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Cancer  
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**CUP** Continuous  
Update  
Project

Analysing research on cancer  
prevention and survival



# Non-alcoholic drinks and the risk of cancer

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 World Cancer Research Fund 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. [Non-alcoholic drinks and the risk of cancer](#) 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 the Third Expert Report

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## Key

See **Glossary** for definitions of terms highlighted in *italics*.

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

## Executive summary

### Background and context

In this part of the Third Expert Report from our Continuous Update Project (CUP) – the world’s largest source of scientific research on cancer prevention and survivorship through diet, nutrition and physical activity – we analyse global research on how consuming non-alcoholic drinks affects the risk of developing cancer.<sup>1</sup> This includes new studies as well as those included in the 2007 Second Expert Report, Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective [1].

Non-alcoholic drinks discussed in this Third Expert Report include water as well as hot drinks such as mate, coffee and tea. Consumption of sugar-sweetened drinks is discussed elsewhere as a cause of weight gain, overweight and *obesity* (see [Energy balance and body fatness](#)).

Access to clean drinking water is essential to health. However, drinking water can be contaminated by harmful substances, including arsenic. Agricultural, mining and industrial practices can contaminate water with arsenic. Arsenic can also occur naturally in water due to natural geological deposits or volcanic activity. The International Agency for Research on Cancer (IARC) has judged drinking water contaminated with arsenic to be carcinogenic to humans (Group 1). The primary regions where high concentrations of arsenic have been measured in drinking water include large areas of Bangladesh, China and West Bengal (India).

Mate is an infusion (brewed using boiling water), which is drunk almost exclusively in parts of South America. It is a type of herbal tea prepared from the dried leaves of the plant

*Ilex paraguariensis*. Mate is traditionally drunk scalding hot through a metal straw. Drinking very hot beverages such as mate is graded by IARC as probably carcinogenic to humans (Group 2A).

Coffee and tea are also infusions and are the two most commonly consumed hot drinks. Coffee is made from ground, roasted coffee beans – the dried seeds of coffee plant berries. Many different qualities, varieties and forms of coffee are available. These include arabica and robusta coffee beans, roasted or green coffee beans, as well as instant coffee and soluble powders made from finely ground coffee beans. There are also various different methods of preparing coffee depending on culture and personal preference. Decaffeinated coffee is produced by various processes, using water, organic solvents or steam, or by interfering with the expression of the gene coding for *caffeine*.

Tea is specifically the infusion of the dried leaves of the plant *Camellia sinensis*. Green tea, which is often preferred in China, is made from leaves that have first been cooked, pressed and dried. To produce black tea, the fresh leaves are withered, rolled repeatedly, allowed to turn deep brown and then air-dried until they are dark in colour.

Evidence on whether consumption of milk affects the risk of cancer is considered along with the evidence on other dairy products (see [Exposures: Meat, fish and dairy products](#)) and is not presented in this part of the Third Expert Report.

### How the research was conducted

The global scientific research on diet, nutrition, physical activity and the risk of cancer was systematically gathered and analysed, and then independently assessed by a panel of leading international scientists to draw conclusions about which factors increase or decrease the risk of developing the disease (see [Judging the evidence](#)).

<sup>1</sup> Cancers at the following sites are reviewed in the CUP: mouth, pharynx and larynx; nasopharynx; oesophagus; lung; stomach; pancreas; gallbladder; liver; colorectum; breast; ovary; endometrium; cervix; prostate; kidney; bladder; and skin.

This Third Expert Report presents in detail findings where the Panel considered the evidence strong enough to make cancer prevention recommendations (where appropriate), and highlights areas where more research is required (where the evidence is suggestive of a causal or protective relationship but is limited in terms of amount or by methodological flaws). Evidence that was considered by the Panel, but was too limited to draw firm conclusions, is not covered in detail in this Third Expert Report.

## Findings

There is **strong evidence** that consuming:

- **arsenic in drinking water increases** the risk of lung cancer, bladder cancer and skin cancer (unspecified)
- **mate, as drunk scalding hot in the traditional style in South America, increases** the risk of oesophageal squamous cell carcinoma
- **coffee decreases** the risk of liver cancer and endometrial cancer

The evidence shows that, in general, the more scalding hot mate people drink, the higher the risk of oesophageal squamous cell carcinoma. In contrast, the evidence shows that, in general, the more coffee people drink, the lower the risk of some cancers. For arsenic in drinking water, conclusions can be drawn only for the levels of arsenic that were investigated.

The Panel uses such strong evidence, where possible, when making Recommendations designed to reduce the risk of developing cancer. However, Recommendations have not been made about coffee as there are still too many unanswered questions (see [Recommendations and public health and policy implications](#), Section 3: Issues of inadequate information – Coffee).

A global recommendation about consumption of mate has not been made as this type of non-alcoholic drink is consumed only in specific parts of the world. Nevertheless, the Panel advises that mate should not be consumed scalding hot in the traditional style (see [Recommendations and public health and policy implications](#), Section 3: Issues relevant only in specific parts of the world – Mate).

There is no global recommendation for arsenic in drinking water, as individuals do not have the power to control whether or not their local water supply is contaminated. However, contamination of water supplies with arsenic is a public health issue. Authorities should ensure that safe water supplies are available when such contamination occurs. Water contaminated with arsenic should not be consumed (see [Recommendations and public health and policy implications](#), Section 3: Issues of public health significance – Arsenic in drinking water).

There is also other evidence on non-alcoholic drinks that is limited (either in amount or by methodological flaws), but is suggestive of an increased or decreased risk of some cancers. Further research is required and the Panel has not used this evidence to make recommendations.

## Recommendations

Our Cancer Prevention Recommendations – for preventing cancer in general – include maintaining a healthy weight, being physically active and eating a healthy diet. The advice is to limit consumption of sugar-sweetened drinks. The Recommendations are listed on the inside back cover.

## 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)

# 1. Non-alcoholic drinks and the risk of cancer: a summary matrix

NON-ALCOHOLIC DRINKS AND THE RISK OF CANCER					
WCRF/AICR GRADING		DECREASES RISK		INCREASES RISK	
		Exposure	Cancer site	Exposure	Cancer site
STRONG EVIDENCE	Convincing			Arsenic in drinking water <sup>1</sup>	Lung 2017
	Probable	Coffee	Liver 2015 Endometrium 2013 <sup>2</sup>	Arsenic in drinking water <sup>1</sup>	Bladder 2015 Skin (unspecified) 2017
				Mate <sup>3</sup>	Oesophagus (squamous cell carcinoma) 2016
LIMITED EVIDENCE	Limited – suggestive	Coffee	Mouth, pharynx and larynx 2018 Skin (basal cell carcinoma [men and women] / malignant melanoma [women]) 2017	Arsenic in drinking water <sup>1</sup>	Kidney 2015
				Mate <sup>3</sup>	Mouth, pharynx and larynx 2018
		Tea	Bladder 2015		
STRONG EVIDENCE	Substantial effect on risk unlikely	None identified			

- 1 The International Agency for Research on Cancer (IARC) has judged arsenic and inorganic arsenic compounds to be carcinogenic to humans (Group 1) [2]. Drinking water contaminated with arsenic is also classed separately as a human carcinogen (Group 1) [2]. Water can become contaminated by arsenic as a result of natural deposits present in the earth, volcanic activity, or agricultural, mining and industrial practices. Countries particularly affected by higher levels of arsenic in drinking water include Bangladesh, China and India.
- 2 The effect of coffee on the risk of endometrial cancer is observed with both caffeinated and decaffeinated coffee so cannot be attributed to caffeine.
- 3 Mate, an aqueous infusion prepared from dried leaves of the plant *Ilex paraguariensis*, is traditionally drunk scalding hot through a metal straw in parts of South America. In 2016, an IARC Working Group declared that drinking very hot beverages, including mate, above 65°C is probably carcinogenic to humans (Group 2A) [3].

Consumption of sugar-sweetened drinks is discussed elsewhere as a cause of weight gain, overweight and *obesity* (see [Energy balance and body fatness](#)); however, there is no direct link to cancer risk. There is no strong evidence in humans to suggest that artificially sweetened drinks with minimal *energy* content, such as diet sodas, are a cause of cancer.

Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, for which the

year given is the year the systematic literature review was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

## Definitions of World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) grading criteria

**‘Strong evidence’:** Evidence is strong enough to support a judgement of a convincing or probable causal (or protective) relationship and generally justify making public health recommendations.

**‘Convincing’:** Evidence is 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.

**‘Probable’:** Evidence is strong enough to support a judgement of a probable causal (or protective) relationship, which generally justifies goals and recommendations designed to reduce the risk of cancer.

**‘Limited evidence’:** Evidence is inadequate to support a probable or convincing causal (or protective) relationship. The evidence may be limited in amount or by methodological flaws, or there may be too much inconsistency in the direction of effect (or a combination), to justify making specific public health recommendations.

**‘Limited – suggestive’:** Evidence is inadequate to permit a judgement of a probable or convincing causal (or protective) relationship, but is suggestive of a direction of effect. The evidence may be limited in amount, or methodological flaws, but shows a generally consistent direction of effect. This judgement generally does not justify making recommendations.

**‘Limited – no conclusion’:** There is enough evidence to warrant Panel consideration, but it is so limited that no conclusion can be made. The evidence may be limited in amount, by inconsistency in the direction of effect, by methodological flaws, or any combination of these. Evidence that was judged to be ‘limited – no conclusion’ is mentioned in Evidence and judgements (**Section 5**).

**‘Substantial effect on risk unlikely’:** Evidence is strong enough to support a judgement that a particular lifestyle factor relating to diet, nutrition, body fatness or physical activity is unlikely to have a substantial causal (or protective) relation to a cancer outcome.

For further information and to see the full grading criteria agreed by the Panel to support the judgements shown in the matrices, please see **Appendix 1**.

The next section describes which evidence the Panel used when making Recommendations.



## 2. Summary of Panel judgements

The conclusions drawn by the CUP Panel are based on the evidence from both epidemiological and mechanistic studies relating specific non-alcoholic drinks to the risk of development of particular cancer types. Each conclusion on the likely causal relationship between a non-alcoholic drink and a 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 Cancer Prevention Recommendations are based on a synthesis of all these separate conclusions, as well as other relevant evidence, and can be found at the end of this Third Expert Report.

The evidence shows that, in general, the more scalding hot mate people drink, the higher the risk of oesophageal squamous cell carcinoma. In contrast, the evidence shows that, in general, the more coffee people drink, the lower the risk of some cancers. For arsenic in drinking water, conclusions can be drawn only for the levels of arsenic that were investigated.

The Panel uses such strong evidence, where possible, when making Recommendations designed to reduce the risk of developing cancer. However, Recommendations have not been made about coffee, as there are still too many unanswered questions. Across the globe, coffee is consumed in different ways. Before a general recommendation on cancer prevention can be made, more research is needed to improve understanding of how the volume and regularity of consumption, type of coffee, and style of preparation and serving (many people add milk and sugar) affect the risk of cancer (see [Recommendations and public health and policy implications](#), Section 3: Issues of inadequate information – Coffee).

### The CUP Panel concluded:

#### STRONG EVIDENCE

##### Convincing

- **Increased risk**
  - **Arsenic in drinking water<sup>4</sup>:** Consumption of arsenic in drinking water is a convincing cause of lung cancer.

##### Probable

- **Decreased risk**
  - **Coffee:** Consumption of coffee probably protects against liver cancer and endometrial cancer<sup>2</sup>.
- **Increased risk**
  - **Arsenic in drinking water<sup>4</sup>:** Consumption of arsenic in drinking water is probably a cause of bladder cancer and skin cancer (unspecified).
  - **Mate<sup>3</sup>:** Regular consumption of mate, as drunk scalding hot in the traditional style in South America, is probably a cause of oesophageal *squamous cell carcinoma*.

A global recommendation about consumption of mate has not been made as this type of non-alcoholic drink is consumed only in specific parts of the world. Nevertheless, the Panel advises that mate should not be consumed scalding hot in the traditional style (see [Recommendations and public health and policy implications](#), Section 3: Issues relevant only in specific parts of the world – Mate).

There is no global recommendation for arsenic in drinking water, as individuals do not have the power to control whether or not their local water supply is contaminated. However, contamination of water supplies with arsenic is a public health issue. Authorities should ensure that safe water supplies are available when such contamination occurs. Water contaminated with arsenic should

not be consumed (see [Recommendations and public health and policy implications](#), Section 3: Issues of public health significance – Arsenic in drinking water).

## LIMITED EVIDENCE

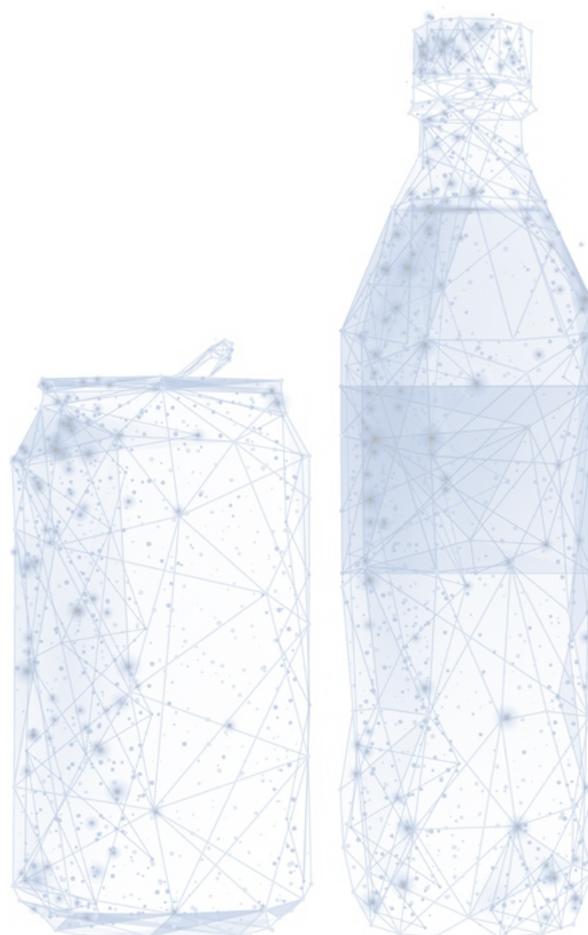
### Limited – suggestive

- **Decreased risk**
  - **Coffee:** The evidence suggesting that consumption of coffee decreases the risk of cancers of the mouth, pharynx and larynx and of skin cancer (*basal cell carcinoma*, and malignant *melanoma* in women) is limited.
  - **Tea:** The evidence suggesting that consumption of tea decreases the risk of bladder cancer is limited.
- **Increased risk**
  - **Arsenic in drinking water<sup>1</sup>:** The evidence suggesting that consumption of arsenic in drinking water increases the risk of kidney cancer is limited.
  - **Mate<sup>3</sup>:** The evidence suggesting that consumption of mate, as drunk scalding hot in the traditional style in South America, increases the risk of cancers of the mouth, pharynx and larynx is limited.

