17)	0	2
	Laryngeal	0.93 (0.80–1.07)	0	3
	Head and neck	0.92 (0.83–1.02)	0	2
<b>CUP 2016 Spirits</b>	Oral cavity	1.11 (1.02 –1.21)	0	2
	Pharyngeal	1.08 (0.89–1.31)	55	2
	Laryngeal	1.04 (0.96–1.13)	0	2
	Head and neck	1.09 (1.02–1.15)	15	2

### **Published pooled analyses and meta-analyses**

No pooled analyses or meta-analyses have been published on beer, wine or spirits and the risk of cancers of the mouth, pharynx and larynx.

### **Mechanisms**

The precise mechanisms underlying the relationship between alcohol consumption and cancers of the mouth, pharynx and larynx are not completely understood. A large body of experimental evidence has shown that acetaldehyde, the major and most toxic metabolite of alcohol, disrupts DNA synthesis and repair and thus may contribute to a carcinogenic cascade [90, 91]. Higher ethanol consumption also induces oxidative stress through increased production of reactive oxygen species, which are potentially genotoxic [92]. It is hypothesised that alcohol may also function as a solvent for cellular penetration of dietary or environmental (for example, tobacco) carcinogens, or interfere with DNA repair mechanisms [93]. High consumers of alcohol may also have diets that are lacking in essential nutrients, such as folate, rendering target tissues more susceptible to carcinogenic effects of alcohol.

## CUP Panel's conclusions:

The evidence was generally consistent, and dose-response meta-analyses showed a significant increased risk with increasing alcohol consumption. For oral cavity cancer and for oral cavity and pharyngeal cancer combined, a stronger association was observed in women. There was no evidence that the effect varied with the type of alcoholic drink, although there was some evidence of an inverse association for wine that was not statistically significant. All studies included in the dose-response meta-analyses for total alcohol were adjusted for smoking. Tests for interaction were in general not conducted in the studies owing to the low numbers of cases in the groups of non-smokers and non-drinkers. Observations for smoking interactions were variable and the number of cases were limited, but several studies noted that the strength of the association was attenuated in never smokers.

The findings were generally consistent with one pooled analysis of case-control studies and two published meta-analyses of cohorts. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded the following:

**Consumption of alcoholic drinks is a convincing cause of cancers of the mouth, pharynx and larynx.**

## 7.6 Body fatness

(Also see CUP Mouth, Pharynx and Larynx SLR 2016: Sections 8.1.1, 8.2.1 and 8.2.3)

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 between visceral, subcutaneous abdominal, intra-muscular, hepatic and other areas of fat accumulation [94]. In addition, relationships between BMI and smoking-related cancers may be confounded by smoking, which has independent effects on body composition.

### Body mass index

The CUP identified seven new studies (seven publications) [81, 86, 95–99] giving a total of seven studies (seven publications) reviewing BMI and cancers of the mouth, pharynx and larynx. Due to the small numbers of studies for each cancer subtype, no meta-analyses were conducted for the CUP.

### Published pooled analyses and meta-analyses

The CUP identified a published pooled analysis of 20 cohorts [100], which included three of the newly identified studies from the CUP [81, 96, 97]. Statistically significant positive associations were reported for head and neck cancer for never smokers in both the categorical and continuous analyses. A significant increased risk was observed for underweight versus normal weight, but the association became non-significant when



restricted to never smokers, probably reflecting early disease among smokers associated with weight loss. The significant inverse association with BMI amongst current smokers probably reflects confounding by smoking (see section 5.2). The results of the pooled analysis are summarised in **Tables 13 and 14**.

**Table 13. Summary of results from published pooled analysis [100] – BMI and head and neck cancer**

	No. Cases	HR (95% CI) Obese ( $\geq 30.0$ ) vs. 21 to $<23$ kg/m <sup>2</sup>	HR (95% CI) Underweight (15.0 to 20.9) vs. 21.0 to $<23$ kg/m <sup>2</sup>	HR (95% CI) Per 5 kg/m <sup>2</sup>	P trend
<b>All</b>	3,760	0.85 (0.76–0.96)	1.28 (1.11–1.46)	0.94 (0.90–0.98)	0.003
<b>Never smokers</b>	796	1.40 (1.08–1.81)	1.17 (0.85–1.61)	1.15 (1.06–1.24)	0.0006
<b>Former smokers</b>	1,508	0.96 (0.79–1.18)	1.24 (0.94–1.63)	0.99 (0.93–1.06)	0.79
<b>Current smokers</b>	1,367	0.58 (0.47–0.72)	1.30 (1.08–1.57)	0.76 (0.71–0.82)	$<0.0001$

