

World
Cancer
Research
Fund



American
Institute for
Cancer
Research

CUP Continuous
Update
Project

Analysing research on cancer
prevention and survival



Wholegrains, vegetables and fruit 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. [Wholegrains, vegetables and fruit 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

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.

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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 wholegrains, vegetables and fruit as well as some individual constituents of these foods affects the risk of developing cancer.¹ 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].

Grains, or cereals, are the seeds and energy stores of cultivated grasses. The main types are wheat, rice, maize (corn), millet, sorghum, barley, oats and rye. Wholegrains are grains and grain products made from the entire grain seed, which consists of the bran, germ and endosperm. Wholegrains contain starch and protein as well as variable amounts of fibre, B vitamins and other *micronutrients* that are most concentrated in the germ and outer layers of the grain. Refining of wholegrains usually removes the germ and outer layers of the grain, thereby reducing the presence of fibre and micronutrients. Consumption of grains in refined forms, such as white rice, bread or pasta, is generally more common than consumption in wholegrain form.

Definitions of dietary fibre vary, but it may be defined briefly as constituents of plant cell walls that are not digested in the small intestine. Pulses (legumes) such as beans, lentils, peas and peanuts (groundnuts) as well as minimally processed grains are particularly concentrated sources of dietary fibre. However, vegetables, fruit, nuts and seeds contain significant amounts of dietary fibre too.

Grains and pulses (legumes) may be contaminated with *mycotoxins* such as *aflatoxins*, which are produced by certain moulds growing on agricultural crops. People can be exposed to aflatoxins by eating contaminated foods. Although moulds that contaminate foods are usually destroyed by cooking, any toxins they produce may remain. All naturally occurring aflatoxins are classified as human carcinogens by the International Agency for Research on Cancer (IARC). Aflatoxins are most problematic in countries with hot, damp climates and poor storage facilities. Levels of aflatoxin contamination tend to be highest in sub-Saharan Africa and South-East Asia, as well as China, and rates of liver cancer are high in these countries. Aflatoxin-contaminated foods are generally consumed in the countries where they are produced, but they may also be exported to neighbouring countries and intercontinentally.

There are two main ways of defining vegetables and fruit: botanical and culinary. Botanical definitions are more precise than culinary definitions, but culinary definitions are more commonly understood as they are based on cultural uses of foods and they align with how most people think of vegetables and fruit. The CUP has therefore used culinary definitions of vegetables and fruit in this Third Expert Report.

The culinary term ‘vegetables’ refers to the edible parts of plants (for example, edible leaves, roots, tubers, bulbs, stems and stalks, flowers and grains that are used as vegetables (such as sweetcorn)) and usually includes fungi (mushrooms, truffles) and algae (seaweed). Vegetables can be separated into groups according to their individual starch content: starchy vegetables such as potatoes, sweet potatoes (yams), cassava (manioc), sago yams and taro contain higher levels of carbohydrate than non-starchy vegetables. Levels of other *nutrients* also vary between the two groups. Examples of non-starchy vegetables include carrots, beets, parsnips, turnips and swedes

¹ 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.

as well as green, leafy vegetables (such as spinach and lettuce); cruciferous vegetables (the cabbage family, for example, bok choy [pak choy], broccoli, cabbage and watercress); and allium vegetables (such as onions, garlic and leeks).

The culinary term 'fruit' refers to the edible part of a plant, tree, bush or vine that contains the seeds and pulpy surrounding tissue and has a sweet or tart taste. Apples, bananas, berries, figs, grapes, mangoes and melons are common types of fruit, as well as citrus fruit such as oranges, grapefruit, lemons and limes, and dried fruit such as apricots, figs and raisins.

The composition of fruit and vegetables depends both on species and on subtype, as well as on the environmental, farming, production and storage conditions. In addition to dietary fibre, vegetables and fruit are sources of a wide variety of vitamins, minerals and other *bioactive compounds*.

Some individual constituents of vegetables and fruit have been identified in this Third Expert Report as being associated with cancer risk based on the evidence reviewed in the CUP. These individual constituents include vitamin C as well as other biologically active compounds such as *carotenoids* (red, orange and yellow pigments found in varying concentrations in all vegetables including beta-carotene) and isoflavones (plant-derived compounds with oestrogen-like properties).

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](#)).

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:

- **wholegrains decreases** the risk of colorectal cancer
- **foods containing dietary fibre decreases** the risk of colorectal cancer
- **beta-carotene in foods or supplements is unlikely to have a substantial effect** on the risk of prostate cancer
- **foods contaminated by aflatoxins increases** the risk of liver cancer
- **foods preserved by salting (including preserved non-starchy vegetables) increases** the risk of stomach cancer

For wholegrains and foods containing dietary fibre the evidence shows that, in general, the more people consume, the lower the risk of some cancers. In contrast, for foods preserved by salting (including preserved non-starchy vegetables) the evidence shows that, in general, the more people consume, the higher the risk of stomach cancer. For foods contaminated by aflatoxins, conclusions can only be drawn for the levels of exposure that were investigated in the studies using *biomarkers*.

The Panel used the strong evidence on wholegrains and foods containing dietary fibre when making Recommendations designed to reduce the risk of developing cancer.

Although contamination of foods with aflatoxins is a public health issue, individuals themselves cannot necessarily influence whether foods are contaminated before being sold. It is therefore inappropriate to make a global recommendation on the consumption of foods contaminated by aflatoxins. Nevertheless, the Panel advises people against eating mouldy grains or mouldy pulses (legumes) and advises governments to ensure facilities for the safe storage of foods are made available in areas at risk of aflatoxin contamination (see [Recommendations and public health and policy implications](#), Section 3: Issues of public health significance).

A global Recommendation about consumption of foods preserved by salting (including preserved non-starchy vegetables) has not been made, as these types of food are mostly consumed only in Asia. Nevertheless, the Panel advises that foods be preserved without using salt (see [Recommendations and public health and policy implications](#), Section 3: Issues relevant only in specific parts of the world – Foods preserved by salting).

There is also evidence on non-starchy vegetables, fruit and their constituents that is limited (either in amount or by methodological flaws) but is suggestive of a decreased risk of many cancers with greater consumption. In addition, consumption of non-starchy vegetables and fruit is a consistent feature of dietary patterns that have been associated with lower risk of cancer and of other non-communicable diseases, as well as *obesity*.

Where possible, the Panel uses only evidence that is judged to be ‘strong’ (either ‘convincing’ or ‘probable’) as a basis for the Cancer Prevention Recommendations. Evidence that is judged to be ‘limited – suggestive’ is not normally sufficient to support Recommendations. However, the Panel notes that while the evidence for links between individual cancers and non-starchy vegetables or fruit is limited, the pattern of association is consistent and in the same

direction, and overall the evidence is more persuasive of a protective effect.

The CUP Panel concluded:

- Overall, greater consumption of non-starchy vegetables or fruit probably protects against a number of aerodigestive cancers.

Therefore, evidence for non-starchy vegetables and fruit and some of their constituents that was judged to be ‘limited – suggestive’ is described in detail in this part of the Third Expert Report. This contrasts with other parts of this Third Expert Report, where less information is provided on ‘limited – suggestive’ evidence.

In addition, there is other evidence on consumption of preserved non-starchy vegetables that is limited (either in amount or by methodological flaws) but is suggestive of an increased risk of nasopharyngeal cancer. 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. Wholegrains, vegetables, fruit and pulses (legumes) such as beans and lentils are a major part of a healthy diet. 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

1. Wholegrains, vegetables and fruit and the risk of cancer: a summary matrix

WHOLEGRAINS, VEGETABLES AND FRUIT AND THE RISK OF CANCER							
WCRF/AICR GRADING		DECREASES RISK		INCREASES RISK			
		Exposure	Cancer site	Exposure	Cancer site		
STRONG EVIDENCE	Convincing			Aflatoxins	Liver 2015 ¹		
	Probable	Wholegrains	Colorectum 2017	Foods preserved by salting (including preserved non-starchy vegetables)	Stomach 2016 ²		
		Foods containing dietary fibre	Colorectum 2017 ³				
		Non-starchy vegetables and fruit (aggregated)	Aerodigestive cancer and some other cancers (aggregated) ⁴				
LIMITED EVIDENCE	Limited – suggestive	Non-starchy vegetables	Mouth, pharynx and larynx 2018	Non-starchy vegetables (low intake)	Colorectum 2017 ⁵		
			Nasopharynx 2017			Preserved non-starchy vegetables	Nasopharynx 2017
			Oesophagus (adenocarcinoma) 2016				
		Oesophagus (squamous cell carcinoma) 2016	Lung (people who smoke or used to smoke tobacco) 2017	Breast (oestrogen receptor-negative) ⁸ 2017			
		Fruit			Oesophagus (squamous cell carcinoma) 2016	Lung (people who smoke or used to smoke tobacco) 2017	
		Citrus fruit	Stomach (cardia) 2016	Fruit (low intake)	Stomach 2016 ⁶		
		Non-starchy vegetables and fruit	Bladder 2015 ⁹			Lung 2017 ¹⁰	Colorectum 2017 ⁷
		Foods containing carotenoids	Breast 2017 ¹¹				
		Foods containing beta-carotene	Lung 2017 ¹²				
Foods containing vitamin C	Lung (people who smoke tobacco) 2017 ¹³						
Foods containing isoflavones	Colorectum (colon) 2017 ¹⁴						
		Lung (people who have never smoked tobacco) 2017 ¹⁵					
STRONG EVIDENCE	Substantial effect on risk unlikely	Beta-carotene: Prostate 2014 ¹⁶					

- 1 The evidence for aflatoxins and liver cancer relates to foods that may be contaminated with aflatoxins and includes cereals (grains) as well as pulses (legumes), seeds, nuts and some vegetables and fruit. The studies reported on elevated levels of biomarkers of aflatoxin exposure.
- 2 For preserved non-starchy vegetables and stomach cancer, there is no separate conclusion. The evidence was included in ‘foods preserved by salting’, which assessed the evidence for salt-preserved vegetables, salt-preserved fish and salt-preserved foods. The term ‘foods preserved by salting’ refers mainly to high-salt foods and salt-preserved foods, including pickled vegetables and salted or dried fish, as traditionally prepared in East Asia.
- 3 The evidence for foods containing dietary fibre and colorectal cancer includes both foods that naturally contain fibre and foods that have had fibre added.
- 4 The Panel notes that while the evidence for links between individual cancers and non-starchy vegetables or fruit is limited, the pattern of association is consistent and in the same direction, and overall the evidence is more persuasive of a protective effect: greater consumption of non-starchy vegetables or fruit probably protects against a number of aerodigestive cancers.
- 5 Although the dose–response meta-analysis for colorectal cancer showed a statistically significant decreased risk with increased consumption of non-starchy vegetables, a non-linear relationship was apparent, which showed a significant increased risk at intakes of 100 grams or less per day when compared with an intake of 200 grams per day. For information on the evidence that led to the Panel’s conclusion, see **Section 5.4.8**.
- 6 An increased risk of stomach cancer was not apparent when the data for fruit were analysed assuming a linear response but became apparent when conducting a non-linear analysis, which showed a significant increased risk at intakes below 45 grams per day when compared with an intake of about 100 grams per day. For information on the evidence supporting the conclusion, see **Section 5.6.4**.
- 7 Although the dose–response meta-analysis for colorectal cancer showed a statistically significant decreased risk with increased consumption of fruit, a non-linear relationship was apparent, which showed a significant increased risk at intakes of 100 grams or less per day when compared with an intake of 200 grams per day. For information on the evidence that led to the conclusion, see **Section 5.6.5**.
- 8 The Panel’s conclusion for non-starchy vegetables and breast cancer relates to evidence for breast cancer overall (menopausal status not specified). The observed association was in oestrogen receptor-negative (ER-negative or ER–) breast cancer only.
- 9 The evidence for non-starchy vegetables and fruit and bladder cancer relates to combined consumption of vegetables and fruit.
- 10 The evidence for foods containing carotenoids and lung cancer is derived from studies on dietary intake and serum levels.
- 11 The Panel’s conclusion for foods containing carotenoids and breast cancer relates to the evidence for breast cancer overall (menopausal status not specified). The evidence is derived from studies on dietary intake and serum or plasma levels and includes both foods that naturally contain carotenoids and foods that have had carotenoids added.
- 12 The evidence for foods containing beta-carotene and lung cancer is derived from studies on dietary intake and serum levels.
- 13 The evidence for foods containing vitamin C and lung cancer in people who smoke tobacco is derived from studies on dietary intake.
- 14 The Panel’s conclusion is for foods containing vitamin C and colon cancer. No conclusion was drawn for foods containing vitamin C and rectal cancer.
- 15 The evidence for foods containing isoflavones and lung cancer in people who have never smoked tobacco is derived from studies on dietary intake.
- 16 The evidence for beta-carotene and prostate cancer is derived from studies on dietary intake and serum or plasma levels, as well as studies on supplement use (20, 30 and 50 milligrams per day).

Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from those for nasopharynx, cervix and skin, where 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 by 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 wholegrains, vegetables and fruit to the risk of development of particular cancer types. Each conclusion on the likely causal relationship between wholegrains, vegetables and fruit 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.

For wholegrains and foods containing dietary fibre the evidence shows that, in general, the more people consume, the lower the risk of some cancers. In contrast, for foods preserved by salting (including preserved non-starchy vegetables) the evidence shows that,

in general, the more people consume, the higher the risk of stomach cancer. For foods contaminated by *aflatoxins*, conclusions can be drawn only for the levels of exposure that were investigated in the studies using *biomarkers*.

The Panel used the strong evidence on wholegrains and foods containing dietary fibre when making Recommendations designed to reduce the risk of developing cancer (see [Recommendations and public health and policy implications](#), Section 2: Recommendations for Cancer Prevention).

Although contamination of foods with aflatoxins is a public health issue, individuals themselves cannot necessarily influence whether foods are contaminated before being sold. It is therefore inappropriate to make a global recommendation on the consumption of foods contaminated by aflatoxins. Nevertheless, the Panel advises against eating mouldy grains or mouldy pulses (legumes) and advises governments to ensure facilities for the safe storage of foods are made available in areas at risk of aflatoxin contamination (see [Recommendations and public health and policy implications](#), Section 3: Issues of public health significance).

The CUP Panel concluded:

STRONG EVIDENCE

Convincing

- **Increased risk**

- **Aflatoxins:** Consumption of *aflatoxin*-contaminated foods is a convincing cause of liver cancer.¹

Probable

- **Decreased risk**

- **Wholegrains:** Consumption of wholegrains probably protects against colorectal cancer.

- **Foods containing dietary fibre:**

Consumption of foods containing dietary fibre probably protects against colorectal cancer.²

- **Increased risk**

- **Foods preserved by salting (including preserved non-starchy vegetables):** Consumption of foods preserved by salting is probably a cause of stomach cancer.³

- **Substantial effect on risk unlikely**

- **Beta-carotene:** Consumption of beta-carotene in foods or supplements is unlikely to have a substantial effect on the risk of prostate cancer.⁴

Please page 13 for explanation of footnotes.

A global Recommendation about consumption of foods preserved by salting (including preserved non-starchy vegetables) has not been made as these types of food are mostly consumed only in Asia. Nevertheless, the

Panel advises that foods are preserved without using salt (see [Recommendations and public health and policy implications](#), Section 3: Issues relevant only in specific parts of the world – Foods preserved by salting).

LIMITED EVIDENCE

Limited – suggestive

● Decreased risk

- **Non-starchy vegetables:** The evidence suggesting that greater consumption of non-starchy vegetables decreases the risk of cancers of the following types is limited: mouth, pharynx and larynx; nasopharynx; oesophagus (*adenocarcinoma* and *squamous cell carcinoma*); lung (in people who smoke or used to smoke tobacco); and breast (oestrogen receptor-negative).⁵
- **Fruit:** The evidence suggesting that greater consumption of fruit decreases the risk of oesophageal cancer (*squamous cell carcinoma*) and lung cancer (people who smoke or used to smoke tobacco) is limited.
- **Citrus fruit:** The evidence suggesting that greater consumption of citrus fruit decreases the risk of stomach cancer (*cardia*) is limited.
- **Non-starchy vegetables and fruit:** The evidence suggesting that greater combined consumption of non-starchy vegetables and fruit decreases the risk of bladder cancer⁶ is limited.
- **Foods containing carotenoids:** The evidence suggesting that greater consumption of foods containing carotenoids decreases the risk of lung cancer⁷ and breast cancer⁸ is limited.
- **Foods containing beta-carotene:** The evidence suggesting that greater consumption of foods containing beta-carotene decreases the risk of lung cancer⁹ is limited.

- **Foods containing vitamin C:** The evidence suggesting that greater consumption of foods containing vitamin C decreases the risk of lung cancer (in people who smoke tobacco)¹⁰ and colon cancer¹¹ is limited.
- **Foods containing isoflavones:** The evidence suggesting that greater consumption of foods containing isoflavones decreases the risk of lung cancer (in people who have never smoked tobacco)¹² is limited.

● Increased risk

- **Non-starchy vegetables (low intake):** The evidence suggesting that low consumption of non-starchy vegetables increases the risk of colorectal cancer¹³ (increased risk was apparent at intakes of 100 grams or less per day when compared with an intake of 200 grams per day or more) is limited.
- **Preserved non-starchy vegetables:** The evidence suggesting that greater consumption of preserved non-starchy vegetables increases the risk of nasopharyngeal cancer is limited.
- **Fruit (low intake):** The evidence suggesting that low consumption of fruit increases the risk of stomach cancer¹⁴ (increased risk was apparent at intakes below about 45 grams per day when compared with an intake of about 100 grams per day) and colorectal cancer¹⁵ (increased risk was apparent at intakes of 100 grams or less per day when compared with an intake of 200 grams per day or more) is limited.

Where possible, the Panel uses only evidence that is judged to be ‘strong’ (either ‘convincing’ or ‘probable’) as a basis for the Cancer Prevention Recommendations. Evidence that is judged to be ‘limited – suggestive’ is not normally sufficient to support Recommendations. However, the Panel notes that while the evidence for links between individual cancers and non-starchy vegetables or fruit is limited, the pattern of association is consistent and in the same direction, and overall the evidence is more persuasive of a protective effect: greater consumption of non-starchy vegetables or fruit probably protects against a number of aerodigestive cancers. In addition, consumption of non-starchy vegetables and fruit is a consistent feature of dietary patterns that have been associated with lower risk of cancer and of other non-communicable diseases, as well as *obesity*.

The CUP Panel concluded:

- **Overall, greater consumption of non-starchy vegetables or fruit probably protects against a number of aerodigestive cancers.**

Therefore, evidence for non-starchy vegetables and fruit and some of their constituents that was judged to be ‘limited – suggestive’ is described in detail in this part of the Third Expert Report. This contrasts with other parts of this Third Expert Report, where less information is provided on ‘limited – suggestive’ evidence.

In addition, there is other evidence on consumption of preserved non-starchy vegetables that is limited (either in amount or by methodological flaws) but is suggestive of an increased risk of nasopharyngeal cancer. Further research is required, and the Panel has not used this evidence to make recommendations.

See Definitions of WCRF/AICR grading criteria (**Section 1: Wholegrains, vegetables and fruit and the risk of cancer: a summary matrix**) for explanations of what the Panel means by ‘strong evidence’, ‘convincing’, ‘probable’, ‘substantial effect on risk unlikely’, ‘limited evidence’ and ‘limited – suggestive’.

- ¹ The evidence for aflatoxins and liver cancer relates to foods that may be contaminated with aflatoxins and includes cereals (grains) as well as pulses (legumes), seeds, nuts and some vegetables and fruit. The studies reported on elevated levels of biomarkers of aflatoxin exposure.
- ² The evidence for foods containing dietary fibre and colorectal cancer includes both foods that naturally contain fibre and foods that have had fibre added.
- ³ For preserved non-starchy vegetables and stomach cancer, there is no separate conclusion. The evidence was included in ‘foods preserved by salting’, which assessed the evidence for salt-preserved vegetables, salt-preserved fish and salt-preserved foods. The term ‘foods preserved by salting’ refers mainly to high-salt foods and salt-preserved foods, including pickled vegetables and salted or dried fish, as traditionally prepared in East Asia.
- ⁴ The evidence for beta-carotene and prostate cancer is derived from studies on dietary intake and serum or plasma levels, as well as studies on supplement use (20, 30 and 50 milligrams per day).
- ⁵ The Panel’s conclusion for non-starchy vegetables and breast cancer relates to evidence for breast cancer overall (menopausal status not specified). The observed association was in oestrogen receptor-negative (ER-negative or ER-) breast cancer only.
- ⁶ The evidence for non-starchy vegetables and fruit and bladder cancer relates to combined consumption of vegetables and fruit.
- ⁷ The evidence for foods containing carotenoids and lung cancer is derived from studies on dietary intake and serum levels.
- ⁸ The Panel’s conclusion for foods containing carotenoids and breast cancer relates to the evidence for breast cancer overall (menopausal status not specified). The evidence is derived from studies on dietary intake and serum or plasma levels, and includes both foods that naturally contain carotenoids and foods that have had carotenoids added.
- ⁹ The evidence for foods containing beta-carotene and lung cancer is derived from studies on dietary intake and serum levels.
- ¹⁰ The evidence for foods containing vitamin C and lung cancer in people who smoke tobacco is derived from studies on dietary intake.
- ¹¹ The Panel’s conclusion is for foods containing vitamin C and colon cancer. No conclusion was drawn for foods containing vitamin C and rectal cancer.
- ¹² The evidence for foods containing isoflavones and lung cancer in people who have never smoked tobacco is derived from studies on dietary intake.
- ¹³ Although the dose–response meta-analysis for colorectal cancer showed a statistically significant decreased risk with increased consumption of non-starchy vegetables, a non-linear relationship was apparent, which showed a significant increased risk at intakes of 100 grams or less per day when compared with an intake of 200 grams per day. For information on the evidence that led to the Panel’s conclusion, see **Section 5.4.8**.
- ¹⁴ An increased risk of stomach cancer was not apparent when the data for fruit were analysed assuming a linear response, but became apparent when conducting a non-linear analysis which showed a significant increased risk at intakes below 45 grams per day when compared with an intake of about 100 grams per day. For information on the evidence supporting the conclusion, see **Section 5.6.4**.
- ¹⁵ Although the dose–response meta-analysis for colorectal cancer showed a statistically significant decreased risk with increased consumption of fruit, a non-linear relationship was apparent, which showed a significant increased risk at intakes of 100 grams or less per day when compared with an intake of 200 grams per day. For information on the evidence that led to the conclusion, see **Section 5.6.5**.

3. Definitions and patterns

3.1 Wholegrains

3.1.1 Definitions and sources

Grains, or cereals, are the seeds and energy stores of cultivated grasses. The main types are wheat, rice, maize (corn), millet, sorghum, barley, oats and rye.

Wholegrains are grains and grain products made from the entire grain seed, usually called the kernel, which consists of the bran, germ and endosperm [2]. If the kernel has been cracked, crushed or flaked, it must retain the same relative proportions of bran, germ, and endosperm as the original grain to be called wholegrain [2]. Wholegrains vary in their dietary fibre content [2]. Some countries define the minimum content of the constituents of the unprocessed grain required to allow a product to be described as wholegrain [3].

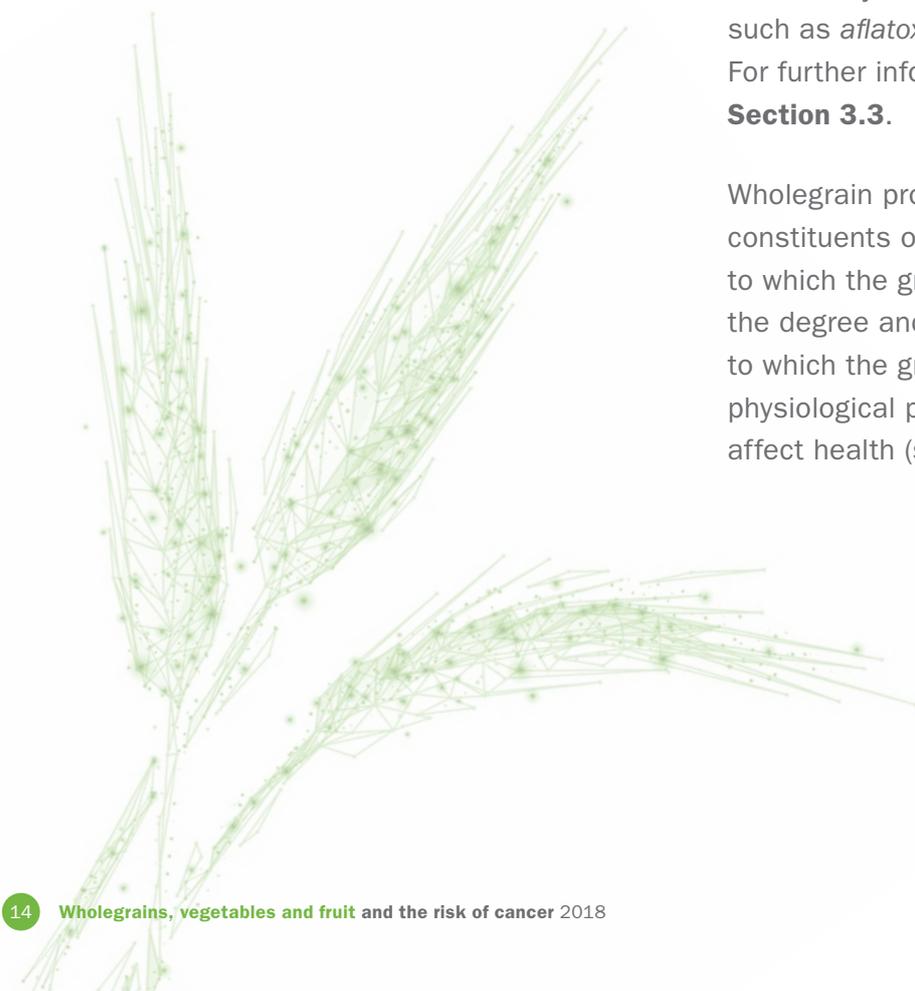
3.1.2 Composition

Starch makes up about 70 per cent of the raw weight of the endosperm of unprocessed grains. The germ is the embryonic part of cereal plants and contains oils, proteins and fibre. The outer parts of the grain (the bran and the aleurone layer, which is the outermost layer of the endosperm) contain non-starch polysaccharides, a type of carbohydrate that is the major component of dietary fibre (for more information about the definition of dietary fibre, see **Section 3.2**). In addition to starch, grains contain protein, oils, B vitamins, vitamin E, iron and various trace elements, as well as *phytochemicals*, some of which are bioactive. As these substances are most concentrated in the germ and the outer layers of the grain, their presence, as well as that of dietary fibre, may be reduced by refining.

Different grains can also contain other specific components. Wheat contains gluten (a mixture of proteins). Rye has high levels of pentosans, and oats contain beta-glucans, both of which are non-starch polysaccharides.

Grains may be contaminated with *mycotoxins* such as *aflatoxins*, as may pulses (legumes). For further information on aflatoxins, see **Section 3.3**.

Wholegrain products generally contain all the constituents of the grain. However, the extent to which the grain remains intact depends on the degree and type of processing. The extent to which the grain is processed can influence physiological processes in the bowel and may affect health (see **Box 1**).



Box 1: Refinement and processing of grains

Many of the grains (cereals) that we consume are refined. All grains contain starch and protein in the endosperm, and unrefined wholegrains contain variable amounts of additional protein, B vitamins and fibre, as well as *phytochemicals*, concentrated in the germ and outer layers (bran and aleurone layer, which is the outermost layer of the endosperm). During refining, grains are first broken into pieces and the bran, germ and, usually, the aleurone layer are sifted away. This removes most of the fibre, oil and B vitamins, as well as approximately 25 per cent of the protein. Polishing, as is often performed on rice, removes additional *nutrients*. Many countries therefore fortify refined grains, including flour, with B vitamins and iron.

Consumption of grains in refined forms, such as white rice, bread or pasta, is generally more common than consumption in wholegrain form. Refined grains are considered easier than wholegrains to cook and to chew, are light in colour (which is attractive to many consumers), have a longer shelf life than wholegrain products (as the oil in bran turns rancid relatively quickly) and cost less to purchase.

Breakfast cereals, particularly in the USA and parts of Europe, also account for a significant proportion of grains eaten. Many breakfast cereals, although based on grains (whole or refined), contain substantial amounts of added sugars.

Grains are further processed to provide ingredients such as corn syrup, starch or alcohol. They also form the basis of many animal feeds.

In general, processed grains have a higher glycaemic index than unprocessed grains, and the greater the degree of processing, the greater the glycaemic index (see [Exposures: Other dietary exposures](#), Section 3.2).

3.1.3 Consumption patterns

As societies moved to more settled, agricultural ways of life 10,000–15,000 years ago, grains from cereal crops became the main staple foods. The types of cereal crops grown depended largely on climate and terrain. Wheat, barley, oats and rye are traditionally staple foods in the Middle East and Europe, rice in Asia, maize (corn) in the Americas, and sorghum and millet in Africa (for information about foods made from grains, see **Box 2**). The market for cereal crops and their products is now global, although the markets for some grains, such as sorghum, remain largely regional.

Cereal crop cultivation and consumption tends to be highest in most of Asia and lowest in Oceania, parts of Europe and North America [4].

Globally, about 150 kilograms per capita per year of grains and their products are available for consumption, which supplies average daily intakes of about 1,300 kilocalories [4]. Diets based on relatively unprocessed grain products tend to be bulky, with a low *energy* density. The availability of grains and their products for consumption is highest in Asia (156 kilograms per capita per year in 2013) and Africa (151), followed by Europe (132) and the Americas (119), and lowest in Oceania (91) [4]. Wheat and wheat products are the main source of grains in all parts of the world except for Asia, where rice is the grain source most commonly eaten [4]. Although more wheat than rice is grown on a global basis, much of it is used for animal feed. Rice is the principal staple for half of the world's population.

Box 2: Foods made from grains

Grain, or cereal, products are very versatile once they have been processed from the raw grain. Wheat is milled mainly to make flour for bread, pastries, cakes and pasta. Maize (corn) is a staple food in Latin America and parts of Asia and Africa, where it is used to make grits, cornmeal (used for polenta as well as cornbreads), corn flour, tortillas, tamales and corn chips. It is also the basis of cornstarch (a thickener), corn syrup (a sweetener) and corn oils. Sweetcorn is also eaten as a vegetable, either on or off the cob.

Rice is usually processed to remove the bran and aleurone layers, turning 'brown rice' into 'white rice'. It is also used to make flour (a replacement for other flours in some gluten-free products), rice powder, noodles, rice paper, rice milk, Japanese mochi and lao-chao (Chinese fermented rice).

Barley is used throughout the world, as animal feed, for malting or as a food for human consumption. The European Union is the largest consumer of barley, followed by Russia, but it is also consumed in Asia (as tsampa and in miso soya paste) and in North Africa (in soups, porridges and flat breads). Whole rye grains are milled and used to make bread in some North and East European countries. Whole oats are made into porridges and used in muesli and baked goods, such as biscuits. Fonio, millet, sorghum, teff and triticale are traditional crops and staples in parts of Africa and Asia.

Many grains are also fermented to make alcoholic drinks (see [Exposures: Alcoholic drinks](#)).

Box 3: 'Dietary fibre', as defined by the Codex Committee on Nutrition and Foods for Special Dietary Uses in 2008 [6]

Dietary fibre is defined as *carbohydrate polymers* with 10 or more *monomeric units*, which are not hydrolysed by the *endogenous* enzymes in the small intestine of humans and belong to the following categories:

- edible carbohydrate polymers naturally occurring in the food as consumed
- carbohydrate polymers, which have been obtained from raw food material by physical, enzymatic or chemical means and which have been shown to have a physiological benefit to health, as demonstrated by generally accepted scientific evidence
- synthetic carbohydrate polymers, which have been shown to have a physiological effect of benefit to health, as demonstrated by generally accepted scientific evidence to competent authorities

3.2 Foods containing dietary fibre

3.2.1 Definitions and sources

Definitions of dietary fibre have varied over the years; however, since 2008 there has been general agreement globally [5]. Dietary fibre may be defined briefly as constituents of plant cell walls that are not digested in the small intestine.

In 2008, the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) agreed on a more detailed definition of dietary fibre for use in analysing and labelling [6] (see **Box 3**).

One important thing to note in the CCNFSDU definition is that carbohydrate polymers that have been isolated from foods, or synthesised, may be classified as dietary fibre only if they have proven health benefits.

Another thing to note is that a footnote to the CCNFSDU definition states that the decision on whether to include non-digestible *oligosaccharides* with three to nine monomeric units in the definition should be left to national authorities [6, 7]. These carbohydrates have potentially beneficial properties that warrant further research [7].

The aim of the CCNFSDU definition is to reflect the current body of scientific knowledge on dietary fibre; to promote the concept that any and all substances that behave like fibre in vivo, regardless of their source, may be considered to be dietary fibre provided that physiological health benefits can be demonstrated for them; and to guide harmonisation for food labelling and food composition tables. Many countries now accept the CCNFSDU definition [8].

Dietary fibre may sometimes be classified according to its source – this generally includes cereal fibre, vegetable fibre and fruit fibre.

3.2.2 Consumption patterns

Pulses (legumes) (see **Box 4**) and minimally processed grains (see **Section 3.1**) are particularly concentrated sources of dietary fibre, but vegetables and fruit (see **Section 3.4**) also contain significant amounts. Parts of plants that are eaten as vegetables such as roots and tubers with the skin on are a source of dietary fibre. Nuts and seeds are also high in dietary fibre, especially when they are eaten with their skins or hulls.

Global data on levels of consumption of dietary fibre are not readily available in a format that allows quick and easy country-by-country comparisons because of variations in the analytical methods used to assess the fibre content of foods (see **Section 4.2.1.1**). However, data on levels of consumption of foods containing dietary fibre provide valuable information.

Box 4: Pulses

Definitions and sources

Leguminous plants are plants that produce their fruit as pods. The dried, edible seeds of this family are often called pulses, although this term is used interchangeably with legumes. They include beans, lentils, peas and peanuts (groundnuts). The dried forms, which have matured and dried on the plant, are eaten most widely.

Some legumes, such as peas, are eaten when green, as a vegetable. The pods are sometimes eaten like this too, for example, green beans and runner beans. Some legumes can also be sprouted (germinated) and eaten, such as beansprouts.

Composition

Dry pulses are seeds and are higher in protein than most other plant foods. Pulses are also typically high in carbohydrates and dietary fibre, and low in fat (though there are exceptions, for example, soya).

Consumption patterns

Globally, about 10 kilograms per capita per year of pulses are available for consumption [4]. Consumption is generally highest in Africa (15 kilograms per capita per year in 2013), followed by the Americas (12) and Asia (10) and lowest in Europe and Oceania (4 each) [4].

In societies with high intakes of meat and other foods of animal origin, pulses are consumed in lower quantities than in countries with lower intakes of meat.

Dietary fibre isolated from plant cell walls and in synthetic forms is increasingly entering the food supply. However, good evidence is lacking to show that the synthetic forms have the same benefits as a diet with a high natural content of fibre – that is, a diet based on fruit, vegetables, pulses and wholegrains [9].