The Panel did not use the limited evidence when making Recommendations designed to reduce the risk of developing cancer. Further research is required into these possible effects on the risk of cancer.

In addition, consumption of sugar-sweetened drinks is a cause of weight gain, overweight and obesity (see [Energy balance and body fatness](#)). There is no strong evidence in humans to suggest that sugar-sweetened drinks or artificially sweetened drinks with minimal energy content, such as diet sodas, are a cause of cancer.

See Definitions of WCRF/AICR grading criteria (**Section 1**: Non-alcoholic drinks and the risk of cancer: a summary matrix) for explanations of what the Panel means by ‘strong evidence’, ‘convincing’, ‘probable’, ‘limited evidence’ and ‘limited – suggestive’.



<sup>1</sup> The International Agency for Research on Cancer (IARC) has judged arsenic and inorganic arsenic compounds to be carcinogenic to humans (Group 1) [2]. Drinking water contaminated with arsenic is also classed separately as a human carcinogen (Group 1) [2]. Water can become contaminated by arsenic as a result of natural deposits present in the earth, volcanic activity, or agricultural, mining and industrial practices. Countries particularly affected by higher levels of arsenic in drinking water include Bangladesh, China and India.

<sup>2</sup> The effect of coffee on the risk of endometrial cancer is observed with both caffeinated and decaffeinated coffee so cannot be attributed to caffeine.

<sup>3</sup> Mate, an aqueous infusion prepared from dried leaves of the plant *Ilex paraguariensis*, is traditionally drunk scalding hot through a metal straw in parts of South America. In 2016, an IARC Working Group declared that drinking very hot beverages, including mate, above 65°C is probably carcinogenic to humans (Group 2A) [3].

### 3. Definitions and patterns

Non-alcoholic drinks discussed in this Third Expert Report include water as well as hot drinks such as mate, coffee and tea. In addition, consumption of sugar-sweetened drinks is discussed elsewhere as a cause of weight gain, overweight and *obesity* (see [Energy balance and body fatness](#)).

#### 3.1 Arsenic in drinking water

People cannot live without drinking water, which is vital for the normal functioning of the body (see **Box 1** and **Box 2**).

Agricultural, mining and industrial practices can contaminate water with arsenic. Arsenic can also occur naturally in water due to natural geological deposits or volcanic activity. Inorganic arsenic (arsenate or arsenite) is the form that predominantly contaminates drinking water.

The primary regions where high concentrations of arsenic have been measured in drinking water include large areas of Bangladesh, China and West Bengal (India), and smaller areas of Argentina, Australia, Chile, Mexico, Taiwan, the USA and Vietnam [2]. In many of these regions, the drinking water comes from groundwater naturally contaminated by arsenic-rich geological formations [2].

#### Box 1: People's need for drinking water

Access to clean drinking water is essential to health.

The water content of the body is around 70 per cent: men tend to have a higher proportion of water in their bodies than women, because women naturally have more body fat, which has minimal amounts of water.

Drinking water can contribute to intakes of essential elements, such as *calcium*, iron and copper, depending on its origin and the piping materials used. It can also provide fluoride either naturally or by fluoridation.

Even mild dehydration (water loss of one to two per cent of body weight) can produce symptoms such as a dry mouth and headaches. Stopping all fluid intake causes death in days, with the exact length of time depending on the health of the individual and environmental conditions such as temperature and humidity.

Approximately 80 per cent of water intake comes from drinks; food provides the other 20 per cent.

Environmental conditions, health, activity levels and other factors determine the amount of water needed, and there is no international recommendation for daily consumption. The Institute of Medicine in the USA recommends 2.7 litres per day total water for women and 3.7 litres for men [4]. Public Health England advises to drink six to eight glasses of fluid a day, around 1.2 litres, to prevent dehydration [5]. Water, lower-fat milk and sugar-free drinks including tea and coffee all count.

Adults produce an average of around 1.5 litres of urine each day though this varies with intake; the body has highly effective mechanisms for conserving water when intakes are low or losses high. An additional litre of water is lost through breathing, from the skin by evaporation or sweating, and in the faeces.

## Box 2: Access to drinking water

Water comes from rain, springs, freshwater lakes, rivers, reservoirs and aquifers accessed by wells. (An aquifer is an underground layer of permeable, water-bearing rock, which acts as a reservoir for groundwater [6].)

More than half of the world's population has access to drinking water through taps in their homes or outside. Around the world, people also drink ground, rain and river waters, often without first treating the water to make sure it is safe.

About 844 million people lack even a basic drinking-water service, including 159 million who are dependent on surface water [7]. Globally, at least 2 billion people use a drinking water source contaminated with faeces [7].

Most people who do not have access to clean drinking water live in Asia, sub-Saharan Africa and some parts of Latin America. In many *low-income countries*, access to clean water is limited for low-income segments of the population and people living in rural areas.

Consumption of bottled water has also increased over the past 5 years; a total of 391 billion litres of bottled water was estimated to be consumed around the world in 2017 [8]. In developed countries, bottled water is generally consumed for taste and convenience, but in developing countries consumption is often due to unreliable and unsafe municipal water supplies [9]. Bottled water can cost between 240 and 10,000 times more than tap water, which may limit consumption of the bottled form in low-income countries where access to clean drinking water can be difficult [9].

In some areas of Japan, Mexico, Thailand, Brazil, Australia and the USA, mining, smelting and other industrial activities have contributed to elevated concentrations of arsenic in local water sources [2].

The International Agency for Research on Cancer (IARC) has judged arsenic and inorganic arsenic compounds to be carcinogenic to humans (Group 1) [2]. Drinking water contaminated with arsenic is also classed separately as a human carcinogen (Group 1) [2].

The joint Food and Agriculture Organization of the United Nations and World Health Organization Expert Committee on Food Additives has set a provisional tolerable weekly intake of 0.015 milligrams of arsenic per kilogram of body weight [10].

The quality of tap water is regulated in most countries according to World Health Organization (WHO) guidelines for drinking water, which cover tap water and bottled water [11]. Provisional WHO guidelines recommend that levels of arsenic in drinking water should not exceed 10 micrograms per litre [11].

Levels of arsenic in affected areas may range from tens to hundreds, or even thousands, of micrograms per litre. In unaffected areas, levels are typically less than 10 micrograms per litre [11–13].



## 3.2 Mate

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### 3.2.1 Definitions and sources

Mate, a type of herbal tea, is an aqueous infusion prepared from the dried leaves of the plant *Ilex paraguariensis* [3, 14].

Mate is traditionally drunk scalding hot (above 65°C) from a gourd through a metal straw following repeated addition of almost boiling water to the infusion [14, 15]. The metal straw is often kept resting in the mouth, rather like the stem of a tobacco pipe [14]. A gourd is a container made from the hollowed and dried skin of a gourd – a fleshy, typically large fruit with a hard skin.

In 2016, an IARC Working Group declared that drinking very hot beverages, including mate, above 65°C is probably carcinogenic to humans (Group 2A) [3].

Mate can also be consumed warm or cold [3]. In 2016, the IARC Working Group concluded that drinking mate that is not very hot is unclassifiable in terms of its carcinogenicity in humans (Group 3) [3].

### 3.2.2 Composition

Mate has stimulant properties similar to coffee and tea. Like coffee and tea, it contains methylxanthines (including caffeine, theophylline and theobromine) and chlorogenic acids [14].

### 3.2.3 Consumption patterns

Mate, as traditionally prepared, is drunk almost exclusively in parts of South America, more specifically in Argentina, Bolivia, Brazil, Chile, Ecuador, Paraguay and Uruguay [14]. To a lesser extent, mate is also consumed in the Middle East, Europe and North America [3].

Mate is drunk in Germany as a cold beverage [14]. It is also drunk chilled in Paraguay and southwestern Brazil, with milk or water and sugar [14]. Burnt sugar, lemon or lime juice are sometimes added instead of milk [14].

## 3.3 Coffee and tea

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There are many similarities between coffee and tea, and therefore information on these drinks is presented together here to avoid unnecessary duplication. More information is presented on coffee, since the Panel judged some of the evidence on the relationship between drinking coffee and the risk of cancer to be strong, whereas all evidence on drinking tea was judged to be limited (see **Section 1**).

### 3.3.1 Definitions and sources

Coffee and tea are the two most commonly consumed hot drinks. Like mate, coffee and tea are infusions (brewed using boiling water) that are usually drunk hot, sometimes very hot.

#### 3.3.1.1 Coffee

The coffee plant is a large bush native to Ethiopia, now cultivated in many hot and humid climates. Coffee is made from ground, roasted coffee beans – the dried seeds of coffee plant berries. The beans naturally contain *caffeine*.

Many different qualities, varieties and forms of coffee are available. These include arabica and robusta coffee beans, roasted or green coffee beans, as well as instant coffee and soluble powders made from finely ground coffee beans [16]. There are also various different methods of preparing coffee depending on culture and personal preference. Coffee may be boiled, infused, filtered, percolated, vaporised under pressure (espresso) or dissolved in water in the form of ‘instant’ granules [14]. Instant coffee comprises the soluble solids derived from dried, double-brewed coffee.

Decaffeinated coffee is produced by various processes, using water, organic solvents or steam, or by interfering with the expression of the gene coding for caffeine.

### 3.3.1.2 Tea

Although many herbal infusions are known as teas, tea is specifically the infusion of the dried leaves of the plant *Camellia sinensis*. Green tea, which is often preferred in China, is made from leaves that have first been cooked, pressed and dried. To produce black tea, the fresh leaves are withered, rolled repeatedly, allowed to turn deep brown and then air-dried until they are dark in colour.

Iced teas are popular in the USA and some other countries: these are sugared and considered as soft drinks in the CUP. Herbal and other teas, which may also be consumed cold, are not considered in the CUP.

### 3.3.2 Composition of coffee

Coffee (like tea) contains various *antioxidants* and phenolic compounds, some of which have been shown to have anti-cancer properties in laboratory experiments [17]. It also contains *caffeine*. There is more caffeine in tea leaves than in coffee beans, but brewed coffee contains more caffeine than brewed tea. Caffeine is bioactive, quickening reaction times, relieving fatigue and stimulating the cardiovascular and central nervous systems.

When drunk without adding milk, cream, sugar, lemon or honey, coffee (like tea) contains no *energy*, trivial amounts of some *micronutrients* and the *bioactive constituents* mentioned above. When consumed frequently, coffee (like tea) may be a substantial dietary source of some of these bioactive constituents. Thus, coffee is a major source of some dietary antioxidants in the USA [18].

The chemical properties of coffee can differ depending on the kind of coffee bush it comes from, how it is processed and roasted, and how it is prepared for drinking [15].

### 3.3.3 Consumption patterns for coffee

After water, coffee and tea are the most commonly consumed drinks around the world.

Today, people are consuming more coffee than ever before [16]. As the middle classes of the developing world continue to swell, as their incomes rise and coffee remains affordable, the luxury of the occasional coffee has become a daily habit in an ever-growing number of countries [16].

Annual output has now reached almost nine million tonnes, one million tonnes more than a decade ago [16]. The gross value of production of green coffee now exceeds US\$16 billion, and its export value reached US\$24 billion in 2012 [16].

Most coffee is produced in developing countries [16]. The top five coffee-producing countries are Brazil, Vietnam, Indonesia, Colombia and India [16].

Globally, around 1.16 kilograms per capita per year of coffee and 0.85 kilograms per capita per year of tea are available for consumption. Consumption of coffee is highest in Oceania (4.42 kilograms per capita per year in 2013), followed by Europe (4.08 kilograms per capita per year in 2013) and the Americas (2.94 kilograms per capita per year in 2013), with less than 1 kilogram per capita per year for Asia and Africa.



## 4. Interpretation of the evidence

### 4.1 General

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

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

### 4.2 Specific

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Specific factors that the Panel bears in mind when interpreting evidence on whether consuming non-alcoholic drinks increases or decreases the risk of developing cancer are described below. Factors that are relevant to specific cancers are presented here too.

#### 4.2.1 Exposures

##### 4.2.1.1 Arsenic in drinking water, mate, coffee and tea

###### **Arsenic in drinking water**

**Definitions.** Agricultural, mining and industrial practices can contaminate water with arsenic. Arsenic can also occur naturally in water due to natural geological deposits or volcanic activity. Inorganic arsenic (arsenate or arsenite) is the form that predominantly contaminates drinking water. The primary regions where high concentrations of arsenic have been measured in drinking water include large areas of Bangladesh, China and West Bengal (India).

The International Agency for Research on Cancer (IARC) has judged arsenic and inorganic arsenic compounds to be carcinogenic to humans (Group 1) [2]. Drinking water contaminated with arsenic is also classed separately as a human *carcinogen* (Group 1) [2].



**Study design.** For skin cancer, there was a limited number of *cohort studies* so the evidence for arsenic in drinking water was supplemented by an IARC review of *case-control* and *ecological studies*. Case-control studies are subject to recall bias, which can occur when participants recall past dietary intake or physical activity. It is differentially affected by whether they are cases or controls in the study. Participants may have different behaviours than non-participants, and such differences may vary between cases and controls. Ecological studies are designed to explore relationships between environmental factors and disease among populations rather than people. These studies have the advantage of being able to compare very wide ranges of exposure that occur worldwide; however, they do not take account of confounding factors and hence it is difficult to identify potentially casual factors (see [Judging the evidence](#)).