**Table 14. Summary of results in never smokers from published pooled analysis [100] – BMI and cancers of the mouth, pharynx and larynx, by cancer type**

Cancer type	Increment	No. Cases	HR (95% CI)	P trend
<b>Oral cavity</b>	per 5 kg/m <sup>2</sup> BMI in never smokers	298	1.10 (0.97–1.25)	0.14
<b>Oral cavity and pharyngeal (not otherwise specified) combined</b>		93	1.36 (1.11–1.66)	0.003
<b>Oropharyngeal</b>		241	0.98 (0.84–1.14)	0.77
<b>Hypo-pharyngeal</b>		22	0.96 (0.55–1.67)	0.88
<b>Laryngeal</b>		142	1.42 (1.19–1.70)	0.0001

Three studies identified in the CUP were included in the pooled analysis [81, 96, 97]. Results of the four studies identified in the CUP but not included in the pooled analysis are summarised in **Table 15** (for more details, see CUP Mouth, Pharynx and Larynx SLR 2016, section 8.1.1).

**Table 15. Summary of studies identified in the CUP but not included in the pooled analysis – BMI**

Cancer type	Study	Contrast/ increment	No. Cases	RR (95% CI)	P trend
Oral cavity	CPRD [95]	Per 5 kg/m <sup>2</sup>	7,976	0.81 (0.74–0.89)	-
		All Never smokers		1.07 (0.91–1.26)	
Laryngeal	Cohort from Sweden, M [98]	Obese vs. normal weight	263	0.94 (0.57–1.56)	>0.35
Oropharyngolar- yngaeal	JAMS, M [86]	≥23.2 kg/m <sup>2</sup> vs. ≤18.9 kg/m <sup>2</sup>	29	0.31 (0.08–1.11)*	-
Upper aerodigestive tract	Cohort from China, M [99]	Per 5 kg/m <sup>2</sup>	706	1.06 (0.83–1.37)	-
		15 –<23.5 kg/m <sup>2</sup> 23.5 –<35 kg/m <sup>2</sup>		0.87 (0.51–1.50)	
	JAMS, M [86]	≥23.2 kg/m <sup>2</sup> vs. ≤18.9 kg/m <sup>2</sup>	52	0.28 (0.09–0.85)*	-

\* Not adjusted for smoking.

### Other published pooled analyses and meta-analyses

One additional pooled analysis of cohort studies [101] and one pooled analysis of case-control studies [70] were identified on BMI and the risk of cancers of the mouth, pharynx and larynx.

The pooled analysis of cohort studies [101] (39 studies) reported significant inverse associations for oropharyngolar- yngaeal and upper aerodigestive tract mortality. No significant associations were observed when results were stratified by BMI group [101] (see CUP Mouth, Pharynx and Larynx SLR 2016 Tables 30 and 32).

The pooled analysis of 15 case-control studies [70] reported inverse associations (many significant) for oral cavity, oropharyngeal, hypo-pharyngeal and laryngeal cancer when comparing high versus low BMI categories. When comparing underweight (BMI <18.5 kg/m<sup>2</sup>) with normal BMI, positive associations (mostly significant) were observed for oral cavity, oropharyngeal, hypo-pharyngeal and laryngeal cancer; for more details, see CUP Mouth, Pharynx and Larynx SLR 2016 section 8.1.1).

Results from the CUP meta-analysis and published pooled analyses are shown in **Table 16**.