3.3 Aflatoxins

Aflatoxins are a family of *mycotoxins* produced by certain moulds (fungi) – principally *Aspergillus flavus* and *A. parasiticus* – found on some agricultural crops [10, 11]. Aflatoxin-producing moulds can contaminate crops in the field, at harvest and during storage [11]. People can be exposed to aflatoxins by eating contaminated foods. Although moulds that contaminate foods are usually destroyed by cooking, any toxins they produce may remain.

All naturally occurring aflatoxins (B_1 , B_2 , G_1 , G_2 and M_1) are classified as human *carcinogens* (Group 1) by the IARC; other mycotoxins, such as fumonisins, are suspected carcinogens [12]. It is common to find co-contamination by more than one species of mycotoxin-producing mould. The European Food Safety Authority recommends that exposure to aflatoxins from all sources be kept as low as possible [13].

Contamination by aflatoxins is common in grains of any type, but especially maize (corn), as well as in peanuts, cottonseed and tree nuts [10]. Meat can become contaminated if farm animals consume feedstuff contaminated by aflatoxins, which can then be secreted in milk or accumulate in tissues. Farmers and other agricultural workers may be exposed to aflatoxins by inhaling dust generated during the handling and processing of contaminated crops and feeds [11].

Aflatoxins are most problematic in countries with hot, damp climates and poor storage facilities. Under these conditions, foods

may become contaminated with moulds and accumulate toxins. Such foods are generally consumed in the countries where they are produced, but they may also be exported to neighbouring countries and intercontinentally. Aflatoxin contamination is therefore an international issue.

Levels of aflatoxin contamination tend to be highest in sub-Saharan Africa and South-East Asia, as well as China, and rates of liver cancer are high in these countries. In general, rates of contamination are low in Europe, but relatively high rates of contamination have on occasion been found in the USA. Levels of aflatoxin exposure through consumption of contaminated foods are low in Europe and Australia, higher in the USA, and high in many *low-income countries*. This is particularly the case in tropical and subtropical regions where grains and nuts are stored for long periods under conditions that encourage mold growth.

Aflatoxin contamination and consumption can be reduced by appropriate storage at low temperatures, inspection of stored products, use of fungicides and screening of imported foods. However, the monitoring of levels of aflatoxin contamination in low-income countries is limited, particularly in regions at greatest risk from high exposure [14].

3.4 Non-starchy vegetables and fruit

3.4.1 Definitions and sources

3.4.1.1 Botanical and culinary definitions

There are two main ways of defining vegetables and fruit: botanical and culinary [15]. Botanical definitions are more precise than culinary definitions. However, culinary definitions are more commonly understood by nutrition researchers and by participants in epidemiological studies, as they are based on cultural uses of foods and they align with how most people think of vegetables and fruit [15].

The CUP therefore uses culinary definitions as far as possible when reviewing evidence on vegetables and fruit and culinary definitions are used in this Third Expert Report.

3.4.1.2 Culinary vegetables

The culinary term ‘vegetables’ refers to the edible parts of plants, usually including fungi (mushrooms, truffles) and algae (seaweed), but not including foods that are generally thought of as fruit, most grains, nuts, peanuts, seeds, coffee, tea, cacao, or herbs and spices [15]. Examples of parts of plants that are eaten as vegetables include edible leaves, roots, tubers, bulbs, stems and stalks, flowers and grains that are used as vegetables (for example, sweetcorn, and fruits such as tomatoes, aubergine (eggplant) and courgette (zucchini)).

The CUP reviews evidence on non-starchy vegetables separately from starchy vegetables when possible (for information about starchy vegetables, see **Box 5**). This is because of the difference in nutrient content; for example, starchy vegetables are higher in carbohydrate. It is also important to separate the two types as they each make contributions to a healthy diet.

There are different ways of classifying non-starchy vegetables into subgroups based on, for example, which part of the plant is eaten (as in the paragraph above), what sort of habitat the plant grows in and what colour the vegetable is [15].

Non-starchy vegetables can be divided into green, leafy vegetables (such as spinach and lettuce); cruciferous vegetables (the cabbage family; for example, bok choy [pak choy], broccoli, cabbage and watercress); and allium vegetables (such as onions, garlic and leeks).

3.4.1.3 Botanical and culinary fruit

The botanical term ‘fruit’, as related to food, refers to the edible part of a plant that consists of the seeds and surrounding tissues [15]. However, this definition does not work well for the purposes of epidemiological studies as it encompasses many foods that people do not think of as fruit at all, such as grains, nuts and seeds. It also encompasses foods that people think of as vegetables, such as cucumbers, peppers, squash, tomatoes, plantains, aubergines or eggplants, okra and courgettes or zucchini [15].

Box 5: Starchy vegetables

Starchy vegetables (which have a higher starch content than non-starchy vegetables and can be eaten as dietary staples – that is, as a main source of *energy*) include some tubers and roots, such as potatoes, sweet potatoes (yams), cassava (manioc), sago yams and taro. Plantains are also eaten as starchy vegetables (although they are botanically a fruit).

Although carrots, beets, parsnips, turnips and swedes (or rutabagas) are root vegetables, they are non-starchy and are classified as non-starchy vegetables in this Third Expert Report.

Although potatoes are sometimes classed as vegetables (in the USA, for instance), they are grouped separately from non-starchy vegetables in the CUP where possible.

Starchy vegetables are less concentrated sources of starch than grains, although starch accounts for almost all their raw weight apart from water. Starch content varies from about 15 to 20 per cent in sweet potatoes to 25 to 30 per cent in cassava and yams, which translates into about 80 to 95 per cent of the dietary energy.

The culinary term ‘fruit’ refers to the edible part of a plant, tree, bush or vine that contains the seeds and pulpy surrounding tissue and has a sweet or tart taste [15]. In essence, culinary fruit is a subset of botanical fruit [15]. People tend to think of apples, bananas, berries, figs, grapes, mangoes and melons as fruit, as well as citrus fruit such as oranges, grapefruit, lemons and limes (see **Section 3.6**), and dried fruit such as apricots, figs and raisins.

3.4.2 Composition

The composition of fruit and vegetables depends both on species and on subtype, as well as on the environmental, farming, production and storage conditions. These include factors such as sun exposure, soil quality, agricultural practices, harvesting time, ripeness, length of time between harvest and consumption, and preservation and preparation methods.

For instance, the outer leaves of lettuces can have higher levels of some *micronutrients* than the inner leaves; and harvested, unripe fruit that ripens in transit may have lower levels of nutrients than fruit ripened on the plant (for information about the bioavailability of nutrients, see **Box 6**) [16].

Vegetables and fruit – as well as pulses (legumes), nuts and seeds – are sources of dietary fibre and a wide variety of vitamins and minerals. Vegetables and fruit also contain other *bioactive compounds*, such as *phytochemicals*. Phytochemicals have been shown either in humans or in laboratory experiments to have potentially beneficial health effects when they are included in diets. However, the bioavailability of these compounds is variable and their ultimate health effects uncertain.

Box 6: Preparation of vegetables and nutrient bioavailability

Some vegetables, often termed ‘salad vegetables’, are commonly eaten raw, but many vegetables are cooked before they are eaten. In most cases, whether a vegetable is eaten raw depends on personal choice.

Most forms of cooking reduce the total nutrient content of vegetables, although the degree to which this happens varies between nutrients and with cooking methods. However, cooking also increases the bioavailability of some nutrients [17]. Therefore, although raw vegetables have higher amounts of nutrients overall, the body may absorb more of a nutrient from the cooked vegetable.

For instance, *carotenoid absorption* in the small intestine is relatively inefficient (5 to 50 per cent); the bioavailability of carotenes is increased by cooking and puréeing vegetables, and particularly by adding oil, because these compounds are fat soluble [18].

Similarly, processing tomatoes increases the bioavailability of lycopene, another carotenoid: it is four times more bioavailable from tomato paste than from fresh tomatoes. Thus, processed tomato products such as pasteurised tomato juice, soup, sauce and ketchup provide the most bioavailable lycopene. Cooking and crushing tomatoes (as in the canning process) and including them in oil-rich dishes (such as pasta sauce or pizza) greatly increases lycopene absorption in the digestive tract.

The ways in which vegetables and fruit are produced and stored may affect nutrient levels as much as cooking, or more. For example, nutrient levels tend to fall rapidly after harvest.

Some constituents of vegetables and fruit have been identified in this Third Expert Report as being associated with cancer risk: carotenoids, including beta-carotene (see **Sections 3.7** and **3.8**), vitamin C (see **Section 3.9**) and isoflavones (see **Section 3.10**).

3.4.3 Consumption patterns

Globally, about 140 kilograms per capita per year of vegetables (not including vegetable oils) are available for consumption [4]. Consumption is generally highest in Asia (177 kilograms per capita per year in 2013), followed by Europe (115), Oceania (101), the Americas (76) and Africa (68) [4].

Globally, about 75 kilograms per capita per year of fruit are available for consumption [4]. Consumption is generally highest in the Americas (96 kilograms per capita per year in 2013), followed by Europe (95), Oceania (88) and Asia (71), and lowest in Africa (52) [4].

Most countries have national recommendations on the amount of vegetables and fruit that should be eaten daily to maintain optimal health. These vary, but they tend to recommend three or more servings per day of vegetables and two or more servings per day of fruit, with a serving being about 80 grams (or half a cup in the USA). In most *high-income countries* for which data are available, daily consumption of vegetables falls short of this target, although this is not due to lack of availability; indeed, availability is high due to the wide use of refrigeration. Fruit consumption tends to be closer to national targets.

3.5 Preserved non-starchy vegetables

Preserved vegetables include those that are salted, dried, fermented or pickled. Pickling, broadly defined, is the use of brine (a concentrated salt solution), vinegar, soy sauce or a spicy solution to preserve and give a unique flavour to a food [19]. Numerous

vegetables can be pickled, not only to preserve them but also to modify their flavour. Some vegetables may also be fermented during pickling.

The preserving processes of particular interest in this Third Expert Report are traditional methods used in some parts of China, Thailand, Singapore and Japan. For further information on the preservation of food and the risk of cancer, see [Exposures: Preservation and processing](#).

3.6 Citrus fruit

Citrus fruit grow on trees and shrubs of the citrus genus, which belongs to the rue family (Rutaceae) [20]. Citrus fruit include oranges, grapefruit, lemons and limes.

Citrus fruit are most commonly thought of as a natural dietary source of vitamin C. They are nutrient-dense foods that also contain many other vitamins, minerals, dietary fibre and carbohydrates.

Globally, about 75 kilograms per capita per year of citrus fruit is available for consumption [4]. Consumption is generally highest in the Americas (30), followed by Europe (29), Oceania (17) and Asia (13), and lowest in Africa (12) [4].



3.7 Foods containing carotenoids

Carotenoids are *phytochemicals*, which comprise a family of more than 600 fat-soluble, red, orange and yellow pigments found in varying concentrations in all vegetables, but particularly in those that are red, orange or yellow [15, 21]. They are the main pigments that give vegetables these colours and they consist of xanthophylls (such as lutein and beta-cryptoxanthin) and carotenes (such as alpha- and beta-carotene and lycopene).

Only about half of the 50 or so carotenoids in human diets can be absorbed. In addition to their contribution to vitamin A intake, they have several other potential bioactivities. Sources of carotenoids include spinach, kale, butternut squash, pumpkin, red (bell) peppers, carrots, tomatoes, sweet potatoes and cantaloupe melon.

3.8 Foods containing beta-carotene

Beta-carotene is a *carotenoid* (see **Section 3.7**) that can be converted by the body to retinol (the active form of vitamin A).

Beta-carotene is found naturally in yellow, orange, red and green fruit, and in green, leafy vegetables. These include cantaloupe melon, oranges, carrots, spinach, lettuce, tomatoes, sweet potatoes, broccoli and winter squash (pumpkin). In general, the greater the intensity of the colour of these fruit or vegetables, the more beta-carotene they contain.

Beta-carotene is also available as supplements in a wide range of doses (for more information about *micronutrient* supplements, see [Exposures: Other dietary exposures](#), Box 3).

3.9 Foods containing vitamin C

Vitamin C (ascorbic acid) is a water-soluble vitamin. It is essential for collagen synthesis and has *antioxidant* activity. Severe deficiency causes scurvy.

Humans, unlike most other animals, cannot synthesise vitamin C, so it is an essential part of the human diet. Due to its antioxidant action, it is added to many foods, including bread and soft drinks, in small amounts as a preservative.

Natural dietary sources of vitamin C are vegetables, potatoes and other tubers, and fruit. These include kiwi fruit, papaya, citrus fruit, strawberries, red or yellow (bell) peppers and broccoli. It is destroyed by heat or contact with the air (for instance, when vegetables are chopped) and lost into cooking water.

3.10 Foods containing isoflavones

Isoflavones are a type of *phytochemical*. More specifically, they are a class of phytoestrogens – plant-derived compounds with oestrogen-like properties [22].

Isoflavones are found in small amounts in a number of legumes, grains and vegetables, but soybeans are by far the most concentrated source of isoflavones in the human diet [23, 24].

Some health effects of soy may be dependent on one's capacity to convert the isoflavone daidzein to equol in the digestive tract, which in turn depends on the composition of the colonic microbiota.

Traditional Asian foods made from soybeans include tofu, tempeh, miso and natto. Edamame is a name for varieties of soybeans that are harvested and eaten in their green phase. Soy products that are gaining popularity in Western countries include soy-based meat substitutes, soy milk, soy cheese and soy yogurt. The isoflavone content of a soy protein isolate depends on the method used to isolate it.

Average dietary isoflavone intakes in Japan, China and other Asian countries range from 25 to 50 milligrams per day [25]. Dietary isoflavone intakes are considerably lower in Western countries, typically lower than 1 milligram per day [26].

4. Interpretation of the evidence

4.1 General

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

Specific factors that the Panel bears in mind when interpreting evidence on whether consuming wholegrains, vegetables and fruit increases or decreases the risk of developing cancer are described in the following subsections. Factors that are relevant to individual cancers are presented here too.

4.2.1 Exposures

As explained in **Section 3**, there can be a lack of precision in exactly how some foods are defined and classified. A lack of globally agreed, standardised definitions means the studies that the CUP considers when analysing global research do not all define, classify or group foods in the same way. When interpreting the findings of analyses, the Panel therefore takes into account how individual studies have defined foods or food groups, and considers these foods in the broader context of wider food categories and as part of overall diet and lifestyle.

The lack of precision in definitions is part of a wider issue of imprecision, also including measurement errors, that the Panel takes into account when interpreting evidence.



4.2.1.1 Wholegrains and foods containing dietary fibre, and their dietary constituents, including isoflavones

Definition. ‘Wholegrains’ is a broad classification, referring to grains, or cereals, and grain products that are made from the entire grain seed, which consists of the bran, germ and endosperm. Definitions of dietary fibre vary, although in 2008 the CCNFSDU agreed on a definition (see **Section 3.2.1**).

Different wholegrains have different nutritional composition and biological effects, as do different types of dietary fibre. It may not be possible to identify specific effects of individual wholegrains, or their constituents, on cancer risk.

Confounding. In *high-income countries*, high intakes of wholegrain products tend to go together with other health-conscious habits. Also, there are possible *confounding* effects between dietary fibre and other dietary constituents, and more generally with ‘healthier’ dietary patterns and ways of life. Data on cancer risk and dietary fibre intake come predominantly from studies on consumption of fibre from foods, as opposed to supplements, so no effect can be confidently attributed to fibre that is not from food. High intakes of *isoflavones* may also relate to a healthier diet in *high-income countries*.

Measurement. Various analytical techniques have been used to assess the fibre content of foods, but they give widely different results. The AOAC method measures all carbohydrates that are not digested or absorbed, plus lignin, and has become the method of choice. It requires enzymic digestion of protein and non-resistant starch, followed by precipitation of soluble fibre with 95 per cent alcohol, followed by weighing. In addition to measuring all fibre content, specific methods have been developed to measure individual fibre types such as

oligosaccharides. However, in the past a variety of methods were used – for example, the Southgate and Englyst method (which measures only non-starch polysaccharide) – and most studies do not report which method of analysis was used for the food composition tables. This makes it difficult to compare studies.

Study design. For nasopharyngeal cancer, there was a lack of *cohort studies*, so the evidence for vegetables came from two published *meta-analyses* of *case-control studies* [27, 28]. 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](#)).

4.2.1.2 Aflatoxins

Definition. Aflatoxins are a family of *mycotoxins* produced by certain moulds or fungi found on some agricultural crops [10, 11]. Aflatoxin-producing fungi can contaminate crops in the field, at harvest and during storage [11]. People can be exposed to aflatoxins by eating contaminated foods.

Measurement. There are two approaches to measuring aflatoxin intake. The first uses local food tables to estimate exposure to aflatoxins from diet. The second approach, which uses *biomarkers* of exposure derived from knowledge of aflatoxin metabolism, is more accurate and precise. In humans, metabolised products of aflatoxins can be detected in blood, urine or breastmilk. However, different studies use different biomarkers, meaning it is not possible to conduct *meta-analyses*.

4.2.1.3 Non-starchy vegetables and fruit, and their dietary constituents

In this Third Expert Report, we present evidence and judgements on both a 'greater intake' and a 'low intake' of non-starchy vegetables and of fruit. See [Recommendations and public health and policy implications](#) for advice on consumption of vegetables and fruit. Mostly, judgements are related to 'greater intake'. However, if the CUP *non-linear analysis* clearly showed a higher level of risk for low intakes than for greater intakes and little change in risk at greater intakes, then the Panel made a judgement related to 'low intakes', even if the *dose-response* analyses showed a statistically significant association.

Definitions. There is no general agreement on classification. In common parlance and in most studies the term 'vegetable' applies to non-starchy vegetables. Potatoes are usually (as in this Third Expert Report) defined as tubers but are sometimes (for example, in the USA) included with vegetables. Some studies have included grains or cereals such as corn as vegetables and plantains as fruit. Bananas, a significant item in many diets, may be (as here) defined as a fruit or with plantains as a starchy food.

Some studies report results only for broad categories (for example, 'vegetables' or 'fruit'), whereas others report results for more narrowly defined subgroups (for example, 'raw vegetables', 'green vegetables' or 'citrus fruit') or for individual food items (for example, 'spinach', 'carrots' or 'tomatoes'). The CUP conducts separate analyses for more specific subgroups of vegetables, or fruit, where possible. Studies reporting only on subgroups of vegetables or fruit, or individual foods, are not included in CUP analyses on the broader categories of 'non-starchy vegetables' or 'fruit'.

In some studies, vegetables and fruit have been categorised according to botanical

classification; in others, categorisation has been done according to culinary usage. In this Third Expert Report, the terms 'vegetables' and 'fruit' are used in accordance with their culinary definition (see **Section 3.4**).

Evidence on pulses is considered separately from evidence on non-starchy vegetables in the CUP; pulses are often analysed separately in studies. However, the CUP does not exclude studies that include pulses with vegetables from CUP analyses on non-starchy vegetables.

Many older studies have not differentiated between retinol and *carotenoids* and simply report on vitamin A.

Confounding. People who smoke often consume fewer vegetables and fruit than people who do not smoke [29, 30]. Fat intake is inversely correlated with intake of vegetables and, particularly, fruit in the USA [31]. Recent studies of the effects of consuming fruit and vegetables and the risk of cancers thought to be caused by smoking tobacco have controlled for the effect of smoking. However, there is still potential for residual *confounding*. The Panel was particularly concerned about residual confounding if statistically significant associations were shown for people who smoke but not for people who have never smoked. Folate intake is positively correlated with intake of non-starch polysaccharide (dietary fibre).

Measurement. When measuring carotenoid exposure, it may be best to use *biomarkers* of intake such as circulating levels of carotenoids, because there are differences in the bioavailability of carotenoids from different foods, and individual differences between carotenoids in *absorption* and metabolism. However, different laboratory methods of assessing level of carotenoids generate different results, often making it difficult to compare studies.

Reporting bias. The majority of studies use self-reporting, which tends to over-report consumption of vegetables and fruit. Where an effect exists, results from such studies are liable to underestimate the extent to which vegetables and fruit modify the risk of cancer.

Patterns and ranges of intake. Most studies of consumption of vegetables, fruit and pulses (legumes) have been conducted in populations that have relatively homogeneous diets.

4.2.1.4 Preserved non-starchy vegetables

Definition. Preserved vegetables include those that are salted, dried, fermented or pickled.

Confounding. People who smoke may consume more preserved vegetables than people who have never smoked. People who consume a lot of preserved vegetables may not have access to fresh vegetables and other fresh foods considered part of a healthy diet.

Study design. For nasopharyngeal cancer, there was a lack of cohort studies, so the evidence for that cancer came from a published meta-analysis of case-control studies [32]. Case-control studies are subject to recall bias, which can occur when participants recall past dietary intake or physical activity. Participants may have different behaviours than non-participants, and such differences may vary between cases and controls (see [Judging the evidence](#)).

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) [33], 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 from mouth and oropharynx (the part of the throat just behind the mouth) cancers worldwide [34].



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 [35].



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 by 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 the consumption of wholegrains, vegetables and fruit and cancers of the mouth, pharynx and larynx have not included data on HPV infection.

4.2.2.2 Nasopharynx

Definition. The nasopharynx is the top of the pharynx (throat), the muscular cavity leading from the nose and mouth to the larynx (voice box). Nasopharyngeal cancer is a type of head and neck cancer.

Classification. Nasopharyngeal cancer is reviewed separately from other types of head and neck cancer in the CUP. Cancers of the nasopharynx arise predominantly from *epithelial* cells, with *squamous cell carcinomas* being the most common. Squamous cell carcinomas constitute 75 to 90 per cent of nasopharyngeal cancers in low-risk populations and virtually 100 per cent in high-risk populations. Nasopharyngeal squamous cell carcinomas are included in this Third Expert Report; other types are not.

Other established causes. Other established causes of nasopharyngeal cancer include the following:



Smoking tobacco

Smoking tobacco is a cause of nasopharyngeal cancer. It is estimated that 23 per cent of cases of nasopharyngeal cancers are attributable to smoking tobacco [36].



Occupational exposure

Occupational exposure to wood dust and formaldehyde is also a cause of this cancer.



Infectious agents

Epstein-Barr virus infection is a cause of nasopharyngeal cancer. Although it is a necessary cause, it is not sufficient [37] as only a fraction of the infected population develops nasopharyngeal cancer [37].

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 by smoking tobacco; that is, not a direct result of the *exposure* examined.

4.2.2.3 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 [38]; however, the proportion of adenocarcinomas is increasing dramatically in affluent nations.

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* [39]. It is estimated that 42 per cent of deaths of oesophageal cancer are attributable to tobacco use [34].



Infection

Between 12 and 39 per cent of oesophageal squamous cell carcinomas worldwide are related to carcinogenic types of HPV [40]. *Helicobacter pylori* (*H. 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 [41, 42].



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 [39]. 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) [39].



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 [43].

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 by smoking tobacco; that is, not a direct result of the *exposure* examined.

For more detailed information on *adjustments* made in CUP analyses, see Evidence and judgements for non-starchy vegetables (**Sections 5.4.3** and **5.4.4**) and fruit (**Section 5.6.1**).

4.2.2.4 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 [44].

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 [45]. Passive smoking (inhalation of tobacco smoke from the surrounding air) is also a cause of lung cancer.



Previous lung disease

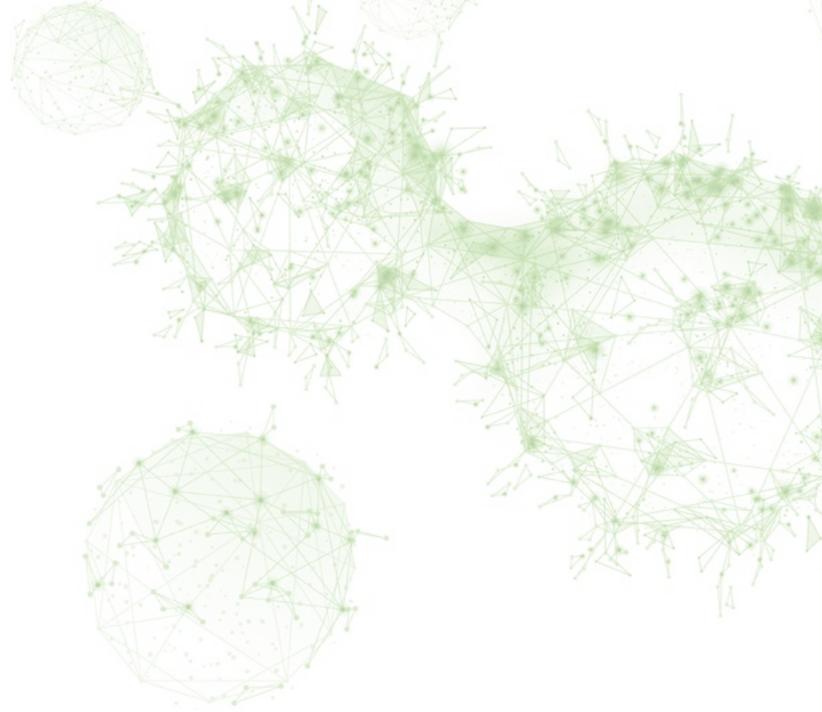
A history of emphysema, *chronic* bronchitis, tuberculosis or pneumonia is associated with an increased risk of lung cancer [46].



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 [47], as is exposure to indoor air pollution from wood and coal burning for cooking and heating [48].

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 also 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 CUP analyses, see Evidence and judgements for non-starchy vegetables (**Section 5.4.5**), fruit (**Section 5.6.2**), foods containing carotenoids (**Section 5.7.1**), foods containing beta-carotene (**Section 5.8.1**), foods containing vitamin C (**Section 5.9.1**) and foods containing isoflavones (**Section 5.10.1**).

4.2.2.5 Stomach

Infection with *H. pylori* is strongly implicated in the aetiology of intestinal *non-cardia stomach cancer*. Other factors may enhance risk of infection, integration and/or persistence.

Definition. The stomach is part of the digestive system, located between the oesophagus and the small intestine. It secretes enzymes and gastric acid to aid in food digestion and acts as a receptacle for masticated food, which is sent to the small intestine through muscular contractions.

Classification. Stomach cancer is usually differentiated by the anatomical site of origin: *cardia stomach cancer* (cardia cancer), which occurs near the gastro-oesophageal junction, and *non-cardia stomach cancer* (non-cardia cancer), which occurs outside this area, in the lower portion of the stomach. Cardia and non-cardia stomach cancer have distinct pathogeneses and aetiologies, but not all studies distinguish between them, particularly older studies. For these studies, there is a greater likelihood that the general term ‘stomach cancer’ may reflect a combination of the two subtypes, and therefore results may be less informative. Furthermore, definitions of cardia cancer classifications sometimes vary according to distance from the gastro-oesophageal junction, raising concerns about misclassification [49].

Other established causes. Other established causes of stomach cancer include the following:



Smoking tobacco

Smoking tobacco is a cause of stomach cancer. It is estimated that 13 per cent of deaths worldwide are attributable to smoking tobacco [34].

Infection

Persistent colonisation of the stomach with *H. pylori* is a risk factor for non-cardia stomach cancer, but in some studies has been found to be inversely associated with the risk of cardia stomach cancer [50, 51].

Industrial chemical exposure

Occupational exposure to dusty and high-temperature environments – as experienced by wood-processing and food-machine operators – has been associated with an increased risk of stomach cancer [52]. Working in other industries, including rubber manufacturing, coal mining, metal processing and chromium production, has also been associated with an elevated risk of this cancer [53, 54].

Family history and ethnicity

Inherited *mutations* of certain genes, particularly the glutathione S-transferase (GSTM1)-null *phenotype*, are associated with an increased risk of stomach cancer [55]. Certain *polymorphisms* of interleukin genes (IL-17 and IL-10) have also been associated with increased risk of stomach cancer, particularly in Asian populations. These polymorphisms may interact with *H. pylori* infection [56] and smoking tobacco [57] to affect cancer risk.

Pernicious anaemia

People with the autoimmune form of pernicious anaemia have an increased risk of stomach cancer [58, 59]. This form of pernicious anaemia involves the autoimmune destruction of parietal cells in the gastric mucosa [59, 60]. These cells produce intrinsic factor, a protein that is needed to absorb vitamin B₁₂ from foods, so the resultant vitamin B₁₂ deficiency hinders the production of fully functioning red blood cells.

Confounding. Smoking tobacco and *H. pylori* infection are possible *confounders* or *effect modifiers*.

For more detailed information on *adjustments* made in CUP analyses, see Evidence and judgements for fruit (**Section 5.6.3**), citrus fruit (**Section 5.6.4**) and preserved non-starchy vegetables (**Section 5.5.1**).

4.2.2.6 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 [61].

Medication

Long-term use of oral contraceptives containing high doses of *oestrogen* and *progesterone* increases the risk of liver cancer [62].

Infection

Chronic infection with the *hepatitis B* or *C* virus is a cause of liver cancer [63].

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 [64, 65]. It is estimated that 14 per cent of deaths worldwide from liver cancer are attributable to smoking tobacco [34].

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

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.

4.2.2.7 Colon and rectum

Definition. The *colon* (large intestine) is the lower part of the intestinal tract, which extends from the *caecum* (an intraperitoneal pouch) to the *rectum* (the final portion of the large intestine which connects to the anus).

Classification. Approximately 95 per cent of colorectal cancers are *adenocarcinomas*. Other types of colorectal cancers include *mucinous carcinomas* and *adenosquamous carcinomas*. *Carcinogens* can interact directly with the cells that line the colon and rectum.

Other established causes. Other established causes of colorectal cancer include the following:

Other diseases

Inflammatory bowel disease (*Crohn's disease* and *ulcerative colitis*) increases the risk of, and so may be seen as a cause of, colon cancer [66].

Smoking tobacco

There is an increased risk of colorectal cancer in people who smoke tobacco. It has been estimated that 12 per cent of cases of colorectal cancer are attributable to smoking cigarettes [67].

Family history

Based on twin studies, up to 45 per cent of colorectal cancer cases may involve a heritable component [68]. Between five and 10 per cent of colorectal cancers are consequences of recognised hereditary conditions [69]. The two major ones are *familial adenomatous polyposis* (FAP) and *hereditary non-polyposis colorectal cancer* (HNPCC, also known as *Lynch syndrome*). A further 20 per cent of cases occur in people who have a family history of colorectal cancer.

Confounding. Smoking tobacco is a possible *confounder*. In postmenopausal women, *menopausal hormone therapy* (MHT) use decreases the risk of colorectal cancer and is a potential confounder.

For more detailed information on *adjustments* made in CUP analyses, see Evidence and judgements for wholegrains (**Section 5.1.1**), foods containing wholegrains (**Section 5.2.1**), non-starchy vegetables (**Section 5.4.6**), fruit (**Section 5.6.5**) and foods containing vitamin C (**Section 5.9.2**).

4.2.2.8 Breast

Definition. Breast tissue comprises mainly fat, glandular tissue (arranged in lobes), ducts and connective tissue. Breast tissue develops in response to *hormones* such as *oestrogens*, *progesterone*, *insulin* and growth factors. The main periods of development are during puberty, pregnancy and lactation. The glandular tissue atrophies after *menopause*.

Classification. Breast cancers are almost all *carcinomas* of the *epithelial* cells lining the breast ducts (the channels in the breast that carry milk to the nipple). Fifteen per cent of breast cancers are lobular carcinoma (from lobes); most of the rest are ductal carcinoma. Although breast cancer can occur in men, it is rare (less than one per cent of cases) and thus is not included in the CUP.

Breast cancers are classified by their receptor type; that is, to what extent the cancer cells have receptors for the sex hormones oestrogen and progesterone, and the growth factor human epidermal growth factor (hEGF), which can affect the growth of the breast cancer cells. Breast cancer cells that have oestrogen receptors are referred to as oestrogen receptor-positive (ER-positive or ER+), while those containing progesterone receptors are called progesterone receptor-positive (PR-positive or PR+) cancers, and those with receptors for hEGF are HER2 receptor-positive (HER2-positive or HER2+). Hormone-receptor-positive cancers are the most common subtypes of breast cancer but vary by population (60 to 90 per cent of cases). They have a relatively better prognosis than hormone-receptor-negative cancers, which are likely to be of higher pathological grade and can be more difficult to treat.

Most data come from *high-income countries*. Breast cancer is hormone related, and factors that modify risk may have different effects on cancers diagnosed in the pre and postmenopausal periods. Due to the

importance of menopausal status as an *effect modifier*, studies should stratify for *menopause* status, but many do not. Breast cancer is now recognised as a heterogeneous disease, with several subtypes according to hormone receptor status or intrinsic molecular markers. Although there is growing evidence that these subtypes have different causes, most studies have limited *statistical power* to evaluate effects by subtype.

There is growing evidence that the impact of *obesity* and dietary exposures on the risk of breast cancer may differ according to these particular molecular subtypes of cancer, but currently there is no information on how nutritional factors might interact with these characteristics.

Other established causes. Other established causes of breast cancer include the following:



Life events

Early *menarche* (before the age of 12), late natural *menopause* (after the age of 55), not bearing children and first pregnancy over the age of 30 all increase lifetime exposure to oestrogen and progesterone and the risk of breast cancer [70–72]. The reverse also applies: late menarche, early menopause, bearing children and pregnancy before the age of 30 all reduce the risk of breast cancer [70, 71].

Because nutritional factors such as obesity can influence these life course processes, their impact on breast cancer risk may depend on the maturational stage at which the exposure occurs. For instance, obesity before menopause is associated with reduced breast cancer risk, probably due to reduced ovarian progesterone production, while in post-menopausal women, in whom ovarian oestrogen production is low, obesity increases breast cancer risk by increasing production of oestradiol through the action of aromatase in *adipose tissue*.



Radiation

Exposure to ionising radiation from medical treatment such as X-rays, particularly during puberty, increases the risk of breast cancer [73, 74].



Medication

MHT containing oestrogen or progesterone increases the risk of breast cancer [75]. Oral contraceptives containing both oestrogen and progesterone also cause a small increased risk of breast cancer in young women, among current and recent users only [76].



Family history

Some inherited *mutations*, particularly in BRCA1, BRCA2 and *p53*, result in a very high risk of breast cancer. However, germline mutations in these genes are infrequent and account for only two to five per cent of all cases of breast cancer [77].

Confounding. Use of MHT is an important possible *confounder* or *effect modifier* in postmenopausal breast cancer. High-quality studies adjust for age, number of reproductive cycles, age at which children were born and the use of hormone-based medications.

For more detailed information on *adjustments* made in CUP analyses on non-starchy vegetables and foods containing carotenoids, see Evidence and judgements (**Sections 5.4.7** and **5.7.2** respectively).

4.2.2.9 Prostate

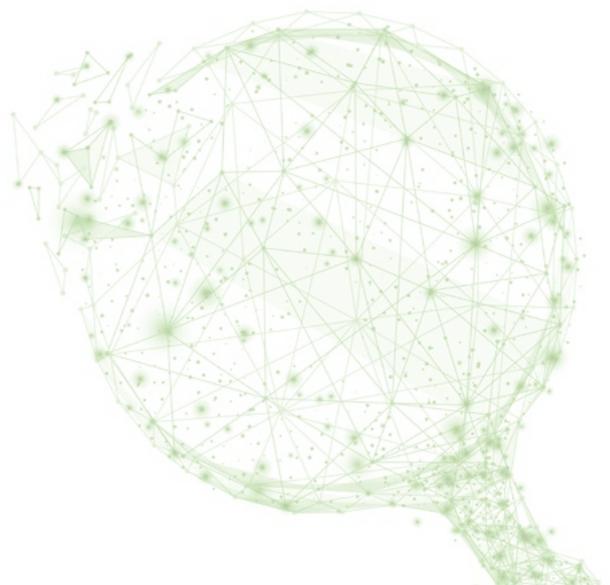
Definition. The prostate is a walnut-sized gland in men that surrounds the top of the urethra just below the bladder outlet; it produces seminal fluid. Male *hormones*, such as testosterone, control its growth and function.