###### **Mate**

**Definitions.** 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 [14]. Mate is consumed mainly in South America, specifically Argentina, Bolivia, Brazil, Chile, Ecuador, Paraguay and Uruguay. These countries correspond to areas of higher incidence of oesophageal *squamous cell carcinoma* within South America [19].

In 2016, an IARC Working Group declared that drinking very hot beverages, including mate, above 65°C is probably carcinogenic to humans (Group 2A) [3]. Mate can also be consumed warm or cold [3]. In 2016, the IARC Working Group concluded that drinking mate that is not very hot is unclassifiable in terms of its carcinogenicity in humans (Group 3) [3].

**Study design.** For mouth, pharynx and larynx cancer and oesophageal cancer (squamous cell carcinoma), there was a lack of *cohort studies* so the evidence for mate came from *case-control studies*. Case-control studies are subject to recall bias, which can occur when participants recall past dietary intake or physical activity. It is differentially affected by whether they are cases or controls in the study. Participants may have different behaviours than non-participants, and such differences may vary between cases and controls (see [Judging the evidence](#)).

### Tea and Coffee

**Definitions.** Coffee is made from ground, roasted coffee beans – the dried seeds of coffee plant berries. The beans naturally contain *caffeine*. Although many herbal infusions are known as teas, tea is specifically the infusion of the dried leaves of the plant *Camellia sinensis*.

Different types of tea and coffee are consumed in different cultures. The ways in which these two drinks are prepared and drunk also vary. For coffee, this includes the degree of roasting, the methods of brewing (which determine the strength and composition) and the different substances added. Similarly, tea may be consumed with or without milk and in different strengths.

Associations between non-alcoholic drinks and the risk of certain cancers that are seen in one population but not another may therefore reflect specific aspects of the drinks as prepared and consumed in that population.

**Confounding.** When interpreting the results of epidemiological studies of all types of drink, confounding effects of other habits should be considered. For example, people who consume large quantities of tea or coffee may also be people who smoke tobacco and drink alcohol.

People who are physically active often consume more liquid than those who are not. Physical activity is therefore a confounder of the relationship between the volume of fluid drunk and cancer risk, but may not be adequately adjusted for.

**Measurement.** Fluid intake is best estimated from urine collection, but this is rarely done. In addition, urine collection gives a measure of overall fluid intake, from all of the drinks and foods that a person consumes. Estimates of the level of consumption of individual drinks – such as mate, coffee and tea – are usually made from food frequency questionnaires.

For arsenic in drinking water, the arsenic content of water is usually based on measurements of arsenic levels in well water. Cumulative exposure to arsenic is usually calculated using people's own reports of the amount of water they consume and the number of years they have lived in the area. There are several cohort studies available; however, for skin cancer the evidence comes mainly from *case-control* and *ecological studies*.

**Reporting bias.** Many people think that drinking large amounts of coffee is unhealthy [20], so studies that depend on self-reporting may disproportionately underestimate consumption.

### 4.2.2 Cancers

The information provided here on 'Other established causes' of cancer is based on judgements made by the International Agency for Research on Cancer (IARC) [21], unless a different reference is given. For more

information on findings from the CUP on diet, nutrition, physical activity and the risk of cancer, see other parts of this [Third Expert Report](#).

#### 4.2.2.1 Mouth, pharynx and larynx

**Definitions.** Organs and tissues in the mouth include the lips, tongue, inside lining of the cheeks (buccal mucosa), floor of the mouth, gums (gingiva), palate and salivary glands. The pharynx (throat) is the muscular cavity leading from the nose and mouth to the larynx (voice box), which includes the vocal cords. Cancers of the mouth, pharynx and larynx are types of head and neck cancer.

**Classification.** In sections of this Third Expert Report where the evidence for cancers of the mouth, pharynx and larynx is discussed, 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 together with oesophageal cancer. Nasopharyngeal cancer is reviewed separately from other types of head and neck cancer in the CUP.

**Other established causes.** Other established causes of cancers of the mouth, pharynx and larynx include the following:



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

Smoking tobacco (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. Smoking tobacco is estimated to account for 42 per cent of deaths worldwide from cancers of the mouth and oropharynx (the part of the throat just behind the mouth) [22].



#### **Infection**

Some human papilloma viruses (HPV) are carcinogenic, and oral infection with these types is a risk factor for mouth, pharynx, and larynx cancer. The prevalence of carcinogenic HPV types in oropharyngeal cancer is estimated to be about 70 per cent in Europe and North America [23].



#### **Environmental exposures**

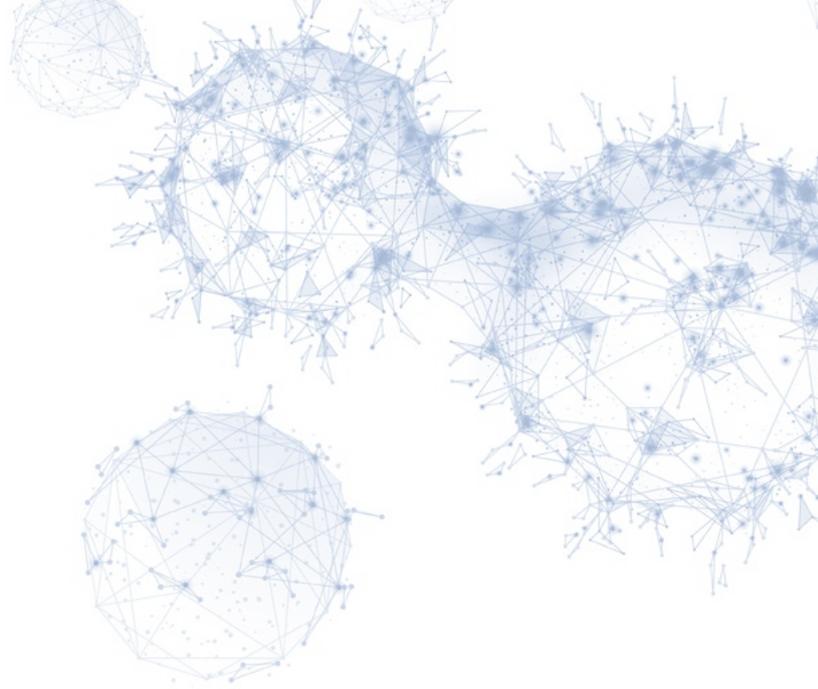
*Exposure* to asbestos increases the risk of laryngeal cancer.

**Confounding.** Smoking tobacco is a potential *confounder*. People who smoke tend to have less healthy diets, less physically active ways of life and lower body weight than people who do not smoke. Therefore a central task in assessing the results of studies is to evaluate the degree to which observed associations in people who smoke may be due to residual confounding effects from smoking tobacco; that is, not a direct result of the exposure examined.

The characteristics of people developing cancers of the mouth, pharynx and larynx are changing. Increasingly, a large cohort of younger people who are infected with the carcinogenic HPV types 16 or 18, and who do not smoke and do not consume a large amount of alcohol, are now developing these cancers. As far as possible, the conclusions for mouth, pharynx and larynx take account of this changing natural history. However, most published epidemiological studies reviewing diet and cancers of the mouth, pharynx and larynx have not included data on HPV infection.

#### 4.2.2.2 Oesophagus

**Definition.** The oesophagus is the muscular tube through which food passes from the pharynx to the stomach.



**Classification.** The oesophagus is lined over most of its length by squamous *epithelial* cells, where *squamous cell carcinomas* arise. The portion just above the gastric junction (where the oesophagus meets the stomach) is lined by columnar epithelial cells, from which *adenocarcinomas* arise. The oesophageal-gastric junction and gastric cardia are also lined with columnar epithelial cells.

Globally, squamous cell carcinoma is the most common type and accounts for 87 per cent of cases [24]; however, the proportion of adenocarcinomas is increasing dramatically in high-income countries.

Squamous cell carcinomas have different geographic and temporal trends from adenocarcinomas and follow a different disease path. Different approaches or definitions in different studies are potential sources of *heterogeneity*.

**Other established causes.** Other established causes of oesophageal cancer include the following:



### Smoking tobacco, chewing tobacco and snuff

Smoking tobacco (or use of smokeless tobacco, sometimes called ‘chewing tobacco’ or ‘snuff’) is a cause of oesophageal cancer. *Squamous cell carcinoma* is more strongly associated with smoking tobacco than *adenocarcinoma* [25]. It is estimated that 42 per cent of deaths from oesophageal cancer are attributable to tobacco use [22].



### Infection

Between 12 and 39 per cent of oesophageal squamous cell carcinomas worldwide are related to carcinogenic types of HPV [26]. *Helicobacter pylori* infection, an established risk factor for *non-cardia stomach cancer*, is associated with a 41 to 43 per cent decreased risk of oesophageal adenocarcinoma [27, 28].



### Other diseases

Risk of adenocarcinoma of the oesophagus is increased by gastro-oesophageal reflux disease, a common condition in which stomach acid damages the lining of the lower part of the oesophagus [25]. This type of oesophageal cancer is also increased by a rare condition, oesophageal achalasia, in which the valve at the end of the oesophagus called the ‘cardia’ fails to open and food gets stuck in the oesophagus [25].



### Family history

Tylosis A, a late-onset, inherited *familial* disease characterised by thickening of the skin of the palms and soles (hyperkeratosis), is associated with a 25 per cent lifetime incidence of oesophageal squamous cell carcinoma [29].

**Confounding.** Smoking tobacco is a potential *confounder*. People who smoke tend to have less healthy diets, less physically active ways of life and lower body weight than those who do not smoke. Therefore a central task in assessing the results of studies is to evaluate the degree to which observed associations in people who smoke may be due to residual confounding effects from smoking tobacco; that is, not a direct result of the *exposure* examined.

For more detailed information on *adjustments* made in CUP analyses on mate, see Evidence and judgements (**Section 5.2.1**).

#### 4.2.2.3 Lung

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

**Classification.** The two main types of lung cancer are small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC).

NSCLC accounts for 85 to 90 per cent of all cases of lung cancer and has three major subtypes: squamous cell carcinoma, *adenocarcinoma* and *large-cell carcinoma*. Adenocarcinoma and squamous cell carcinoma are the most frequent histologic subtypes, accounting for 50 per cent and 30 per cent of NSCLC cases, respectively [30].

SCLC accounts for 10 to 15 per cent of all lung cancers; this form is a distinct pathological entity characterised by aggressive biology, propensity for early *metastasis* and overall poor prognosis.

**Other established causes.** Other established causes of lung cancer include the following:



#### Smoking tobacco

Smoking tobacco is the main cause of lung cancer and increases the risk of all the main subtypes. However, *adenocarcinoma* is the most common subtype among those who have never smoked. It is estimated that over 90 per cent of cases among men and over 80 per cent among women worldwide are attributable to smoking tobacco [31]. Passive smoking (inhalation of tobacco smoke from the surrounding air) is also a cause of lung cancer.



#### Previous lung disease

A history of emphysema, *chronic* bronchitis, tuberculosis or pneumonia is associated with an increased risk of lung cancer [32].



#### Other exposures

Occupational exposure to asbestos, crystalline silica, radon, mixtures of polycyclic aromatic hydrocarbons and some heavy metals is associated with an increased risk of lung cancer [33], as is exposure to indoor air pollution from wood and coal burning for cooking and heating [34].

**Confounding.** Smoking tobacco is the main cause of lung cancer. People who smoke also tend to have less healthy diets, less physically active ways of life and lower body weight than those who do not smoke. Therefore a central task in assessing the results of studies is to evaluate the degree to which observed associations in people who smoke may be due to residual *confounding* effects by smoking tobacco; that is, not a direct result of the exposure examined.

However, this evaluation may not completely mitigate the problem. Stratification by smoking status (for example, dividing the study population into people who smoke, those who used to smoke and those who have never smoked) can be useful, but typically the number of lung cancers in people who have never smoked is limited. Moreover, if an association is observed in people who currently smoke but not in people who have never smoked, residual confounding effects in the former group may be an explanation, but it is also plausible that the factor is only operative in ameliorating or enhancing the effects of tobacco smoke.

It is important to differentiate residual confounding effects from a true effect limited to people who smoke. Because smoking tobacco is such a strong risk factor for lung cancer, residual confounding effects remain a likely explanation, especially when the estimated risks are of moderate magnitudes.

For more detailed information on *adjustments* made in the published cohort studies on arsenic in drinking water, see Evidence and judgements (**Section 5.1.1**).

#### 4.2.2.4 Liver

**Definition.** The liver is the largest internal organ in the body. It processes and stores nutrients and produces *cholesterol* and proteins such as albumin, clotting factors and the lipoproteins that carry cholesterol. It also secretes *bile* and performs many metabolic functions, including detoxification of several classes of *carcinogens*.

**Classification.** Most of the available data are on *hepatocellular carcinoma*, the best characterised and most common form of liver cancer. However, different outcomes are reported for unspecified primary liver cancer than for hepatocellular carcinoma and *cholangiocarcinoma* so the different types of liver cancer may be a cause of heterogeneity among the study results.

**Other established causes.** Other established causes of liver cancer include the following:

#### Disease

*Cirrhosis* of the liver increases the risk of liver cancer [35].

#### Medication

Long-term use of oral contraceptives containing high doses of *oestrogen* and *progesterone* increases the risk of liver cancer [36].

#### Infection

Chronic infection with the *hepatitis B* or *C* virus is a cause of liver cancer [37].

#### Smoking tobacco

Smoking tobacco increases the risk of liver cancer generally, but there is a further increase in risk among people who smoke and have the *hepatitis B* or *hepatitis C* virus infection and also among people who smoke and consume large amounts of alcohol [38, 39]. It is estimated that 14 per cent of deaths worldwide from liver cancer are attributable to smoking tobacco [22].