**Table 16: Summary of other published pooled analyses of cancers of the mouth, pharynx and larynx – BMI**

Analysis	Cancer type	Contrast/ Increment	RR (95% CI)	I <sup>2</sup> /P trend	No. Studies	No. Cases	
<b>Parr, 2010 [101]</b>	Oropharyngeal and laryngeal combined, mortality	Per 5 kg/m <sup>2</sup>	0.66 (0.46–0.95)*	-	39 cohort studies	159	
	Upper aerodigestive tract, mortality	Per 5 kg/m <sup>2</sup>	0.78 (0.62–0.98)*	-		388	
<b>Lubin, 2011 [70]</b>	Oral cavity	BMI ≥ 35 kg/m <sup>2</sup> vs. BMI 18.5– 24.9 kg/m <sup>2</sup>			15 Case- control studies		
		M	0.65 (0.4–1.1)**	<0.01		1,516	
	W	0.92 (0.5–1.6)**	<0.01	925			
	Oropharyngeal	BMI ≥ 35 kg/m <sup>2</sup> vs. BMI 18.5– 24.9 kg/m <sup>2</sup>					
		M	0.48 (0.3–0.7)**	<0.01		1,733	
	W	0.35 (0.2–0.7)**	<0.01	564			
	Hypo-pharyngeal	BMI 30.0–34.9 kg/m <sup>2</sup> vs. BMI<18.5 kg/m <sup>2</sup>					
		M	0.24 (0.1–0.5)**	0.10		412	
	W	0.24 (0.1–0.8)**	<0.01	96			
	Laryngeal	BMI ≥ 35 kg/m <sup>2</sup> vs. BMI 18.5– 24.9 kg/m <sup>2</sup>					
M		0.77 (0.4–1.4)**	<0.01	1,503			
W	0.27 (0.1–0.8)**	<0.01	237				

\* Hazard ratios \*\* Odds ratios

No cohort studies relating to body fatness were identified in the 2005 SLR. For BMI, a meta-analysis of seven case-control studies was conducted and showed a significant inverse association (RR 0.89 (95% CI 0.85–0.92) per 1 kg/m<sup>2</sup>). The CUP SLR included several new studies as well as information from two published pooled analyses of cohort studies and one published pooled analysis of case-control studies.

### Waist circumference

The CUP identified one new study (one publication) [96], giving a total of one study reviewing waist circumference and cancers of the mouth, pharynx and larynx. This study reported significant positive associations in categorical analyses for oral cavity (RR 2.00 (95% CI 1.24–3.23)) and for head and neck cancer (RR 1.42 (95% CI 1.04–1.93)). No significant associations were reported for oro- and hypo-pharyngeal cancers combined (RR 1.53 (95% CI 0.72–3.25)) or for laryngeal cancer (RR 0.98 (95% CI 0.58–1.66)). This study included adjustment for smoking.

### Published pooled analyses and meta-analyses

One published pooled analysis of 20 cohorts was identified [100], which included the study identified in the CUP Mouth, Pharynx and Larynx SLR 2016. Significant positive associations were observed in never smokers for both the categorical and continuous analyses for head and neck cancer, and in the continuous analyses in never smokers for oral cavity cancer (see **Table 17**; CUP Mouth, Pharynx and Larynx SLR 2016 Table 33).

**Table 17. Summary of results for waist circumference from published pooled analysis [100] – head and neck cancer**

	No. Cases	HR (95% CI) highest vs. lowest	RR (95% CI) Per 5 cm*	P trend
<b>All</b>	1,931	1.08 (0.93–1.25)	1.04 (1.03–1.05)	<0.0001
<b>Never smokers</b>	441	1.51 (1.09–2.08)	1.07 (1.01–1.14)	0.022
<b>Former smokers</b>	706	1.21 (0.94–1.55)	1.06 (1.01–1.11)	0.01
<b>Current smokers</b>	745	0.80 (0.62–1.04)	1.04 (1.02–1.05)	<0.0001

\* controlling for BMI



## Waist-hip ratio

The CUP identified one new study (one publication) [96], giving a total of one study reviewing waist-hip ratio and cancers of the mouth, pharynx and larynx. This study reported a significant positive association in categorical analyses for oral cavity cancer (RR 1.58 (95% CI 1.10–2.28)). No significant associations were reported for oro- and hypo-pharyngeal cancers combined (RR 0.77 (95% CI 0.43–1.37)), for laryngeal cancer (RR 1.01 (95% CI 0.67–1.52)), or for head and neck cancer (RR 1.13 (95% CI 0.89–1.43)). This study included adjustment for smoking.

## Published pooled analyses and meta-analyses

One published pooled analysis of 20 cohorts was identified [100], which included the study identified in the CUP Mouth, Pharynx and Larynx SLR 2016. For head and neck cancer, significant positive associations were observed in both the categorical and continuous analyses, but statistical significance was lost when the analyses were restricted to never smokers. For continuous analyses in never smokers, a significant positive association for oral cavity cancer and a significant inverse association for oropharyngeal cancer were reported (see **Table 18**; CUP Mouth, Pharynx and Larynx SLR 2016 Table 35). For the same comparison, non-significant positive associations were observed for oral and pharyngeal (not otherwise specified) combined, oropharyngeal, hypo-pharyngeal, and laryngeal cancer.