Classification. Almost all cases of prostate cancer are *adenocarcinoma*, a glandular malignancy. The clinical course and natural history of diagnosed prostate cancer vary considerably. Although prostate cancer can spread locally and metastasise, and may be fatal, many men, especially at older ages, are found to have previously undetected and presumably asymptomatic prostate cancers at autopsy.

There are several ways of characterising prostate cancers according to grade (aggression) or stage. The term ‘advanced’ prostate cancer is sometimes employed in epidemiologic studies and is variably defined as higher grade, later stage, presence of metastatic disease or death. Further research is needed to better define the biological potential of newly diagnosed prostate cancer.

In the CUP, advanced prostate cancer is defined as cancers reported in any of the following ways:

- stage 3–4 in the American Joint Committee on Cancer (AJCC) 1992 classification
- advanced cancer
- advanced or metastatic cancer
- metastatic cancer
- stage C or D on the Whitmore/Jewett scale
- fatal cancer (prostate specific mortality)
- high stage or grade
- Gleason grade ≥ 7



Other established causes. Other established causes of prostate cancer include the following:



Family history and ethnicity

Approximately nine per cent of all prostate cancers may result from heritable susceptible genes [78]. Genetic susceptibility has been linked to African heritage and familial disease [79]. In the USA, African American men are 1.6 times more likely to develop prostate cancer than Caucasian men. A large number of single-nucleotide *polymorphisms* that modestly affect risk have also been identified [80].

Confounding. Screening for prostate cancer is a potential *confounder* or *effect modifier*.

For more detailed information on *adjustments* made in CUP analyses on foods containing beta-carotene, see Evidence and judgements (**Section 5.8.2**).

Prostate-specific antigen (PSA) screening.

Prostate cancer leads to an elevated blood concentration of PSA. Although it is highly sensitive for prostate cancer, it is not specific. Levels may be raised due to non-malignant disease, for example, benign prostatic *hyperplasia*. Furthermore, when only modestly raised, PSA alone cannot be used to distinguish between early stage or indolent tumours (which may never be of clinical significance) and more aggressive or later-stage cancers.

Cancers detected at an older age with indolent features can be monitored by a process called active surveillance. Consequently, studies of the natural history of screen-detected cancers, and of prostate cancers generally in screened populations, will be dominated by the behaviour of the more common but less clinically relevant low-grade or indolent tumours. In some populations, such as in the USA, PSA screening is widely used. However, in other populations, such as in Europe, PSA screening is less

common. The number of cases of prostate cancer identified by PSA screening is not consistently reported in studies, and few report epidemiological results based on the grade or stage of cancer detected.

4.2.2.10 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 [34].



Infection and infestation

Infection from the parasitic worm, *Schistosoma haematobium*, causing schistosomiasis, is a major risk factor, especially for squamous cell carcinomas [79]. 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) [79].



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 [81]. 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 [81].



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 [82, 83].

Confounding. Smoking tobacco is a potential *confounder*.

For more detailed information on *adjustments* made in CUP analyses on non-starchy vegetables and fruit, see Evidence and judgements (**Section 5.4.8**).

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,¹ there is also a CUP cancer report. CUP cancer reports summarise findings from the SLRs, again focusing on a specific cancer site. The section also presents findings from the SLRs, but from a different perspective: it brings together all of the key findings on wholegrains, vegetables and fruit and the risk of cancer.

Where possible, the Panel uses only evidence that is judged to be ‘strong’ (either ‘convincing’ or ‘probable’) as a basis for the Cancer Prevention Recommendations. Evidence that is judged to be ‘limited – suggestive’ is not normally sufficient to support Recommendations. However, for non-starchy vegetables and fruit, and constituents of these foods, the Panel noted that although the evidence is not strong in relation to specific cancers, both the pattern of association and direction of effect are consistent across cancers and overall the evidence is persuasive of a protective effect. In addition, consumption of non-starchy vegetables and fruit is a consistent feature of dietary patterns that have been associated with lower risk of cancer and of other non-communicable diseases, as well as obesity.

¹ 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.



Therefore, evidence that was judged to be ‘limited – suggestive’ is described in detail in this part of the Third Expert Report. This contrasts with other parts of this Third Expert Report, where less information is provided on ‘limited – suggestive’ evidence.

Note that throughout this section, if *Egger’s test* or *non-linear analysis* are not mentioned for a particular exposure and cancer, it can be assumed that no analyses were conducted. This is often because there were too few studies with the required information. If stratified analyses are not mentioned where there is strong evidence, it can also be assumed that no analyses were conducted. For limited – suggestive evidence, details of stratified analyses are included only for tobacco smoking and only if they influenced the CUP Panel’s conclusion.

5.1 Wholegrains

Table 5.1 summarises the main findings from the CUP *dose–response meta-analysis of cohort studies* on consumption of wholegrains and the risk of colorectal cancer.

There was no discussion specifically on wholegrains and any other cancer considered in the CUP as there were too few studies, although cereals (grains) and their products were discussed.

Table 5.1: CUP dose–response meta-analysis for consumption of wholegrains and the risk of colorectal cancer

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I ² (%)	Conclusion ¹	Date of CUP cancer report ²
Colorectum	6	6	8,320	0.83 (0.78–0.89)	90 g/day	18	Probable: Decreases risk	2017

1 See Definitions of WCRF/AICR grading criteria (**Section 1:** Wholegrains, vegetables and fruit and the risk of cancer: a summary matrix) for explanations of what the Panel means by ‘probable’.

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.

The strong evidence on the effects of eating wholegrains on the risk of cancer is described in the following subsection. 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.

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.

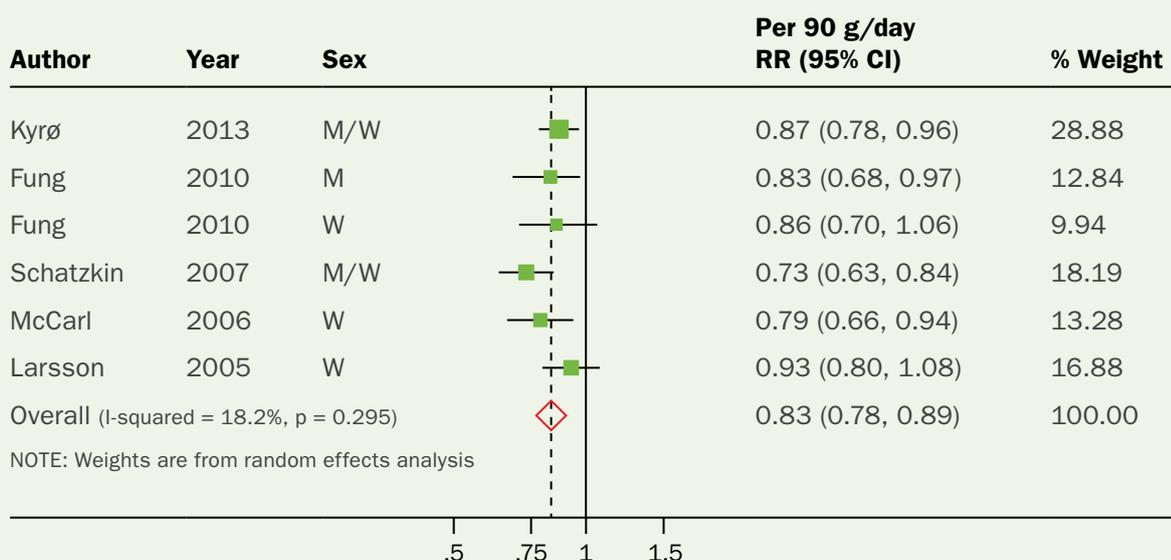
5.1.1 Colorectum

(Also see CUP colorectal cancer report 2017: Section 7.1 and CUP colorectal cancer SLR 2016: Section 2.1.1.4.)

5.1.1.1 CUP dose–response meta-analyses

All six identified studies were included in the dose–response meta-analysis, which showed a statistically significant 17 per cent decreased risk of colorectal cancer per 90 grams increase in wholegrains consumed per day (*relative risk* [RR] 0.83 [95% confidence interval [CI] 0.78–0.89]; n = 8,320 cases) (see **Figure 5.1**). Low *heterogeneity* was observed (I² = 18%). There was no evidence of small study bias with *Egger’s test* (p = 0.72).

Figure 5.1: CUP dose–response meta-analysis¹ for the risk of colorectal cancer, per 90 grams increase in wholegrains consumed per day



Source: Kyrø, 2013 [84]; Fung, 2010 [85]; Schatzkin, 2007 [86]; McCarl, 2006 [87]; Larsson, 2005 [88].

Stratified analyses for the risk of colorectal cancer per 90 grams increase in wholegrains consumed per day were conducted for geographic location and cancer type. Stratification by sex was not possible.

When stratified by geographic location, a statistically significant decreased risk was observed in Europe (RR 0.89 [95% CI 0.81–0.97]) and North America (RR 0.79 [95% CI 0.72–0.86]; see [CUP colorectal cancer SLR 2016](#), Table 8). When stratified by cancer type, a significant decreased risk was observed for colon cancer (RR 0.82 [95% CI 0.73–0.92]), but not rectal cancer (see [CUP colorectal cancer report 2017](#), Table 1 and [CUP colorectal cancer SLR 2016](#), Figures 8 and 12, respectively).

There was no evidence of a non-linear dose–response relationship ($p = 0.33$).

All studies included in the dose–response meta-analysis adjusted for age, physical activity, body mass index (BMI), alcohol consumption, tobacco smoking, red meat and menopausal hormone therapy (MHT) use in women. For information on the *adjustments* made in individual studies, see [CUP colorectal cancer SLR 2016](#), Table 10.

5.1.1.2 Published pooled analyses and meta-analyses

One published *pooled analysis* (see [Table 5.2](#)) and one other published meta-analysis on consumption of wholegrains and the risk of colorectal cancer were identified. In the pooled analysis, no statistically significant association was observed when comparing the highest with the lowest level of wholegrains consumed. The published meta-analysis reported the results from the 2010 CUP colorectal cancer SLR [89] (see [CUP colorectal cancer SLR 2016](#), Table 9).

¹ A total of six studies were analysed in the CUP dose–response meta-analysis. One publication (Fung 2010 [85]) included two studies, one in men and the other in women.

Table 5.2: Summary of published pooled analyses for consumption of wholegrains and the risk of colorectal cancer

Publication	Contrast	RR (95% CI)	No. of studies (cohort)	No. of cases
Pooling Project [90]	Highest vs lowest	0.92 (0.84–1.00)	13	8,081

5.1.1.3 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 are currently prevailing 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](#).

Wholegrains provide various nutrients including vitamin E, selenium, copper, zinc and bioactive non-nutrient compounds such as lignans, phytoestrogens and phenolic compounds as well as dietary fibre. Many of these compounds, which are largely found in the bran and germ of the grain, have plausible anti-carcinogenic properties. For instance, several phenolic acids have been shown in experimental studies to stimulate anti-oxidative activity [91, 92]. Alkylresorcinols, which are *biomarkers* of wholegrain wheat and rye intake, were shown to be inversely related to colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) [93]. Wholegrains may also protect against colorectal cancer by binding *carcinogens* and regulating glycaemic response.

5.1.1.4 CUP Panel's conclusion

The evidence for colorectal cancer was generally consistent, with a clear dose–response relationship showing a statistically significant decreased risk with increased consumption of wholegrains, with low *heterogeneity*. There was no evidence of a non-linear dose–response relationship. Stratification by cancer type showed a significant decreased risk for colon cancer, but not rectal cancer. One published *pooled analysis* reported no significant association. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded:

- **Consumption of wholegrains probably protects against colorectal cancer.**



5.2 Foods containing dietary fibre

Table 5.3 summarises the main findings from the CUP dose–response meta-analysis of cohort studies on consumption of foods containing dietary fibre and the risk of colorectal cancer.

Evidence for cancers of the following types was discussed in the CUP but was too limited to draw a conclusion:¹ mouth, pharynx and larynx (2018); oesophagus (adenocarcinoma and squamous cell carcinoma; 2016); lung (2017); stomach (2016); breast (pre and postmenopause; 2017); ovary (2014); endometrium (2013); prostate (2014); and kidney (2015).

The strong evidence on the effects of eating foods containing dietary fibre on the risk of cancer is described in the following subsection. 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.

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 Colorectum

(Also see [CUP colorectal cancer report 2017: Section 7.2](#) and [CUP colorectal cancer SLR 2016: Section 5.1.2](#))

5.2.1.1 CUP dose–response meta-analyses

Twenty-one of 23 identified studies (including a *pooled analysis* of 13 studies [90]) were included in the dose–response meta-analysis, which showed no statistically significant association between the risk of colorectal cancer and consumption of foods containing dietary fibre (RR 0.93 [95% CI 0.87–1.00]), per 10 grams increase per day; n = 16,562 cases) (see **Figure 5.2**). High *heterogeneity* was observed ($I^2 = 72\%$).

There was evidence of small study bias with *Egger’s test* ($p = 0.002$). Inspection of the funnel plot showed asymmetry, with one study [94] reporting a larger decreased risk than expected (see [CUP colorectal cancer SLR 2016, Figure 296](#)).

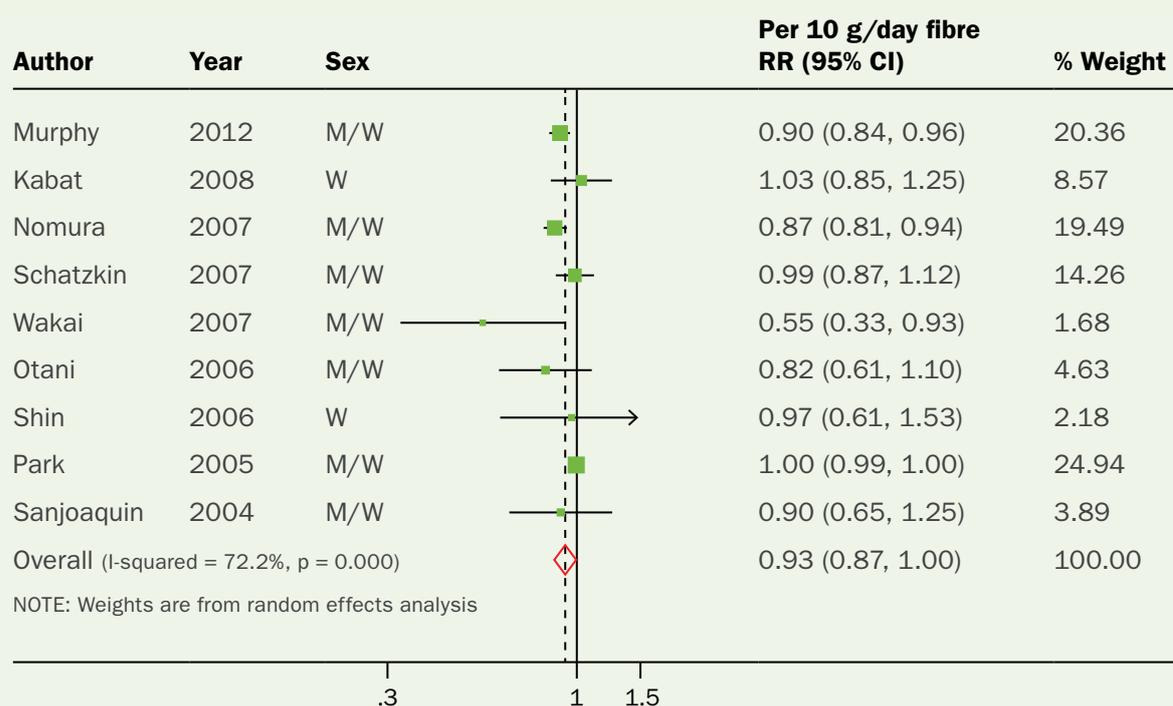
Table 5.3: CUP dose–response meta-analysis for consumption of foods containing dietary fibre and the risk of colorectal cancer

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I^2 (%)	Conclusion ¹	Date of CUP cancer report ²
Colorectum ³	23	21	16,562	0.93 (0.87–1.00)	10 g/day	72	Probable: Decreases risk	2017

- 1 See Definitions of WCRF/AICR grading criteria (**Section 1: Wholegrains, vegetables and fruit and the risk of cancer: a summary matrix**) for explanations of what the Panel means by ‘probable’.
- 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 evidence for foods containing dietary fibre and colorectal cancer includes both foods that naturally contain fibre and foods that have had fibre added.

¹ **‘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.

Figure 5.2: CUP dose–response meta-analysis¹ for the risk of colorectal cancer, per 10 grams increase in dietary fibre consumed per day



Source: Murphy, 2012 [95]; Kabat, 2008 [96]; Nomura, 2007 [97]; Schatzkin, 2007 [86]; Wakai, 2007 [94]; Otani, 2006 [98]; Shin, 2006 [99]; Park, 2005 [90]; Sanjoaquin, 2004 [100].

Another CUP analysis was conducted using the results of individual studies from the *pooled analysis* [90] separately (instead of using the overall pooled analysis result), along with other studies. Fifteen studies (including the seven studies that had published relevant results from the pooled analysis) were included in this second dose–response meta-analysis, which showed a statistically significant nine per cent decreased risk of colorectal cancer per 10 grams increase in dietary fibre consumed per day (RR 0.91 [95% CI 0.88–0.94]; n = 14,876 cases) (see **Figure 5.3**). No *heterogeneity* was observed.

Stratified analyses, using individual study results from the pooled analysis, for the risk of colorectal cancer per 10 grams increase in dietary fibre consumed per day were conducted for sex, geographic location and cancer type and by adjustment for folate.

When stratified by sex, a statistically significant decreased risk was observed for men (RR 0.89 [95% CI 0.82–0.96]) and women (RR 0.91 [95% CI 0.87–0.96]); see [CUP colorectal cancer report 2017](#), Table 3, and [CUP colorectal cancer SLR 2016](#), Figure 297). These analyses did not include the results of the pooled analysis [90] but used results from the individual published studies. When stratified by geographic location, a significant decreased risk was observed in North America (RR 0.92 [95% CI 0.88–0.96]) and Europe (RR 0.90 [95% CI 0.85–0.96]; see [CUP colorectal cancer SLR 2016](#), Figure 298), but not Asia.

When stratified by cancer type, no significant increase or decrease in the risk of colon or rectal cancer was observed with consumption of dietary fibre (see [CUP colorectal cancer report 2017](#), Table 3, and [CUP colorectal cancer SLR 2016](#), Figures 304 and 313,

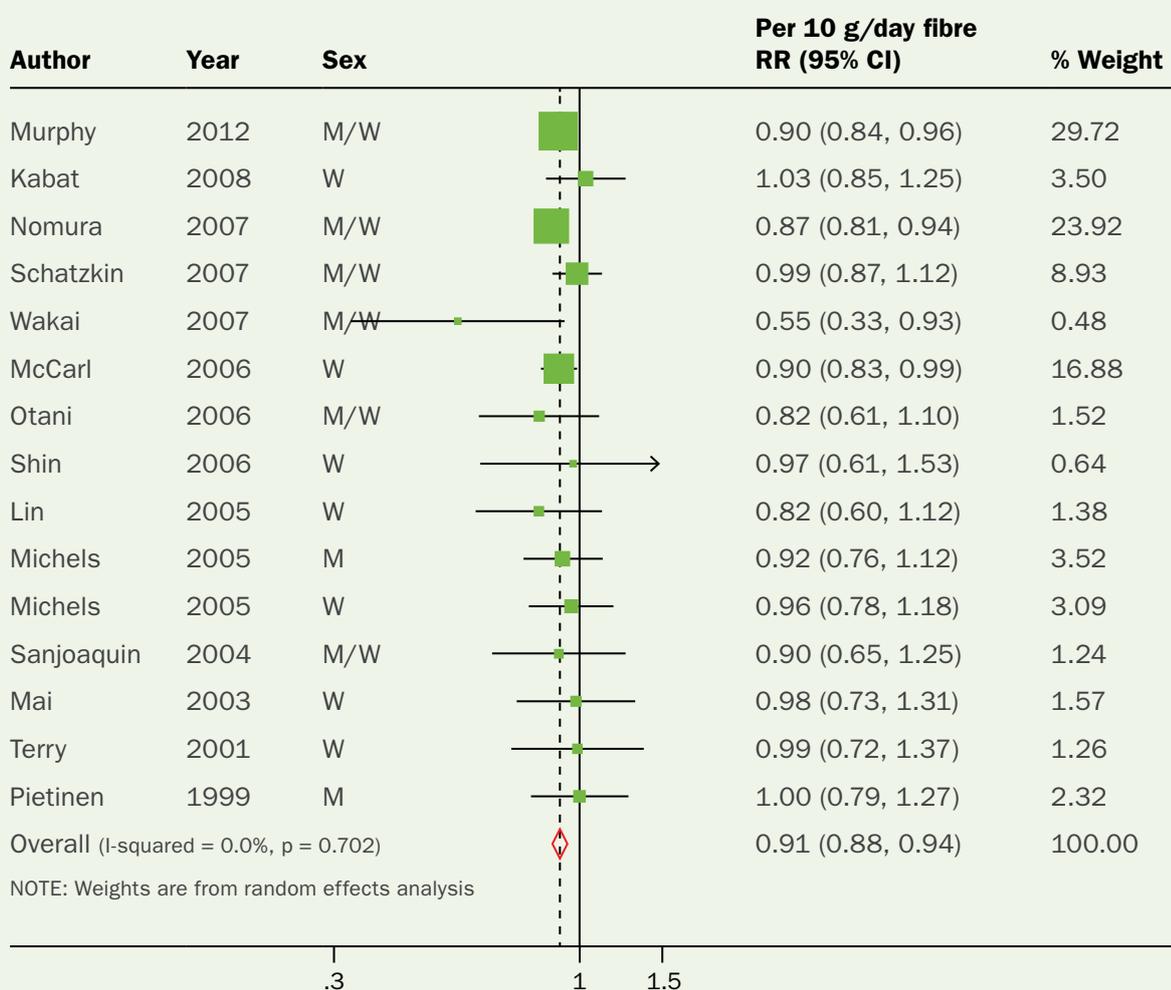
¹ The CUP dose–response meta-analysis included one pooled analysis (Park, 2005 [90]), which included 13 of the identified studies.

respectively). Similarly, no significant increase or decrease in risk was observed when studies were adjusted for folate intake.

There was no evidence of a non-linear dose–response relationship ($p = 0.06$) (see [CUP colorectal cancer SLR 2016](#), Figure 300 and Table 170).

All studies included in the dose–response meta-analysis adjusted for at least age, and most studies adjusted for the majority of the main colorectal cancer risk factors, including physical activity, BMI, alcohol consumption, tobacco smoking, red meat and MHT use in women. For information on the *adjustments* made in individual studies, see [CUP colorectal cancer SLR 2016](#), Table 168.

Figure 5.3: CUP dose–response meta-analysis¹ for the risk of colorectal cancer, per 10 grams increase in dietary fibre consumed per day (individual study results from the pooled analysis, not the overall result)



Source: Murphy, 2012 [95]; Kabat, 2008 [96]; Nomura, 2007 [97]; Schatzkin, 2007 [86]; Wakai, 2007 [94]; McCarl, 2006 [87]; Otani, 2006 [98]; Shin, 2006 [99]; Lin, 2005 [101]; Michels, 2005 [102]; Sanjoaquin, 2004 [100]; Mai, 2003 [103]; Terry, 2001 [104]; Pietinen, 1999 [105].

¹ A total of 15 studies were analysed in the CUP dose–response meta-analysis. One publication, (Michels 2005 [102]), included two studies.

5.2.1.2 Published pooled analyses and meta-analyses

Two published *pooled analyses* (see **Table 5.4**) and one other published meta-analysis on consumption of dietary fibre and the risk of colorectal cancer were identified. One of the published pooled analyses was included in the CUP dose–response meta-analysis [90]. When this pooled analysis stratified the data by source of fibre (cereal, vegetable and fruit fibre), no statistically significant association was observed for any fibre source. The other published pooled analysis reported a significant decreased risk when comparing the highest with the lowest level of fibre consumed, as assessed by food diaries [106]. The published meta-analysis reported the results from the 2010 CUP colorectal cancer SLR [89] (see [CUP colorectal cancer SLR](#), Table 167).

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 are currently prevailing 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](#).

In humans, different types of fibre can, to varying degrees, be fermented or metabolised by the colonic microflora, and this ability can influence the types and patterns of bacterial populations found in the *colon*. Microbial fermentation within the large bowel forms short-chain *fatty acids*, such as butyrate, that have been shown in experimental studies to have anti-proliferative effects for colon cancer cells [91, 107]. Other mechanisms by which greater dietary fibre intake may lower colorectal cancer risk include the reduction of intestinal transit time and increased faecal bulk, which would lessen the potential for faecal mutagens to interact with the colon mucosa, and a reduction of secondary bile acid production [91, 107]. High-fibre diets may also reduce *insulin resistance*, which is a risk factor for colorectal cancer [108]. Overall, there is moderate mechanistic evidence linking dietary fibre intake with a reduced risk of colorectal cancer.

Table 5.4: Summary of published pooled analyses for consumption of foods containing dietary fibre and the risk of colorectal cancer

Publication	Contrast	Source of fibre	RR (95% CI)	No. of studies (cohort)	No. of cases
Pooling Project of Prospective Studies on Diet and Cancer [90]	Highest vs lowest	Cereal fibre (g/day)	0.94 (0.86–1.03)	13	8,081
		Vegetable fibre (g/day)	1.00 (0.93–1.08)		
		Fruit fibre (g/day)	0.96 (0.89–1.04)		
UK Dietary Cohort Consortium [106]	Highest vs lowest	Dietary fibre intake density (g/MJ) assessed by food diaries	0.66 (0.45–0.96)	7	579
		Dietary fibre intake density (g/MJ) assessed by food frequency questionnaires	0.88 (0.57–1.36)		

5.2.1.4 CUP Panel's conclusion

The overall evidence was generally consistent, showing a decreased risk of colorectal cancer with increased consumption of dietary fibre. The CUP dose–response meta-analysis showed no statistically significant association, high *heterogeneity* was observed and there was evidence of small study bias. However, when individual studies from the *pooled analysis* rather than the pooled estimate were included in the CUP dose–response meta-analysis, a significant decreased risk was observed. There was no evidence of a non-linear dose–response relationship. Analyses stratified by sex and those for Europe and North America showed a significant decreased risk. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded:

- Consumption of foods containing dietary fibre probably protects against colorectal cancer.

5.3 Aflatoxins

Table 5.5 summarises the main findings from four published *cohort* and *nested case-control studies* on consumption of foods contaminated by aflatoxins and the risk of liver cancer. Highest versus lowest and dose–response meta-analyses could not be conducted in the CUP because measures of exposure varied between studies (see **Table 5.6**).

There was no discussion of aflatoxins and any other cancer considered in the CUP as there were too few studies.

The strong evidence on the effects of eating foods contaminated by aflatoxins on the risk of cancer is described in the following subsection. 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 published cohort and nested case-control studies on consumption of foods contaminated by aflatoxins and the risk of liver cancer

Cancer	Total no. of studies	No. of analyses	No. of cases (No. of controls)	No. of analyses reporting a statistically significant increased risk	Increment	Conclusion ¹	Date of CUP cancer report ²
Liver ³	4	11	350 (1,541)	8	Biomarkers of exposure above mean vs below mean or Biomarkers of exposure detectable vs undetectable	Convincing: Increases risk	2015

- 1 See Definitions of WCRF/AICR grading criteria (**Section 1**: Wholegrains, vegetables and fruit and the risk of cancer: a summary matrix) for explanations of what the Panel means by ‘convincing’.
- 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 evidence for aflatoxins and liver cancer relates to foods that may be contaminated with aflatoxins and includes cereals (grains) as well as pulses (legumes), seeds, nuts and some vegetables and fruit. The studies reported on elevated levels of biomarkers of aflatoxin exposure.

Table 5.6: Summary of published nested case-control and cohort studies for aflatoxins (as measured by any biomarker of exposure) and the risk of liver (hepatocellular) cancer

Study description	Publication	No. of cases/controls	RR (95% CI)	Contrast
Community-based Cancer Screening Cohort, Taiwan	Wu 2009 [109]	241 cases 1,052 controls	1.54 (1.01–2.36)	AFB ₁ -albumin adducts above vs below mean (59.8 fmol/mg)
			1.76 (1.18–2.58)	Urinary AFB ₁ above vs below mean (55.2 fmol/ml)
	Sun 2001 [110]	HBsAg carriers 75 cases 140 controls	2.0 (1.1–3.7)	AFB ₁ -albumin adducts detectable vs non-detectable
	Wang 1996 [111]	56 cases 220 controls	1.6 (0.4–5.5)	Serum level aflatoxin albumin detectable vs non-detectable
3.8 (1.1–12.8)			Urinary levels of aflatoxin high vs low	
Shanghai Cohort Study, China	Yuan 2006 [112]	50 cases 265 controls	3.25 (1.63–6.48)	Urinary aflatoxin biomarker positive vs negative
	Qian 1994 [113]	55 cases 267 controls	5.0 (2.1–11.8)	Any urinary aflatoxin biomarker vs none
	Ross 1992 [114]	22 cases 110 controls	2.4 (1.0–5.9)	Any urinary aflatoxin biomarker vs none
Qidong Cohort, China	Sun 1999 [115]	22 cases 149 controls	3.3 (1.2–8.7)	Urinary AFM ₁ detectable (above 3.6 ng/l) vs non-detectable
Cohort Government Clinics, Taiwan	Yu 1997 [116]	HBsAg carriers 21 cases 63 controls	12.0 (1.2–117.4)	Both markers (urinary AFM ₁ and AFB ₁ -N7-guanine adducts) vs none
	Chen 1996 [117]	HBsAg carriers 32 cases 73 controls	3.8 (1.0–14.5)	AFB ₁ -albumin adducts high vs undetectable

Abbreviations: AFB₁, aflatoxin B₁; AFM₁, aflatoxin M₁; HBsAg, hepatitis B surface antigen.

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 7.1 and CUP liver cancer SLR 2014: Section 4.2.2.2.2.)

A dose–response meta-analysis could not be conducted in the CUP, as a variety of measures were used to collect the data.

5.3.1.1 Published nested case-control and cohort studies

Four *cohort* and *nested case-control studies* were identified, all of which reported an increase in the risk of liver cancer with elevated levels of biomarkers for exposure to aflatoxins (see **Table 5.6**). Most of the findings were statistically significant.

An *ecological study* (not included as part of the CUP) showed that a fall in the exposure to aflatoxins was associated with a significant decrease in mortality from liver cancer. A reduction in aflatoxin exposure from 100 per cent to 23 per cent of samples positive for aflatoxin–albumin adducts was accompanied by in an estimated population-attributable

benefit of 65 per cent for reduction in the rate of primary liver cancer. Because of the strong synergy between aflatoxin and hepatitis B virus, only 17 per cent of the population-attributable benefit was estimated to be due to the reduction of aflatoxin among those without infection [118].

5.3.1.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. One recent published meta-analysis on aflatoxins and the risk of liver cancer was identified, which included *nested case-control* and *case-control studies* from China, Taiwan and sub-Saharan Africa [119]. A statistically significant increased risk was observed for the nine studies that reported on the general population after adjustment for HBsAg (RR 4.75 [95% CI 2.78–8.11]) [119].

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 are currently prevailing 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](#).

Aflatoxin, and specifically aflatoxin B₁, is a *mycotoxin* produced by moulds of the *Aspergillus* species that contaminates many food crops stored in warm and moist conditions, a problem most evident in areas of Africa and Asia. Aflatoxin B₁ is metabolised in the liver by members of the cytochrome P450 family, specifically CYP3A4 and CYP3A5, to its reactive intermediate, 8,9-exo-epoxide, which can form aflatoxin-N⁷-guanine adducts. The products of aflatoxin biotransformation in the liver are known to be highly *genotoxic* to the organ [120], and *hepatocellular carcinomas*

from regions with high exposure to aflatoxin tend to bear a high *mutation* load in TP53 characteristic of aflatoxin adduct formation [121–123].

5.3.1.4 CUP Panel's conclusion

The overall evidence for a relationship between aflatoxins and liver cancer was consistent. No meta-analysis was conducted in the CUP, but all of the studies identified reported increased risks, most of which were statistically significant. Results were also consistent with recent reviews published on aflatoxins and the risk of liver cancer. The Panel noted that although the main areas affected by higher aflatoxin exposure are Africa and Asia, it is a global issue of public health relevance. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded:

- **Higher exposure to aflatoxins and consumption of aflatoxin-contaminated foods are convincing causes of liver cancer.**

5.4 Non-starchy vegetables

Table 5.7 summarises the main findings from the CUP dose–response meta-analyses of cohort studies on consumption of vegetables and the risk of cancer. In general terms and in most studies, the term ‘vegetable’ applies to non-starchy vegetables. Potatoes are usually (as in this Third Expert Report) defined as tubers, but are sometimes (in the USA especially) included with vegetables (for more information, see **Section 4.2.1.3**). For this reason the Panel’s conclusion is for non-starchy vegetables, although the term ‘vegetable’ is used throughout this section for consistency with the information reported in the individual studies.

In this section, the evidence for each cancer relates to consumption of vegetables, apart from the evidence for bladder cancer, which is for consumption of vegetables and fruit

combined. All of the evidence relates to a greater intake of these foods, apart from the evidence for colorectal cancer, which is for low intake of vegetables.

Table 5.7: Summary of CUP dose–response meta-analyses of vegetable intake and the risk of cancer

Cancer	Type	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I ² (%)	Conclusion ¹	Date of CUP cancer report ²
Mouth, pharynx and larynx³	Vegetables	3	0	–	Statistically significant decreased risk in 1 study ³	–	–	Limited – suggestive: Decreases risk	2018
Nasopharynx⁴	Vegetables	2 meta-analyses	–	–	Statistically significant decreased risk in 2 meta-analyses ⁴	–	–	Limited – suggestive: Decreases risk	2017
Oesophagus (adenocarcinoma)	Vegetables	3	3	415	0.89 (0.80–0.99)	100 g/day	0	Limited – suggestive: Decreases risk	2016
Oesophagus (squamous cell carcinoma)	Vegetables	4	4	2,273	0.91 (0.81–1.03)	100 g/day	31	Limited – suggestive: Decreases risk	2016
Lung (people who smoke tobacco)⁵	Vegetables	9	6	6,520	0.88 (0.79–0.99)	100 g/day	81	Limited – suggestive: Decreases risk ⁵	2017
Lung (people who used to smoke tobacco)⁵		6	4	3,771	0.97 (0.91–1.05)		25		
Breast (oestrogen receptor-negative)⁶	Vegetables	3	3	1,346	0.79 (0.63–0.98)	200 g/day	37	Limited – suggestive: Decreases risk	2017
Bladder⁷	Vegetables and fruit combined	9	8	2,508	0.97 (0.95–0.99)	80 g/day	0	Limited – suggestive: Decreases risk	2015
Colorectum⁸	Vegetables	23	9	–	1.08 (1.06–1.10)	Non-linear dose–response analysis 100 vs 200 g/day	0	Limited – suggestive: Increases risk with low consumption	2017

Please see next page for explanation of footnotes.