**Confounding.** Smoking tobacco and *hepatitis B* and *C* viruses are possible *confounders* or *effect modifiers*.

For more detailed information on *adjustments* made in CUP analyses on coffee, see Evidence and judgements (**Section 5.3.1**).

The Panel is aware that alcohol is a cause of *cirrhosis*, which predisposes to liver cancer. Studies identified as focusing exclusively on patients with hepatic *cirrhosis* (including only patients with *cirrhosis*), *hepatitis B* or *C* viruses, alcoholism or history of alcohol abuse were not included in the CUP.

#### 4.2.2.5 Endometrium

**Definition.** The endometrium is the lining of the uterus (womb). It is subject to a process of cyclical change during the fertile years of a woman's life.

**Classification.** The majority of cancers that occur in the body of the uterus are endometrial cancers, mostly *adenocarcinomas* [40]. Because endometrial cancer is *hormone* related, factors that modify risk might have different effects at different times of life.

**Other established causes.** Other established causes of endometrial cancer include the following:



### Life events

Not bearing children and late natural *menopause* (after the age of 55) both increase the risk of endometrial cancer [41]. The reverse also applies: bearing children and early menopause both reduce the risk of endometrial cancer [42–46].



### Medication

Oral contraceptives, which contain either a combination of *oestrogen* and *progesterone*, or progesterone only, protect against endometrial cancer [45, 47]. *Menopausal oestrogen hormone therapy* unaccompanied by progesterone is a cause of this cancer. Menopausal oestrogen-only hormone therapy is normally prescribed only to women who have had a hysterectomy [45, 47]. Tamoxifen, a hormonal therapy used for breast cancer, can also increase the risk of endometrial cancer.



### Family history

Women with a family history of endometrial or colorectal cancer have a higher risk of endometrial cancer [48]. Lifetime risk of endometrial cancer in women with Lynch syndrome *mutations* MLH1 or MSH2 is approximately 40 per cent, with a median age of 49. Women with MSH6 mutations have a similar risk of endometrial cancer but a later age of diagnosis [49].

**Confounding.** Including data on women who were at high risk of endometrial cancer who have had hysterectomies may have influenced the results. Menopausal hormone therapy (MHT) is an *effect modifier*; in women who have never used MHT there is a stronger association between body mass index and endometrial cancer than in women who have ever used it [50].

For more detailed information on *adjustments* made in CUP analyses on coffee, see Evidence and judgements (**Section 5.3.2**).

### 4.2.2.6 Kidney

**Definition.** The kidneys are a pair of organs located at the back of the abdomen outside the peritoneal cavity. They filter waste products and water from the blood, producing urine, which empties into the bladder through the ureters.

**Classification.** Different subtypes of kidney cancer likely have different aetiologies, yet some epidemiologic studies do not distinguish the *clear cell subtype*, the predominant parenchymal renal cancer, from *papillary* or other subtypes. Cancers of the renal pelvis are typically *transitional cell carcinomas*, which probably share aetiologic risk factors such as smoking tobacco with other transitional cell carcinomas of the ureter and bladder.

**Other established causes.** Other established causes of kidney cancer include the following:



### Smoking tobacco

Smoking tobacco is a cause of kidney cancer. People who smoke have a 52 per cent increased risk of kidney cancer, and people who used to smoke have a 25 per cent increased risk, compared with those who have never smoked [51].



### Medication

Painkillers containing phenacetin are known to cause cancer of the renal pelvis. Phenacetin is no longer used as an ingredient in painkillers [52].



### Kidney disease

Polycystic kidney disease predisposes people to developing kidney cancer [53].



### Hypertension

High blood pressure is associated with a higher risk of kidney cancer [54].

### Family history

Inherited genetic predisposition accounts for only a minority of kidney cancers [55]. Von hippel-Lindau syndrome is the most common, with up to 40 per cent of those inheriting the mutated gene developing kidney cancer [56].

**Confounding.** Smoking tobacco is a possible *confounder*.

#### 4.2.2.7 Bladder

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

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

**Other established causes.** Other established causes of bladder cancer include the following:

### Smoking tobacco

Smoking tobacco increases the risk of bladder cancer. It is estimated that 28 per cent of deaths from bladder cancer worldwide are attributable to smoking tobacco [22].

### Infection and infestation

Infection from the parasitic worm, *Schistosoma haematobium*, causing schistosomiasis, is a major risk factor, especially for squamous cell carcinomas [57]. This is a less common type of bladder cancer that occurs more frequently in countries with high parasitic infection rates (notably in Africa and the Middle East) [57].

### Occupational exposure

People who work with metalworking fluids – such as sheet metalworkers and machine operators – have a significantly higher risk of bladder cancer, which increases with duration of employment [58]. Exposure to aromatic amines and polyaromatic hydrocarbons (chemicals used in the plastic and chemical industries) has also been strongly associated with an elevated risk for this cancer [58].

### Family history

*Mutations* in the *p53 tumour suppressor gene*, as well as abnormalities in chromosome 9, are common in invasive bladder cancer. Inherited mutations of two other genes, glutathione S-transferase (GSTM1) and n-acetyltransferase (NAT2), also increase risk for bladder cancer [59, 60].

**Confounding.** Smoking tobacco is a potential *confounder*.

For more detailed information on *adjustments* made in the published *cohort and case-control studies* on arsenic in drinking water, see Evidence and judgements (**Section 5.1.2**).

#### 4.2.2.8 Skin

**Definition.** The skin is the outer covering of the body and is one of the largest organs in terms of surface area and weight. Its primary function is to act as a barrier between the body and the external environment.

**Classification.** There are two main types of skin cancer: *melanoma* and non-melanoma. The most common non-melanoma tumours are *basal cell carcinoma* and *squamous cell carcinoma*, which together account for 90 per cent of skin cancers. Melanoma accounts for four per cent of skin cancers<sup>1</sup>.

**Other established causes.** Other established causes of skin cancer include the following:

##### Radiation

Over-exposure to ultraviolet radiation (mainly from sunlight, but also from ultraviolet-emitting tanning devices) is the chief cause of melanoma and non-melanoma skin cancers [61, 62].

##### Medication

Immune suppression medication following organ transplantation is associated with an increased risk of skin cancers, especially squamous cell carcinoma [63].

##### Infection and infestation

HPV can cause squamous cell carcinomas of the skin, especially in immunocompromised people [63]. Patients with AIDS, who are immunocompromised, are also at increased risk of squamous cell carcinoma, but development of Kaposi's sarcoma, which is otherwise rare, is a characteristic complication.

##### Occupational exposure

Exposure to polychlorinated biphenyls (chemicals used in the plastic and chemical industries) has also been strongly associated with an elevated risk for this cancer.

##### Genetics and family history

There are some rare, high-penetrance genetic mutations known to cause melanoma, such as mutations in the CDKN2A gene, but these do not make a large contribution to the total number of melanoma cases<sup>2</sup>. People who have a family history of melanoma are predisposed to this cancer [62]<sup>3,4</sup>.

##### Skin pigmentation

There is an inverse relationship between risk of skin cancer and skin pigmentation, with highest risks observed in populations with the fairest skin. This is likely due to lower production of the protective skin pigment melanin [59].

**Confounding.** Sun exposure is an important *confounder*.

For more detailed information on *adjustments* made in the published cohort study on arsenic in drinking water, see Evidence and judgements (**Section 5.1.3**).

<sup>1</sup> Kufe D et al. *Holland Frei Cancer Medicine*. 6 ed. Hamilton, Ontario: BC Decker, 2003.

<sup>2</sup> Berwick M et al. *Cancer Epidemiol Biomarkers Prev* 2006; 15: 1520-5

<sup>3</sup> Ward SV et al. *Cancer Epidemiol* 2015; 39: 346-5

<sup>4</sup> Chen T et al. *Eur J Cancer* 2014; 50: 2659-67

## 5. Evidence and judgements

For information on study types, methods of assessment of exposures and methods of analysis used in the CUP, see [Judging the evidence](#).

Full systematic literature reviews (SLRs) for each cancer are available online. For most cancer sites considered in the CUP,<sup>1</sup> there is also a CUP cancer report. CUP cancer reports summarise findings from the SLRs, again focusing on a specific cancer site. The following subsections also present findings from the SLRs, but from a different perspective: they bring together all of the key findings on non-alcoholic drinks and the risk of cancer.

Note that, throughout this section, if *Egger's test*, *non-linear analysis* or stratified analyses are not mentioned for a particular exposure and cancer, it can be assumed that no such analyses were conducted. This is often because there were too few studies with the required information.

### 5.1 Arsenic in drinking water

**Table 5.1** summarises the main findings from published *cohort studies* on consumption of arsenic in drinking water and the risk of cancer. Highest versus lowest and dose–response meta-analyses could not be conducted in the CUP.

There was no discussion on consumption of arsenic in drinking water and any other cancer considered in the CUP as there were too few studies.

The strong evidence on the effects of consuming arsenic in drinking water on the risk of cancer is described in the following subsections. This strong evidence includes analyses performed in the CUP and/or other published analyses, and information on mechanisms that could plausibly influence the risk of cancer.

For more information on the evidence for consuming arsenic in drinking water and the risk of cancer that was graded by the Panel as ‘limited – suggestive’ and suggests a direction of effect, see the CUP documents listed:

- [CUP kidney cancer report 2015](#): Section 7.1 and [CUP kidney cancer SLR 2015](#): Section 4.1.2.7.2.

Also, see **Appendix 2** for information on mechanisms that could plausibly influence the risk of cancer.

Please note that the information on mechanisms included in the following subsection and in the appendix (see **Appendix 2**) supersedes that in CUP cancer reports published before this Third Expert Report.

<sup>1</sup> Cancers at the following sites are reviewed in the CUP: mouth, pharynx and larynx; nasopharynx; oesophagus; lung; stomach; pancreas; gallbladder; liver; colorectum; breast; ovary; endometrium; cervix; prostate; kidney; bladder; and skin. CUP cancer reports not are currently available for nasopharynx, cervix and skin.



**Table 5.1: Summary of published cohort studies for consumption of arsenic in drinking water<sup>1</sup> and the risk of cancer**

Cancer	Total no. of studies	Exposure level	Total no. of studies	No. of studies showing statistically significant increased risk	No. of studies showing no statistically significant association	No. of studies showing statistically significant decreased risk	Conclusion <sup>2</sup>	Date of CUP cancer report <sup>3</sup>
Lung	4 <sup>4</sup>	High	3	3	0	0	Convincing: Increases risk	2017
		Low	1	0	1	0		
Bladder	7	High	3	2	1	0	Probable: Increases risk	2015
		Low	4	0	4	0		
Skin <sup>5</sup>	3	High	1	1	0	0	Probable: Increases risk	2017
		Low	2	0	2	0		
Kidney	4	High	1	1	0	0	Limited – suggestive: Increases risk	2015
		Low	3	0	3	0		

- 1 The International Agency for Research on Cancer (IARC) has judged arsenic and inorganic arsenic compounds to be carcinogenic to humans (Group 1) [2]. Drinking water contaminated with arsenic is also classed separately as a human carcinogen (Group 1) [2]. Water can become contaminated by arsenic as a result of natural deposits present in the earth, volcanic activity, or agricultural, mining and industrial practices. Countries particularly affected by higher levels of arsenic in drinking water include Bangladesh, China and India.
- 2 See Definitions of WCRF/AICR grading criteria (**Section 1:** Non-alcoholic drinks and the risk of cancer: a summary matrix) for explanations of what the Panel means by ‘convincing’, ‘probable’ and ‘limited – suggestive’.
- 3 Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.
- 4 A fifth study reported on dietary arsenic intake from foods (see CUP lung cancer report 2017: Section 7.1 and CUP lung cancer SLR 2015: Section 4.1.2.7.2).
- 5 Evidence from a published IARC review of case-control and ecological studies on consumption of arsenic in drinking water and skin cancer [2] was also considered by the Panel. Four out of six case-control studies and most ecological studies reported a statistically significant increased risk for skin cancer (histological type not specified).

### 5.1.1 Lung

(Also see [CUP lung cancer report 2017: Section 7.1](#) and [CUP lung cancer SLR 2015: Section 4.1.2.7.2](#))

The evidence for consumption of arsenic in drinking water is presented in the following subsections. Highest versus lowest or dose–response meta-analyses could not be conducted in the CUP due to the variability in median arsenic exposure and outcomes across studies. The evidence is from individual published cohort studies. For information on a study that considered evidence on dietary arsenic intake from foods [65], see [CUP lung cancer report 2017: Section 7.1](#) and [CUP lung cancer SLR 2015: Section 4.1.2.7.2](#).

#### 5.1.1.1 Published cohort studies

##### 5.1.1.1.1 Nature of studies

Four published cohort studies on consumption of arsenic in drinking water and the risk of lung cancer were identified (see **Table 5.2**).

Three of the studies reporting on arsenic in drinking water were in populations with high exposure to arsenic [66–68] and one study was from an area with low exposure to arsenic [69]. Further publications from the four studies are shown in the [CUP lung cancer report 2017: Section 7.1](#).

Measurements of people's level of exposure to arsenic in drinking water were based on arsenic levels in well water. Cumulative exposure was calculated from the amount of water consumed and the years of residence in the area.

All of the studies apart from one [67] adjusted for tobacco smoking. For information on the *adjustments* made in individual studies, see [CUP lung cancer SLR 2015](#), Table 98.

#### 5.1.1.1.2 Findings

The findings of the published cohort studies are summarised in **Table 5.2** (see [CUP lung cancer SLR 2015](#), Table 98, for more detailed information).

Two studies from areas with high exposure to arsenic [67, 68] showed a statistically significant increased risk of lung cancer with increasing levels of cumulative exposure to arsenic from drinking water, and one reported a statistically significant increased risk for

men and women separately, but not for men and women overall [66]. No statistically significant increase or decrease in risk was observed in the Danish Cohort Study, which is in a population with low levels of exposure to arsenic in drinking water [69].

#### 5.1.1.1 Published pooled analyses and meta-analyses

No published pooled analyses and no published meta-analyses on consumption of arsenic in drinking water and the risk of lung cancer were identified.