**Table 18. Summary of results from published pooled analysis (NCI consortium [100]) reviewing waist-hip ratio and head and neck cancer**

	No. Cases	RR (95% CI) Highest vs. lowest	RR (95% CI) Per 0.1 unit	P trend
<b>All</b>	1,677	1.30 (1.12–1.50)	1.06 (1.04–1.09)	<0.0001
<b>Never smokers</b>	382	1.23 (0.89–1.69)	1.08 (0.96–1.22)	0.2013
<b>Former smokers</b>	577	1.25 (0.98–1.59)	1.10 (1.01–1.20)	0.0351
<b>Current smokers</b>	685	1.38 (1.09–1.75)	1.06 (1.02–1.10)	0.0017

## Mechanisms

Specific mechanisms to support the relationship between body fatness and mouth, pharynx and larynx cancers have not been proposed to date. However, greater body fatness is associated with metabolic and endocrine abnormalities such as hyperinsulinemia and elevated levels of bioavailable oestrogen and in other tissues, insulin and oestrogen have been shown to stimulate mitogenesis [102] and inhibit apoptosis [103, 104] leading to enhanced cell proliferation. Obesity has also been shown to stimulate the inflammatory response and thus may also promote tumorigenesis [105]. Further research is needed on the mechanisms underlying the link between obesity and cancers of the mouth, pharynx and larynx.

### CUP Panel's conclusions:

For BMI and waist circumference, one pooled analysis of 20 cohort studies reported significant positive associations for head and neck cancer for never smokers in both the categorical and continuous analyses. The increased risk observed for underweight compared to normal weight may be due to pre-existing disease. There were few individual cohort studies reviewing each cancer published, so no meta-analysis was possible. There is evidence of plausible mechanisms. The CUP Panel concluded the following:

**Greater body fatness (marked by BMI, waist circumference and waist-to-hip ratio) is probably a cause of cancers of the mouth, pharynx and larynx.**

## 7.7 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 matrix on **page 8**.

The evidence for fruits and foods containing carotenoids, previously judged as 'probable decreases risk' in the Second Expert Report [1], was less consistent, and the Panel could not draw any conclusions about the updated evidence.

Evidence for the following exposures, previously judged as 'limited – no conclusion' in the Second Expert Report, remains unchanged after updating the analyses with new data identified in the CUP Mouth, Pharynx and Larynx SLR 2016: cereals (grains) and their products; starchy roots, tubers, and plantains; dietary fibre; pulses (legumes); meat; poultry; fish; eggs; milk and dairy products; total fat; animal fats; plant oils; tea; frying, grilling (broiling) and barbecuing (charbroiling); protein; vitamin A; retinol; thiamin; riboflavin; niacin; folate; vitamin C; vitamin E; calcium; iron; selenium and 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: red meat, processed meat, soft drinks, fruit juices, vitamin D, cooked food acrylamide, other patterns of diet (not related to healthy dietary indices), physical activity, and height.

## 8. Comparison with the Second Expert Report

Throughout this review of the evidence for cancers of the mouth, pharynx and larynx, new evidence specific to cancer types was included that was not available for the Second Expert Report [1]. Much of the new evidence was on body fatness and coffee, which were both previously judged as 'limited – no conclusion' in the Second Expert Report. The updated evidence on non-starchy vegetables, fruits, and foods containing carotenoids was less strong than in the Second Expert Report. The increase in the amount and quality of the evidence has highlighted the need for further research, particularly in non-smokers.

## 9. Conclusions

### Convincing evidence

**Alcoholic drinks:** Consumption of alcoholic drinks is a convincing cause of cancers of the mouth, pharynx and larynx.

### Probable evidence

**Body fatness:** Greater body fatness (marked by BMI, waist circumference and waist-hip ratio) is probably a cause of cancers of the mouth, pharynx and larynx.

### Limited – suggestive evidence

**Non-starchy vegetables:** The evidence suggesting that greater consumption of non-starchy vegetables decreases the risk of cancers of the mouth, pharynx and larynx is limited.