- 1 See Definitions of WCRF/AICR grading criteria (**Section 1**: Wholegrains, vegetables and fruit 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.
- 3 A dose–response meta-analysis on vegetables and cancers of the mouth, pharynx and larynx could not be conducted in the CUP. One of three identified published studies reported a statistically significant decreased risk of oral cavity cancer (RR 0.84 [95% CI 0.73–0.95], per serving/1,000 kcal, n = 319), and of head and neck cancer (RR 0.89 [95% CI 0.82–0.97], per serving/1,000 kcal, n = 787), with increased consumption of vegetables in dose–response meta-analyses [124].
- 4 A dose–response meta-analysis on vegetables and nasopharyngeal cancer could not be conducted in the CUP. Two published meta-analyses of case-control studies on vegetable intake and nasopharyngeal cancer were identified, both of which showed a statistically significant decreased risk of nasopharyngeal cancer when comparing the highest with the lowest level of vegetables consumed (RR 0.60 [95% CI 0.47–0.76] [27] and RR 0.64 [95% CI 0.48–0.85] [28]).
- 5 A separate dose–response meta-analysis on green leafy vegetables and lung cancer also showed a significant decreased risk. For more information on the evidence that led to the conclusion, see **Section 5.4.5**.
- 6 The Panel’s conclusion for non-starchy vegetables (greater intake) and breast cancer relates to evidence for breast cancer overall (menopausal status not specified). The observed association was in oestrogen receptor-negative (ER-negative or ER–) breast cancer only.
- 7 The evidence for vegetables and fruit and bladder cancer relates to combined consumption of vegetables and fruit and is summarised in **Section 5.4.7** and **Table 5.15**.
- 8 Although the dose–response meta-analysis for colorectal cancer showed a statistically significant decreased risk with increased consumption of vegetables, a non-linear relationship was apparent, which showed a significant increased risk at intakes of 100 grams or less per day when compared with an intake of 200 grams per day. For information on the evidence that led to the Panel’s conclusion, see **Section 5.4.8**.

Evidence for cancers of the following types was discussed in the CUP but was too limited to draw a conclusion¹: lung (people who have never smoked; 2017), stomach (2016), pancreas (2012), liver (2015), breast cancer (ER-positive; 2017), ovary (2014), endometrium (2013), cervix (2017), prostate (2014), kidney (2015) and skin (2017).

The evidence on the effects of eating vegetables and the risk of cancer that was graded by the Panel as ‘limited – suggestive’ is described in the following subsections.

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

5.4.1 Mouth, pharynx and larynx

(Also see [CUP mouth, pharynx and larynx cancer report 2018](#): Section 7.1 and [CUP mouth, pharynx and larynx cancer SLR 2016](#): Section 2.2.1.)

The evidence for vegetables and the risk of the following cancers is presented in the following subsections: oral cavity cancer, oro- and hypopharyngeal cancer combined, laryngeal cancer, head and neck cancer, and upper aerodigestive tract cancer. For information on specific types of vegetables, see [CUP mouth, pharynx and larynx cancer SLR 2016](#), Section 2.2.1.1. Dose–response meta-analyses could not be conducted in the CUP, as there were too few studies.

¹ ‘**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.

5.4.1.1 Published dose–response analyses from individual cohort studies

Three published dose–response cohort studies on consumption of vegetables and cancers of the mouth, pharynx and larynx were identified. One study reported a statistically significant decreased risk for oral cavity cancer and head and neck cancer (see **Table 5.8**). All studies adjusted for tobacco smoking. For information on the *adjustments* made in individual studies, see [CUP mouth, pharynx and larynx cancer SLR 2016](#), Table 3.

One of these published studies [124] stratified analyses by tobacco smoking and reported a statistically significant decreased risk of head and neck cancer per one serving increase in vegetables consumed per 1,000 kilocalories

in people who used to smoke (RR 0.83 [95% CI 0.73–0.94]). No significant association was reported for people who smoke (RR 0.88 [95% CI 0.77–1.02]) or those who have never smoked (RR 1.11 [95% CI 0.94–1.32]).

5.4.1.2 Published pooled analyses and meta-analyses

One published *pooled analysis* of case-control studies on consumption of vegetables and the risk of cancers of the mouth, pharynx and larynx was identified (see **Table 5.9**). No published meta-analyses have been identified. A significant decreased risk was reported for various cancer subtypes (head and neck, oral, oropharyngeal, pharyngeal and laryngeal separately) [127].

Table 5.8: Summary of published dose–response analyses from individual cohort studies on consumption of vegetables and the risk of cancers of the mouth, pharynx and larynx

Cancer site	Study	Increment	No. of cases	RR (95% CI)
Oral cavity	Netherlands cohort study [125]	25 g/day	131	0.95 (0.89–1.02)
	NIH-AARP [124]	serving/1,000 kcal	319	0.84 (0.73–0.95)
Oro- and hypopharyngeal combined	Netherlands cohort study [125]	25 g/day	88	0.94 (0.85–1.04)
	NIH-AARP [124]	serving/1,000 kcal	142	0.90 (0.74–1.09)
Laryngeal	Netherlands cohort study [125]	25 g/day	193	0.98 (0.92–1.04)
	NIH-AARP [124]	serving/1,000 kcal	279	0.91 (0.79–1.05)
Head and neck	Netherlands cohort study [125]	25 g/day	415	0.96 (0.92–1.01)
	NIH-AARP [124]	serving/1,000 kcal	787	0.89 (0.82–0.97)
Upper aerodigestive tract	European Prospective Investigation into Cancer and Nutrition [126]	40 g/day	352	0.89 (0.78–1.02)

Table 5.9: Summary of published pooled analyses of vegetable intake and the risk of head and neck cancer

Publication	Contrast	RR (95% CI)	No. of studies (case control)	No. of cases
Chuang, 2012 [127]	Highest vs lowest	0.66 (0.49–0.90)	22	12,968

5.4.1.3 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 are currently prevailing 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](#).

Vegetables comprise a diverse group of foods, and their consumption provides exposure to a wide array of *nutrients* and *phytochemicals*. Although there is a substantial body of evidence demonstrating potential anti-tumorigenic effects of many components found in vegetables, including *carotenoids*; vitamins A, C, and E; selenium; phenolic acids; *flavonoids*; and glucosinolates, among others, in a range of different tissue types, experimental models of *de novo* *carcinogenesis* of the oral, oropharyngeal, pharyngeal and laryngeal mucosa are limited. Thus, the number of studies of the effects of vegetables or extracts, or specific phytochemicals on these tissues remains modest. This approach is complemented by studies of *tumorigenesis* using transplantable models that employ human *squamous cell carcinoma* cells in immune-deficient mice. In parallel, *in vitro* studies examine how specific substances affect various aspects of carcinogenesis and cancer cell growth [128]. Human *randomised controlled trials* of vegetable intake or components from vegetables are few, limited in size, and often focus on *biomarkers* or premalignant oral conditions, such as leukoplakia [129]. It is likely that the epidemiological relationships between vegetables and reduced risk of cancers of the mouth, pharynx and larynx are mediated by multiple components that are themselves mediated by a range

of mechanisms [130]. Future studies focusing upon how diets rich in vegetables or specific vegetables and their unique phytochemicals may affect cancers of the mouth, pharynx and larynx are necessary.

5.4.1.4 CUP Panel's conclusion

The evidence from cohort studies suggesting increased consumption of non-starchy vegetables decreases the risk of cancers of the mouth, pharynx and larynx was limited but generally consistent. All the studies identified in the CUP adjusted for tobacco smoking; however, no statistically significant association was observed in people who have never smoked in the only study that stratified by tobacco smoking, suggesting that there is potential for residual confounding due to tobacco smoking. Overall, findings from the studies identified in the CUP were generally consistent with a published *pooled analysis* of *case-control studies*. There is evidence of plausible mechanisms in humans.

The CUP Panel concluded:

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

5.4.2 Nasopharynx

(Also see [CUP nasopharyngeal cancer SLR 2017](#): Section 2.2.1.)

A dose–response meta-analysis could not be conducted in the CUP as no cohort studies were identified.

5.4.2.1 Published meta-analyses of case-control studies

Two published meta-analyses of *case-control studies* on consumption of vegetables and the risk of nasopharyngeal cancer were identified

[27, 28], both of which showed a statistically significant decreased risk when comparing the highest with the lowest level of vegetables consumed (see **Table 5.10**).

When one of these published meta-analyses was restricted to studies that adjusted for tobacco smoking, the statistically significant decreased risk remained (RR 0.57 [95% CI 0.39–0.84]) for six case-control studies [27]. No study adjusted for Epstein-Barr virus.

The studies in one published meta-analysis [27] mostly adjusted or accounted for age and sex; about half adjusted for tobacco smoking, and some for alcohol and dietary factors. All studies in the other published meta-analysis [28] adjusted for age, sex and smoking. No study adjusted for Epstein-Barr virus.

5.4.2.2 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 are currently prevailing 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](#).

Fruit and non-starchy vegetables contain a large number of potential anti-tumorigenic agents, such as dietary fibre, *carotenoids*, vitamins C and E, selenium, dithiolthiones, glucosinolates and indoles, isothiocyanates, *flavonoids*, phenols, protease inhibitors, plant sterols, allium compounds and limonene [131]. It is likely that a combination of these *nutrients* is responsible for the lower risk of nasopharyngeal cancer that has been observed among high consumers of fruit and non-starchy vegetables.

5.4.2.3 CUP Panel's conclusion

No cohort studies were identified. The evidence from two meta-analyses of *case-control studies* suggesting that increased consumption of non-starchy vegetables decreases the risk of nasopharyngeal cancer was limited, but generally consistent. Although studies that adjusted for tobacco smoking showed a statistically significant decreased risk, there were no analyses in people who have never smoked. There is evidence of plausible mechanisms in humans.

The CUP Panel concluded:

- The evidence suggesting that greater consumption of non-starchy vegetables decreases the risk of nasopharyngeal cancer is limited.

Table 5.10: Summary of published highest versus lowest meta-analyses for consumption of vegetables and the risk of nasopharyngeal cancer

Publication	Contrast	RR (95% CI)	P value	No. of studies (case control)	No. of cases
Jin, 2014 [27]	Highest vs lowest total or fresh vegetable intake	0.60 (0.47–0.76)	0.03	11 (all studies)	3,749
		0.47 (0.38–0.58)	0.18	4 (hospital-based studies)	
		0.80 (0.65–0.99)	0.84	7 (population-based studies)	
Gallicchio, 2006 [28]	Highest vs lowest non-preserved vegetable intake	0.64 (0.48–0.85)	0.09	5 (all studies)	1,695

5.4.3 Oesophagus (adenocarcinoma)

(Also see CUP oesophageal cancer report 2016: Section 7.1 and CUP oesophageal cancer SLR 2015: Section 2.2.1.)

The evidence for vegetables and the risk of oesophageal adenocarcinoma is presented in the following subsection. For evidence specifically on vegetables and oesophageal squamous cell carcinoma, see **Section 5.4.4**. For information on green leafy vegetables and cruciferous vegetables/other vegetables, see CUP oesophageal cancer SLR 2015, Sections 2.2.1.4 and 2.2.1.2, respectively.

5.4.3.1 CUP dose–response meta-analyses

All three identified studies were included in the dose–response meta-analysis, which showed a statistically significant 11 per cent decreased risk of oesophageal adenocarcinoma per 100 grams increase in vegetables consumed per day (RR 0.89 [95% CI 0.80–0.99]; $n = 415$ cases) (see **Figure 5.4**). No *heterogeneity* was observed. There was no evidence of small study bias with *Egger’s test* for oesophageal cancer overall ($p = 0.15$; there was no separate analysis for adenocarcinoma), but inspection of the funnel plot suggested small studies showing an increased risk may be missing (see CUP oesophageal cancer SLR 2015, Figure 4).

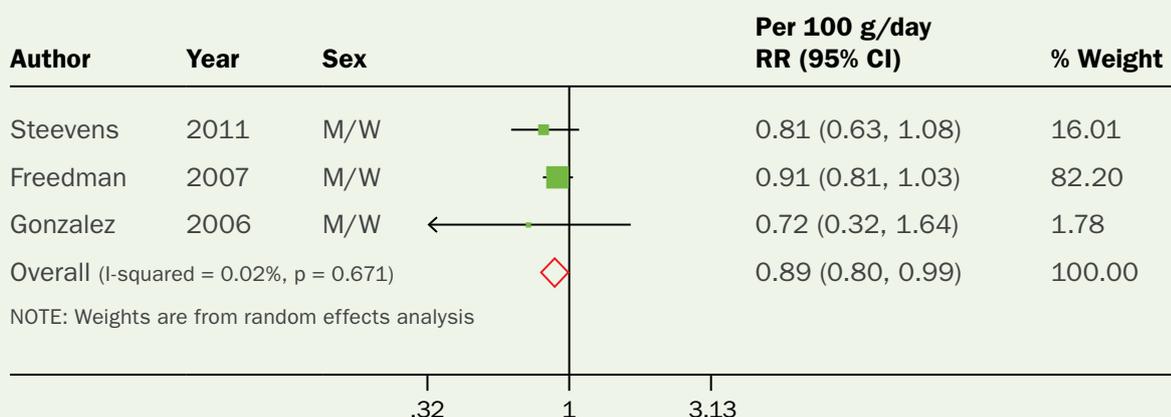
One published study that was included in the dose–response meta-analysis [132] reported results by tobacco smoking. A statistically significant decreased risk of oesophageal adenocarcinoma was observed per 25 grams increase in vegetables consumed per day in people who smoke (RR 0.85 [95% CI 0.75–0.97]) but not in people who used to smoke (RR 1.02 [95% CI 0.93–1.11]) or those who have never smoked (RR 0.97 [95% CI 0.84–1.13]).

All studies included in the dose–response meta-analysis adjusted for age, sex, alcohol consumption and tobacco smoking, as well as frequency and duration of tobacco smoking. No studies adjusted for *H. pylori* status. For information on the *adjustments* made in individual studies, see CUP oesophageal cancer SLR 2015, Table 7.

5.4.3.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. One other published meta-analysis on consumption of vegetables and the risk of oesophageal adenocarcinoma was identified [135]. The meta-analysis included both cohort and *case-control studies*; no statistically significant association was observed when the cohort studies were analysed [135].

Figure 5.4: CUP dose–response meta-analysis for the risk of oesophageal adenocarcinoma, per 100 grams increase in vegetables consumed per day



Source: Steevens, 2011 [132]; Freedman, 2007 [133]; Gonzalez, 2006 [134].

5.4.3.3 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 are currently prevailing 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](#).

Fruit and non-starchy vegetables contain a large number of potential anti-tumorigenic agents, such as dietary fibre, *carotenoids*, vitamins C and E, selenium, dithiolthiones, glucosinolates and indoles, isothiocyanates, *flavonoids*, phenols, protease inhibitors, plant sterols, allium compounds and limonene [131]. It is likely that a combination of these *nutrients* is responsible for the lower risk of oesophageal cancer that has been observed among high consumers of fruit and non-starchy vegetables.

5.4.3.4 CUP Panel's conclusion

For oesophageal adenocarcinoma, the evidence for consumption of vegetables was limited but generally consistent. The CUP dose–response meta-analysis showed a statistically significant decreased risk with greater vegetable consumption; however, this included only three studies. No *heterogeneity* was observed. Although studies adjusted for tobacco smoking, there is the potential for residual confounding due to tobacco smoking. There is evidence of plausible mechanisms in humans.

The CUP Panel concluded:

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

5.4.4 Oesophagus (squamous cell carcinoma)

(Also see [CUP oesophageal cancer report 2016](#): Section 7.1 and [CUP oesophageal cancer SLR 2015](#): Section 2.2.1.)

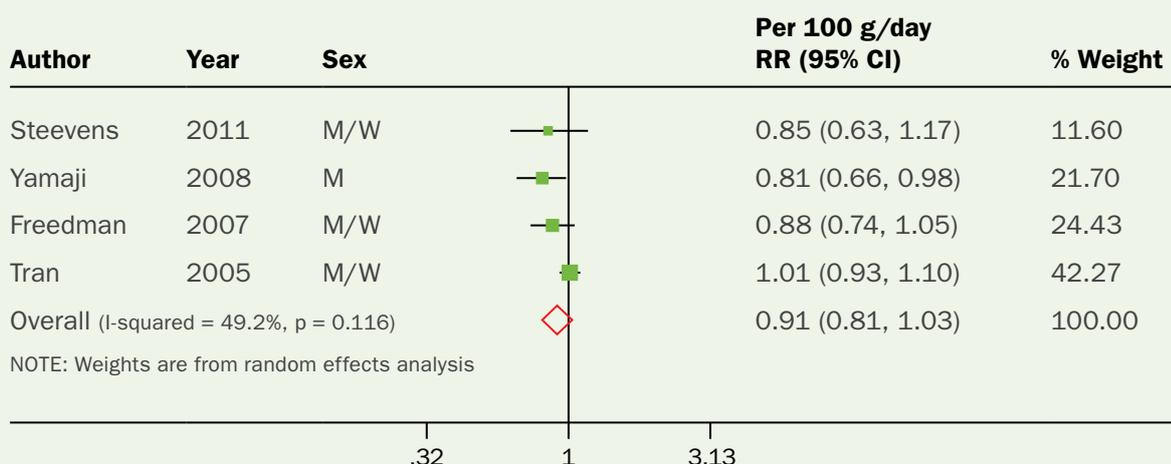
The evidence for vegetables and the risk of oesophageal squamous cell carcinoma is presented in the following subsection. For evidence specifically on vegetables and oesophageal adenocarcinoma, see **Section 5.4.3**. For information on green leafy vegetables and cruciferous vegetables/other vegetables, see [CUP oesophageal cancer SLR 2015](#), Sections 2.2.1.4 and 2.2.1.2, respectively.

5.4.4.1 CUP dose–response meta-analyses

All four identified studies were included in the dose–response meta-analysis, which showed no statistically significant association between the risk of oesophageal squamous cell carcinoma and consumption of vegetables (RR 0.91 [95% CI 0.81–1.03], per 100 grams increase per day; $n = 2,273$ cases) (see **Figure 5.5**). Moderate *heterogeneity* was observed ($I^2 = 31\%$). There was no evidence of small study bias with *Egger's test* for oesophageal cancer overall ($p = 0.15$; there was no separate analysis for squamous cell carcinoma), but inspection of the funnel plot suggested small studies showing an increased risk may be missing (see [CUP oesophageal cancer SLR 2015](#), Figure 4). One study reported a non-significant increased risk; this study was conducted in Linxian, China, an area that is characterised by poor nutritional status and has a high rate of oesophageal cancer [136].

One published study that was included in the dose–response meta-analysis [132] reported results by tobacco smoking. A statistically significant decreased risk of oesophageal squamous cell carcinoma was observed per 25 grams increase in vegetables consumed per day in people who smoke (RR 0.90 [95% CI 0.81–0.99]), but not in those who used to smoke (RR 0.96 [95% CI 0.83–1.11]) or in people who have never smoked (RR 1.08 [95% CI 0.98–1.19]).

Figure 5.5: CUP dose–response meta-analysis for the risk of oesophageal squamous cell carcinoma, per 100 grams increase in vegetables consumed per day



Source: Steevens, 2011 [132]; Yamaji, 2008 [137]; Freedman, 2007 [133]; Tran, 2005 [136].

All studies included in the dose–response meta-analysis adjusted for age and sex, and all but one [136] adjusted for alcohol consumption and tobacco smoking, as well as frequency and duration of tobacco smoking. For information on the *adjustments* made in individual studies, see [CUP oesophageal cancer SLR 2015](#), Table 7.

5.4.4.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. One other published meta-analysis on consumption of vegetables and the risk of oesophageal squamous cell carcinoma was identified [138]. The meta-analysis included both cohort and *case-control studies*; no statistically significant association was observed when the cohort studies were analysed [138].

5.4.4.3 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 are currently prevailing 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](#).

Fruit and non-starchy vegetables contain a large number of potential anti-tumorigenic agents, such as dietary fibre, *carotenoids*, vitamins C and E, selenium, dithiolthiones, glucosinolates and indoles, isothiocyanates, *flavonoids*, phenols, protease inhibitors, plant sterols, allium compounds and limonene [131]. It is likely that a combination of these *nutrients* is responsible for the lower risk of oesophageal cancer that has been observed among high consumers of fruit and non-starchy vegetables.

5.4.4.4 CUP Panel's conclusion

For oesophageal squamous cell carcinoma, the evidence for consumption of vegetables was limited but generally consistent. Although the CUP dose–response meta-analysis showed no statistically significant association, it included only four studies with moderate *heterogeneity*; three of the four studies reported decreasing risk with increasing consumption of vegetables. Although most studies adjusted for tobacco smoking, there is the potential for residual confounding due to tobacco smoking. There is evidence of plausible mechanisms in humans.

The CUP Panel concluded:

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

5.4.5 Lung (people who smoke/used to smoke tobacco)

(Also see [CUP lung cancer report 2017](#): Section 7.3 and [CUP lung cancer SLR 2015](#): Section 2.2.1.)

The evidence for vegetables and green leafy vegetables and the risk of lung cancer, stratified by tobacco smoking, is presented in the following subsections. For information on vegetables, green leafy vegetables and cruciferous vegetables (all not stratified by tobacco smoking), see [CUP lung cancer SLR 2015](#), Sections 2.2.1, 2.2.1.4 and 2.2.1.2, respectively.

5.4.5.1 CUP dose–response meta-analyses stratified by tobacco smoking

Six of nine identified studies reporting results on people who smoke were included in a dose–response meta-analysis stratified by tobacco smoking, which showed a statistically significant 12 per cent decreased risk of lung cancer in

people who smoke per 100 grams increase in vegetables consumed per day (RR 0.88 [95% CI 0.79–0.99]; $n = 6,520$) (see [Figure 5.6](#)). High *heterogeneity* was observed ($I^2 = 81\%$).

No significant association was observed between the risk of lung cancer and consumption of vegetables in people who used to smoke (RR 0.97 [95% CI 0.91–1.05]; $n = 3,771$) or people who have never smoked (RR 1.00 [95% CI 0.91–1.14]; $n = 680$). Low *heterogeneity* was observed in both analyses (see [Figure 5.6](#)).

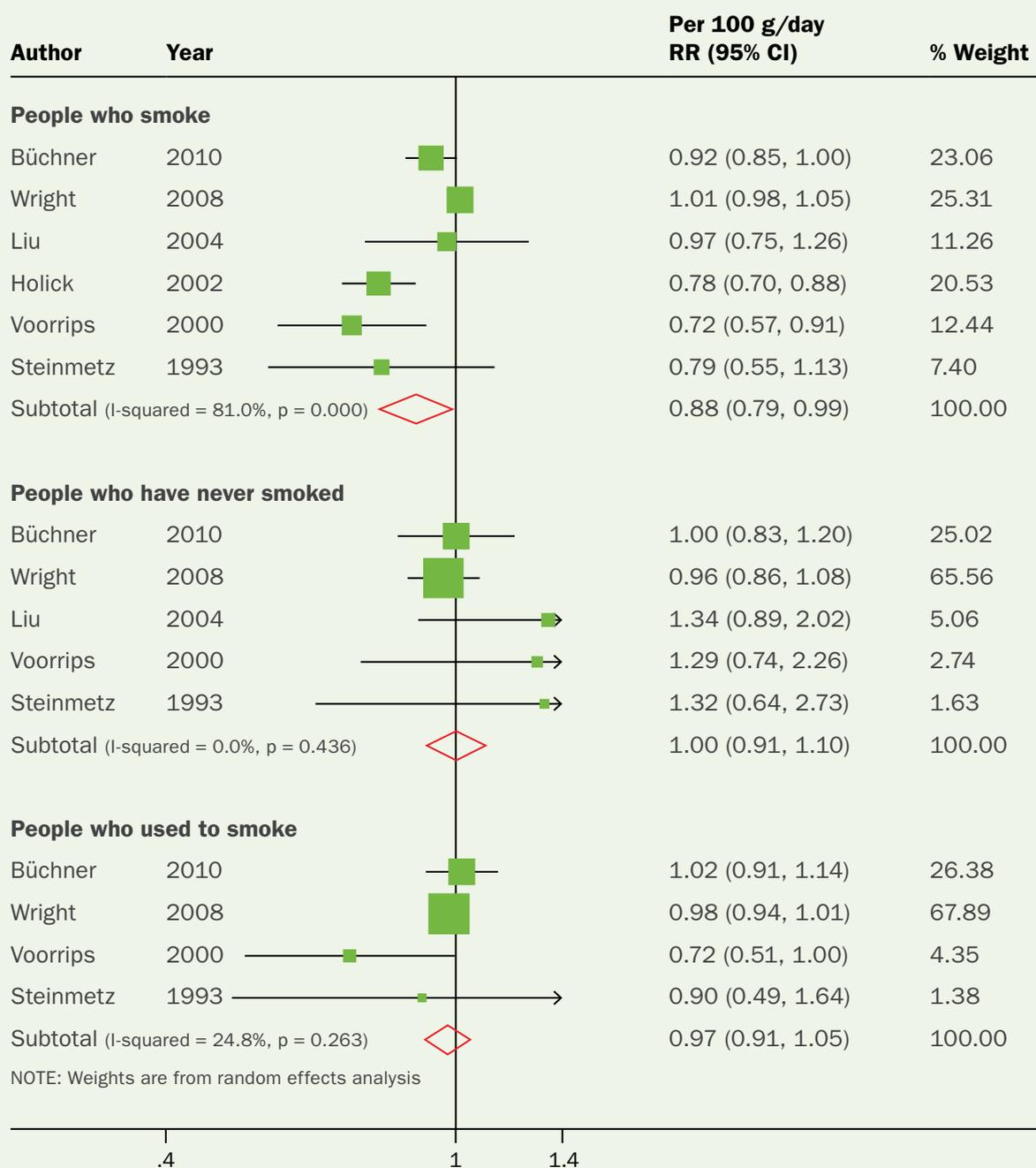
All studies included in the dose–response analysis adjusted for age and sex. For information on the *adjustments* made in individual studies, see [CUP lung cancer SLR 2015](#), Table 15.

A dose–response meta-analysis for the risk of lung cancer stratified by tobacco smoking was also possible per 50 grams increase in green leafy vegetables consumed per day. A statistically significant decreased risk was observed for people who used to smoke (RR 0.63 [95% CI 0.41–0.95] for three studies), but not for people who smoke (RR 0.83 [95% CI 0.66–1.06] for four studies), or for those who have never smoked (RR 0.96 [95% CI 0.76–1.22] for four studies) ([CUP lung cancer SLR 2015](#), Figure 33).

5.4.5.2 Published pooled analyses and meta-analyses

One published *pooled analysis* on consumption of vegetables and the risk of lung cancer was identified (see [Table 5.11](#)). No other published meta-analyses have been identified. In the pooled analysis, no statistically significant association was observed when comparing the highest with the lowest level of vegetables consumed in people who smoke, people who used to smoke or people who have never smoked [145].

Figure 5.6: CUP dose–response meta-analysis^{1,2} for the risk of lung cancer stratified by tobacco smoking, per 100 grams increase in vegetables consumed per day



Source: Büchner, 2010 [139]; Wright, 2008 [140]; Liu, 2004 [141]; Holick, 2002 [142]; Voorrips, 2000 [143]; Steinmetz, 1993 [144].

When the results of the pooled analysis [145] were combined with non-overlapping studies identified in the CUP, a significant decreased risk of lung cancer was observed when comparing the highest with the lowest amount

of vegetables consumed for all participants (RR 0.93 [95% CI 0.88–0.98]) as well as in people who smoke (RR 0.88 [95% CI 0.80–0.97]); see [CUP lung cancer report 2017, Table 5](#).

¹ For people who smoke, three studies could not be included in the dose–response meta-analysis as they did not provide sufficient information. For further details, see CUP lung cancer SLR 2015, Tables 15 and 16.

² For people who used to smoke, two studies could not be included in the dose–response meta-analysis as they did not provide sufficient information. For further details, see CUP lung cancer SLR 2015, Tables 15 and 16.

Table 5.11: Summary of published pooled analyses of vegetable intake and the risk of lung cancer

Publication	Contrast	Subgroup	RR (95% CI)	No. of studies (cohort)	No. of cases
Pooling Project of Prospective Studies on Diet and Cancer [145]	Quintile 4 vs Quintile 1	People who smoke	0.86 (0.74–1.00)	5	1,915
		People who used to smoke	0.97 (0.76–1.24)		981
		People who have never smoked	0.90 (0.58–1.40)		259

5.4.5.3 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 are currently prevailing 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](#).

Vegetables comprise a diverse food group, and their consumption provides exposure to a wide array of *phytochemicals*. Although there is a substantial body of evidence demonstrating the potential anti-tumorigenic effects of many agents found in vegetables including *carotenoids*, vitamins A, C, and E, selenium, phenolic acids, *flavonoids* and glucosinolates in a range of different tissue types, experimental models of *de novo carcinogenesis* of the lung are limited. Thus, the number of studies of the effects of vegetables or extracts or specific phytochemicals on lung tissue remains modest. It is likely that the epidemiological relationships between vegetables and reduced risk of lung cancer are mediated by multiple components and through a range of mechanisms. Vegetables are a source of carotenoids, and there are suggestive epidemiologic and mechanistic data linking their intake to lower risk of lung cancer, see **Section 5.7.1**. Future studies focusing on how

diets rich in vegetables or specific vegetables and their unique phytochemicals may affect lung cancer development are warranted.

5.4.5.4 CUP Panel's conclusion

The evidence for consumption of vegetables and the risk of lung cancer was limited but generally consistent. The CUP dose–response meta-analysis showed a statistically significant decreased risk only for people who smoke; however, high *heterogeneity* was observed. Although no significant association was observed for people who used to smoke, results were consistent with the decreased risk observed for people who smoke. The results for people who had never smoked showed no evidence of an effect. The dose–response meta-analysis for green leafy vegetables showed a significant decreased risk in people who used to smoke, with low *heterogeneity*. Although studies adjusted for tobacco smoking, there is the potential for residual confounding due to tobacco smoking. There is evidence of plausible mechanisms in humans.

The CUP Panel concluded:

- **The evidence suggesting that greater consumption of non-starchy vegetables decreases the risk of lung cancer in people who smoke and people who used to smoke tobacco is limited.**



5.4.6 Breast (oestrogen receptor-negative)

(Also see CUP breast cancer report 2017: Section 7.1 and CUP breast cancer SLR 2017: Section 2.2.1.)

The evidence for vegetables and the risk of breast cancer (pre or postmenopause not specified), stratified by hormone receptor status, is presented in the following subsections. For information on premenopausal breast cancer and postmenopausal breast cancer (both not stratified by hormonal status), see CUP breast cancer SLR, Section 2.2.1.

5.4.6.1 CUP dose-response meta-analysis stratified by hormone receptor status

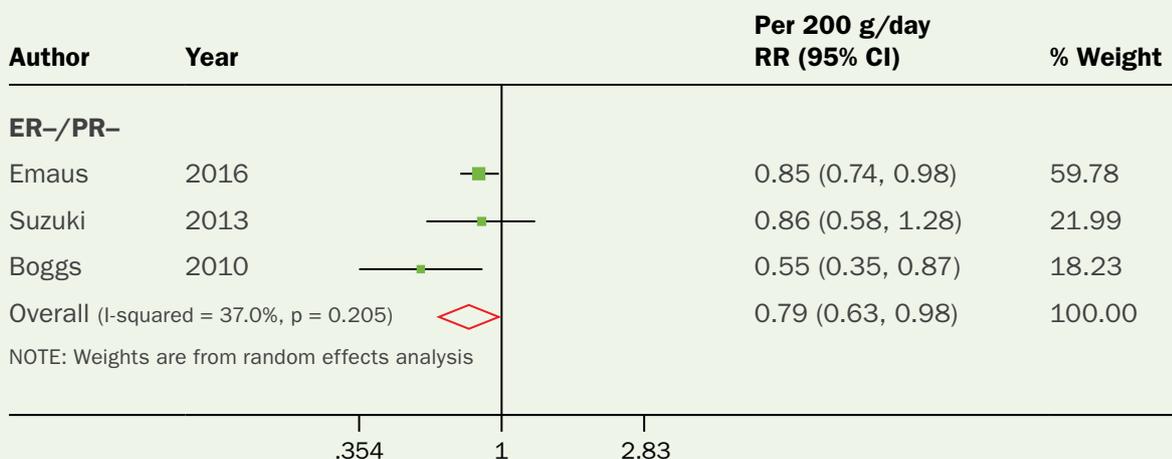
All three identified studies reporting results by hormone receptor status were included in the dose-response meta-analysis, which showed a statistically significant 21 per cent decreased risk of ER-negative/progesterone receptor-negative (PR-negative or PR-) breast cancer per 200 grams increase in vegetables consumed per day (RR 0.79 [95% CI 0.63–0.98]; n = 1,346 cases) (see Figure 5.7). Moderate heterogeneity was observed ($I^2 = 37\%$).

No significant association was observed between the risk of breast cancer and consumption of vegetables for tumours that were ER-positive/PR-positive (RR 0.96 [95% CI 0.81–1.13]; n = 3,950; moderate heterogeneity) or ER-positive/PR-negative (RR 0.89 [95% CI 0.79–1.01]; n = 1,229; no heterogeneity) (see Figure 5.7).

There were not enough studies to conduct stratified analyses by menopausal status.

All studies included in the dose-response meta-analysis adjusted for at least age, and most of the studies adjusted for parity, age at menarche, age at menopause, physical activity, BMI and alcohol consumption. For information on the adjustments made in individual studies, see CUP breast cancer SLR 2017, Table 34.

Figure 5.7: CUP dose-response meta-analysis for the risk of oestrogen receptor-negative/progesterone receptor-negative breast cancer, per 200 grams increase in vegetables consumed per day



Source: Emaus, 2016 [146]; Suzuki, 2013 [147]; Boggs, 2010 [148].

Table 5.12: Summary of published pooled analyses of vegetable intake and the risk of oestrogen receptor-negative breast cancer

Publication	Increment/contrast	RR (95% CI)	No. of studies (cohort)	No. of cases
Pooling Project of Prospective Studies on Diet and Cancer 2013 [149]	Quintile 5 vs Quintile 1	0.82 (0.74–0.90)	20	4,820
	Per 300 g/day	0.88 (0.81–0.95)		

5.4.6.2 Published pooled analyses and meta-analyses

A recent published *pooled analysis* of cohort studies on consumption of vegetables and the risk of breast cancer according to hormone receptor status was identified (see **Table 5.12**). A statistically significant decreased risk of ER-negative breast cancer was observed when comparing the highest with the lowest levels of vegetables consumed [149]. No significant association was observed for ER-positive/PR-negative or PR-positive breast cancer. A statistically significant decreased risk of ER-negative breast cancer was also observed per 300 grams increase in vegetables consumed per day (approximately three servings per day).