#### 5.1.1.2 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that currently prevail and is not based on a systematic or exhaustive search of the literature.

**Table 5.2: Summary of published cohort studies for consumption of arsenic in drinking water and the risk of lung cancer**

Study description	Total no. of cases	Sex	RR (95% CI)	Increment/contrast
<b>High-exposure areas</b>				
<b>Chung, 2013 South-western Taiwan cohort, 1989–1996 [66]</b>	71	Men and women	1.47 (0.66–3.31)	≥ 19.5 vs < 9.1 µg/litre/year
	43	Men	SMR 6.05 (4.38–8.15)	
	28	Women	SMR 7.18 (4.77–10.38)	
<b>Chen, 2010 North-eastern Taiwan cohort [68]</b>	178	Men and women	2.08 (1.33–3.27)	≥ 10,000 vs < 400 µg/litre/year
<b>Tsuda, 1995 Japanese cohort, 1959–1992 [67]</b>	9	Men and women	SMR 15.69 (7.38–31.02)	≥ 1 ppm
<b>Low-exposure areas</b>				
<b>Baastrop, 2008 Danish Diet, Cancer and Health cohort [69]</b>	402	Men and women	IRR 0.99 (0.90–1.08)	Per 1 µg/litre
			IRR 1.00 (0.98–1.03)	Per 5 mg/litre

Abbreviations: IRR, incident rate ratio; SMR, standardised mortality ratio.

For further information on general processes involved in the development of cancer, see [The cancer process](#).

The mechanisms linking arsenic in drinking water with cancer development are poorly understood. Experimental studies suggest that exposure to arsenic and its metabolites induces the production of *reactive oxygen species* inducing DNA damage, altering transcription factor function and modulating the expression of genes involved in cell growth, survival and cancer risk [70, 71]. It is currently uncertain, however, whether these mechanisms are specifically relevant for lung cancer.

#### 5.1.1.4 CUP Panel's conclusion

Overall the evidence was consistent, showing a statistically significant increased risk of lung cancer with consumption of arsenic in drinking water in high-exposure areas. In these areas, risk estimates were particularly large, indicating a strong effect. No dose–response meta-analysis was possible in the CUP. In addition, arsenic is a recognised *carcinogen*. There is robust evidence for plausible mechanisms operating in humans.

#### The CUP Panel concluded:

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

## 5.1.2 Bladder

(Also see [CUP bladder cancer report 2015: Section 7.3](#) and [CUP bladder cancer SLR 2014: Section 4.1.2.7.1](#).)

The evidence for consumption of arsenic in drinking water is presented in the following subsections. Highest versus lowest or dose–response meta-analyses could not be conducted in the CUP due to the variability in arsenic exposure assessment across studies. The evidence is from individual published cohort studies and one nested case-control study.

### 5.1.2.1 Published cohort and nested case-control studies

#### 5.1.2.1.1 Nature of studies

Seven studies on consumption of arsenic in drinking water and the risk of bladder cancer were identified (see [Table 5.3](#)).

Three studies on consumption of arsenic in drinking water were in populations with high exposure to arsenic [66, 67, 72], and four studies were from an area with low exposure to arsenic [69, 73–75]. Further publications from the studies conducted in Taiwan are shown in the [CUP bladder cancer report 2015: Section 7.3](#).

In six of the studies, measurements of people's exposure to arsenic in drinking water were based on arsenic levels in well water. Cumulative exposure was calculated from the duration of consumption and amount of water consumed. In one of the studies, exposure to arsenic was assessed by toenail arsenic concentration [73].

Three studies did not report *adjustment* for tobacco smoking. Of these studies, two were conducted in areas of high exposure to arsenic and reported data on tobacco smoking; the third was conducted in a low-exposure area



and estimated a low prevalence of tobacco smoking. For information on the adjustments made in individual studies, see [CUP bladder cancer SLR 2014](#), Table 82.

### 5.1.2.1.2 Findings

The findings of the studies are summarised in **Table 5.3** (see [CUP bladder cancer SLR 2014](#), Table 82, for more detailed information).

Two of the three studies [67, 72] from areas with high exposure to arsenic showed a statistically significant increased risk of bladder cancer with increasing levels of cumulative exposure to arsenic from drinking water. No statistically significant increase or decrease in risk was observed in the studies from areas with low exposure to arsenic [69, 73–75].

### 5.1.2.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. Two published meta-analyses of *cohort* and *case-control studies* on consumption of arsenic in drinking water and the risk of bladder cancer were identified. One, which was funded by the Wood Preservative Science Council, Virginia, USA, in populations with low levels of exposure to arsenic in drinking water, showed no statistically significant increased or decreased risk of bladder cancer when comparing the highest with the lowest levels of exposure [76]. The other, a dose–response analysis from areas with high and low levels of arsenic in drinking water, also reported no significant increased or decreased risk [77].

**Table 5.3: Summary of published cohort and nested case-control studies for consumption of arsenic in drinking water and the risk of bladder cancer**

Publication	Total no. of cases	Sex	RR (95% CI)	Increment/contrast
<b>High-exposure areas</b>				
<b>Chung, 2013</b> South-western Taiwan cohort, 1989–1996 [66]	43	Men and women	7.74 (0.97–61.51)	≥ 19.5 vs 9.1 µg /litre/year
<b>Chen, 2010</b> North-eastern Taiwan cohort, 1991/1994–2006 [72]	45	Men and women	12.6 (3.40–46.8)	≥ 10,000 vs < 400 µg/litre
<b>Tsuda, 1995</b> Japanese cohort, 1959–1992 [67]	3	Men and women	SMR 31.18 (8.62–91.75)	≥ 1 ppm
<b>Low-exposure areas</b>				
<b>Baastrop, 2008</b> Danish Diet, Cancer and Health cohort [69]	214	Men and women	1.00 (0.91–1.11)	Per µg/litre
<b>Michaud, 2004</b> ATBC study <sup>1</sup> [73]	280	Men	1.13 (0.70–1.81)	Toenail arsenic level > 0.161 vs < 0.05 µg/gram
<b>Lewis, 1999</b> Cohort of Mormons, USA <sup>2</sup> [75]	–	Men	SMR 0.42 (0.08–1.22)	≥ 5,000 ppb-year
		Women	SMR 0.81 (0.10–2.93)	
<b>Kurttio, 1999</b> Finnish cohort, 1981–1995 [74]	61	Men and women	1.00 (0.91–1.11)	3 to 9 years before cancer diagnosis ≥ 2.0 vs < 0.5 mg

Abbreviations: SMR, standardised mortality ratio.

<sup>1</sup> The ATBC study [73] is a nested case-control study.

<sup>2</sup> The Lewis Cohort study [75] is retrospective cohort study of mortality.

### 5.1.2.3 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that currently prevail and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see [The cancer process](#).

The mechanisms linking arsenic in drinking water with cancer development are poorly understood. Experimental studies suggest that exposure to arsenic and its metabolites induces excessive *reactive oxygen species* inducing DNA damage, altering transcription factor function and modulating the expression of genes involved in cell growth, survival and cancer risk [70, 71]. It is currently uncertain, however, whether these mechanisms are specifically relevant for bladder cancer.

### 5.1.2.4 CUP Panel's conclusion

Overall, the evidence was generally consistent, showing a statistically significant increased risk of bladder cancer with consumption of arsenic in drinking water in high-exposure areas. In these areas, risk estimates were particularly large, indicating a strong effect. No dose–response meta-analysis was possible in the CUP. In addition, arsenic is a recognised *carcinogen*. There is robust evidence for plausible mechanisms operating in humans.

#### **The CUP Panel concluded:**

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

### 5.1.3 Skin

(Also see [CUP skin cancer SLR 2017](#): Section 4.1.2.7.2)

The evidence for consumption of arsenic in drinking water is presented in the following subsections. Highest versus lowest or dose–response meta-analyses could not be conducted in the CUP due to the variability in arsenic exposure assessment across studies. The evidence is from individual published cohort studies. The Panel also considered evidence from a published IARC review of *case-control* and *ecological studies* on consumption of arsenic in drinking water and skin cancer [2].

#### 5.1.3.1 Published cohort studies

Three published cohort studies on consumption of arsenic in drinking water and the risk of skin cancer were identified. One study, conducted in areas of Taiwan where *arseniasis* is hyperendemic, reported a statistically significant increased risk of skin cancer when comparing the highest with the lowest arsenic concentration in drinking water [78]. No statistically significant increase or decrease in risk was observed in two other studies from populations with low levels of exposure to arsenic in drinking water [69, 75].

Most studies adjusted or accounted for age and sex.

The findings of the published cohort studies are summarised in **Table 5.4** (see [CUP skin cancer SLR 2017](#), Section 4.1.2.7.2, for more detailed information).



**Table 5.4: Summary of published cohort studies for consumption of arsenic in drinking water and the risk of skin cancer**

Study description	Total no. of cases	Sex	RR (95% CI)	Increment/contrast
<b>High-exposure areas</b>				
<b>Hsueh, 1997</b> <b>South-western Taiwan cohort 1989–1992 [78]</b>	26	Men and women	Skin cancer 8.69 (1.08–65.50)	0.71–1.1 vs 0 mg/litre
<b>Low-exposure areas</b>				
<b>Baastrup, 2008</b> <b>Danish Diet, Cancer and Health cohort [69]</b>	147	Men and women	Malignant melanoma IRR 0.80 (0.59–1.08)	Per 1 µg/litre Time-weighted average exposure
			Non-melanoma skin cancer IRR 0.99 (0.94–1.06)	Per 1 µg/litre Time-weighted average exposure
<b>Lewis, 1999</b> <b>Cohort of Mormons, USA<sup>1</sup> [75]</b>	3	Men	Malignant melanoma SMR 0.83 (0.17–2.43)	≥ 5,000 vs <1,000 ppb-years
	4	Women	Malignant melanoma SMR 1.82 (0.50–4.66)	

**Abbreviations:** IRR, incident rate ratio; SMR, standardised mortality ratio.

### 5.1.3.2 Published pooled analyses and meta-analyses

No published pooled analyses and no published meta-analyses on consumption of arsenic in drinking water and the risk of skin cancer were identified. One published review from IARC [2] of *case-control* and *ecological studies* on arsenic intake and skin cancer was identified. Results are shown in the [CUP skin cancer SLR 2017](#), Appendix 4. In summary, four of six case-control studies reported a statistically significant increased risk for non-melanoma skin cancer or for skin cancer (histological type not specified); and of 17 ecological studies, where the outcomes were mostly skin cancer and histological type was not specified, most reported a significant increased risk.

### 5.1.3.3 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever

possible. This section covers the primary hypotheses that currently prevail and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see [The cancer process](#).

The mechanisms linking arsenic in drinking water with cancer development are poorly understood. Experimental studies suggest that arsenic exhibits tumour-promoting properties by inducing oxidative DNA damage, activating transcription factors and modulating the expression of genes involved in cell growth [70, 71]. It is currently uncertain, however, whether these mechanisms are applicable specifically to skin cancer.

### 5.1.3.4 CUP Panel's conclusion

Overall, the evidence was generally consistent. A statistically significant increased risk of skin cancer with consumption of arsenic in drinking

<sup>1</sup> The Lewis Cohort study [75] is a retrospective cohort study of mortality.

water was reported in one study from a high-exposure area. Results were not significant in the other; however, there were very few cases of malignant *melanoma*. The IARC review of *case-control* and *ecological studies* supported the evidence from the cohort studies. No dose–response meta-analysis was possible in the CUP. In addition, arsenic is a recognised *carcinogen*<sup>1</sup>. There is robust evidence for plausible mechanisms operating in humans.

**The CUP Panel concluded:**

- **Consumption of arsenic in drinking water is probably a cause of skin cancer (unspecified).**

**5.2 Mate**

**Table 5.5** summarises the main findings from the CUP *dose–response meta-analyses* of *case-control studies* on consumption of mate and the risk of cancer.

Evidence for oesophageal adenocarcinoma (2016) was discussed in the CUP but was too limited to draw a conclusion<sup>2</sup>.

The strong evidence on the effects of consuming mate on the risk of cancer is described in the following subsections. This strong evidence includes analyses performed in the CUP and/or other published analyses, and information on mechanisms that could plausibly influence the risk of cancer.

**Table 5.5: Summary of CUP dose–response meta-analyses from case-control studies for consumption of mate<sup>1</sup> and the risk of cancer**

Cancer	Total no. of studies	No. of studies in meta-analysis	Total no. of cases	Risk estimate (95% confidence interval [CI])	Increment	I <sup>2</sup> (%)	Conclusion <sup>2</sup>	Date of CUP cancer report <sup>3</sup>
Oesophagus (squamous cell carcinoma)	8	5 <sup>4</sup>	1,162	1.16 (1.07–1.25)	Cup per day	89	Probable: Increases risk	2016 <sup>5</sup>
Mouth, pharynx and larynx <sup>6</sup>	5	0	–	Statistically significant increased risk in 3 studies	–	–	Limited – suggestive: Increases risk	2018

1 Mate, an aqueous infusion prepared from dried leaves of the plant *Ilex paraguariensis*, is traditionally drunk scalding hot through a metal straw in parts of South America. In 2016, an IARC Working Group declared that drinking very hot beverages, including mate, above 65°C is probably carcinogenic to humans (Group 2A) [3].

2 See Definitions of WCRF/AICR grading criteria (Section 1: Non-alcoholic drinks and the risk of cancer: a summary matrix) for explanations of what WCRF means by ‘probable’ and ‘limited – suggestive’.

3 Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

4 Four of the studies on consumption of mate and oesophageal cancer reported on oesophageal squamous cell carcinoma and the fifth did not specify a cancer subtype.

5 Data presented are from the 2005 oesophageal cancer SLR (see CUP Oesophageal cancer SLR 2015, Appendix 3). No analysis was conducted in the CUP.

6 A dose–response meta-analysis of cohort studies could not be conducted in the CUP. Three of five studies identified on consumption of mate and cancers of the mouth, pharynx and larynx reported a statistically significant increased risk for people who had ever consumed mate compared with those who had never consumed mate, or for people who consumed greater amounts of mate compared with those who had consumed the least (see CUP mouth, pharynx and larynx report 2018, Table 5).