**Healthy dietary patterns:** The evidence suggesting that healthy dietary patterns (marked by greater healthy dietary index scores) decrease the risk of cancers of the mouth, pharynx and larynx is limited.

**Coffee:** The evidence suggesting that greater consumption of coffee decreases the risk of cancers of the mouth, pharynx and larynx is limited.

**Mate:** The evidence suggesting that greater consumption of mate, as consumed in South America, increases the risk of cancers of the mouth, pharynx and larynx 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 62.

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

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

# Acknowledgements

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## Abbreviations

<b>ACS</b>	American Cancer Society
<b>AICR</b>	American Institute for Cancer Research
<b>aMED</b>	alternative Mediterranean Diet
<b>BMI</b>	body mass index
<b>CI</b>	confidence interval
<b>CUP</b>	Continuous Update Project
<b>DNA</b>	deoxyribonucleic acid
<b>HEI-2005</b>	Healthy Eating Index-2005
<b>HPV</b>	human papilloma virus
<b>HR</b>	hazard ratio
<b>IARC</b>	International Agency for Research on Cancer
<b><i>n</i></b>	number of cases
<b>NCI</b>	National Cancer Institute
<b>NIH-AARP</b>	National Institute of Health Retired Person Diet and Health Study
<b>OR</b>	odds ratio
<b>RR</b>	relative risk
<b>SLR</b>	systematic literature review
<b>WCRF</b>	World Cancer Research Fund

## Glossary

### **Adjustment**

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

### **aMED (Mediterranean) score**

The aMed score is a modified Mediterranean Diet score that includes consumption of vegetables (excluding potatoes), legumes, fruit, nuts, whole grains, fish, ratio of monounsaturated to saturated fat, red and processed meat and alcohol.

### **American Cancer Society Guidelines score**

The ACS score includes maintaining a healthy body weight, engaging in moderate to vigorous physical activity, making healthy dietary choices and limiting alcohol intake.

### **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**).

### **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 the study type or analysis (see **selection bias**).

### **Body mass index (BMI)**

Body weight expressed in kilograms divided by the square of height expressed in metres (BMI = kg/m<sup>2</sup>). Provides an indirect measure of body fatness.

### **Carcinogen**

Any substance or agent capable of causing cancer.

### **Case-control study**

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

### **Chronic**

Describing a 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) and 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, tobacco 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 with 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 association of tobacco smoking and 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/confounding factors**

A variable that is associated with both 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 tobacco 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.

### **Diet, nutrition and physical activity**

In the CUP, these three exposures are taken to mean the following: **diet**, the food and drink people habitually consume, including dietary patterns and individual constituent nutrients as well as other constituents, which may or may not have physiological bioactivity in humans; **nutrition**, the process by which organisms obtain energy and nutrients (in the form of food and drink) for growth, maintenance and repair, often marked by nutritional biomarkers and body composition (encompassing body fatness); and **physical activity**, any body movement produced by skeletal muscles that requires energy expenditure.

**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.

**Dose–response**

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

**Exposure**

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

**Free radicals**

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

**Hazard ratio**

A measure of a risk of an outcome (for example, death) associated with an exposure of interest. Hazard ratios do not reflect a time unit of the study, but represent instantaneous risk over the study time period. Hazard ratios are often treated as a ratio of death probabilities.

**Head and neck cancer**

Includes cancers of the oral cavity, pharynx and larynx, nasal cavity and salivary glands.

**Healthy Eating Index-2005**

The HEI-2005 score assesses concordance with 2005 Dietary Guidelines for Americans and includes intakes of plant foods, milk, meat, saturated fat, sodium, energy from solid fat, alcohol and added sugar.

**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 an average annual gross national income per capita of US\$12,236 or more in 2016. This term is more precise than and used in preference to 'economically developed countries'.

**Hyperinsulinemia**

High blood concentrations of insulin.

**Immune response**

The production of antibodies or specialised cells, for instance, 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. Inflammation may be acute (such as in response to infection or injury) or chronic (as part of several conditions, including obesity).

**Insulin-like growth factor (IGF)**

Polypeptides with high sequence similarity to insulin that are part of a complex system that cells use to communicate with their physiologic environment. IGF-I is the main mediator of growth hormone activity.