No other published meta-analyses on consumption of vegetables and the risk of breast cancer according to hormone receptor status have been identified.

5.4.6.3 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 are currently prevailing 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](#).

Vegetables are a source of many *nutrients* and thus may increase levels of pro-vitamin A *carotenoids*, vitamins C and E, folate, selenium and other nutrients that are hypothesised to affect the risk of certain cancers. Plants also provide a source of fibre in the diet, which may affect the colonic microbiota and host metabolism to alter cancer risk. Plants are also a rich source of chemical substances collectively referred to as *phytochemicals*. Many of these compounds are used by the plants as part of their hormonal environment and protect the plant from stress due to heat, cold, sunlight, infections and predators, in addition to playing a role in reproduction. We now appreciate that many phytochemicals have potential anti-carcinogenic and anti-tumorigenic properties. These include many classes of compounds such as dithiolthiones, glucosinolates and indoles, isothiocyanates, *flavonoids*, phenols, protease inhibitors, plant sterols, allium compounds and limonene [131]. A possible protective effect of *bioactive constituents* in vegetables may be more detectable in the less hormonally dependent ER-negative tumours than in ER-positive tumours, where a dominant effect of oestrogens might obscure a smaller effect on risk from vegetables. Epidermal growth factor receptor (EGFR) tends to be overexpressed in ER-negative breast tumours, and some phytochemicals found in vegetables have been suggested to reduce the level of EGFR, which may, in turn, reduce the risk of developing ER-negative breast cancer [149].

5.4.6.4 CUP Panel's conclusion

The evidence for consumption of vegetables and the risk of breast cancer was limited but generally consistent. When stratified by *hormone receptor status*, the CUP dose–response meta-analysis observed a statistically significant decreased risk with increasing intake of vegetables for ER-negative/PR-negative breast cancers and not for other hormone receptor types. This finding was supported by results from a published *pooled analysis*, which also reported a significant decreased risk for ER-negative breast cancers only. There is evidence of plausible mechanisms operating in humans.

The CUP Panel concluded:

- **The evidence suggesting that greater consumption of non-starchy vegetables decreases the risk of oestrogen receptor-negative breast cancer is limited.**

5.4.7 Bladder

(Also see [CUP bladder cancer report 2015](#): Section 7.1 and [CUP bladder cancer SLR 2014](#): Section 2.2.)

The evidence for vegetables and fruit combined and the risk of bladder cancer is presented in the following subsections. Evidence on vegetables and fruit reviewed separately showed no statistically significant association with bladder cancer risk (see [CUP bladder cancer SLR 2014](#), Sections 2.2.1 and 2.2.2, respectively). The Panel advised that the evidence relating to vegetables and fruit separately was limited and that no specific conclusions could be drawn. For information on cruciferous vegetables, green leafy vegetables and citrus fruit, see [CUP bladder cancer SLR 2014](#), Sections 2.2.1.2, 2.2.1.4 and 2.2.2.1, respectively.

5.4.7.1 CUP dose–response meta-analysis

Eight of nine identified studies were included in the dose–response meta-analysis, which showed a statistically significant three per cent decreased risk of bladder cancer per 80 grams increase in vegetables and fruit consumed per day (RR 0.97 [95% CI 0.95–0.99]; n = 2,508 cases) (see **Figure 5.8**). No *heterogeneity* was observed, and there was no evidence of small study bias with *Egger's test* (p = 0.09).

One study [150] contributed 55 per cent weight in the dose–response meta-analysis. When this study was removed, no significant association was observed (RR 0.98 [95% CI 0.95–1.01]).

One published study that was included in the CUP dose–response meta-analysis reported results by tobacco smoking and found that the decreased risk of bladder cancer observed with consumption of vegetables was not affected by tobacco smoking [150].

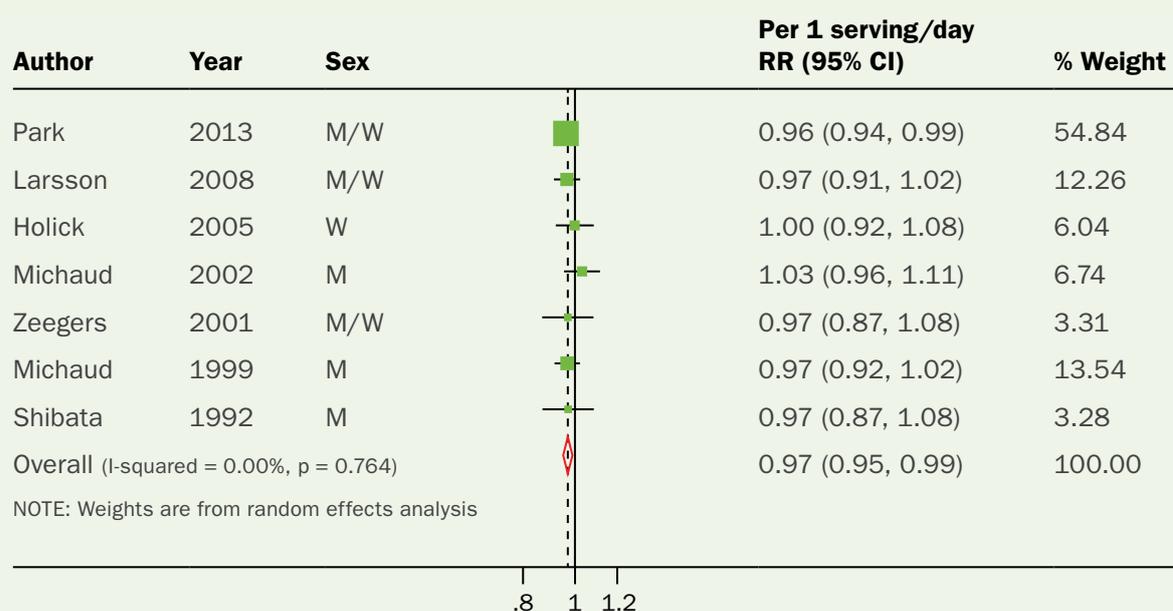
There was no evidence of a non-linear dose–response relationship (p = 0.06).

All studies included in the dose–response meta-analysis adjusted for intensity and duration of tobacco smoking, except one study that adjusted for tobacco smoking only and reported similar results.

5.4.7.2 Published pooled analyses and meta-analyses

No published pooled analyses and no other published meta-analyses on combined consumption of vegetables and fruit and the risk of bladder cancer were identified.

Figure 5.8: CUP dose–response meta-analysis¹ for the risk of bladder cancer, per 80 grams increase in vegetables and fruit consumed per day



Source: Park, 2013 [150]; Larsson, 2008 [151]; Holick, 2005 [152]; Michaud, 2002 [153]; Zeegers, 2001 [154]; Michaud, 1999 [155]; Shibata, 1992 [156].

5.4.7.3 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 are currently prevailing 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](#).

Fruit and vegetables contain a large number of potential anti-tumorigenic agents, such as dietary fibre, *carotenoids*, vitamins C and E, selenium, dithiolthiones, glucosinolates and indoles, isothiocyanates, *flavonoids*, phenols, protease inhibitors, plant sterols, allium compounds and limonene [131]. It is likely that a combination of these *nutrients* is responsible for a lower risk of bladder cancer being associated with greater consumption of fruit and vegetables. A better understanding of the exact mechanisms is required.

5.4.7.4 CUP Panel's conclusion

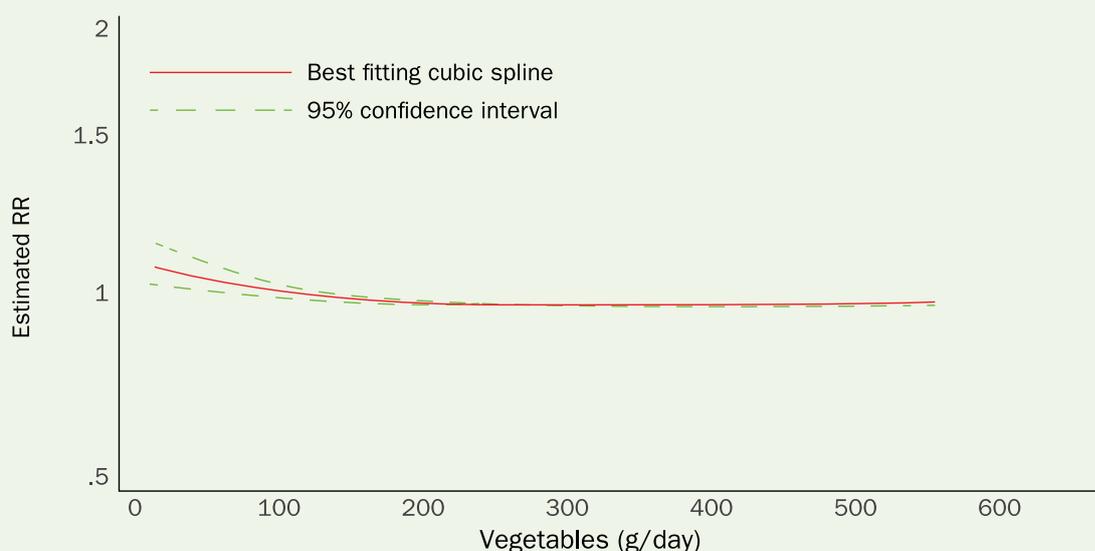
The evidence for combined consumption of vegetables and fruit and the risk of bladder cancer was limited but generally consistent and showed a statistically significant decreased risk with increasing vegetables and fruit intake. No *heterogeneity* was observed. However, the decreased risk observed was strongly influenced by a single study, and it was not possible to conduct analyses stratified by tobacco smoking. There is evidence of plausible mechanisms operating in humans.

The CUP Panel concluded:

- **The evidence suggesting that greater consumption of non-starchy vegetables and fruit decreases the risk of bladder cancer is limited.**

¹ The CUP dose–response meta-analysis included one publication (Larsson, 2008 [151]) that included two studies.

Figure 5.9: CUP non-linear dose–response association of vegetable intake and the risk of colorectal cancer



5.4.8 Colorectum – low intake of vegetables

(Also see CUP colorectal cancer report 2017: Section 7.3.2 and CUP colorectal cancer SLR 2016: Section 2.2.1.)

The evidence for **low intake** of vegetables and the risk of colorectal cancer is presented in the following subsections. For information on garlic, see CUP colorectal cancer SLR 2016, Section 2.2.1.3.1.

5.4.8.1 CUP dose–response meta-analyses

Eleven of 23 identified studies were included in the dose–response meta-analysis,¹ which showed a statistically significant two per cent decreased risk of colorectal cancer per 100 grams increase in vegetables consumed per day (RR 0.98 [95% CI 0.96–0.99]); n = 14,136 cases) (see CUP colorectal cancer SLR 2016, Figure 34). No *heterogeneity* was observed ($I^2 = 0\%$), and there was no evidence of small study bias with *Egger’s test* ($p = 0.92$).

¹ Twelve studies could not be included in the dose–response meta-analysis; two reported on mortality, four reported on subtypes of colorectal cancer and six did not provide sufficient information. For further details, see CUP colorectal cancer SLR 2016, Tables 25 and 26.

There was evidence of a non-linear dose–response relationship ($p < 0.0001$; see **Figure 5.9**). A significant increased risk was observed for low intakes (100 grams or less per day) and a significant decreased risk was observed for intakes of 300 grams or more per day compared with an intake of 200 grams per day (see **Table 5.13**).

Table 5.13: CUP non-linear dose–response estimates of vegetable intake and the risk of colorectal cancer

Vegetable intake (grams per day)	RR (95% CI)
22	1.16 (1.11–1.21)
100	1.08 (1.06–1.10)
200	1.00
300	0.96 (0.95–0.97)
400	0.95 (0.95–0.96)
500	0.96 (0.96–0.96)

All studies included in the dose–response meta-analysis adjusted for age, and most of the studies also adjusted for the majority of established colorectal cancer risk factors, including physical activity, BMI, alcohol

consumption, tobacco smoking, red meat and MHT use in women. For information on the *adjustments* made in individual studies, see [CUP colorectal cancer SLR 2016](#), Table 25.

5.4.8.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. Two other published meta-analyses on consumption of vegetables and the risk of colorectal cancer have been identified. One published meta-analysis [157] reported no statistically significant association when comparing the highest with the lowest level of vegetables consumed. The other published meta-analysis reported results from the 2010 CUP colorectal cancer SLR [158].

5.4.8.3 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 are currently prevailing 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](#).

Vegetables are a diverse food group, and consumption of vegetables provides a large number of potential anti-carcinogenic *nutrients* and bioactive *phytochemicals* such as dietary fibre, *carotenoids*, vitamins C and E, selenium, folate, dithiolthiones, glucosinolates and indoles, isothiocyanates, *flavonoids*, phenols, protease inhibitors, plant sterols, allium compounds and limonene [131]. A substantial body of experimental data exists linking many of these compounds with anticarcinogenic activity in colorectal cancer cells in both animal and *in vitro* models [159]. However, robust evidence from human studies supporting a relationship between specific

vegetables and compounds found within vegetables and colorectal cancer is currently lacking. It is possible that a combination of these nutrients is responsible for the lower risk of colorectal cancer associated with vegetable consumption. Mechanistic evidence supporting the inverse relationship between vegetables and colorectal cancer is moderate in strength.

5.4.8.4 CUP Panel's conclusion

The evidence for consumption of vegetables and the risk of colorectal cancer was limited but generally consistent. The CUP dose–response meta-analysis showed a statistically significant decreased risk of colorectal cancer with increasing intake of vegetables. There was evidence of a non-linear dose–response relationship, with a significant increased risk being observed at low levels of intake (100 grams or less per day). There is evidence of plausible mechanisms in humans.

The CUP Panel concluded:

- **The evidence suggesting that low consumption of non-starchy vegetables increases the risk of colorectal cancer is limited.**



5.5 Preserved non-starchy vegetables

This section includes evidence on preserved non-starchy vegetables for nasopharyngeal cancer. For stomach cancer, there is no separate conclusion. The evidence for salt-preserved non-starchy vegetables was grouped with salt-preserved fish and salt-preserved foods.

Table 5.14 summarises the main findings from the CUP dose–response meta-analyses of cohort studies on consumption of preserved vegetables and the risk of cancer.

Evidence for oesophageal cancer (adenocarcinoma and squamous cell carcinoma; 2016) and foods preserved by salting was discussed in the CUP but was too limited to draw a conclusion.¹

There was no discussion of preserved vegetables and any other cancer considered in the CUP as there were too few studies.

The strong evidence on the effects of eating salt-preserved foods 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 5.14: Summary of CUP dose–response meta-analyses of preserved vegetable intake and the risk of cancer

Cancer	Type	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment /contrast	I ² (%)	Conclusion ¹	Date of CUP cancer report ²
Stomach ³	Salt-preserved vegetables	14	9	3,932	1.09 (1.05–1.13)	20 g/day	0	Probable: Increases risk	2016
	Salt-preserved foods ⁴	6	5	635	1.70 (1.18–2.45)	Highest vs lowest	–		
Naso-pharynx ⁵	Preserved vegetables	14	5	3,924	1.42 (1.04–1.93)	once/week	76	Limited – suggestive: Increases risk	2017

- 1 See Definitions of WCRF/AICR grading criteria (**Section 1**: Wholegrains, vegetables and fruit 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 For preserved non-starchy vegetables and stomach cancer, there is no separate conclusion. The evidence was included in ‘foods preserved by salting’, which assessed the evidence for salt-preserved vegetables, salt-preserved fish and salt-preserved foods. The term ‘foods preserved by salting’ refers mainly to high-salt foods and salt-preserved foods, including pickled vegetables and salted or dried fish, as traditionally prepared in East Asia. There was no significant association for salt-preserved fish in the CUP dose–response meta-analysis. See Exposures: Preservation and the processing of foods.
- 4 A dose–response meta-analysis on salt-preserved foods and stomach cancer could not be conducted in the CUP as there were too few studies. Evidence is from a CUP highest versus lowest meta-analysis.
- 5 A dose–response meta-analysis of cohort studies could not be conducted in the CUP. Evidence is from a CUP dose–response meta-analysis of case-control studies on preserved vegetable intake and nasopharyngeal cancer.

¹ ‘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 eating preserved vegetables and the risk of cancer that was graded by the Panel as ‘limited – suggestive’ and suggests a direction of effect, see the CUP document listed:

- CUP nasopharyngeal cancer SLR 2017, Section 2.2.1.5.

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

Please note that the information on mechanisms included in the following subsections and in the appendix supersedes that in CUP cancer reports published before this Third Expert Report.

5.5.1 Stomach

(Also see CUP stomach cancer report 2016: Section 7.3 and CUP stomach cancer SLR 2015: Sections 2.2.1.5, 2.5.2 and 4.2.5.3.)

The evidence for salt-preserved vegetables, salt-preserved fish and salt-preserved foods and the risk of stomach cancer is presented in the following subsections.

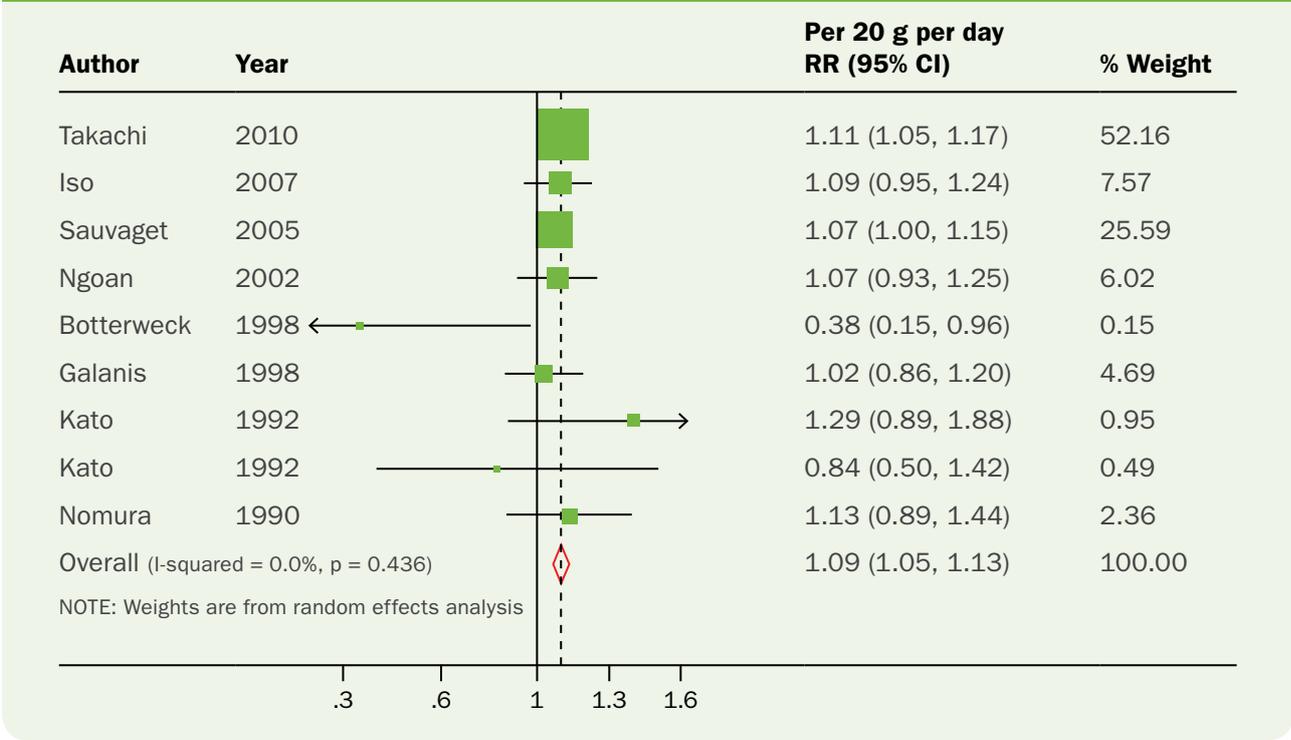
5.5.1.1 Salt-preserved vegetables

5.5.1.1.1 CUP dose–response meta-analyses

Nine of 14 identified studies were included in the dose–response meta-analysis, which showed a statistically significant nine per cent increased risk of stomach cancer per 20 grams increase in salt-preserved vegetables consumed per day (RR 1.09 [95% CI 1.05–1.13]; n = 3,932 cases) (see **Figure 5.10**). No *heterogeneity* was observed, and there was no evidence of small study bias with *Egger’s test* (p = 0.14).

A stratified analysis for the risk of stomach cancer per 20 grams increase in salt-preserved vegetables consumed per day

Figure 5.10: CUP dose–response meta-analysis¹ for the risk of stomach cancer, per 20 grams increase in salt-preserved vegetables consumed per day



Source: Takachi, 2010 [160]; Iso, 2007 [161]; Sauvaget, 2005 [162]; Ngoan, 2002 [163]; Botterweck, 1998 [164]; Galanis, 1998 [165]; Kato, 1992 [166]; Kato, 1992 [167]; Nomura, 1990 [168].

¹ Five studies could not be included in the dose–response meta-analysis, mainly because sufficient information was not provided. For further details, see CUP stomach cancer SLR 2015, Table 33.

was conducted for outcome; a statistically significant increased risk was observed for incidence (RR 1.09 [95% CI 1.02–1.16]), but not mortality (see [CUP stomach cancer SLR 2015](#), Figure 38). For details of other stratified analyses that have been conducted, see [CUP stomach cancer SLR 2015](#), Section 2.2.1.5.

Some of the studies included in the dose–response meta-analysis adjusted for tobacco smoking. None of the studies adjusted for *H. pylori* status. For information on the adjustments made in individual studies, see [CUP stomach cancer SLR 2015](#), Table 32.

5.5.1.1.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. Two other published meta-analyses on consumption of salt-preserved and pickled vegetables and the risk of stomach cancer have been identified, both of which reported a statistically significant increased risk for the highest compared with the lowest level consumed (RR 1.27 [95% CI 1.09–1.49] [169] and RR 1.32 [95% CI 1.10–1.59] [170]).

5.5.1.2 Salt-preserved fish

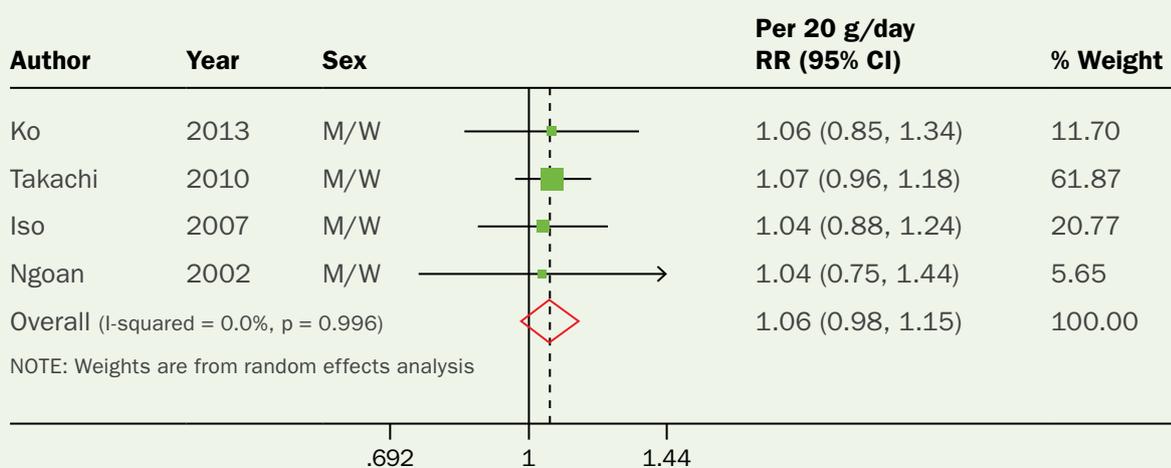
A brief summary of the evidence for salt-preserved fish and risk of stomach cancer is included as this forms part of the conclusion for salt-preserved foods.

CUP analyses

Four of 11 identified studies were included in the dose–response meta-analysis, which showed no statistically significant association between the risk of stomach cancer and consumption of salt-preserved fish (RR 1.06 [95% CI 0.98–1.15]; per 20 grams increase per day, n = 2,110 cases) (see [Figure 5.11](#)). No heterogeneity was observed.

As many studies could not be included in the dose–response meta-analysis, an analysis comparing the highest with the lowest level of consumption was conducted for eight studies, which showed a significant increased risk of stomach cancer (RR 1.15 [95% CI 1.01–1.31]). When one study [160] was removed from the analysis, the risk estimate was no longer significant.

Figure 5.11: CUP dose–response meta-analysis¹ for the risk of stomach cancer, per 20 grams increase in salt-preserved fish consumed per day



Source: Ko, 2013 [171]; Takachi, 2010 [160]; Iso, 2007 [161]; Ngoan, 2002 [163].

¹ Seven studies could not be included in the dose–response meta-analysis; one reported very low intakes of salted fish and six did not provide sufficient information. For further details, see [CUP stomach cancer SLR 2015](#), Table 89.

All studies included in the dose–response meta-analysis adjusted for tobacco smoking and alcohol, except for one study that adjusted only for age and residence area [161]. None of the studies adjusted for *H. pylori* status. For information on the *adjustments* made in individual studies, see [CUP stomach cancer SLR 2015](#), Table 88.

5.5.1.2.1 Published pooled analyses and meta-analyses

No published pooled analyses were identified. One other published meta-analysis on consumption of salt-preserved fish and the risk of stomach cancer was identified, which reported a significant increased risk for the highest compared with the lowest level consumed (RR 1.24 [95% CI 1.03–1.50]) [169].

5.5.1.3 Salt-preserved foods

5.5.1.3.1 CUP highest versus lowest meta-analysis

A dose–response meta-analysis could not be conducted in the CUP as there were too

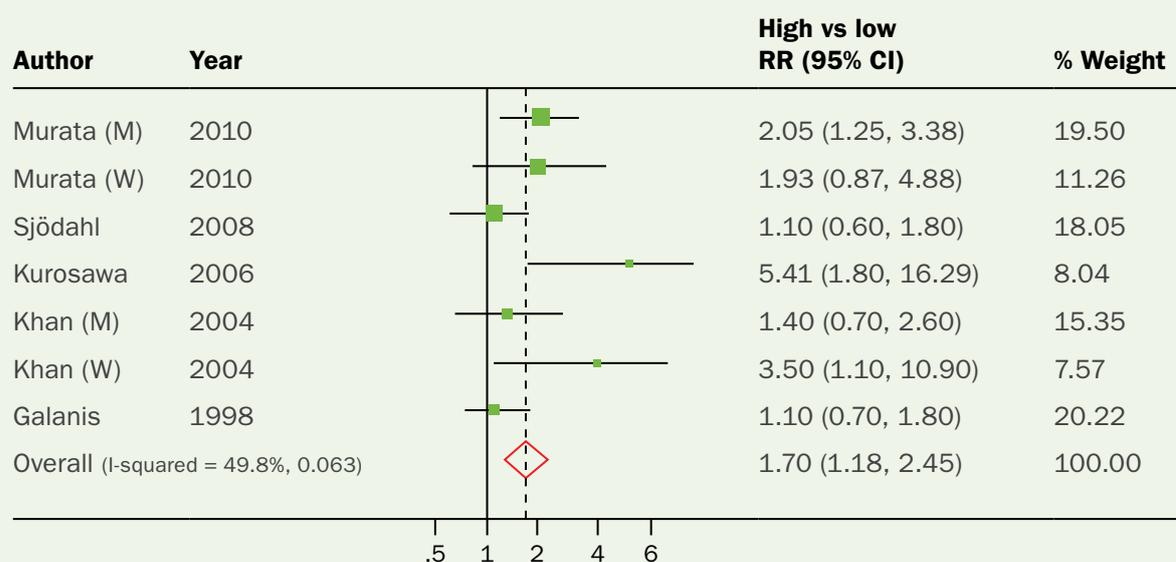
few studies. Five of six identified studies were included in the highest versus lowest meta-analysis, which showed a statistically significant increased risk of stomach cancer for the highest compared with the lowest level of salt-preserved foods consumed (RR 1.70 [95% CI 1.18–2.45]; n = 635 cases) (see **Figure 5.12**).

All studies included in the highest versus lowest meta-analysis except one [165] adjusted for tobacco smoking. None of the studies adjusted for *H. pylori* status. For information on the *adjustments* made in individual studies, see [CUP stomach cancer SLR 2015](#), Table 139.

5.5.1.3.2 Published pooled analyses and meta-analyses

No published pooled analyses and no other published meta-analyses on consumption of salt-preserved foods and the risk of stomach cancer were identified.

Figure 5.12: CUP highest versus lowest meta-analysis¹ for consumption of salt-preserved foods and the risk of stomach cancer



Source: Murata, 2010 [172]; Sjödahl, 2008 [173], Kurosawa, 2006 [174], Khan, 2004 [175], Galanis, 1998 [165].

¹ A total of five studies were analysed in the CUP highest versus lowest meta-analysis. In some studies, the relative risks for men and women were reported separately.



5.5.1.4 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 are currently prevailing 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](#).

Animal models have shown that high salt levels alter the viscosity of the mucus protecting the stomach and enhance the formation of *N-nitroso compounds* [176]. In addition, high salt intake may stimulate the colonization of *H. pylori*, the strongest known risk factor for stomach cancer [177]. Finally, in animal models, high salt levels have been shown to be responsible for the primary cellular damage that results in the promotion of stomach cancer development [178].

5.5.1.5 CUP Panel's conclusions

The evidence was generally consistent for salt-preserved vegetables, salt-preserved fish and salt-preserved foods in showing an increased risk of stomach cancer with higher consumption. The dose–response meta-analysis for salt-preserved vegetables was statistically significant with no *heterogeneity*. Evidence on salt-preserved foods and salt-preserved fish showed a statistically significant increased risk from analyses comparing the highest with the lowest level of intake. For salt-preserved fish, the result was no longer significant after one study was removed from analysis. Studies did not adjust for *H. pylori* status. There is evidence of plausible mechanisms in humans.

The CUP Panel concluded:

- Consumption of foods preserved by salting is probably a cause of stomach cancer.

5.6 Fruit

Table 5.15 summarises the main findings from the CUP dose–response meta-analyses of cohort studies on consumption of fruit and the risk of cancer. In this section, the evidence for each cancer relates to consumption of fruit, apart from the evidence for stomach cancer (cardia), which is for citrus fruit only. All of the evidence relates to a greater intake of these foods, apart from the evidence for stomach cancer (all types) and colorectal cancer, which is for low intake of fruit.

Evidence for cancers of the following types was discussed in the CUP but was too limited to draw a conclusion:¹ mouth, pharynx and larynx (2018); nasopharynx (2017), oesophagus (adenocarcinoma; 2016); pancreas (2012); liver (2015); breast (pre and postmenopause; 2017); ovary (2014); endometrium (2013); prostate (2014) and kidney (2015).

The evidence on the effects of eating fruit and the risk of cancer that was graded by the Panel as ‘limited – suggestive’ is described in the following subsections. For the evidence on eating non-starchy vegetables and fruit and the risk of bladder cancer, see **Section 5.4.7**.

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

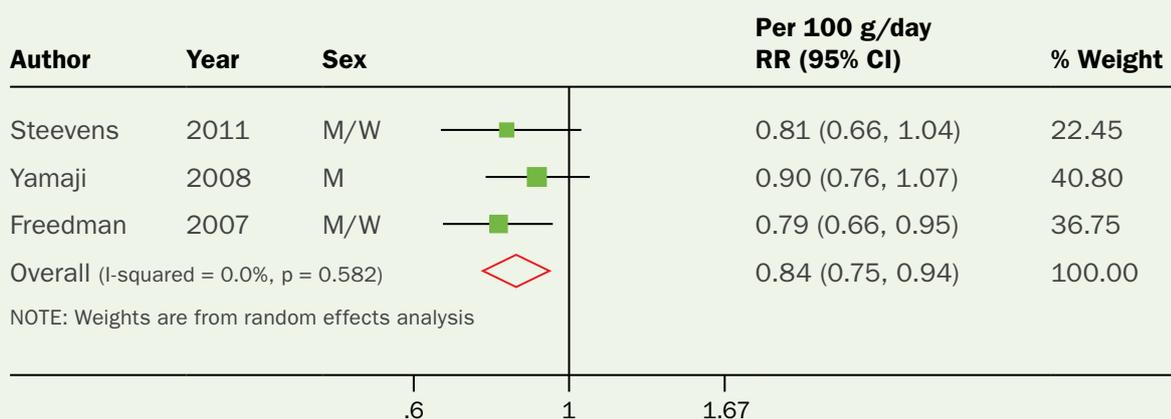
¹ ‘**Limited – no conclusion**’: There is enough evidence to warrant Panel consideration, but it is so limited that no conclusion can be made. The evidence may be limited in amount, by inconsistency in the direction of effect, by methodological flaws, or by any combination of these.

Table 5.15: Summary of CUP dose–response meta-analyses of fruit intake and the risk of cancer

Cancer	Type	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I ² (%)	Conclusion ¹	Date of CUP cancer report ²
Oesophagus (squamous cell carcinoma)	Fruit	4	3	320	0.84 (0.75–0.94)	100 g/day	0	Limited – suggestive: Decreases risk	2016
Lung (people who smoke tobacco)	Fruit	11	9	7,141	0.91 (0.85–0.98)	100 g/day	57	Limited – suggestive: Decreases risk	2017
Lung (people who used to smoke tobacco)		7	5	3,828	0.97 (0.92–1.02)	100 g/day	0		
Stomach (cardia)	Citrus fruit	3	3	555	0.76 (0.58–0.99)	100 g/day	53	Limited – suggestive: Decreases risk	2016
Bladder³	Vegetables and fruit combined	9	8	2,508	0.97 (0.95–0.99)	80 g/day	0	Limited – suggestive: Decreases risk	2015
Stomach⁴	Fruit	24	7	–	1.08 (1.05–1.11)	Non-linear dose–response analysis 43 vs 86 g/day	–	Limited – suggestive: Increases risk with low consumption	2016
Colorectum⁵	Fruit	21	9	–	1.07 (1.05–1.09)	Non-linear dose–response analysis 100 vs 200 g/day	–	Limited – suggestive: Increases risk with low consumption	2017

- 1 See Definitions of WCRF/AICR grading criteria (**Section 1**: Wholegrains, vegetables and fruit 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.
- 3 The evidence for non-starchy vegetables and fruit and bladder cancer relates to combined consumption of vegetables and fruit and is included in **Section 5.4.7**.
- 4 An increased risk of stomach cancer was not apparent when the data for fruit were analysed assuming a linear response, but became apparent when conducting a non-linear analysis. The Panel’s conclusion for fruit (low intake) and stomach cancer relates to intakes below 45 grams per day when compared with an intake of about 100 grams per day. For information on the evidence supporting the conclusion, see **Section 5.6.4**.
- 5 No statistically significant association was observed between consumption of fruit and the risk of colorectal cancer when the data were analysed assuming a linear response. A significant increased risk became apparent when a non-linear analysis was conducted. The Panel’s conclusion for fruit (low intake) and colorectal cancer relates to intakes of 100 grams or less per day when compared with an intake of 200 grams per day. For information on the evidence that led to the conclusion, see **Section 5.6.5**.

Figure 5.13: CUP dose–response meta-analysis for the risk of oesophageal squamous cell carcinoma, per 100 grams increase in fruit consumed per day



Source: Steevens, 2011 [132]; Yamaji, 2008 [137]; Freedman, 2007 [133].