<sup>1</sup> The CUP Panel noted the strength of the evidence from IARC judging arsenic as a ‘Group 1’ carcinogen, and this evidence acts as a special upgrading factor (see Appendix 1).

<sup>2</sup> ‘Limited – no conclusion’: There is enough evidence to warrant Panel consideration, but it is so limited that no conclusion can be made. The evidence may be limited in amount, by inconsistency in the direction of effect, by methodological flaws, or by any combination of these.

For more information on the evidence for consuming mate and the risk of cancer that was graded by the Panel as ‘limited-suggestive’ and suggests a direction of effect, see the CUP documents listed:

- CUP mouth, pharynx and larynx cancer report 2018: Section 7.3 and CUP mouth, pharynx and larynx cancer SLR 2016: Section 3.6.3.

Also, see **Appendix 2** for information on mechanisms that could plausibly influence the risk of cancer.

Please note that the information on mechanisms included in the following subsection and in the appendix (see **Appendix 2**) supersedes that in CUP cancer reports published before this Third Expert Report.

### 5.2.1 Oesophagus (squamous cell carcinoma)

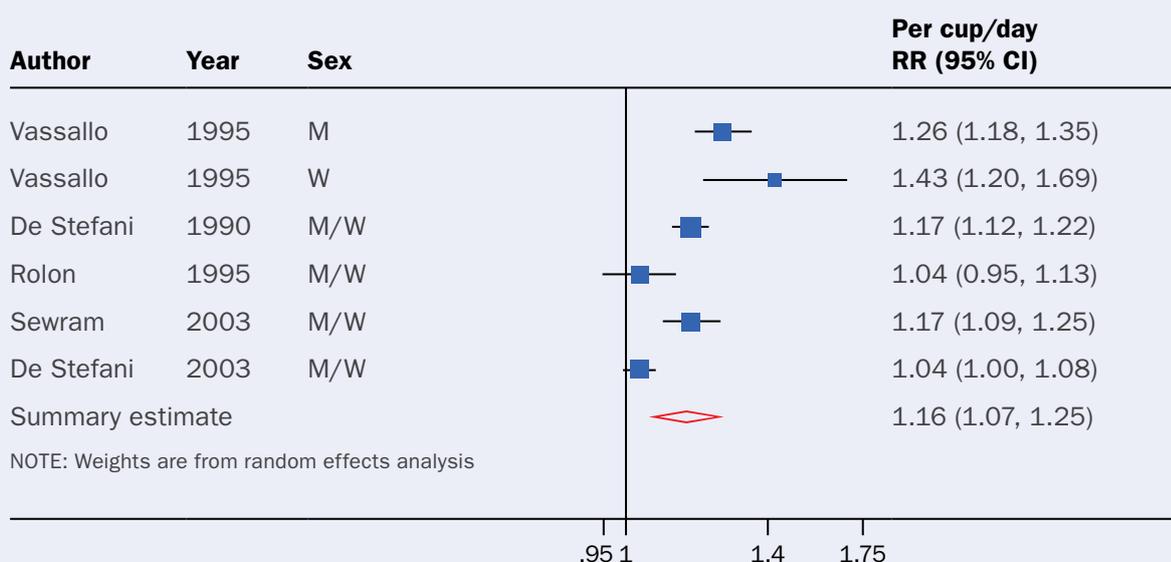
(Also see CUP oesophageal cancer report 2016: Section 7.4 and CUP oesophageal cancer SLR 2015: Section 3.6.3.)

#### 5.2.1.1 CUP dose–response meta-analysis

No cohort studies were identified in the CUP. Five of eight *case-control studies* identified were included in the dose–response meta-analysis in the 2005 oesophageal cancer SLR, which showed a statistically significant 16 per cent increased risk of oesophageal *squamous cell carcinoma* per cup increase in mate consumed per day (RR 1.16 [95% CI 1.07–1.25]; 1,162 cases) (**Figure 5.1**). Four of these studies reported on oesophageal squamous cell carcinoma and the fifth reported on unspecified oesophageal cancer. High *heterogeneity* was observed ( $I^2 = 89\%$ ), which was due to variations in the size of the effect. There was no evidence of small study bias with *Egger’s test* ( $p = 0.85$ ).

All five of the studies included in the dose–response meta-analysis adjusted for tobacco smoking.

**Figure 5.1: CUP dose–response meta-analysis<sup>1,2</sup> for the risk of oesophageal squamous cell carcinoma, per cup increase in mate consumed per day**



Source: Vassallo, 1985 [79]; De Stefani, 1990 [80]; Rolon, 1995 [81]; Sewram, 2003 [82]; De Stefani, 2003 [83].

<sup>1</sup> Three studies could not be included in the dose–response meta-analysis as sufficient information was not provided.

<sup>2</sup> A total of five studies was analysed in the CUP dose–response meta-analysis. In one study, the relative risk for men and women was reported separately.

**Table 5.6: Summary of published pooled analyses for consumption of mate and the risk of oesophageal squamous cell carcinoma**

Publication	Contrast	RR (95% CI)	No. of studies (case-control)	No. of cases
Lubin, 2014 <sup>1</sup> [84]	Ever vs never	1.60 (1.2–2.2)	2	1,391
	Warm vs never	1.20 (0.8–1.7)		168
	Hot vs never	1.61 (1.2–2.2)		929
	Very hot vs never	2.15 (1.5–3.1)		213

### 5.2.1.2 Published pooled analyses and meta-analyses

One published pooled analysis (see **Table 5.6**) and one other published meta-analysis on consumption of mate and the risk of oesophageal squamous cell carcinoma were identified. The pooled analysis of *case-control studies* reported a statistically significant increased risk in people who had ever consumed mate compared with those who had never consumed mate [84].

The published meta-analysis [85] (which included the two studies included in the pooled analysis) also reported a significant increased risk of oesophageal squamous cell carcinoma for the highest compared with the lowest levels of mate consumed (RR 2.57 [95% CI 1.66–3.98]).

### 5.2.1.3 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that currently prevail and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see [The cancer process](#).

Mate is an infusion made from the dried leaves of the plant *Ilex paraguariensis*. Habitually consumed in South America, mate can be drunk hot or cold. Any carcinogenic effects of mate are believed to be due to consumption at very hot temperatures (over 65°C) increasing the incidence of *nitrosamine*-induced tumours [3, 86].

### 5.2.1.4 CUP Panel's conclusion

The evidence from *case-control studies* reviewed in the 2005 oesophageal cancer SLR was generally consistent. The dose–response meta-analysis showed a statistically significant increased risk of oesophageal squamous cell carcinoma with increased consumption of scalding hot mate. High *heterogeneity* was observed; however, this was explained by variations in the size of the effect. This was consistent with findings from recent published pooled and meta-analyses. There is robust evidence for plausible mechanisms.

#### The CUP Panel concluded:

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

<sup>1</sup> In the Lubin, 2014 study [84] the *odds ratios* increased linearly with cumulative mate consumption.

We are aware that in May 2016, after the SLR on which this Report is based was completed and the evidence judged by the CUP Panel, the International Agency for Research on Cancer (IARC) published a report on the carcinogenicity of coffee, mate and very hot beverages. They concluded that drinking coffee or mate that was not very hot was unclassifiable in terms of its carcinogenicity in humans (Grade 3), but that drinking very hot (greater than 65°C) beverages, including mate, was probably carcinogenic in humans (Grade 2A) [3]. Epidemiological studies of oesophageal cancer and drinking mate were an important basis for their conclusion. The IARC report is consistent with the conclusions in this Third Expert Report.

## 5.3 Coffee

**Table 5.7** summarises the main findings from the CUP dose–response meta-analyses of cohort studies on consumption of coffee and the risk of cancer.

Evidence for cancers of the following types was discussed in the CUP but was too limited to draw a conclusion<sup>1</sup>: oesophagus (adenocarcinoma and squamous cell carcinoma, 2016), lung (2017), stomach (2016), pancreas (2012), gallbladder (2015), colorectum (2017), breast (pre and postmenopause; 2017), ovary (2014), prostate (2014), kidney (2015) and bladder (2015).

**Table 5.7: Summary of CUP dose–response meta-analyses for consumption of coffee and the risk of cancer**

Cancer	Type	Total no. of studies	No. of studies in meta-analysis	Total no. of cases	Risk estimate (95% CI)	Increment	I <sup>2</sup> (%)	Conclusion <sup>2</sup>	Date of CUP cancer report <sup>3</sup>
Liver	Coffee	8	6	1,582	0.86 (0.81–0.90)	Cup per day	18	Probable: Decreases risk	2015
Endometrium <sup>3</sup>	Coffee	8	7	3,571	0.93 (0.91–0.96)	Cup per day	10	Probable: Decreases risk	2013
	Decaffeinated coffee	3	3	2,585	0.92 (0.87–0.97)	Cup per day	0		
Mouth, pharynx and larynx <sup>4</sup>	Coffee	6	0	–	Statistically significant increased risk in 3 studies	–	–	Limited – suggestive: Decreases risk	2018
Skin (basal cell carcinoma [men and women] / malignant melanoma [women])	Coffee	5	3	23,109	0.96 (0.94–0.97)	Cup per day	0	Limited – suggestive: Decreases risk	2017
		4	4	1,830	0.91 (0.86–0.96)		36		

- 1 See Definitions of WCRF/AICR grading criteria (**Section 1**: non-alcoholic drinks and the risk of cancer: a summary matrix) for explanations of what the Panel means by ‘probable’ and ‘limited – suggestive’.
- 2 Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.
- 3 The effect of coffee on the risk of endometrial cancer is observed with both caffeinated and decaffeinated coffee so cannot be attributed to caffeine.
- 4 A dose–response meta-analysis of cohort studies could not be conducted in the CUP. Three of six studies identified on consumption of coffee and cancers of the mouth, pharynx and larynx reported a statistically significant decreased risk for people who consumed the highest compared with the lowest level of coffee consumed or when conducting a dose–response analysis per cup per day (see CUP mouth, pharynx and larynx report 2018, Table 6).

<sup>1</sup> ‘Limited – no conclusion’: There is enough evidence to warrant Panel consideration, but it is so limited that no conclusion can be made. The evidence may be limited in amount, by inconsistency in the direction of effect, by methodological flaws, or any combination of these.

The strong evidence on the effects of consuming coffee on the risk of cancer is described in the following subsections. This strong evidence includes analyses performed in the CUP and/or other published analyses, and information on mechanisms that could plausibly influence the risk of cancer.

For more information on the evidence for consuming coffee and the risk of cancer that was graded by the Panel as ‘limited – suggestive’ and suggests a direction of effect, see the CUP documents listed:

- CUP mouth, pharynx and larynx cancer report 2018: Section 7.4 and CUP mouth, pharynx and larynx cancer SLR 2016: Section 3.6.1.
- CUP skin cancer SLR 2017: Section 3.6.1.

Also, see **Appendix 2** for information on mechanisms that could plausibly influence the risk of cancer.

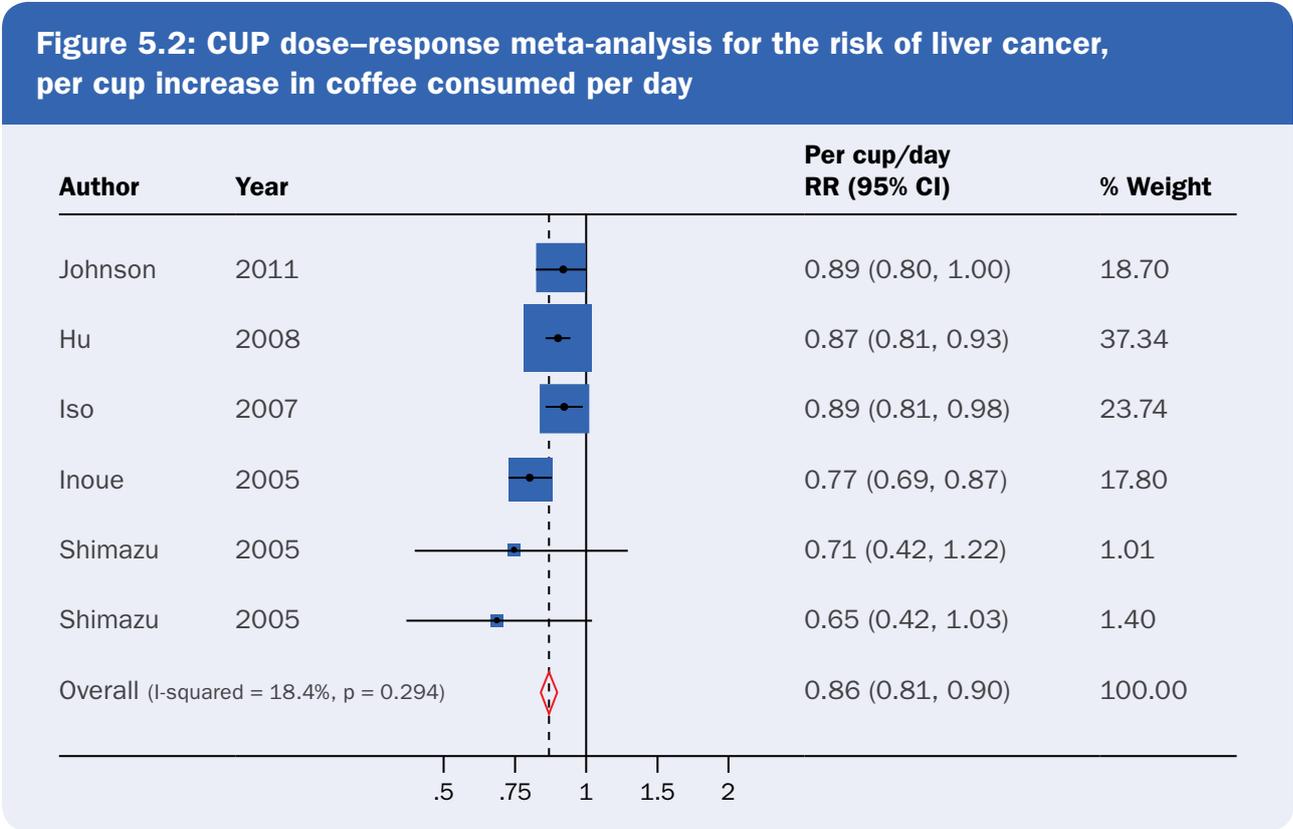
Please note that the information on mechanisms included in the following subsection and in the appendix (see **Appendix 2**) supersedes that in CUP cancer reports published before this Third Expert Report.