**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 an average annual gross national income per capita of US\$1,005 or less in 2016. 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**

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

**Mutation**

A permanent change in 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-communicable diseases (NCDs)**

Diseases which are not transmissible from person to person. The most common NCDs are cancer, cardiovascular disease, chronic respiratory diseases, and diabetes.

**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.

**Oral cavity cancer**

Cancers of the oral cavity include malignancies of the lips, tongue, inside lining of the cheeks (buccal mucosa), floor of the mouth, gums (gingiva), palate and salivary glands. Most studies in this report excluded cancer of the lip and salivary glands.

**Pathogenesis**

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

**Pharyngeal cancer**

Cancer of the pharynx includes tumours of the nasopharynx, the oropharynx (including tonsils) and the hypopharynx. Studies on nasopharyngeal cancer were not reviewed for this report.

**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**

Meats transformed through salting, curing, fermentation, smoking or other processes to enhance flavour or improve preservation (see [Exposures: Meat, fish and dairy products](#)).

**Prostaglandins**

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

**Relative risk (RR)**

The ratio of the rate of an outcome (for example, 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 power**

The power of any test of statistical significance, defined as the probability that it will reject a false null hypothesis.

**Statistical significance**

The probability that any observed result has or has not occurred by chance. Conventionally, a probability of less than five per cent ( $p < 0.05$ ) that a study result has occurred by chance is considered 'statistically significant' (see **confidence interval**).

**Systematic literature review (SLR)**

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

**Upper aerodigestive tract cancer**

Cancers of the upper aerodigestive tract (UADT) include head and neck cancers and oesophageal cancers.

**Waist-hip ratio (WHR)**

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

**WCRF/AICR score**

The WCRF/AICR score was constructed on the basis of the WCRF/AICR recommendations on weight management, physical activity, foods and drinks that promote weight gain, plant foods, animal foods, alcoholic drinks and breastfeeding (in women).

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## Appendix: Criteria for grading evidence for cancer prevention

See also [Judging the evidence](#), section 8.

Adapted from Chapter 3 of the 2007 Second Expert Report. Listed here are the criteria agreed by the Panel that were necessary to support the judgements shown in the matrices. The grades shown here are ‘convincing’, ‘probable’, ‘limited – suggestive’, ‘limited – no conclusion’, and ‘substantial effect on risk unlikely’. In effect, the criteria define these terms.

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

### **CONVINCING (STRONG EVIDENCE)**

Evidence strong enough to support a judgement of a convincing causal (or protective) relationship, which justifies making recommendations designed to reduce the risk of cancer. The evidence is robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates.

All of the following are generally required:

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

## **PROBABLE (STRONG EVIDENCE)**

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

All of the following are generally required:

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

## **LIMITED – SUGGESTIVE**

Evidence that is too limited to permit a probable or convincing causal judgement but is suggestive of a direction of effect. The evidence may be limited in amount or by methodological flaws but shows a generally consistent direction of effect. This judgement is broad and includes associations where the evidence falls only slightly below that required to infer a probably causal association through to those where the evidence is only marginally strong enough to identify a direction of effect. This judgement is very rarely sufficient to justify recommendations designed to reduce the risk of cancer; any exceptions to this require special, explicit justification.

All of the following are generally required:

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

## **LIMITED – NO CONCLUSION**

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

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

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

### **SUBSTANTIAL EFFECT ON RISK UNLIKELY (STRONG EVIDENCE)**

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

All of the following are generally required:

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

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

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

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

## **SPECIAL UPGRADING FACTORS**

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

Factors may include the following:

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

## Our Cancer Prevention Recommendations

### **Be a healthy weight**

Keep your weight within the healthy range and avoid weight gain in adult life

### **Be physically active**

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

### **Eat a diet rich in wholegrains, vegetables, fruit and beans**

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

### **Limit consumption of ‘fast foods’ and other processed foods high in fat, starches or sugars**

Limiting these foods helps control calorie intake and maintain a healthy weight

### **Limit consumption of red and processed meat**

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

### **Limit consumption of sugar sweetened drinks**

Drink mostly water and unsweetened drinks

### **Limit alcohol consumption**

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

### **Do not use supplements for cancer prevention**

Aim to meet nutritional needs through diet alone

### **For mothers: breastfeed your baby, if you can**

Breastfeeding is good for both mother and baby

### **After a cancer diagnosis: follow our Recommendations, if you can**

Check with your health professional what is right for you

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

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

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