5.6.1 Oesophagus (squamous cell carcinoma)

(Also see [CUP oesophageal cancer report 2016](#): Section 7.2 and [CUP oesophageal cancer SLR 2015](#): Section 2.2.2.)

The evidence for fruit and the risk of oesophageal squamous cell carcinoma is presented in the following subsections. For information on fruit (oesophageal adenocarcinoma) and citrus fruit (oesophageal adenocarcinoma and squamous cell carcinoma), see [CUP oesophageal cancer SLR 2015](#), Sections 2.2.2 and 2.2.2.1, respectively.

5.6.1.1 CUP dose–response meta-analysis

Three of four identified studies were included in the dose–response meta-analysis, which showed a statistically significant 16 per cent decreased risk of oesophageal squamous cell carcinoma per 100 grams increase in fruit consumed per day (RR 0.84 [95% CI 0.75–0.94]; n = 320 cases) (see **Figure 5.13**).

No *heterogeneity* was observed.

One published study that was included in the CUP dose–response meta-analysis reported results by tobacco smoking and found that the risk of oesophageal squamous cell carcinoma observed with consumption of fruit was not affected by tobacco smoking [132].

All studies included in the dose–response meta-analysis adjusted for tobacco smoking. For information on the *adjustments* made in individual studies, see [CUP oesophageal cancer SLR 2015](#), Table 16.

5.6.1.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. One other published meta-analysis on consumption of fruit and the risk of oesophageal squamous cell carcinoma was identified. The meta-analysis included both cohort and *case-control studies*; a statistically significant decreased risk was observed when the cohort studies were analysed (RR 0.87 [95% CI 0.82–0.91], per 100 grams increase in fruit consumed per day) [138]. The meta-analysis also reported a significant decreased risk when comparing the highest with the lowest level of fruit consumed.

5.6.1.3 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 are currently prevailing 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](#).

Fruit and non-starchy vegetables contain a large number of potential anti-tumorigenic agents, such as dietary fibre, *carotenoids*, vitamins C and E, selenium, dithiolthiones, glucosinolates and indoles, isothiocyanates, *flavonoids*, phenols, protease inhibitors, plant sterols, allium compounds and limonene [131]. It is likely that a combination of these *nutrients* is responsible for the lower risk of oesophageal cancer that has been observed among high consumers of fruit and non-starchy vegetables.

5.6.1.4 CUP Panel's conclusion

For oesophageal squamous cell carcinoma, the evidence for consumption of fruit was limited but generally consistent. The CUP dose-response meta-analysis showed a statistically significant decreased risk of squamous cell carcinoma with higher consumption of fruit; however, this included only three studies and a limited number of cases. No *heterogeneity* was observed. Although studies adjusted for tobacco smoking, there is the potential for residual confounding due to tobacco smoking. There is evidence of plausible mechanisms in humans.

The CUP Panel concluded:

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

5.6.2 Lung (people who smoke/used to smoke tobacco)

(Also see [CUP lung cancer report 2017](#): Section 7.4 and [CUP lung cancer SLR 2015](#): Section 2.2.2.)

The evidence for fruit and the risk of lung cancer, stratified by tobacco smoking, is presented in the following subsections. For information on fruit (not stratified by tobacco smoking) and citrus fruit (with and without stratification by tobacco smoking), see [CUP lung cancer SLR 2015](#), Sections 2.2.2 and 2.2.2.1, respectively.

5.6.2.1 CUP dose-response meta-analyses stratified by tobacco smoking

Nine of 11 identified studies reporting results on people who smoke were included in a dose-response meta-analysis stratified by tobacco smoking, which showed a statistically significant nine per cent decreased risk of lung cancer in people who smoke per 100 grams increase in fruit consumed per day (RR 0.91 [95% CI 0.85–0.98]; n = 7,141 cases) (see [Figure 5.14](#)). High *heterogeneity* was observed ($I^2 = 57%$).

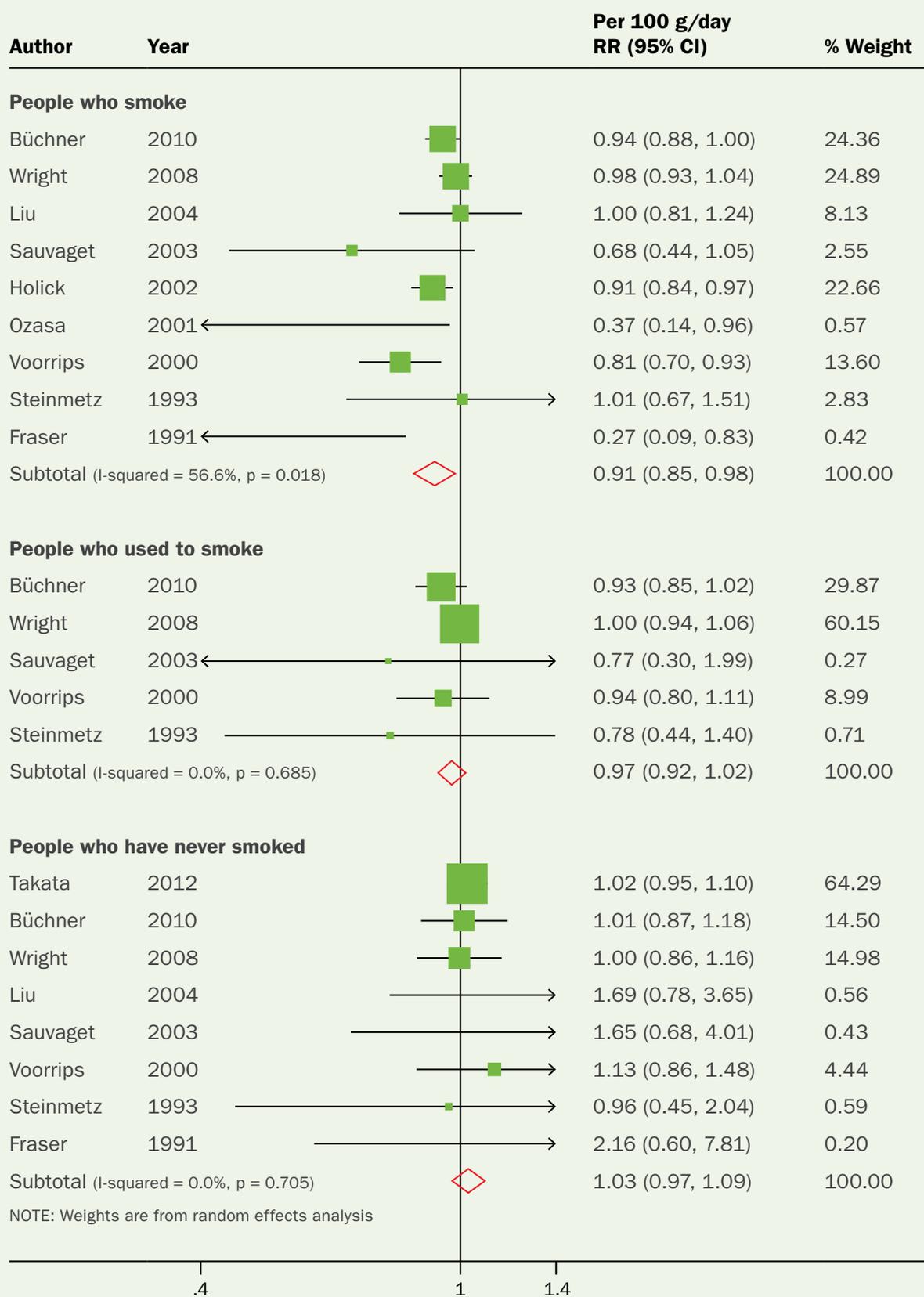
No significant association was observed between the risk of lung cancer and consumption of fruit in people who used to smoke (RR 0.97 [95% CI 0.92–1.02]; n = 3,828 cases) or people who have never smoked (RR 1.03 [95% CI 0.97–1.09]; n = 1,260 cases). No *heterogeneity* was observed in either analysis (see [Figure 5.14](#)).

All studies included in the dose-response meta-analysis adjusted for age and sex. For information on the *adjustments* made in individual studies, see [CUP lung cancer SLR 2015](#), Table 33.

5.6.2.2 Published pooled analyses and meta-analyses

One published *pooled analysis* (see [Table 5.16](#)) on consumption of fruit and the risk of lung cancer was identified. No other published meta-analyses have been identified. The pooled analysis reported a statistically significant decreased risk for the highest compared with the lowest level of fruit consumed in people who smoke [145].

Figure 5.14: CUP dose–response meta-analysis for the risk of lung cancer stratified by tobacco smoking, per 100 grams increase in fruit consumed per day



Source: Takata, 2012 [179]; Büchner, 2010 [139]; Wright, 2008 [140]; Liu, 2004 [141]; Sauvaget, 2003 [180]; Voorrips, 2000 [143]; Steinmetz, 1993 [144]; Fraser, 1991 [181]; Holick, 2002 [142]; Ozasa, 2001 [182].

Table 5.16: Summary of published pooled analyses of fruit intake and the risk of lung cancer

Publication	Contrast	Subgroup	RR (95% CI)	No. of studies (cohort)	No. of cases
Pooling Project of Prospective Studies on Diet and Cancer [145]	Quintile 4 vs Quintile 1	People who smoke	0.82 (0.68–0.99)	5	1,915
		People who used to smoke	0.85 (0.69–1.05)		981
		People who have never smoked	0.59 (0.34–1.04)		259

An additional CUP analysis, which combined the results of the published pooled analysis with non-overlapping studies identified in the CUP, showed a significant decreased risk of lung cancer when comparing the highest with the lowest level of fruit consumed in people who smoke (RR 0.83 [95% CI 0.75–0.92]) and in those who used to smoke (RR 0.89 [95% CI 0.81–0.99]).

5.6.2.3 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 are currently prevailing 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](#).

Fruit are a source of vitamins C and E as well as numerous *bioactive compounds* that may have anti-tumorigenic potential including *carotenoids*, *flavonoids* and polyphenols. Many of these compounds have anti-oxidative properties that could inhibit cellular damage and exposure to *reactive oxygen species*. Some fruit are a source of carotenoids, and there are suggestive epidemiologic and mechanistic data linking their intake to lower risk of lung cancer (see **Section 5.7.1**). Future studies focusing on how diets rich in fruit or specific fruits and

their unique *phytochemicals* may affect lung cancer development are warranted.

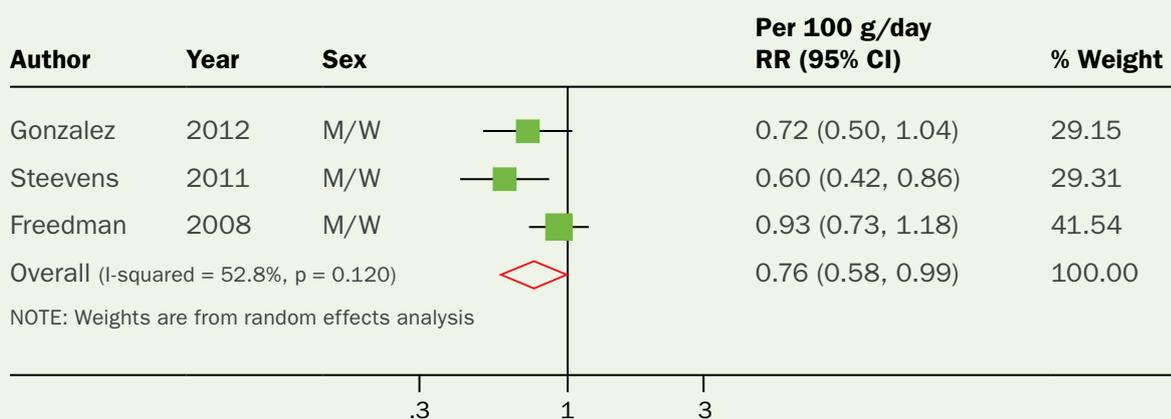
5.6.2.4 CUP Panel's conclusion

Overall, the evidence for consumption of fruit and the risk of lung cancer in people who smoke and those who used to smoke was limited but generally consistent. The CUP dose–response meta-analysis showed a decreased risk with increased consumption of fruit which was significant for people who smoke but not for those who used to smoke, although high *heterogeneity* was observed in the stratified analysis for people who smoke. When the *pooled analysis* was combined with non-overlapping studies from the CUP, a statistically significant decreased risk was observed for both people who smoke and those who used to smoke. Although studies adjusted for tobacco smoking, there is the potential for residual confounding due to tobacco smoking. There is evidence of plausible mechanisms in humans.

The CUP Panel concluded:

- **The evidence suggesting that greater consumption of fruit decreases the risk of lung cancer in people who smoke and people who used to smoke tobacco is limited.**

Figure 5.15: CUP dose–response meta-analysis for the risk of cardia stomach cancer, per 100 grams increase in citrus fruit consumed per day



Source: Gonzalez, 2012 [183]; Steevens, 2011 [132]; [184].

5.6.3 Stomach (cardia)

(Also see [CUP stomach cancer report 2016](#): Section 7.2 and [CUP stomach cancer SLR 2015](#): Section 2.2.2.1.)

The evidence for citrus fruit and the risk of cardia stomach cancer is presented in the following subsections. For evidence on low intake of fruit and stomach cancer (unspecified), see **Section 5.6.4**. For information on citrus fruit (non-cardia stomach cancer), see [CUP stomach cancer SLR 2015](#), Section 2.2.2.1.

5.6.3.1 CUP dose–response meta-analysis

All three identified studies were included in the dose–response meta-analysis, which showed a statistically significant 24 per cent decreased risk of cardia cancer per 100 grams increase in citrus fruit consumed per day (RR 0.76 [95% CI 0.58–0.99]; n = 555 cases) (see **Figure 5.15**). Moderate heterogeneity was observed ($I^2 = 53\%$).

All studies included in the dose–response meta-analysis adjusted for age, sex and tobacco smoking. No study adjusted for *H. pylori* status. For information on the adjustments made in individual studies, see [CUP stomach cancer SLR 2015](#), Table 43.

5.6.3.2 Published pooled analyses and meta-analyses

No published pooled analyses and no other published meta-analyses on consumption of citrus fruit and the risk of cardia stomach cancer were identified.

5.6.3.3 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 are currently prevailing 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](#).

Citrus fruit contain a large number of potential anti-tumorigenic agents, such as dietary fibre, *carotenoids*, vitamin C, *flavonoids* and folate [131]. It is likely that a combination of these *nutrients* is responsible for a lower risk of *cardia stomach cancer* being associated with greater consumption of citrus fruit. A better understanding of the exact mechanisms is required.

5.6.3.4 CUP Panel's conclusion

Overall, the evidence for consumption of citrus fruit and the risk of stomach cancer was limited but generally consistent. The CUP dose–response meta-analysis showed a statistically significant decreased risk, although with a limited number of cases. Moderate *heterogeneity* was observed. No published pooled or meta-analyses were identified. There is evidence of plausible mechanisms in humans.

The CUP Panel concluded:

- The evidence suggesting that greater consumption of citrus fruit decreases the risk of stomach cardia cancer is limited.

5.6.4 Stomach – low intake of fruit

(Also see [CUP stomach cancer report 2016](#): Section 7.1 and [CUP stomach cancer SLR 2015](#): Section 2.2.2.)

The evidence for low intake of fruit and the risk of stomach cancer is presented in the following subsections. For evidence specifically on citrus fruit and cardia stomach cancer, see **Section 5.6.3**. For information on citrus fruit (non-cardia stomach cancer), see [CUP stomach cancer SLR 2015](#), Section 2.2.2.1.

5.6.4.1 CUP dose–response meta-analyses

Thirteen of 24 identified studies were included in the dose–response meta-analysis,¹ which showed no statistically significant association between the risk of stomach cancer and consumption of fruit (RR 0.98 [95% CI 0.94–1.02], per 100 grams increase per day;

¹ Eleven studies could not be included in the dose–response meta-analysis; participants in one study had very low fruit consumption, three reported on subtypes of stomach cancer and seven did not provide sufficient information. For further details, see [CUP stomach cancer SLR 2015](#), Tables 37 and 38.

n = 4,905 cases) (see [CUP stomach cancer SLR 2015](#), Figure 41). Low *heterogeneity* was observed ($I^2 = 8\%$), and there was no evidence of small study bias with *Egger's test* ($p = 0.49$).

When the CUP dose–response meta-analysis was stratified by cancer subtype, no statistically significant association was observed between consumption of fruit (per 100 grams increase per day) and the risk of cardia or non-cardia cancer. When stratified by tobacco smoking, a significant decreased risk was observed for people who smoke (RR 0.89 [95% CI 0.81–0.97]), but not those who used to smoke (RR 1.02 [95% CI 0.95–1.09]) or those who have never smoked (RR 0.99 [95% CI 0.92–1.06]) and stomach cancer; see [CUP stomach cancer SLR 2015](#), Figures 49, 48 and 47, respectively).

There was evidence of a non-linear dose–response relationship ($p < 0.001$; see **Figure 5.16**). A significant increased risk was observed for low intakes (less than approximately 45 grams per day) and a significant decreased risk was observed for intakes of more than approximately 140 grams per day compared with an intake of 86 grams per day (see **Table 5.17**).

All studies included in the dose–response meta-analysis adjusted for age. The majority also adjusted for sex and tobacco smoking. No study adjusted for *H. pylori* status. For information on the *adjustments* made in individual studies, see [CUP stomach cancer SLR 2015](#), Table 37.

5.6.4.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. One other published meta-analysis on consumption of fruit and the risk of stomach cancer was identified, which reported a statistically significant decreased risk (RR 0.95 [95% CI 0.91–0.99], per 100 grams increase in fruit consumed per day) [185].

Figure 5.16: CUP non-linear dose–response association of fruit intake and the risk of stomach cancer

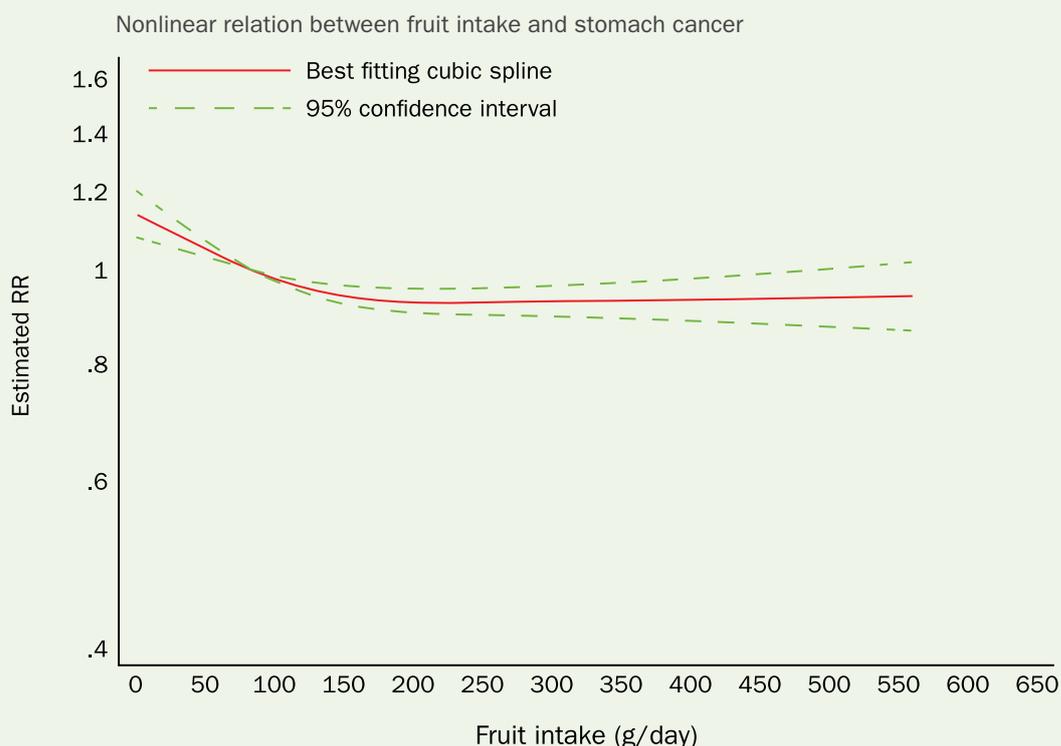


Table 5.17: CUP non-linear dose–response estimates of fruit intake and the risk of stomach cancer

Fruit intake (grams per day)	RR (95% CI)
0	1.18 (1.11–1.26)
43	1.08 (1.05–1.11)
86	1.00
137	0.95 (0.93–0.97)
196	0.94 (0.92–0.97)
236	0.95 (0.92–0.98)

5.6.4.3 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 are currently prevailing 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](#).

Fruit contains multiple potential anti-tumorigenic agents, such as dietary fibre, folate, carotenoids, vitamins C and E, selenium, *flavonoids*, phenols and limonene [131]. For example, vitamins C and E can act as *antioxidants* by donating electrons to *free radicals*, which can block their damaging activity. Several other plant-derived compounds (*phytochemicals*) display antioxidant activity in laboratory experiments. It is likely that a combination of these *nutrients* is responsible for any relationship between low fruit intake and stomach cancer.

5.6.4.4 CUP Panel's conclusion

Overall, the evidence for low consumption of fruit and the risk of stomach cancer was limited, but generally consistent, although

no statistically significant association was observed in the CUP dose–response meta-analysis. There was evidence of a non-linear dose–response relationship in which a statistically significant increased risk was observed for intake of fruit lower than approximately 45 grams (about 0.5 portion) per day; and a significant decreased risk was observed at higher intakes, from about 140 grams (about 1.75 portions) per day. A published meta-analysis also showed a significant decreased risk of stomach cancer per 100 grams increase in fruit consumed per day. There is evidence of plausible mechanisms in humans.

The CUP Panel concluded:

- The evidence suggesting that low intake of fruit increases the risk of stomach cancer is limited.

5.6.5 Colorectum – low intake of fruit

(Also see [CUP colorectal cancer report 2017](#): Section 7.3.3 and [CUP colorectal cancer SLR 2016](#): Section 2.2.2.)

The evidence for low intake of fruit and the risk of colorectal cancer is presented in the following subsections.

5.6.5.1 CUP dose–response meta-analyses

Thirteen of 21 identified studies were included in the dose–response meta-analysis,¹ which showed no statistically significant association between the risk of colorectal cancer and consumption of fruit (RR 0.96 [95% CI 0.93–1.00], per 100 grams increase per day; $n = 16,355$ cases) (see [CUP colorectal cancer SLR 2016](#), Figure 54). High *heterogeneity* was observed ($I^2 = 68\%$), which appeared to be

explained by one study [100] reporting a much lower decreased risk than the other studies.

Although there was no evidence of small study bias with *Egger’s test* ($p = 0.07$), inspection of the funnel plot suggested asymmetry, which appeared to be driven by the same study [100], and when that study was excluded, *Egger’s test* was no longer significant ($p = 0.14$).

In the influence analysis, when the EPIC study [186] (with the largest weighting) was removed, a significant decreased risk was observed (RR 0.95 [95% CI 0.92–0.99]).

There was evidence of a non-linear dose–response relationship ($p < 0.0001$, see [Figure 5.17](#)). A significant increased risk was observed for low intakes (100 grams or less per day) and a decreased risk was observed for intakes of 300 grams or more per day compared with an intake of 200 grams per day (see [Table 5.18](#)).

Most of the studies included in the dose–response meta-analysis adjusted for physical activity, BMI, alcohol consumption, tobacco smoking, red meat consumption and MHT use in women. For information on the *adjustments* made in individual studies, see [CUP colorectal cancer SLR 2016](#), Table 36.

5.6.5.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. Two other published meta-analyses on consumption of fruit and the risk of colorectal cancer have been identified. One published meta-analysis reported no statistically significant association when comparing the highest with the lowest level of fruit consumed [157]. The other reported results from the CUP 2010 colorectal cancer SLR [158] (see [CUP colorectal cancer SLR 2016](#), Table 35).

¹ Eleven studies could not be included in the dose–response meta-analysis; one reported on mortality, four reported on subtypes of colorectal cancer and three did not provide sufficient information. For further details, see [CUP colorectal cancer SLR 2016](#), Tables 36 and 37.

Figure 5.17: CUP non-linear dose–response association of fruit intake and the risk of colorectal cancer

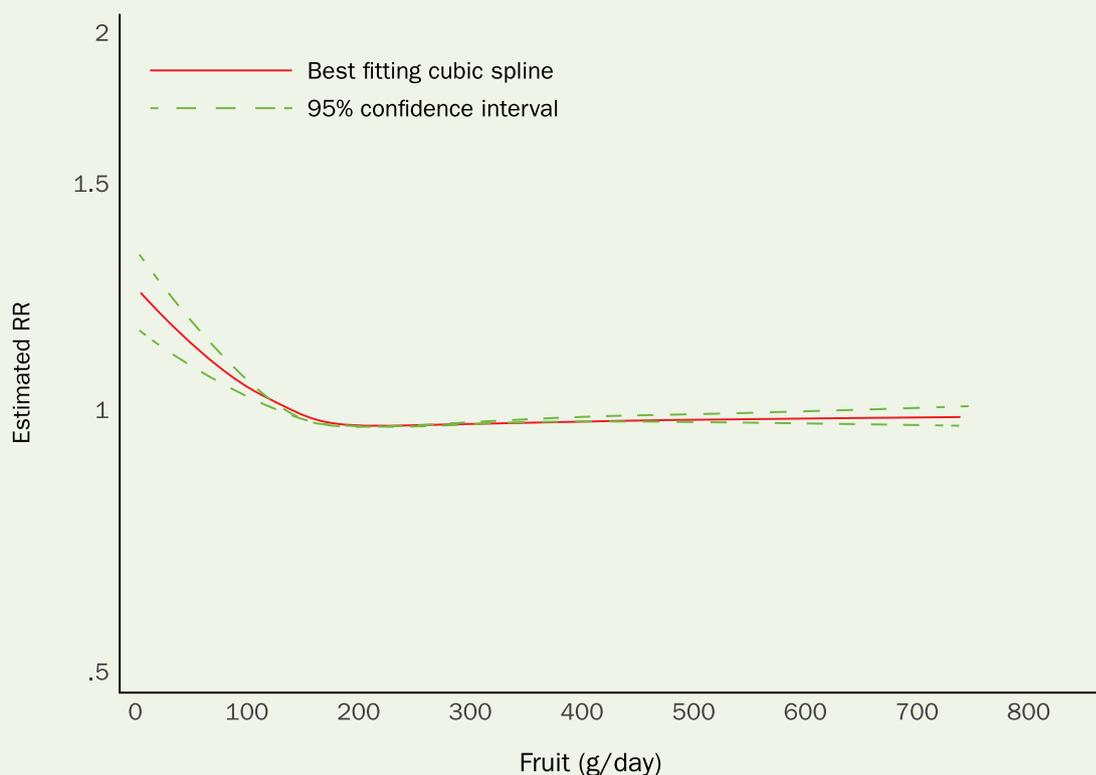


Table 5.18: CUP non-linear dose–response estimates of fruit intake and the risk of colorectal cancer

Fruit intake (grams per day)	RR (95% CI)
2	1.21 (1.15–1.26)
100	1.07 (1.05–1.09)
200	1.00
300	0.99 (0.98–0.99)
400	0.99 (0.98–0.99)
500	0.99 (0.98–1.00)

5.6.5.3 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 are currently prevailing 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](#).

In addition to their fibre content, fruit are a source of vitamins C and E as well as numerous *bioactive compounds* that may have anti-tumorigenic potential. These include folate, *flavonoids*, polyphenols and limonene. Many of these compounds have anti-oxidative properties that could inhibit cellular damage and exposure to *reactive oxygen species* [187].

5.6.5.4 CUP Panel's conclusion

The evidence for low consumption of fruit and the risk of colorectal cancer was limited but generally consistent. The CUP dose–response meta-analysis showed no statistically significant association. However, there was evidence of a non-linear dose–response relationship that showed a significant

increased risk at low levels of fruit intake (100 grams or less per day). There is evidence of plausible mechanisms in humans.

The CUP Panel concluded:

- **The evidence suggesting that low consumption of fruit increases the risk of colorectal cancer is limited.**

5.7 Foods containing carotenoids

This section includes evidence supporting conclusions for foods containing carotenoids. For a summary of the main findings for the evidence supporting conclusions for consumption of foods containing beta-carotene and the risk of cancer, see **Section 5.8**.

Table 5.19 summarises the main findings from the CUP dose–response meta-analyses of cohort studies on consumption of foods containing carotenoids and the risk of cancer.

Table 5.19: Summary of CUP dose–response meta-analyses for consumption of foods containing carotenoids and the risk of cancer

Cancer	Type	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I ² (%)	Conclusion ¹	Date of CUP cancer report ²
Lung ³	Dietary carotenoids	9	7	4,491	0.98 (0.97–0.99)	1,000 µg/day	37	Limited – suggestive: Decreases risk	2017
	Serum carotenoids ⁴	5	5	724	0.64 (0.44–0.93)	Highest vs lowest	–		
Breast ^{5,6}	Serum/plasma carotenoids	9	9	3,407	0.82 (0.71–0.96)	100 µg/100 ml	0	Limited – suggestive: Decreases risk	2017
	Dietary beta-carotene ⁷	24	18	3,055	1.00 (0.98–1.02)	5000 µg/day	0		
	Serum/plasma beta-carotene	13	11	3,558	0.78 (0.66–0.92)	50 µg/100 ml	0		

- 1 See Definitions of WCRF/AICR grading criteria (**Section 1**: Wholegrains, vegetables and fruit 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.
- 3 The evidence for foods containing carotenoids and lung cancer is derived from studies on dietary intake and serum levels.
- 4 A dose–response meta-analysis for serum carotenoids and lung cancer could not be conducted in the CUP as there were not enough studies. Evidence is from a CUP highest versus lowest meta-analysis.
- 5 The Panel’s conclusion for foods containing carotenoids and breast cancer relates to the evidence for breast cancer overall (menopausal status not specified). The evidence is derived from studies on dietary intake and serum/plasma levels and includes both foods that naturally contain carotenoids and foods that have had carotenoids added.
- 6 For additional information on breast cancer and other carotenoids, such as alpha-carotene, lutein, beta-cryptoxanthin and lycopene, see **Section 5.7.2.4**.
- 7 A dose–response meta-analysis was not conducted in the CUP for dietary beta-carotene and breast cancer, as all identified studies were superseded by a published pooled analysis. Evidence is from the published pooled analysis of 18 cohort studies [188].



Evidence for cancers of the following types was discussed in the CUP but was too limited to draw a conclusion:¹ mouth, pharynx and larynx (2018); oesophagus (adenocarcinoma and squamous cell carcinoma; 2016); cervix (2017); and skin (2017).

The evidence on eating foods containing carotenoids and the risk of cancer that was graded by the Panel as ‘limited – suggestive’ is described in the following subsections.

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

5.7.1 Lung

(Also see [CUP lung cancer report 2017](#): Section 7.5 and [CUP lung cancer SLR 2015](#): Sections 5.5.2 and 5.5.2.1.)

The evidence for dietary carotenoids and serum carotenoids and the risk of lung cancer is presented in the following subsections. These measures include all types of carotenoids. For evidence specifically on beta-carotene and lung cancer, see **Section 5.8.1**. For information on other individual carotenoids,

see the following sections of the [CUP lung cancer SLR 2015](#): alpha-carotene (Section 5.5.1.2), beta-cryptoxanthin (Section 5.5.1.2), lycopene (Section 5.5.2), and lutein and zeaxanthin combined (Section 5.5.2).

5.7.1.1 Dietary carotenoids

5.7.1.1.1 CUP dose–response meta-analysis

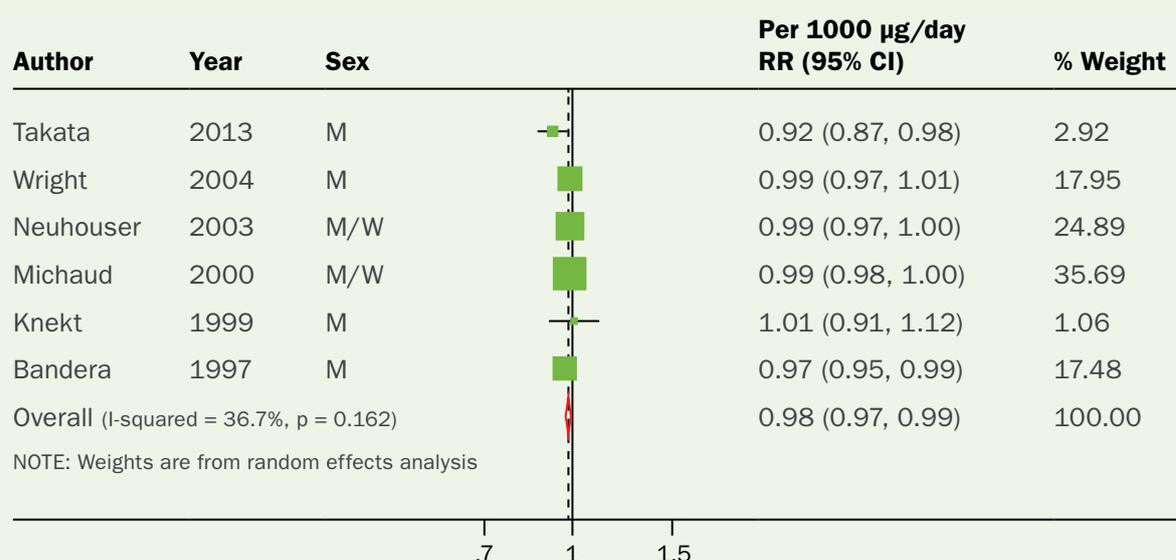
Seven of nine identified studies were included in the dose–response meta-analysis, which showed a statistically significant two per cent decreased risk of lung cancer per 1,000 micrograms increase in dietary carotenoids consumed per day (RR 0.98 [95% CI 0.97–0.99]; n = 4,491 cases) (see **Figure 5.18**). Moderate *heterogeneity* was observed ($I^2 = 37\%$), and there was no evidence of small study bias with *Egger’s test* ($p = 0.31$).

There were not enough studies to stratify the CUP dose–response meta-analysis by tobacco smoking. However, several published studies that were included in the CUP dose–response meta-analysis reported results by tobacco smoking for the risk of lung cancer with the highest compared with the lowest level of dietary carotenoids consumed. In one study [189], a statistically significant decreased risk was observed among people who smoke a lot of tobacco, but not in people who do not smoke or those who smoke a low amount of tobacco. Two other studies [193, 194] reported no significant association in either people who smoke (irrespective of the amount of tobacco) or those who do not smoke. Two studies on people who smoke or populations exposed to asbestos [190, 191] reported no significant association.

All studies included in the dose–response meta-analysis adjusted for at least tobacco smoking; all except one [193] adjusted for intensity, duration of tobacco smoking and other smoking variables. For information on the *adjustments* made in individual studies, see [CUP lung cancer SLR 2015](#), Table 173.

¹ ‘**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.

Figure 5.18: CUP dose–response meta-analysis¹ for the risk of lung cancer, per 1,000 micrograms increase in dietary intake of carotenoids per day



Source: Takata, 2013 [189]; Wright, 2004 [190]; Neuhouser, 2003 [191]; Michaud, 2000 [192]; Knekt, 1999 [193]; Bandera, 1997 [194].