**5.3.1 Liver**

(Also see CUP liver cancer report 2015: Section 7.3 and CUP liver cancer SLR 2014: Section 3.6.1.)

**5.3.1.1 CUP dose–response meta-analysis**

Six of eight identified studies were included in the dose–response meta-analysis, which showed a statistically significant 14 per cent decreased risk of liver cancer per cup increase in coffee consumed per day (RR 0.86 [95% CI 0.81–0.90]; n = 1,582 cases) (see **Figure 5.2**). Low *heterogeneity* was observed ( $I^2 = 18\%$ ) and there was no evidence of small study bias with *Egger’s test* ( $p = 0.20$ ).



Source: Johnson, 2011 [87]; Hu, 2008 [88]; Iso, 2007 [89]; Inoue, 2005 [90]; Shimazu 2005 [91].

Stratified analyses for the risk of liver cancer per cup increase in coffee consumed per day were conducted for sex; a statistically significant decreased risk was observed in men (RR 0.84 [95% CI 0.78–0.90]), but not women (RR 0.91 [95% CI 0.83–1.01]); see [CUP liver cancer report 2015](#), Table 2 and [CUP liver cancer SLR 2014](#), Figure 22).

All studies included in the dose–response meta-analysis adjusted for tobacco smoking except for one [89].

### 5.3.1.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. Three other published meta-analyses of *cohort* and *case-control studies* on consumption of coffee and the risk of liver cancer were identified. One published meta-analysis [92] reported a statistically significant decreased risk per cup increase in coffee consumed per day in cohort studies (RR 0.83 [95% CI 0.78–0.88]). The second meta-analysis [93] reported a statistically significant decreased risk in cohort studies for people who drank the highest volume of coffee compared with those who never or almost never consumed coffee (RR 0.48 [95% CI 0.38–0.62]). The third meta-analysis [94] also reported a statistically significant decreased risk per two cups increase in coffee consumed per day for cohort studies (RR 0.56 [95% CI 0.46–0.69]).

### 5.3.1.3 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that currently prevail and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see [The cancer process](#).

Coffee is rich in a large number of bioactive compounds including *caffeine*, chlorogenic acids and numerous phenolic compounds. Emerging evidence suggests that these compounds may have beneficial effects on the liver ranging from *antioxidant*, anti-inflammatory properties to the inhibition of *angiogenesis*, but the main underlying mechanisms of the role of coffee in liver cancer development are not fully elucidated [95]. Coffee is also associated with improved insulin sensitivity [96], decreased incidence of metabolic syndrome [97] and reduced level of liver injury [98], which could represent additional mechanisms by which coffee drinking may reduce the risk of liver cancer development.

### 5.3.1.4 CUP Panel's conclusion

The evidence for coffee was generally consistent, and the CUP dose–response meta-analysis showed a statistically significant decreased risk of liver cancer with increased consumption of coffee. Low *heterogeneity* was observed. When stratified by sex, the decreased risk was significant for men but not for women. No threshold was identified, and there was no evidence regarding specific components of coffee that were attributable to the decreased risk. The CUP findings were consistent with findings from three published meta-analyses. There is evidence of plausible mechanisms operating in humans.

#### The CUP Panel concluded:

- Consumption of coffee probably protects against liver cancer.



### 5.3.2 Endometrium

(Also see [CUP endometrial cancer report 2013](#): Section 7.2 and [CUP endometrial cancer SLR 2012](#): Sections 3.6.1 and 3.6.1.1.)

The evidence for coffee and decaffeinated coffee is presented in the following subsections.

#### 5.3.2.1 Coffee

##### 5.3.2.1.1 CUP dose–response meta-analysis

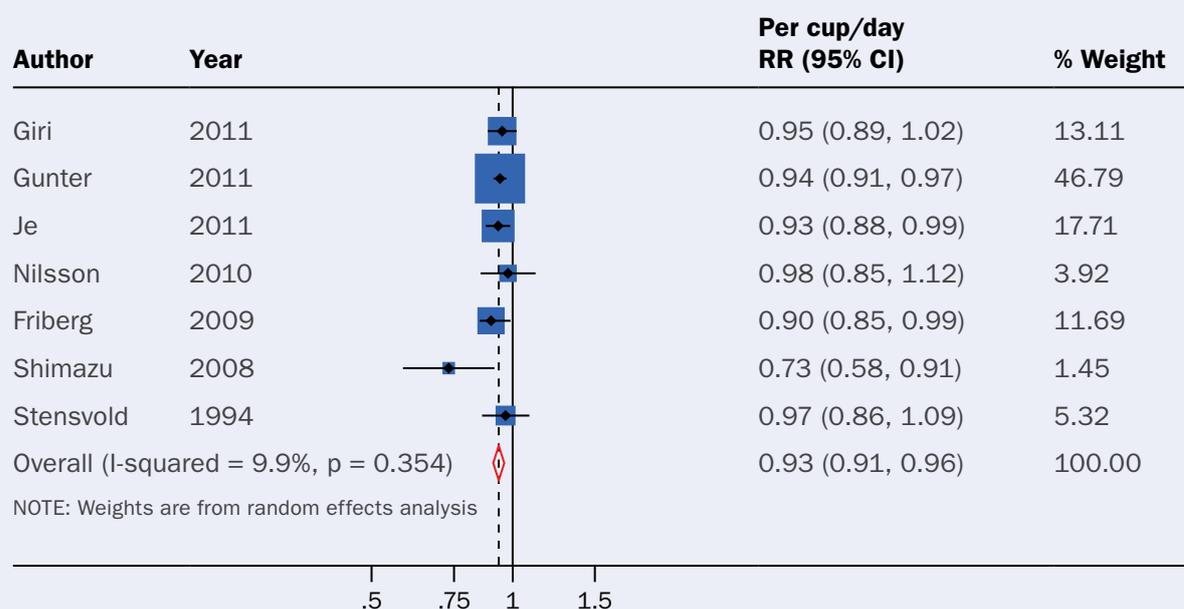
Seven of eight identified studies were included in the dose–response meta-analysis, which showed a statistically significant seven per cent decreased risk of endometrial cancer per cup increase in coffee consumed per day (RR 0.93 [95% CI 0.91–0.96];  $n = 3,571$  cases) (see **Figure 5.3**). Low *heterogeneity* was observed ( $I^2 = 10\%$ ). There was no evidence of small study bias with Egger’s test ( $p = 0.39$ ), but inspection of the funnel plot suggested that a small study [99] reported a larger decreased risk than the other studies (see [CUP endometrial cancer SLR 2012](#), Figure 15).

All studies included in the dose–response meta-analysis adjusted for age and tobacco smoking. Most adjusted for BMI and MHT use and some for reproductive factors, dietary factors and/or physical activity.

##### 5.3.2.1.2 Published pooled analyses and meta-analyses

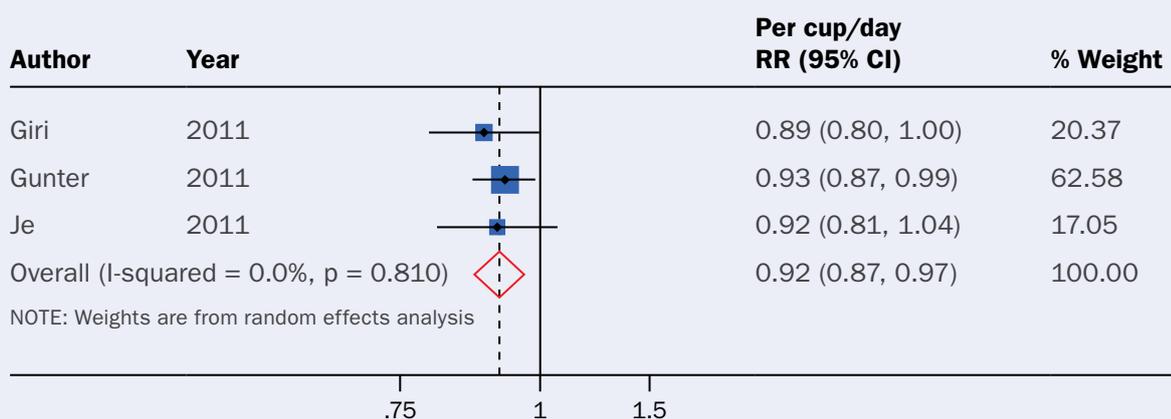
No published pooled analyses were identified. Three other published meta-analyses on consumption of coffee and the risk of endometrial cancer were identified. One reported a statistically significant decreased risk per cup increase in coffee consumed per day (RR 0.94 [95% CI 0.90–0.97]) [106]. Another meta-analysis reported a significant decreased risk for people who drank the highest amount of coffee compared with those who drank the lowest amount (RR 0.74 [95% CI 0.63–0.84]) [107]. The third meta-analysis reported no significant association per cup increase in coffee consumed per day or for the highest compared with the lowest level of coffee consumed [108].

**Figure 5.3: CUP dose–response meta-analysis for the risk of endometrial cancer, per cup increase in coffee consumed per day**



Source: Giri, 2011 [100]; Gunter, 2011 [101]; Je, 2011 [102]; Nilsson, 2010 [103]; Friberg, 2009 [104]; Shimazu, 2008 [99]; Stensvold, 1994 [105].

**Figure 5.4: CUP dose–response meta-analysis for the risk of endometrial cancer, per cup increase in decaffeinated coffee consumed per day**



Source: Giri, 2011 [100]; Gunter, 2011 [101]; Je, 2011 [102].

### 5.3.2.2 Decaffeinated coffee

#### 5.3.2.2.1 CUP dose–response meta-analysis

All three identified studies were included in the dose–response meta-analysis, which showed a statistically significant eight per cent decreased risk of endometrial cancer per cup increase in decaffeinated coffee consumed per day (RR 0.92 [95% CI 0.87–0.97]; n = 2,585 cases) (see **Figure 5.4**). No *heterogeneity* was observed and there was no evidence of publication bias with *Egger’s test* (p = 0.40).

All studies included in the dose–response meta-analysis adjusted for age, tobacco smoking, BMI and MHT use.

#### 5.3.2.2.2 Published pooled analyses and meta-analyses

No published pooled analyses and no other published meta-analyses on consumption of decaffeinated coffee and the risk of endometrial cancer were identified.

### 5.3.2.3 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary

hypotheses that currently prevail and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see [The cancer process](#).

The mechanisms linking coffee consumption to a decrease in endometrial cancer risk remain unclear but may involve lower circulating levels of bioavailable sex-steroids or insulin and higher insulin sensitivity in people who drink coffee [109–111]. Coffee drinking is correlated with higher levels of sex hormone-binding globulin (SHBG), which may decrease exposure to bioavailable oestradiol levels [109, 112, 113]. A large cross-sectional study of more than 1,200 women in the Nurses’ Health Study reported that in premenopausal women, coffee intake was associated with lower luteal phase total and free oestradiol levels, while in postmenopausal women *caffeine* and coffee intake were positively associated with SHBG levels [114]. Coffee drinking is also associated with reduced insulin levels, particularly among overweight women [110], and it has been hypothesised that coffee may reduce the risk of endometrial cancer through an insulin-mediated

mechanism. Coffee has also been shown to alter *adipokines* and inflammatory pathways and lead to an increase in *adiponectin* levels [111, 115] – an adipokine that is down-regulated in *obesity* and has been linked to endometrial cancer development [116, 117].

**5.3.2.4 CUP Panel's conclusion**

The evidence for coffee and decaffeinated coffee was generally consistent, and the CUP dose–response meta-analyses showed a statistically significant decreased risk of endometrial cancer with increased consumption of coffee. Little or no *heterogeneity* was observed. The findings for coffee were also consistent with results from other published meta-analyses. There is evidence of plausible mechanisms operating in humans.

**The CUP Panel concluded:**

- **Consumption of coffee probably protects against endometrial cancer.**



**5.4 Tea**

**Table 5.8** summarises the main findings from the CUP dose–response meta-analysis of cohort studies on consumption of tea and the risk of bladder cancer.

Evidence on tea or green tea for cancers of the following types was discussed in the CUP but was too limited to draw a conclusion<sup>1</sup>: mouth, pharynx and larynx (2018), nasopharynx (2017), lung (2017), stomach (2016), pancreas (2012), gallbladder (2015), liver (2015), colorectum (2017), breast (pre and postmenopause; 2017), ovary (2014), endometrium (2013), prostate (2014) and kidney (2015).

**Table 5.8: CUP dose–response meta-analysis for consumption of tea and the risk of bladder cancer**

Cancer	Total no. of studies	No. of studies in meta-analysis	Total no. of cases	Risk estimate (95% CI)	Increment	I <sup>2</sup> (%)	Conclusion <sup>1</sup>	Date of CUP cancer report <sup>2</sup>
Bladder	4	4	1,446	0.94 (0.89–0.98)	Cup per day	0	Limited – suggestive: Decreases risk	2015

**1** See Definitions of WCRF/AICR grading criteria (**Section 1**: Non-alcoholic drinks and the risk of cancer: a summary matrix) for explanations of what the Panel means by ‘limited – suggestive’.

**2** Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

<sup>1</sup> **‘Limited – no conclusion’**: There is enough evidence to warrant Panel consideration, but it is so limited that no conclusion can be made. The evidence may be limited in amount, by inconsistency in the direction of effect, by methodological flaws, or by any combination of these.

For more information on the evidence for drinking tea and the risk of cancer that was graded by the Panel as ‘limited – suggestive’ and suggests a direction of effect, see the CUP documents listed:

- [CUP bladder cancer report 2015](#): Section 7.2 and [CUP bladder cancer SLR 2014](#): Section 3.6.2.

Also, see **Appendix 2** for information on mechanisms that could plausibly influence the risk of cancer.

Please note that the information on mechanisms included in the appendix (see **Appendix 2**) supersedes that in CUP cancer reports published before this Third Expert Report.

## 5.5 Other

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The effect of other non-alcoholic drinks on the risk of cancer was evaluated, as well as those that were graded by the Panel as ‘limited-suggestive’, ‘probable’ or ‘convincing’. These included fruit juices and soft drinks. The effect of total fluid intake has also been evaluated. However, data were either of too low quality or too inconsistent, or the number of studies too few to allow conclusions to be reached.

Evidence on whether consumption of milk affects the risk of cancer is considered along with the evidence on other dairy products (see [Exposures: Meat, fish and dairy products](#)) and is not presented in this section.

## 6. Comparison with the 2007 Second Expert Report

In 2007, there was strong evidence that consuming arsenic in drinking water increases the risk of two cancers (lung and skin). The evidence for those two cancers has remained strong. There is new strong evidence that the risk of bladder cancer is increased too, bringing the total to three cancers.

Evidence for oesophageal cancer, which is now considered by subtype in the CUP, supports the conclusion that drinking very hot mate is probably a cause of squamous cell carcinoma but not of adenocarcinoma. In 2007, the conclusion that mate is probably a cause of oesophageal cancer was for oesophageal cancer overall.

There is new strong evidence that drinking coffee probably protects against two cancers (liver and endometrium).

In 2007, the Panel judged that drinking coffee is unlikely to have a substantial effect on the risk of two cancers (pancreas and kidney). The CUP analyses included additional studies; the summary risk estimate was not close to null and there was more variability between the studies. The evidence for those two cancers is now judged to be too limited for conclusions to be drawn.



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## Abbreviations

<b>AICR</b>	American Institute for Cancer Research
<b>CI</b>	Confidence interval
<b>CUP</b>	Continuous Update Project
<b>DNA</b>	Deoxyribonucleic acid
<b>HPV</b>	Human papilloma viruses
<b>IARC</b>	International Agency for Research on Cancer
<b>IRR</b>	Incident rate ratio
<b>MHT</b>	Menopausal hormone therapy
<b>NSCLC</b>	Non-small-cell lung cancer
<b>RR</b>	Relative risk
<b>ROS</b>	Reactive oxygen species
<b>SCLC</b>	Small-cell lung cancer
<b>SLR</b>	Systematic literature review
<b>SMR</b>	Standardised mortality ratio
<b>WCRF</b>	World Cancer Research Fund

# Glossary

## **Adenocarcinoma**

Cancer of glandular epithelial cells.

## **Adipokines**

Cytokines (cell signalling proteins) secreted by adipose tissue.

## **Adiponectin**

A protein secreted by adipose tissue that is inversely related to body fatness. High concentrations have been associated with a lower risk of kidney cancer.

## **Adjustment**

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

## **Angiogenesis**

The process of generating new blood vessels.

## **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**).

## **Apoptosis**

The death of cells that occurs as a normal and controlled part of the cell cycle.

## **Arseniasis**

Chronic arsenic poisoning.

## **Basal cell carcinoma**

A type of cancer of the basal cells at the bottom of the epidermis. The most common form of skin cancer. Basal cell carcinomas are usually found on areas of the body exposed to the sun. They rarely metastasise (spread) to other parts of the body.

## **Bile**

A greenish-yellow fluid secreted by the liver and stored in the gallbladder. Bile plays an important role in the intestinal absorption of fats. Bile contains cholesterol, bile salts and waste products such as bilirubin.

## **Bioactive constituents**

Compounds that have an effect on a living organism, tissue or cell. In nutrition, bioactive compounds are distinguished from nutrients.

## **Caffeine**

An alkaloid found in coffee, tea, kola nuts, chocolate and other foods that acts as a stimulant and a diuretic.

**Calcium**

An essential nutrient for many regulatory processes in all living cells, in addition to playing a structural role in the skeleton. Calcium plays a critical role in the complex hormonal and nutritional regulatory network related to vitamin D metabolism, which maintains the serum concentration of calcium within a narrow range while optimising calcium absorption to support host function and skeletal health.

**Carcinogen**

Any substance or agent capable of causing cancer.

**Carcinogenesis**

The process by which a malignant tumour is formed.

**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.

**Cholangiocarcinoma**

A malignant tumour in the ducts that carry bile from the liver to the small intestine.

**Cholesterol**

The principal sterol in animal tissues, synthesised in the body; an essential component of cell membranes and the precursor of the steroid hormones and vitamin D.

**Chronic**

Describing a condition or disease that is persistent or long lasting.

**Cirrhosis**

A condition in which normal liver tissue is replaced by scar tissue (fibrosis), with nodules of regenerative liver tissue.

**Clear cell renal cell carcinoma (CCRCC)**

The most common type of kidney cancer in adults, characterised by malignant epithelial cells with clear cytoplasm.

**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.

### **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.

### **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.

### **DNA methylation**

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

### **Dose–response**

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

### **Ecological study**

A study in which differences in patterns of exposure, for instance in consumption of a particular nutrient or food, are compared at aggregate level, with populations (rather than individual people) as the unit of analysis.

### **Effect modification**

Effect modification (or effect-measure modification) occurs when the effect of an exposure differs according to levels of another variable (the modifier).

### **Egger's test**

A statistical test for small study effects such as publication bias.

### **Energy**

Energy, measured as calories or joules, is required for all metabolic processes. Fats, carbohydrates, proteins and alcohol from foods and drinks release energy when they are metabolised in the body.

### **Epithelial (see epithelium)**

**Epithelium**

The layer of cells covering internal and external surfaces of the body, including the skin and mucous membranes lining body cavities such as the lung, gut and urinary tract.

**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.

**Familial**

Relating to or occurring in a family or its members.

**Head and neck cancer**

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

***Helicobacter pylori (H. pylori)***

A gram-negative bacterium that lives in the human stomach. It colonises the gastric mucosa and elicits both inflammatory and lifelong immune responses.

**Hepatitis**

Inflammation of the liver, which can occur as the result of a viral infection or autoimmune disease, or because the liver is exposed to harmful substances, such as alcohol.

**Hepatocellular carcinoma**

Primary malignant tumour of the liver.

**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<sup>2</sup> test.

**Hormone**

A substance secreted by specialised cells that affects the structure and/or function of cells or tissues in another part of the body.

**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'.

**Melanoma**

Malignant tumour of the skin derived from the pigment-producing cells (melanocytes).

**Menopausal hormone therapy (MHT)**

Treatment with oestrogens and progesterones with the aim of alleviating menopausal symptoms or osteoporosis. Also known as hormone replacement therapy.

**Meta-analysis**

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

**Metastasis/metastatic spread**

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

**Micronutrient**

Vitamins and minerals present in foods and required in the diet for normal body function in small quantities conventionally of less than 1 gram per day.

**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.

**Nitrosamine**

A compound created from a reaction between nitrites and amino compounds, which may occur during meat curing. Many nitrosamines are known carcinogens.

**Non-cardia stomach cancer**

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

**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.

**Non-linear analysis**

A non-linear dose–response meta-analysis does not assume a linear dose–response relationship between exposure and outcome. It is useful for identifying whether there is a threshold or plateau.

**Obesity**

Excess body fat to a degree that increases the risk of various diseases. Conventionally defined as a BMI of 30 kg/m<sup>2</sup> or more. Different cut-off points have been proposed for specific populations.

**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.

**Oestrogen**

The female sex hormones, produced mainly by the ovaries during reproductive life and also by adipose tissue.

**p53**

A protein central to regulation of cell growth. Mutations of the p53 gene are important causes of cancer.

**Phytochemicals**

Non-nutritive bioactive plant substances that may have biological activity in humans.

**Progesterone**

Female sex hormone, produced mainly by the ovaries during reproductive life and by the placenta during pregnancy.

**Reactive oxygen species (ROS)**

Oxygen-containing radical species or reactive ions that can oxidise DNA (remove electrons), for example, hydroxyl radical (OH<sup>-</sup>), hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) or superoxide radical (O<sup>2-</sup>).

**Selection bias**

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

**Squamous cell carcinoma**

A malignant cancer derived from squamous epithelial cells.

**Statistical power**

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

**Systematic literature review (SLR)**

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

**Transitional cell carcinomas**

Cancer that develops in the lining of the renal pelvis, ureter or bladder.

**Tumorigenesis**

The process of tumour development.

**Tumour suppressor gene**

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

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## Appendix 1: Criteria for grading evidence for cancer prevention

Adapted from Chapter 3 of the [2007 Second Expert Report](#) [1]. 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.

## Appendix 2: Mechanisms

The evidence on mechanisms has been based on human and animal studies. Though not a systematic or exhaustive search, the expert reviews represent the range of currently prevailing hypotheses.

### Arsenic in drinking water

#### Lung

The mechanisms linking arsenic in drinking water with cancer development are poorly understood. Experimental studies suggest that exposure to arsenic and its metabolites induces production of *reactive oxygen species* inducing DNA damage, altering transcription factor function, and modulating the expression of genes involved in cell growth, survival and cancer risk [70, 71]. It is currently uncertain, however, whether these mechanisms are specifically relevant for lung cancer.

#### Bladder

The mechanisms linking arsenic in drinking water with cancer development are poorly understood. Experimental studies suggest that exposure to arsenic and its metabolites induces excessive *reactive oxygen species* inducing DNA damage, altering transcription factor function and modulating the expression of genes involved in cell growth, survival and cancer risk [70, 71]. It is currently uncertain, however, whether these mechanisms are specifically relevant for bladder cancer.

#### Skin

The mechanisms linking arsenic in drinking water with cancer development are poorly understood. Experimental studies suggest that arsenic exhibits tumour-promoting properties by inducing oxidative DNA damage, activating transcription factors and modulating the expression of genes involved in cell growth [70, 71]. It is currently uncertain, however, whether these mechanisms are applicable specifically to skin cancer.

#### Kidney

The mechanisms linking arsenic in drinking water with cancer development are poorly understood. Experimental studies suggest that exposure to arsenic and its metabolites induces excessive *reactive oxygen species* inducing DNA damage, altering transcription factor function, and modulating the expression of genes involved in cell growth, survival and cancer risk [70, 71]. It is currently uncertain, however, whether these mechanisms are specifically relevant for kidney cancer.

### Mate

#### Oesophagus (squamous cell carcinoma)

Mate is an infusion made from the dried leaves of the plant *Ilex paraguariensis*. Habitually consumed in South America, mate can be drunk hot or cold. Any carcinogenic effects of mate are believed to be due to consumption at very hot temperatures (over 65°C), increasing the incidence of *nitrosamine*-induced tumours [3, 86].

## Mouth, pharynx and larynx

Mate is an infusion made from the dried leaves of the plant, *Ilex paraguariensis*. Habitually consumed in South America, mate can be consumed hot or cold. Any carcinogenic effects of mate are believed to be due to consumption at very hot temperatures (over 65°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 [3, 86].

## Coffee

### Liver

Coffee is rich in a large number of bioactive compounds including *caffeine*, chlorogenic acids and numerous phenolic compounds. Emerging evidence suggests that these compounds may have beneficial effects on the liver ranging from *antioxidant*, anti-inflammatory properties to the inhibition of *angiogenesis*, but the main underlying mechanisms of the role of coffee in liver cancer development are not fully elucidated [95]. Coffee is also associated with improved insulin sensitivity [96], decreased incidence of metabolic syndrome [97] and reduced level of liver injury [98], which could represent additional mechanisms by which coffee drinking may reduce the risk of liver cancer development.

### Endometrium

The mechanisms linking coffee consumption to a decrease in endometrial cancer risk remain unclear but may involve lower circulating levels of bioavailable sex steroids or insulin and higher insulin sensitivity in people who drink coffee [109–111]. Coffee drinking is correlated with higher levels of sex hormone-binding globulin (SHBG), which may decrease exposure to bioavailable oestradiol levels [109, 112, 113]. A large cross-sectional study of more than 1,200 women in the Nurses' Health Study reported that in premenopausal women, coffee intake was associated with lower luteal phase total and free oestradiol levels, while in postmenopausal women *caffeine* and coffee intake were positively associated with SHBG levels [114]. Coffee drinking is also associated with reduced insulin levels, particularly among overweight women [110], and it has been hypothesised that coffee may reduce the risk of endometrial cancer through an insulin-mediated mechanism. Coffee has also been shown to alter *adipokines* and inflammatory pathways and lead to an increase in *adiponectin* levels [111, 115] – an adipokine that is down-regulated in *obesity* and has been linked to endometrial cancer development [116, 117].

## Mouth, pharynx and larynx

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 [118, 119]. Coffee is also a source of natural diterpenes, such as cafestol and kahweol, which have been shown to induce *apoptosis* and have anti-oxidative and anti-inflammatory effects [120, 121]. 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.

### **Skin (basal cell carcinoma [men and women] and malignant melanoma [women])**

The exact biological mechanisms linking coffee consumption to malignant *melanoma* and basal cell carcinoma are uncertain. Coffee drinking provides exposure to a range of biologically active compounds, many of which have been demonstrated in *in vitro* and animal studies to have anti-oxidant and anti-tumorigenic properties. These include high levels of certain phenolic *phytochemicals*, such as the anti-oxidants caffeic acid and chlorogenic acid, and natural diterpenes, such as cafestol and kahweol, which have been shown to inhibit changes in *DNA methylation* [119], induce *apoptosis*, and have anti-oxidative and anti-inflammatory effects [120–123].

### **Tea**

#### **Bladder**

Tea is a rich source of biologically active compounds, including polyphenols. Animal models have shown that certain polyphenols found within green tea inhibited bladder cancer tumour growth [124]. However, more evidence is required to assess any possible anti-tumorigenic role of tea consumption on bladder cancer.

# 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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