5.7.1.1.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. One other published meta-analysis on consumption of carotenoids and the risk of lung cancer was identified, which reported a statistically significant decreased risk (RR 0.98 [95% CI 0.97–0.99], per 1,000 micrograms increase in carotenoids consumed per day) [195].

5.7.1.2 Serum carotenoids

5.7.1.2.1 CUP highest versus lowest meta-analysis

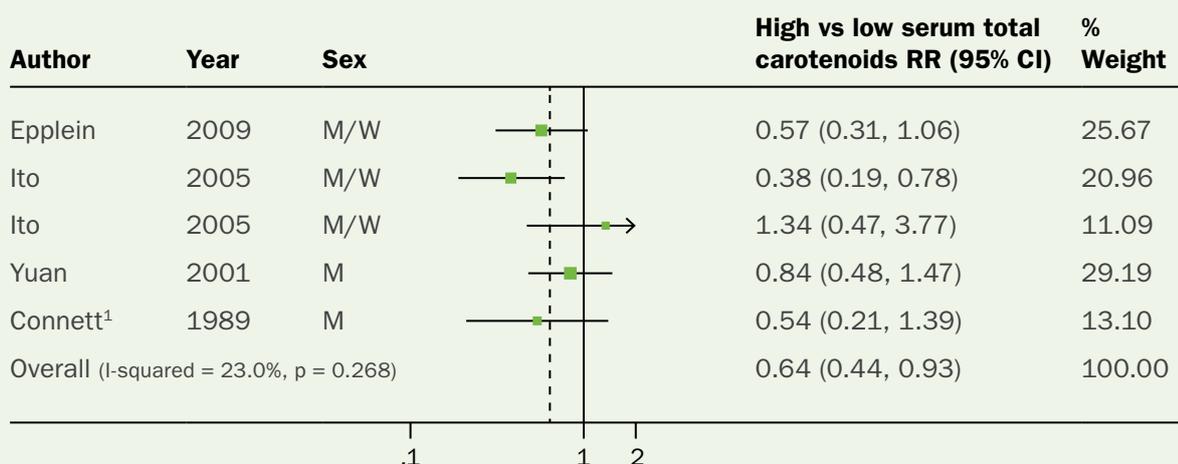
A dose–response meta-analysis could not be conducted, as there were not enough studies. All five identified studies were included in the highest versus lowest meta-analysis, which showed a statistically significant decreased risk of lung cancer for the highest compared with the lowest level of serum carotenoids (RR 0.64 [95% CI 0.44–0.93]; n = 724 cases) (see **Figure 5.19**).

There were not enough studies to stratify the CUP dose–response meta-analysis by tobacco smoking. However, two published studies that were included in the CUP highest versus lowest meta-analysis reported results by tobacco smoking. In one study, a statistically significant decreased risk of lung cancer was observed for the highest compared with the lowest level of serum carotenoids in people who smoke, but not in people who have ever smoked [199]. Another study reported a decreased risk of lung cancer with serum carotenoids, and there was no evidence of a different relationship between people who had ever or never smoked [196].

All studies included in the highest versus lowest meta-analysis adjusted for main confounders including age and tobacco smoking. All studies adjusted for intensity, duration of tobacco smoking and other smoking variables in addition to smoking status. For information on the *adjustments* made in individual studies, see **CUP lung cancer SLR 2015**, Table 173.

¹ The CUP dose–response meta-analysis included one publication (Michaud, 2000 [192]) that included two studies.

Figure 5.19: CUP highest versus lowest meta-analysis for levels of serum carotenoids and the risk of lung cancer



Source: Epplein, 2009 [196]; Ito, 2005 [197]; Ito, 2005 [198]; Yuan, 2001 [199]; Connett, 1989 [200].

5.7.1.2.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. One other published meta-analysis on serum carotenoids and the risk of lung cancer risk was identified, which reported a statistically significant decreased risk (RR 0.64 [95% CI 0.46–0.88], per 0.75 micromole increase in carotenoids per litre of serum) [195].

5.7.1.3 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 are currently prevailing 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](#).

A number of human studies and *meta-analyses* have shown that higher circulating levels of *carotenoids*, including beta-carotene, lycopene

and beta-cryptoxanthin, are associated with lower risk of lung cancer [202]. Further, evidence from both animal and laboratory studies has shown that carotenoids can block certain carcinogenic processes and inhibit tumour cell growth [203, 204]. Some proposed mechanisms for these actions include (1) functioning as an *antioxidant* [203, 205]; (2) acting as a precursor for retinoic acid [206, 207]; (3) enhancing immunologic function [208, 209]; (4) inducing *carcinogen-metabolising enzymes* [210]; (5) inhibiting *cell proliferation*; and (6) inducing *apoptosis*.

5.7.1.4 CUP Panel's conclusion

The evidence for consumption of foods containing carotenoids was limited but generally consistent. The CUP dose–response meta-analysis showed a statistically significant decreased risk of lung cancer per 1,000 micrograms increase in dietary carotenoids per day. Moderate *heterogeneity* was observed. No analysis by tobacco smoking was possible. A significant decreased risk was observed for the highest compared with the lowest level of serum carotenoids. Both these findings were

¹ In the MRFIT study [200], the RRs were recalculated using the Hamling method [201].

supported by another published meta-analysis, which also showed a significant decreased risk of lung cancer. Smoking tobacco may affect serum carotenoid levels. Residual confounding could not be excluded. There is evidence of plausible mechanisms in humans.

The CUP Panel concluded:

- **The evidence suggesting that greater consumption of foods containing carotenoids decreases the risk of lung cancer is limited.**

5.7.2 Breast

(Also see [CUP breast cancer report 2017](#): Section 7.2 and [CUP breast cancer SLR 2017](#): Sections 5.5.1.2.1, 5.5.1.2.2, 5.5.1.2.3, 5.5.2, 5.5.2.1 and 5.5.2.3.)

The evidence for the following carotenoids and the risk of breast cancer is presented in the following subsections: serum/plasma carotenoids (which includes all types of carotenoids); dietary beta-carotene; serum/plasma beta-carotene; and serum/plasma levels of other individual carotenoids such

as alpha-carotene, lutein, beta-cryptoxanthin and lycopene. For information on foods containing carotenoids and the risk of breast cancer according to menopausal status (pre and postmenopausal breast cancer), see the specific sections of the CUP breast cancer SLR 2017 noted above.

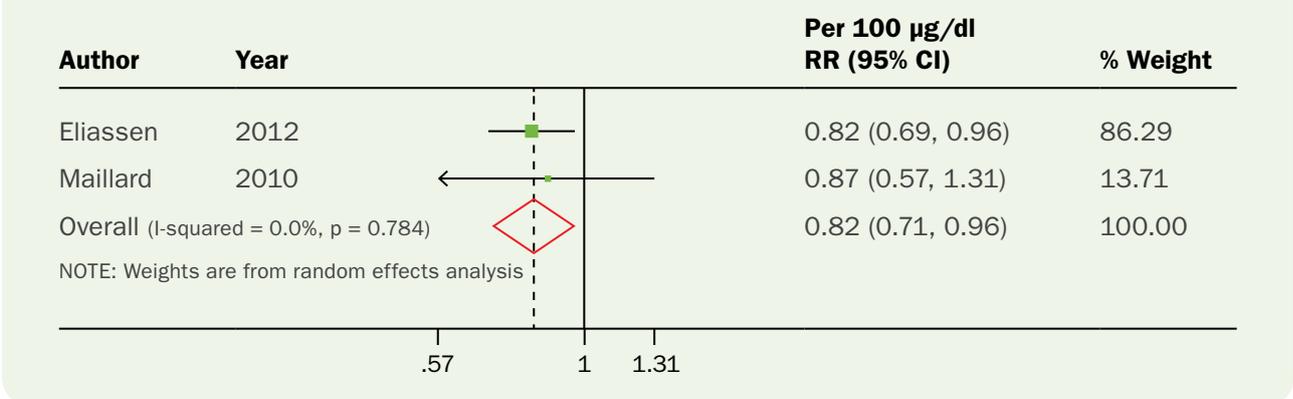
5.7.2.1 Serum/plasma carotenoids

5.7.2.1.1 CUP dose-response meta-analyses

All nine identified studies (including one published *pooled analysis*) were included in the dose-response meta-analysis, which showed a statistically significant 18 per cent decreased risk of breast cancer per 100 micrograms increase in carotenoids per 100 millilitres of serum/plasma (RR 0.82 [95% CI 0.71–0.96]; n = 3,407 cases) (see **Figure 5.20**). No *heterogeneity* was observed.

When the CUP dose-response meta-analysis was stratified by menopausal status, no statistically significant increase or decrease in the risk of breast cancer was observed per 100 micrograms increase in carotenoid levels per 100 millilitres of serum/plasma for pre or postmenopausal women (see [CUP breast cancer SLR 2017](#), Figures 414 and 415).

Figure 5.20: CUP dose-response meta-analysis¹ for the risk of breast cancer, per 100 micrograms increase in carotenoids per 100 millilitres of serum/plasma



Source: Eliassen, 2012 [211]; Maillard, 2010 [212].

¹ The CUP dose-response meta-analysis included one pooled analysis (Eliassen, 2012 [211]), which included eight of the identified studies.

The *pooled analysis* that was included in the CUP dose–response meta-analysis (86 per cent weight) reported results by tobacco smoking and found that the decreased risk of breast cancer observed with serum/plasma carotenoid levels was not affected in people who smoke or in those who do not smoke. [211].

All studies included in the dose–response meta-analyses adjusted for age at first birth, and most adjusted for age, reproductive factors and MHT use. For information on the *adjustments* made in individual studies, see [CUP breast cancer SLR 2017, Table 324](#).

5.7.2.2 Dietary beta-carotene

5.7.2.2.1 Published pooled analysis

For dietary beta-carotene, all studies identified in the CUP were superseded by a published *pooled analysis* [188], so no dose–response meta-analysis was conducted. The published pooled analysis of 18 studies reported no statistically significant association per 5,000 micrograms increase in dietary beta-carotene consumed per day (RR 1.00 [95% CI 0.98–1.02; n = 3,055 cases). No *heterogeneity* was observed.

The published pooled analysis adjusted for age, number of reproductive cycles, menopausal status and age at first birth, as well as several other factors.

5.7.2.3 Serum/plasma beta-carotene

5.7.2.3.1 CUP dose–response meta-analyses

Eleven of 13 identified studies (including one published *pooled analysis*) were included in the dose–response meta-analysis, which showed a statistically significant 12 per cent decreased risk of breast cancer per 50 micrograms increase in beta-carotene per 100 millilitres of serum/plasma (RR 0.78 [95% CI 0.66–0.92]; n = 3,558 cases) (see **Figure 5.21**). No *heterogeneity* was observed.

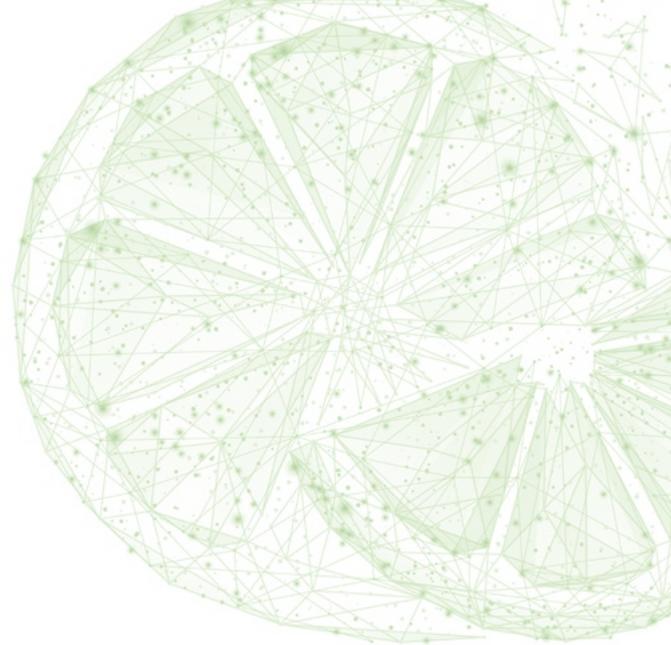
When the CUP dose–response meta-analysis was stratified by menopausal status, no statistically significant increase or decrease in the risk of breast cancer was observed per 50 micrograms increase in beta-carotene per 100 millilitres of plasma/serum for pre or postmenopausal women (see [CUP breast cancer SLR 2017, Figures 403 and 404](#)).

Figure 5.21: CUP dose–response meta-analysis¹ for the risk of breast cancer, per 50 micrograms increase in beta-carotene per 100 millilitres of plasma/serum



Source: Pouchieu, 2014 [213]; Eliassen, 2012 [211]; Maillard, 2010 [212]; Wald, 1984 [214].

¹ The CUP dose–response meta-analysis included one pooled analysis (Eliassen, 2012 [211]), which included eight of the identified studies.



Most studies included in the dose–response meta-analysis adjusted for age, number of reproductive cycles, age at first birth and use of hormone-based medications. For information on the *adjustments* made in individual studies, see [CUP breast cancer SLR 2017](#), Table 314.

5.7.2.4 Other carotenoids

In addition to the studies on serum/plasma carotenoids, dietary beta-carotene and serum/plasma beta-carotene presented above, the CUP identified studies on serum/plasma levels of alpha-carotene, lutein, beta-cryptoxanthin and lycopene. Dose–response meta-analyses were possible on all of these exposures. The results are presented in **Table 5.20**.

5.7.2.5 Published pooled analyses and meta-analyses

Two published *pooled analyses* and one other published meta-analysis on foods containing carotenoids and the risk of breast cancer were identified.

One published pooled analysis [211] reported on most of the carotenoid-related exposures included in the CUP. This pooled analysis was included in the CUP dose–response meta-analyses for all exposures except circulating lutein. Another published pooled

analysis identified by the CUP [188] reported no statistically significant association per 5,000 micrograms increase in dietary beta-carotene consumed per day (see **Table 5.19**). This pooled analysis superseded all studies identified in the CUP, and no CUP dose–response analysis was necessary for dietary beta-carotene.

One other published meta-analysis [215], which reported results from the CUP, was identified. It reported on all of the carotenoid exposures.

For further details of the published pooled analyses and meta-analysis, see the relevant sections in the [CUP breast cancer SLR 2017](#).

Table 5.20: Summary of CUP dose–response meta-analyses for other carotenoid exposures and the risk of breast cancer

Serum/ plasma levels	Total no. of studies ¹	No. studies on meta-analysis	RR (95% CI)	Increment	I ² (%)	No. of cases
Alpha-carotene	11	10	0.90 (0.77–1.05)	10 µg/100 ml	0	3,506
Lutein	7	7	0.72 (0.55–0.93)	25 µg/100 ml	0	1,296
Beta-cryptoxanthin	11	10	0.87 (0.68–1.11)	15 µg/100 ml	59	3,517
Lycopene	11	10	0.90 (0.70–1.16)	25 µg/100 ml	39	3,506

¹ For information about the studies included in each dose–response meta-analysis, see [CUP breast cancer SLR 2017](#), Tables 306, 329, 319 and 334, respectively.

5.7.2.5.1 Hormone receptor status

Two published *pooled analyses* [188, 211] and other individual studies [216–218] have reported on carotenoid exposures and breast cancer risk by *hormone receptor status*. The results from the published pooled analyses are presented in **Table 5.21**.

Results indicated overall a greater decreased risk with ER-negative breast cancers, with statistically significant decreased risks

reported for dietary beta-carotene, serum/plasma alpha-carotene and serum/plasma beta-carotene.

In addition to the results presented in **Table 5.21**, the EPIC study [216] showed a significant decreased risk of ER-negative breast cancer for plasma alpha-carotene and beta-carotene only, and of ER-positive breast cancer for plasma lutein only, and no differences by hormone receptor status for plasma carotenoids, beta-cryptoxanthin and lycopene.

Table 5.21: Summary of published pooled analyses for any carotenoid and the risk of breast cancer stratified by hormone receptor status

Exposure/publication	Increment/contrast	ER status	RR (95% CI)	No. of studies (cohort)	No. of cases
Serum/plasma carotenoids Eliassen 2012 [211]	Quintile 5 vs Quintile 1	ER–	0.81 (0.56–1.16)	8	417
	Quintile 5 vs Quintile 1	ER+	0.86 (0.69–1.07)		1,481
Dietary beta-carotene Zhang 2012 [188]	5,000 µg/day	ER–	0.93 (0.88–0.99)	18	4,463
	5,000 µg/day	ER+	1.02 (0.99–1.05)		19,282
Serum/plasma beta-carotene Eliassen 2012 [211]	Quintile 5 vs Quintile 1	ER–	0.52 (0.36–0.77)	8	417
	Quintile 5 vs Quintile 1	ER+	0.83 (0.66–1.04)		1,481
Dietary alpha-carotene Zhang 2012 [188]	5,000 µg/day	ER–	0.95 (0.90–1.01)	18	4,463
	5,000 µg/day	ER+	1.01 (0.99–1.03)		19,282
Serum/plasma alpha-carotene Eliassen 2012 [211]	Quintile 5 vs Quintile 1	ER–	0.61 (0.40–0.93)	8	417
	Quintile 5 vs Quintile 1	ER+	0.85 (0.65–1.12)		1,481
Dietary beta-cryptoxanthin Zhang 2012 [188]	5,000 µg/day	ER–	0.97 (0.93–1.00)	18	4,463
	5,000 µg/day	ER+	0.99 (0.97–1.00)		19,282
Serum/plasma beta-cryptoxanthin Eliassen 2012 [211]	Quintile 5 vs Quintile 1	ER–	1.03 (0.69–1.53)	8	417
	Quintile 5 vs Quintile 1	ER+	1.09 (0.86–1.39)		1,481
Dietary lycopene Zhang 2012 [188]	5,000 µg/day	ER–	0.98 (0.93–1.03)	18	4,463
	5,000 µg/day	ER+	1.01 (0.99–1.03)		19,282
Serum/plasma lycopene Eliassen 2012 [211]	Quintile 5 vs Quintile 1	ER–	0.72 (0.44–1.17)	8	417
	Quintile 5 vs Quintile 1	ER+	0.83 (0.60–1.15)		1,481

5.7.2.6 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 are currently prevailing 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](#).

Carotenoids may act as *antioxidants* by quenching *free radicals* and protecting against macromolecular damage, including DNA damage [219, 220]. Carotenoids such as beta-carotene may have direct effects on cell signalling as well, such as reducing *cell proliferation* and inducing *apoptosis* [221, 222]. Circulating concentrations of carotenoids are also used in epidemiologic and clinical studies as *biomarkers* of intake of fruit and vegetables, which contain an array of *bioactive compounds*, including fibre, *flavonoids* and other antioxidants, and these may act synergistically to reduce breast cancer risk [215]. Alpha-carotene, beta-carotene and beta-cryptoxanthin may decrease cancer risk indirectly through their metabolism to vitamin A (retinol), which in turn regulates cell growth, differentiation and apoptosis through direct and indirect effects on gene expression [188]. Carotenoids may also be directly anticarcinogenic by several other mechanisms, including enhanced immune system functioning. Experimental evidence has also shown that some carotenoids can inhibit the growth of both ER-positive and ER-negative breast cancer *cell lines*, and

it is possible that an effect of carotenoids on ER-positive tumours is masked by the *hormone*-related associations that dominate as risk factors for ER-positive tumours [188].

5.7.2.7 CUP Panel's conclusion

The evidence for breast cancer was limited but generally consistent, and there was evidence of a decreased risk for several carotenoid-related exposures, including serum/plasma carotenoids, serum/plasma beta-carotene and serum/plasma lutein. No *heterogeneity* was observed for most of the dose–response meta-analyses. Results from two published *pooled analyses* (one of which was included in the CUP dose–response meta-analyses for most exposures) overall supported the CUP findings. Fewer studies reported on menopausal status, and results from the CUP dose–response meta-analyses were not significant. The Panel also notes the evidence suggesting that the decreased risk is stronger for ER-negative breast cancers, as a significant decreased risk was shown for both dietary and serum/plasma levels of some exposures – for example, beta-carotene. There is evidence of plausible mechanisms operating in humans.

The CUP Panel concluded:

- **The evidence suggesting that greater consumption of foods containing carotenoids decreases the risk of breast cancer is limited.**

5.8 Foods containing beta-carotene

For breast cancer the evidence related to foods containing beta-carotene is included in the conclusion for foods containing carotenoids; see **Sections 5.7.2.2** and **5.7.2.3**.

Table 5.22 summarises the main findings from the CUP dose–response meta-analyses of cohort studies on consumption of foods containing beta-carotene 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:¹ oesophagus (adenocarcinoma and squamous cell

carcinoma; 2016), stomach (2016), colorectum (2017), ovary (2014), endometrium (2013), cervix (2017), kidney (2015), bladder (2015), and skin (2017).

The strong evidence on the effects of eating foods containing beta-carotene 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. The evidence that was graded by the Panel as ‘limited – suggestive’ is also described in the following subsections.

Table 5.22: Summary of CUP dose–response meta-analyses for consumption of foods containing beta-carotene and the risk of cancer

Cancer	Type	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I ² (%)	Conclusion ¹	Date of CUP cancer report ²
Lung ³	Dietary	15	13	7,560	0.99 (0.98–1.00)	700 µg/day	5	Limited – suggestive: Decreases risk	2017
	Serum	17	9	2,958	0.92 (0.87–0.97)	10 µg/100 ml	40		
Prostate ⁴	Dietary	11	10	12,219	1.00 (0.99–1.00)	700 µg/day	0	Substantial effect on risk unlikely	2014
	Serum/plasma	14	9	3,449	0.99 (0.95–1.04)	10 µg/100 ml	38		
	Supplements	8	0	–	No statistically significant association in 8 studies	–	–		

- 1 See Definitions of WCRF/AICR grading criteria (**Section 1**: Wholegrains, vegetables and fruit and the risk of cancer: a summary matrix) for explanations of what the Panel means by ‘substantial effect on risk unlikely’ 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 Panel made two separate conclusions on lung cancer and beta-carotene: one on ‘foods containing beta-carotene’, which is based on evidence on dietary intake and serum levels, and another on ‘high-dose beta-carotene supplements’. The evidence for foods containing beta-carotene is presented here. For information on high-dose beta-carotene supplements, see Exposures: Other dietary exposures, Section 5.10.
- 4 The Panel made one conclusion for prostate cancer and beta-carotene, which is based on evidence derived from studies on dietary intake and serum levels, as well as studies on high-dose supplement use (20, 30 and 50 mg/day). A dose–response meta-analysis could not be conducted in the CUP for prostate cancer and beta-carotene supplements. Evidence is from five cohort studies and three randomised controlled trials which all reported no statistically significant association.

¹ ‘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.

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

5.8.1 Lung

(Also see [CUP lung cancer report 2017: Section 7.6](#) and [CUP lung cancer SLR 2015: Section 5.5.1.2.](#))

The evidence for dietary and serum beta-carotene and the risk of lung cancer is presented in the following subsections. For evidence specifically on foods containing carotenoids and the risk of lung cancer, see

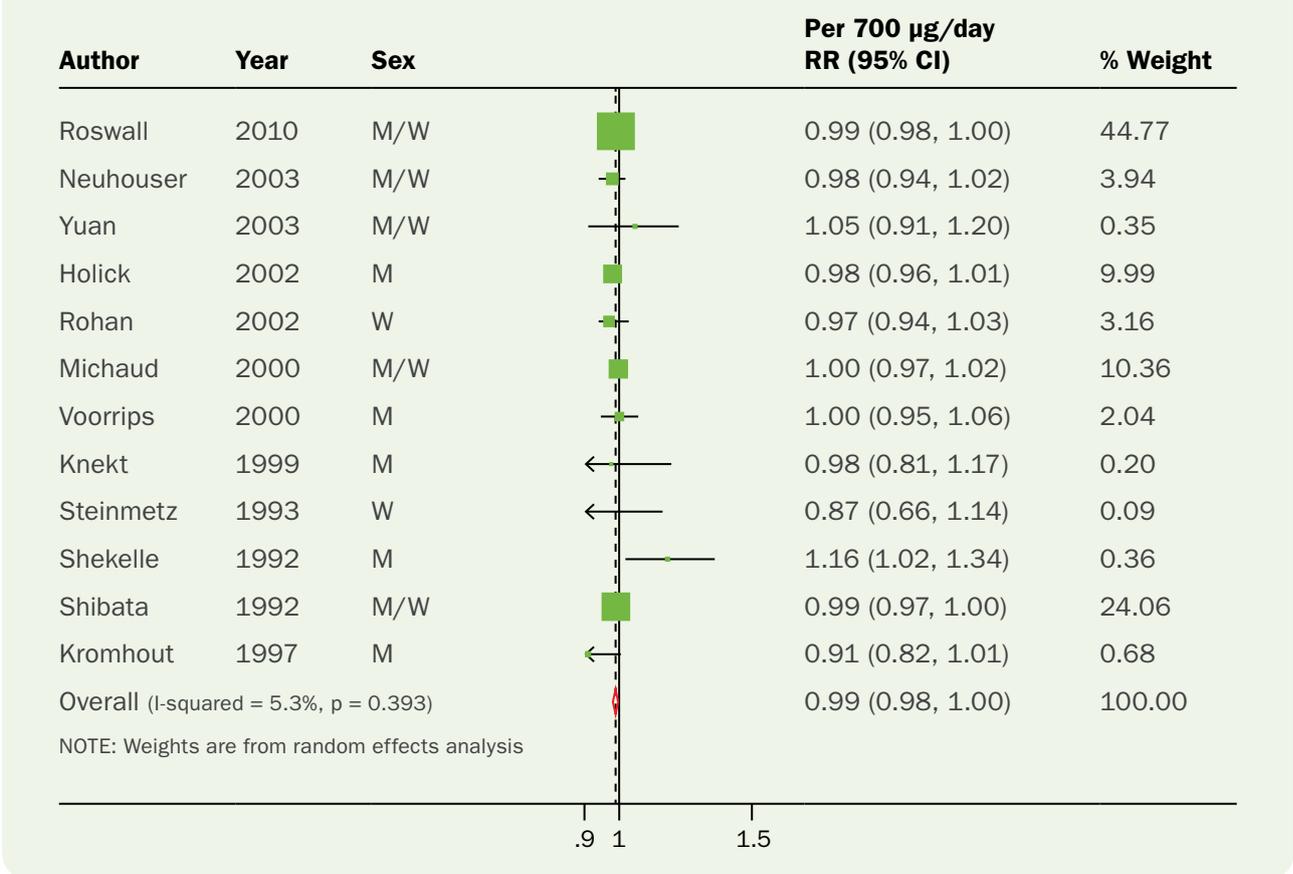
Section 5.7.1. For information on high-dose beta-carotene supplements, see [Exposures: Other dietary exposures](#), Section 5.10.

5.8.1.1 Dietary beta-carotene

5.8.1.1.1 CUP dose–response meta-analyses

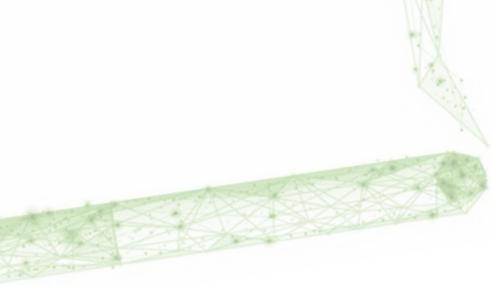
Thirteen of 15 identified studies were included in the dose–response meta-analysis, which showed no statistically significant association between the risk of lung cancer and consumption of dietary beta-carotene (RR 0.99 [95% CI 0.98–1.00], per 700 micrograms consumed per day; n = 7,560 cases) (see **Figure 5.22**). Low *heterogeneity* was observed ($I^2 = 5\%$), and there was no evidence of small study bias with *Egger’s test* ($p = 0.52$).

Figure 5.22: CUP dose–response meta-analysis for the risk of lung cancer, per 700 micrograms increase in dietary beta-carotene consumed per day



Source: Roswall, 2010 [223]; Neuhaus, 2003 [191]; Yuan, 2003 [224]; Holick, 2002 [142]; Rohan, 2002 [225]; Michaud, 2000 [192]; Voorrips, 2000 [143]; Knekt, 1999 [193]; Steinmetz, 1993 [144]; Shekelle, 1992 [226]; Shibata, 1992 [156]; Kromhout, 1987 [227].

¹ The CUP dose–response meta-analysis included one publication (Michaud, 2000 [192]) that included two studies.



When stratified by tobacco smoking, no statistically significant association was observed between the risk of lung cancer and dietary beta-carotene (per 700 micrograms consumed per day) in people who smoke, people who used to smoke or people who have never smoked (see [CUP lung cancer SLR 2015](#), Table 132 and Figure 162).

There was no evidence of a non-linear dose-response relationship ($p > 0.05$).

All studies included in the dose-response meta-analysis adjusted for intensity, duration of tobacco smoking and other smoking variables in addition to smoking status. For information on the *adjustments* made in individual studies, see [CUP lung cancer SLR 2015](#), Table 134.

5.8.1.1.2 Published pooled analyses and meta-analyses

One published *pooled analysis* (see [Table 5.23](#)) and one other published meta-analysis on consumption of dietary beta-carotene and the risk of lung cancer were identified. The pooled analysis reported no statistically significant association for the highest compared with the lowest level of dietary beta-carotene consumed [228]. The meta-analysis reported no significant association in both a dose-response and a highest versus lowest meta-analysis [195].

5.8.1.2 Serum beta-carotene

5.8.1.2.1 CUP dose-response meta-analysis

Nine of 17 identified studies were included in the dose-response meta-analysis, which showed a statistically significant eight per cent decreased risk of lung cancer per 10 micrograms increase in beta-carotene levels per 100 ml of serum (RR 0.92 [95% CI 0.87–0.97]; $n = 2,958$ cases) (see [Figure 5.23](#)). Moderate *heterogeneity* was observed ($I^2 = 40\%$), and there was no evidence of small study bias with *Egger's test* ($p = 0.28$).

There were not enough data to stratify by tobacco smoking status.

There was no evidence of non-linear dose-response relationship ($p > 0.05$).

All studies included in the dose-response meta-analysis adjusted for intensity, duration of tobacco smoking and other smoking variables, in addition to smoking status. For information on the *adjustments* made in individual studies, see [CUP lung cancer SLR 2015](#), Table 141.

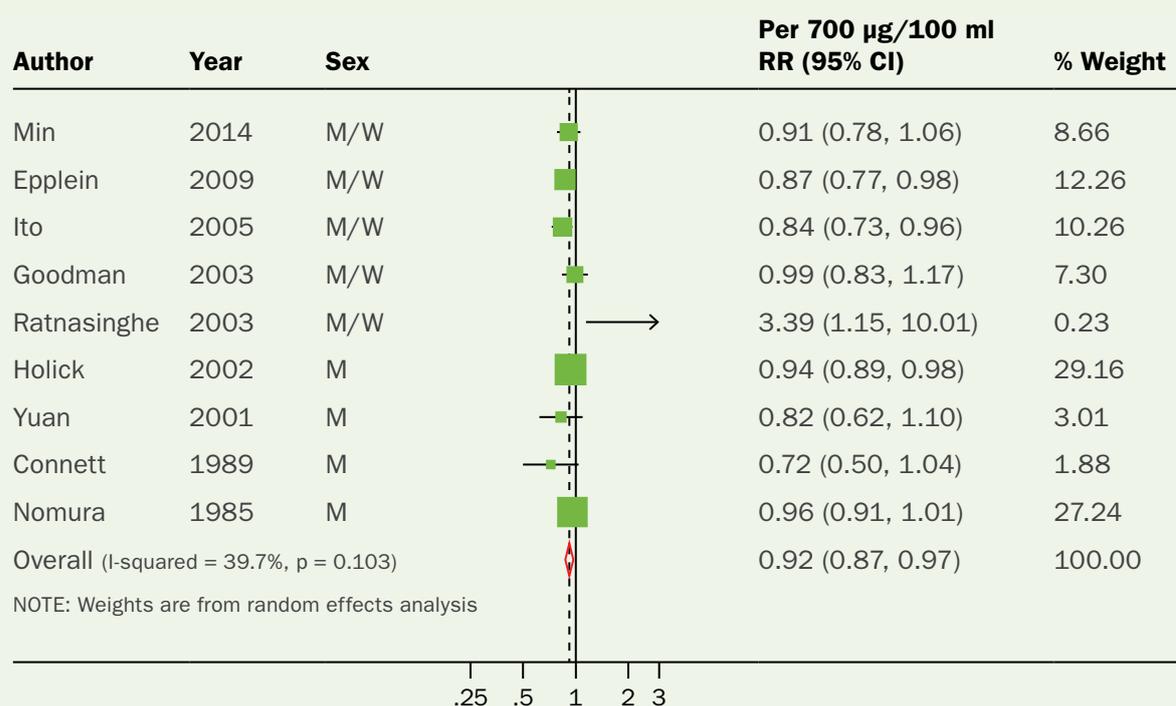
5.8.1.2.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. One other published meta-analysis on serum/plasma beta-carotene and the risk of lung cancer was identified, which reported no statistically significant association per 0.1 micromol/L increase in serum beta-carotene [195].

Table 5.23: Summary of published pooled analyses of dietary beta-carotene intake and the risk of lung cancer

Publication	Contrast	RR (95% CI)	No. of studies (cohort)	No. of cases
Männistö 2004 [228]	Quintile 5 vs Quintile 1	0.98 (0.87–1.11)	7	3,155

Figure 5.23: CUP dose–response meta-analysis¹ for the risk of lung cancer, per 10 micrograms increase in beta-carotene per 100 millilitres of serum



Source: Min, 2014 [229]; Epplein, 2009 [196]; Ito, 2005 [197]; Goodman, 2003 [230]; Ratnasinghe, 2003 [231]; Holick, 2002 [142]; Yuan, 2001 [199]; Connett, 1989 [200]; Nomura, 1985 [232].

5.8.1.3 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 are currently prevailing 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](#).

A number of human studies and *meta-analyses* have shown that higher circulating levels of *carotenoids*, including beta-carotene, lycopene, and beta-cryptoxanthin, are associated with lower risk of lung cancer [202]. A number

of human studies and *meta-analyses* have shown that higher circulating levels of beta-carotene are associated with a lower risk of lung cancer [202]. Further, evidence from both animal and laboratory studies have shown that carotenoids can block certain carcinogenic processes and inhibit tumour cell growth [203, 204]. Some proposed mechanisms for these actions include (1) functioning as an *antioxidant* [205, 233], (2) acting as a precursor for retinoic acid [206, 207], (3) enhancing immunologic function [208, 209], (4) inducing *carcinogen*-metabolising enzymes [210], (5) inhibiting *cell proliferation* and (6) inducing *apoptosis*.

¹ Eight studies could not be included in the dose–response meta-analysis because they did not provide sufficient information. For further details, see CUP lung cancer SLR 2015, Table 142.

5.8.1.4 CUP Panel's conclusion

The evidence for consumption of foods containing beta-carotene and the risk of lung cancer was limited but generally consistent. The CUP dose–response meta-analysis of dietary beta-carotene intake showed no statistically significant association, with low *heterogeneity* observed, and no significant association was observed in people who smoke, people who used to smoke and those who have never smoked in analyses stratified by tobacco smoking. There was no evidence of a non-linear dose–response relationship. The analysis of serum beta-carotene showed a significant eight per cent decreased risk of lung cancer per 10 micrograms increase in beta-carotene per 100 millilitres of serum, with moderate *heterogeneity*, and there were not enough data to stratify by tobacco smoking. However, because smoking tobacco lowers serum beta-carotene levels, residual confounding cannot be excluded. There is evidence of plausible mechanisms in humans.

The CUP Panel concluded:

- **The evidence suggesting that greater consumption of foods containing beta-carotene decrease the risk of lung cancer is limited.**

5.8.2 Prostate

(Also see [CUP prostate cancer report 2014](#): Section 7.3 and [CUP prostate cancer SLR 2014](#): Section 5.5.1.2.)

The conclusion is based on evidence for beta-carotene (dietary intake, serum/plasma levels and supplement use) and the risk of prostate cancer. A dose–response meta-analysis could not be conducted in the CUP for supplement use.

5.8.2.1 Dietary beta-carotene

5.8.2.1.1 CUP highest versus lowest meta-analyses

Ten of 11 identified studies on consumption of dietary beta-carotene and the risk of prostate cancer were included in a highest versus lowest meta-analysis (see **Figure 5.24**). Most of the risk estimates were close to 1.0.

5.8.2.1.2 CUP dose–response meta-analysis

Ten of 11 identified studies were included in the dose–response meta-analysis, which showed no statistically significant association between the risk of prostate cancer and consumption of dietary beta-carotene (RR 1.00 [95% CI 0.99–1.00], per 700 micrograms increase per day; $n = 12,219$ cases) (see **Figure 5.25**). No *heterogeneity* was observed, and there was no evidence of small study bias with *Egger's test* ($p = 0.13$).

It was not possible to conduct stratified dose–response meta-analyses for advanced or aggressive prostate cancer. All studies included in the dose–response meta-analysis adjusted or accounted for age; some studies adjusted for combinations of other dietary factors, alcohol consumption, tobacco smoking, BMI and physical activity.

5.8.2.1.3 Published pooled analyses and meta-analyses

No published pooled analyses and no other published meta-analyses on consumption of dietary beta-carotene and the risk of prostate cancer were identified.

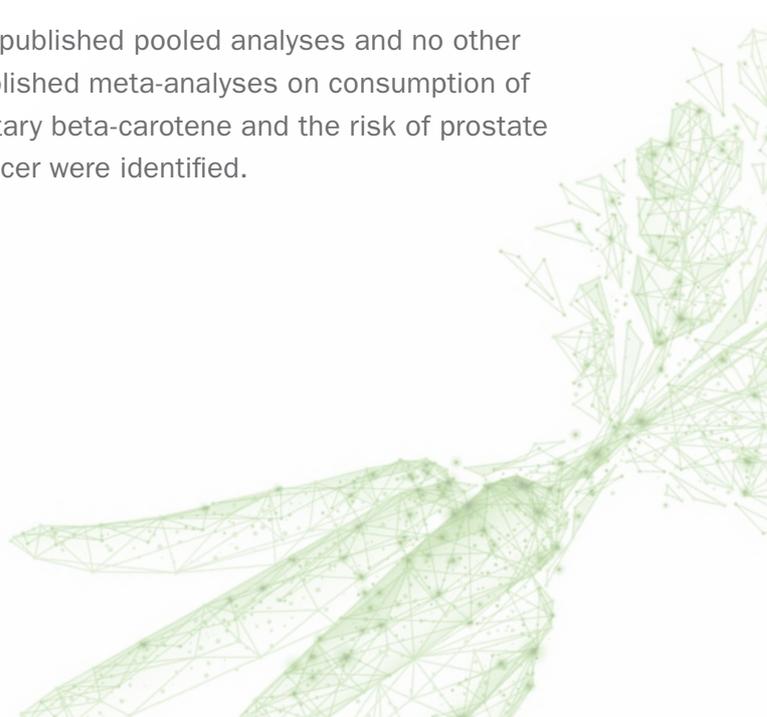
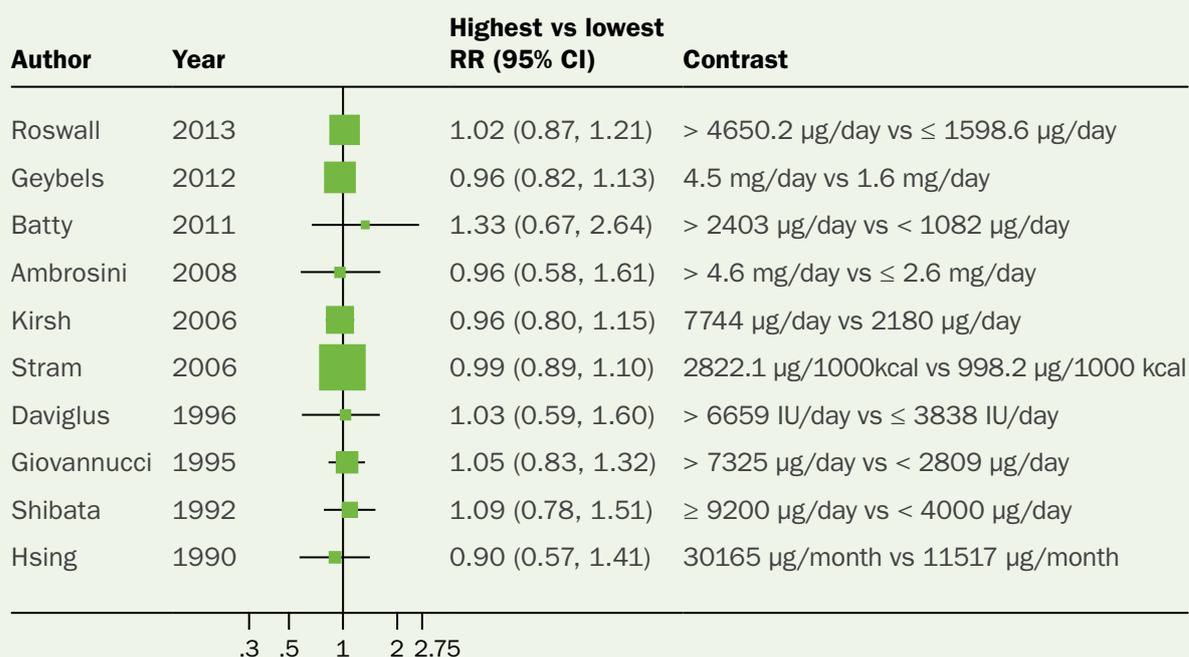
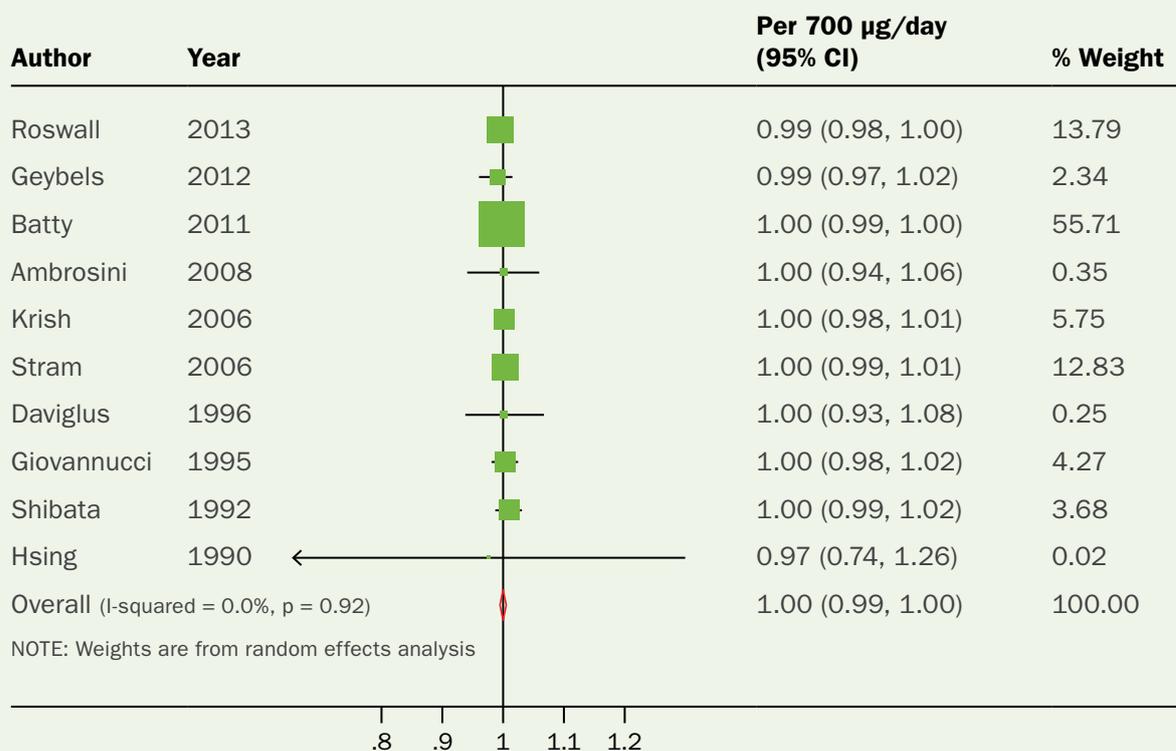


Figure 5.24: CUP highest versus lowest meta-analysis for dietary beta-carotene intake and the risk of prostate cancer



Source: Roswall, 2013 [234]; Geybels, 2012 [235]; Batty, 2011 [236]; Ambrosini, 2008 [237]; Kirsh, 2006 [238]; Stram, 2006 [239]; Daviglus, 1996 [240]; Giovannucci, 1995 [241]; Shibata, 1992 [156]; Hsing, 1990 [242].

Figure 5.25: CUP dose–response meta-analysis for the risk of prostate cancer, per 700 micrograms increase in dietary beta-carotene consumed per day



Source: Roswall, 2013 [234]; Geybels, 2012 [235]; Batty, 2011 [236]; Ambrosini, 2008 [237]; Kirsh, 2006 [238]; Stram, 2006 [239]; Daviglus, 1996 [240]; Giovannucci, 1995 [241]; Shibata, 1992 [156]; Hsing, 1990 [242].

5.8.2.2 Serum/plasma beta-carotene

5.8.2.2.1 CUP highest versus lowest meta-analyses

Thirteen of 14 identified studies on serum/plasma beta-carotene levels and the risk of prostate cancer were included in a highest versus lowest meta-analysis (see **Figure 5.26**). No apparent pattern of increased or decreased risk was observed.

5.8.2.2.2 CUP dose-response meta-analysis

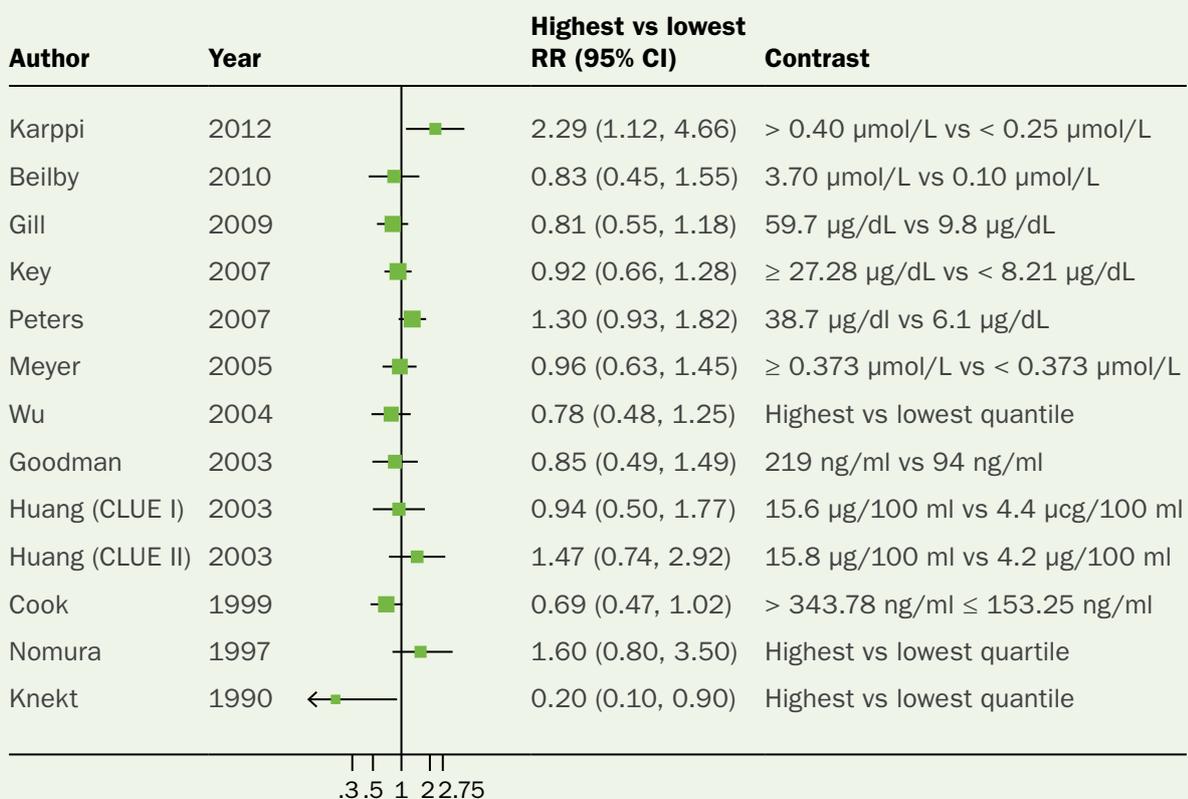
Nine of 14 identified studies were included in the dose-response meta-analysis, which showed no statistically significant association between the risk of prostate cancer and serum/plasma (see **Figure 5.27**). Moderate heterogeneity was observed ($I^2 = 38\%$), and

there was no evidence of small study bias with Egger's test ($p = 0.47$).

A stratified analysis for the risk of prostate cancer per 10 micrograms increase in beta-carotene per 100 millilitres of serum/plasma was conducted for cancer progression; no statistically significant association was observed for three studies on advanced prostate cancer (RR 0.97 [95% CI 0.85–1.12]; see **CUP prostate cancer SLR 2014**, Figure 189).

All studies included in the dose-response meta-analysis adjusted or accounted for age; some studies adjusted for combinations of alcohol consumption, tobacco smoking, BMI and physical activity.

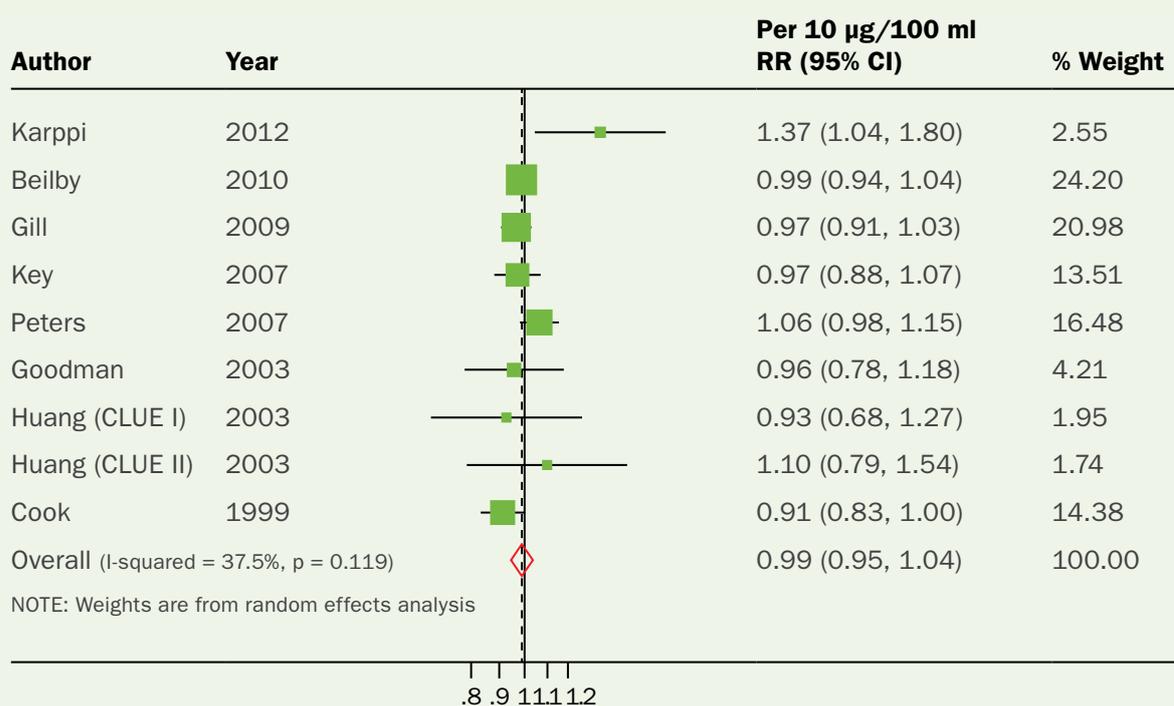
Figure 5.26: CUP highest versus lowest meta-analysis¹ for serum/plasma levels of beta-carotene and the risk of prostate cancer



Source: Karppi, 2012 [243]; Beilby, 2010 [244]; Gill, 2009 [245]; Key, 2007 [246]; Peters, 2007 [247]; Meyer, 2005 [248]; Wu, 2004 [249]; Goodman, 2003 [230]; Huang, 2003 [250]; Cook, 1999 [251]; Nomura, 1997 [252]; Knekt, 1990 [253].

¹ In Cook 1999 [251], the RRs were recalculated using the Hamling method [201].

Figure 5.27: CUP dose–response meta-analysis^{1,2} for the risk of prostate cancer, per 10 micrograms increase in beta-carotene per 100 millilitres of serum/plasma



Source: Karppi, 2012 [243]; Beilby, 2010 [244]; Gill, 2009 [245]; Key, 2007 [246]; Peters, 2007 [247]; Goodman, 2003 [230]; Huang, 2003 [250]; Cook, 1999 [251].

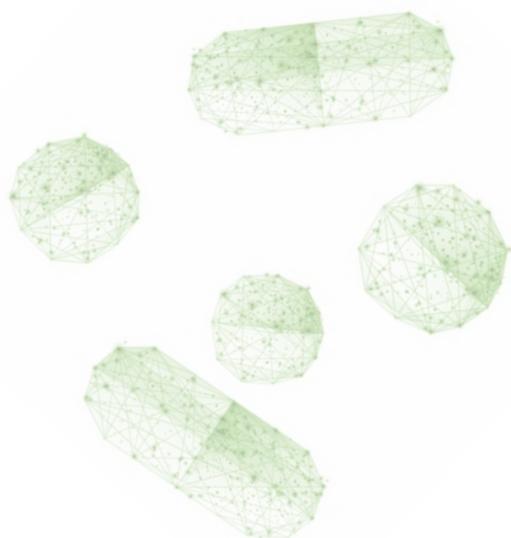
5.8.2.2.3 Published pooled analyses and meta-analyses

No published pooled analyses and no other published meta-analyses on serum/plasma levels of beta-carotene and the risk of prostate cancer were identified.

5.8.2.3 High-dose beta-carotene supplements

5.8.2.3.1 Published cohort studies and randomised controlled trials

Five published cohort studies and three randomised controlled trials on beta-carotene supplements and the risk of prostate cancer were identified. Dose–response and highest versus lowest meta-analyses could not be conducted in the CUP as too few studies could be included. All five cohort studies [234, 238, 249, 251, 254] reported no statistically significant association between consumption of high-dose beta-carotene supplements and the risk of prostate cancer. In addition, the three randomised controlled trials all reported no significant association (see **Table 5.24**).



¹ Five studies could not be included in the dose–response meta-analysis because they did not provide sufficient information. For further details, see CUP prostate cancer SLR 2014, Table 172.

² One publication (Huang, 2003 [250]) included two studies.

Table 5.24: Summary of published randomised controlled trials for consumption of beta-carotene supplements and the risk of prostate cancer

Trial name	No. of participants	Intervention	Intervention length (years)	Follow-up (years)	RR (95% CI)
Beta-Carotene and Retinol Efficacy Trial (CARET) [255, 256]	18,314 at high risk of developing lung cancer	30 mg beta-carotene and 25,000 IU retinyl palmitate	4 (trial ended early)	5	1.01 (0.80–1.27)
Physicians' Health Study (PHS) [257]	22,071	50 mg beta-carotene taken on alternate days	13		1.00 (0.90–1.10)
Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study (men who smoke tobacco) [258, 259]	29,133	20 mg of beta-carotene only or with 50 mg of <i>alpha-tocopherol</i>	5–8	6–8	1.26 (0.98–1.62) for the 1985–1993 follow-up period

5.8.2.3.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. One published meta-analysis on consumption of beta-carotene supplements and the risk of prostate cancer was identified, which included a randomised controlled trial, a case-control study and a cohort study, and reported no statistically significant association [260].

5.8.2.4 Mechanisms

This judgement requires the absence of strong and plausible experimental evidence; hence, no mechanisms are presented.

5.8.2.5 CUP Panel's conclusion

There is strong evidence from good-quality cohort studies on dietary intake, serum levels and supplement use that consistently fail to demonstrate an association between foods containing beta-carotene and the risk of prostate cancer. No *heterogeneity* was observed for dietary beta-carotene. There was no evidence of an adverse or protective effect using supplements at doses of 20, 30, and 50 milligrams per day.

The CUP Panel concluded:

- **Consuming beta-carotene in supplements or foods is unlikely to have substantial effect on the risk of prostate cancer.**

5.9 Foods containing vitamin C

Table 5.25 summarises the main findings from the CUP dose–response meta-analyses of cohort studies on consumption of foods containing vitamin C 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:¹ mouth, pharynx and larynx (2018); oesophagus (adenocarcinoma and squamous cell carcinoma; 2016); lung (people who used to smoke or have never smoked; 2017); stomach (2016); pancreas (2012); gallbladder (2015); liver (2015); breast (pre and postmenopause; 2017); ovary (2014); endometrium (2013); prostate (2014); kidney (2015); bladder (2015); and skin (2017).

¹ **'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.

Table 5.25: Summary of CUP dose–response meta-analyses for consumption of foods containing vitamin C and the risk of cancer

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I ² (%)	Conclusion ¹	Date of CUP cancer report ²
Lung (people who smoke tobacco) ³	5	4	1,664	0.87 (0.79–0.96)	40 mg/day	62	Limited – suggestive: Decreases risk	2017
Colorectum (colon) ⁴	18	6	4,391	0.94 (0.89–0.99)	40 mg/day	50	Limited – suggestive: Decreases risk	2017

- 1 See Definitions of WCRF/AICR grading criteria (**Section 1**: Wholegrains, vegetables and fruit 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.
- 3 The evidence for foods containing vitamin C and lung cancer in people who smoke tobacco is derived from studies on dietary intake.
- 4 The Panel’s conclusion is for foods containing vitamin C and colon cancer. No conclusion was drawn for foods containing vitamin C and rectal cancer.

The evidence on eating foods containing vitamin C and the risk of cancer that was graded by the Panel as ‘limited – suggestive’ is described in the following subsections.

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

5.9.1 Lung (people who smoke tobacco)

(Also see CUP lung cancer report 2017: Section 7.7 and CUP lung cancer SLR 2015: Section 5.5.9.)

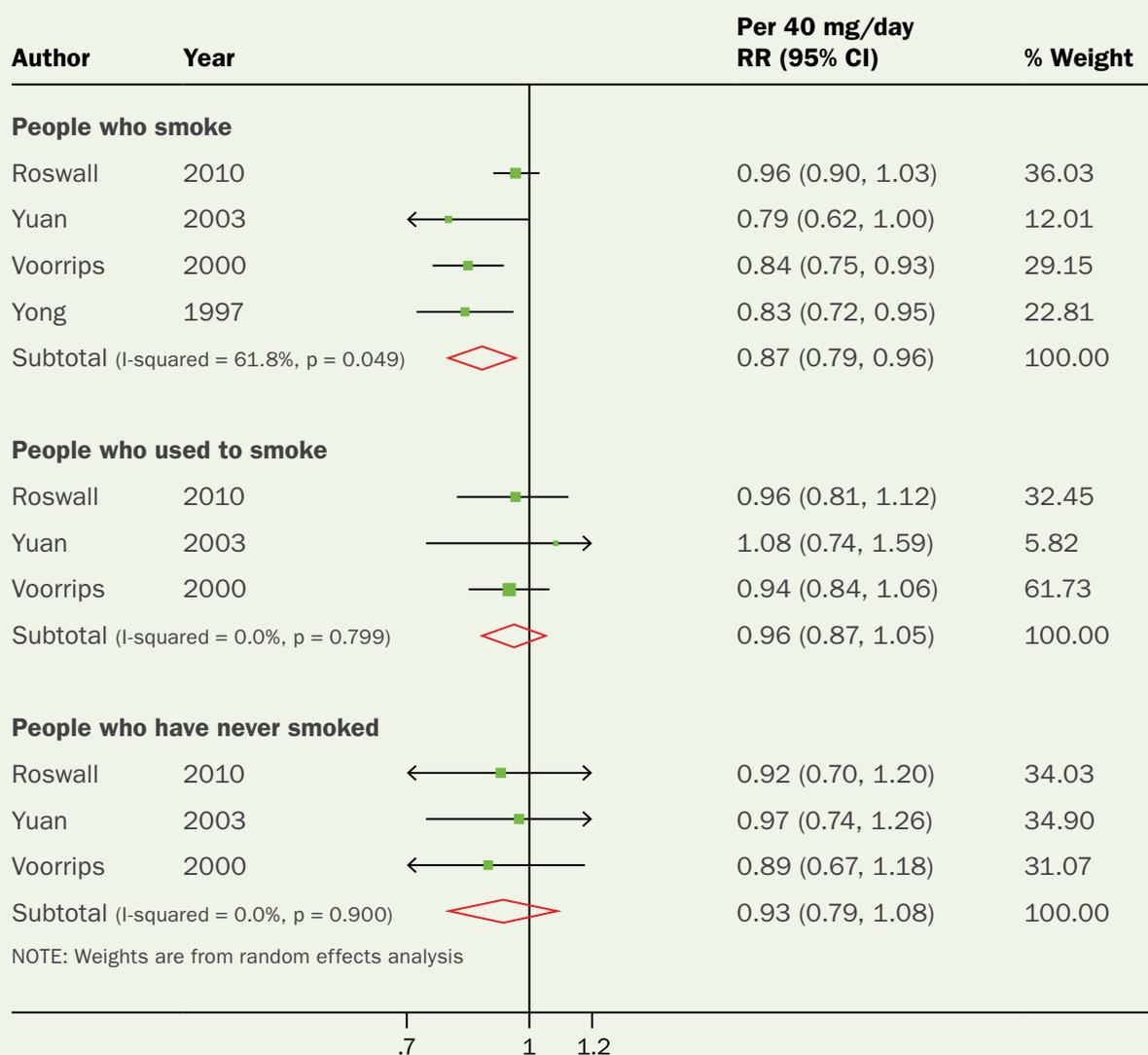
The evidence for dietary vitamin C and the risk of lung cancer, stratified by tobacco smoking, is presented in the following subsections. No studies on serum/plasma vitamin C were identified. For information on dietary vitamin C (not stratified by tobacco smoking) and on vitamin C supplements, see CUP lung cancer SLR 2015, Section 5.5.9.

5.9.1.1 CUP dose–response meta-analysis stratified by tobacco smoking

Four of five identified studies reporting results on people who smoke were included in a dose–response meta-analysis stratified by tobacco smoking, which showed a statistically significant 13 per cent decreased risk of lung cancer in people who smoke per 40 milligrams increase in dietary vitamin C consumed per day (RR 0.87 [95% CI 0.79–0.96]; n = 1,664 cases) (see **Figure 5.28**). High *heterogeneity* was observed (I² = 62%).

No significant association was observed between the risk of lung cancer and dietary vitamin C intake in people who used to smoke (RR 0.96 [95% CI 0.87–1.05]; n = 582) or people who have never smoked (RR 0.93 [95% CI 0.79–1.08]; n = 225). No *heterogeneity* was observed in either analysis (see **Figure 5.28**).

Figure 5.28: CUP dose–response meta-analysis for the risk of lung cancer stratified by tobacco smoking, per 40 milligrams increase in dietary vitamin C consumed per day



Source: Roswall, 2010 [223]; Yuan, 2003 [224]; Voorrips, 2000 [143]; Yong, 1997 [261].

All studies in the dose–response meta-analysis adjusted for age and sex. For information on the *adjustments* made in individual studies, see [CUP lung cancer SLR 2015](#), Table 191.

5.9.1.2 Published pooled analyses and meta-analyses

One published *pooled analysis* (see [Table 5.26](#)) and one other published meta-analysis on consumption of vitamin C and the risk of lung cancer were identified. The pooled analysis reported no statistically significant association for people who smoke, people who used to smoke and people who have never smoked [262]. The meta-analysis of *cohort* and *case-control studies* reported a significant decreased risk for people who smoke (RR 0.64 [95% CI 0.44–0.92]); no significant association was observed for people who used to smoke and those who have never smoked [263].

Table 5.26: Summary of published pooled analyses of vitamin C intake and the risk of lung cancer

Publication	Contrast	RR (95% CI)	No. of studies (cohort)	No. of cases
Pooling Project of Prospective Studies on Diet and Cancer (people who smoke) [262]	Highest vs lowest	0.85 (0.70–1.02)	8	1,915

5.9.1.3 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 are currently prevailing 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](#).

Vitamin C is a potent antioxidant, reducing levels of *reactive oxygen species*, inhibiting *lipid peroxidation* and reducing nitrates [187]. Vitamin C has also been shown to inhibit the formation of *carcinogens* in experimental models and to protect DNA from mutagenic insults [264].

5.9.1.4 CUP Panel's conclusion

The evidence for consumption of foods containing vitamin C and the risk of lung cancer was limited but generally consistent. The CUP dose–response meta-analysis showed a statistically significant decreased risk in people who smoke tobacco but not in those who used to smoke or who have never smoked. High *heterogeneity* was observed in the analyses for people who smoke. Although studies adjusted for tobacco smoking and for intensity and duration of tobacco smoking, there is the potential for residual confounding due to tobacco smoking.

Other published meta-analyses reported a significant decreased risk of lung cancer in people who smoke. There is evidence of plausible mechanisms in humans.

The CUP Panel concluded:

- **The evidence suggesting that greater consumption of foods containing vitamin C decreases the risk of lung cancer in people who smoke tobacco is limited.**

5.9.2 Colorectum (colon)

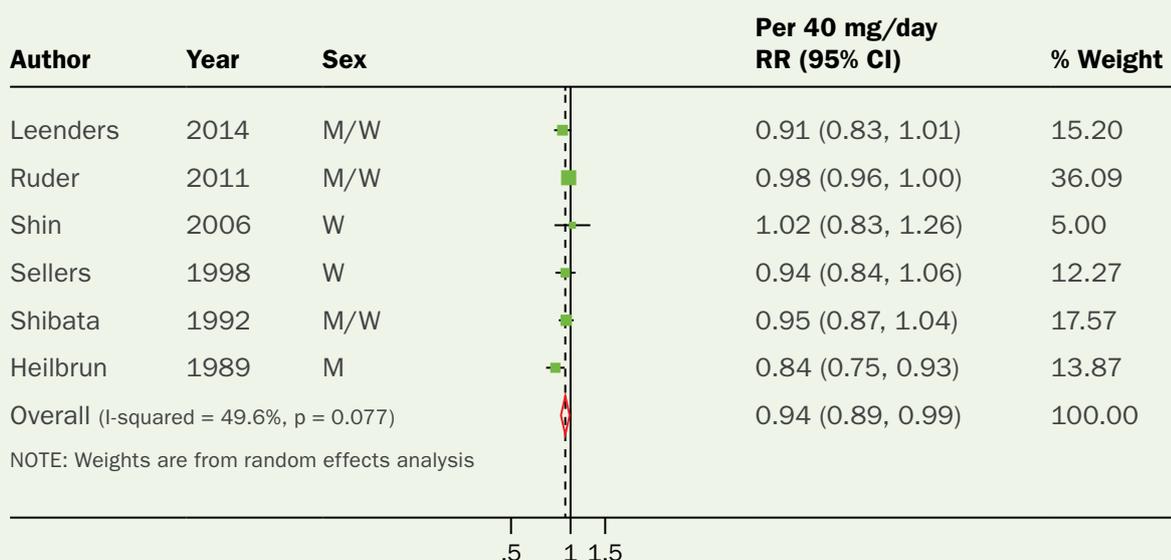
(Also see [CUP colorectal cancer report 2017: Section 7.4](#) and [CUP colorectal cancer SLR 2016: Section 5.5.9](#).)

The evidence for dietary vitamin C and the risk of colon cancer is presented in the following subsections. Dose–response meta-analyses could not be conducted in the CUP for colorectal or rectal cancer, as there were too few studies.

5.9.2.1 CUP dose–response meta-analysis

Six of 18 identified studies were included in the dose–response meta-analysis, which showed a statistically significant six per cent decreased risk of colon cancer per 40 milligrams increase in dietary vitamin C consumed per day (RR 0.94 [95% CI 0.89–0.99]; n = 4,391 cases) (see [Figure 5.29](#)). Moderate *heterogeneity* was observed ($I^2 = 50\%$), and there was no evidence of small study bias with *Egger's test* ($p = 0.06$).

Figure 5.29: CUP dose–response meta-analysis¹ for the risk of colon cancer, per 40 milligrams increase in dietary vitamin C consumed per day



Source: Leenders, 2014 [265]; Ruder, 2011 [266]; Shin, 2006 [99]; Sellers, 1998 [267]; Shibata, 1992 [156]; Heilbrun, 1989 [268].

Table 5.27: Summary of published pooled analyses of dietary vitamin C intake and the risk of colon cancer

Publication	Contrast	RR (95% CI)	No. of studies (cohort)	No. of cases
Pooling Project of Prospective Studies on Diet and Cancer [269]	Highest vs lowest	1.06 (0.95–1.18)	13	5,454

Most of the studies included in the dose–response meta-analysis adjusted for physical activity, BMI, alcohol consumption, tobacco smoking, red meat and MHT use in women. For information on the *adjustments* made in individual studies, see [CUP colorectal cancer SLR 2016](#), Table 278.

5.9.2.2 Published pooled analyses and meta-analyses

One published *pooled analysis* on consumption of dietary vitamin C and the risk of colon cancer was identified (see **Table 5.27**). No other published meta-analyses have been identified. In the pooled analysis, no statistically significant association was

observed in the multivariate adjusted model, which compared the highest with the lowest amount of dietary vitamin C consumed [269].

5.9.2.3 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 are currently prevailing 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](#).

¹ It was possible to include only six of the 18 studies in the dose–response meta-analysis as the pooled analysis of 13 studies reported a highest versus lowest category risk estimate only [269]. One study from the pooled analysis was published as a separate publication (Sellers, 1998 [267]).

Table 5.28: CUP highest versus lowest meta-analysis for consumption of foods containing isoflavones and the risk of lung cancer

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Conclusion ¹	Date of CUP cancer report ²
Lung (people who have never smoked tobacco) ³	4	3	714	0.66 (0.51–0.84)	Limited – suggestive: Decreases risk	2017

- 1 See Definitions of WCRF/AICR grading criteria (**Section 1:** Wholegrains, vegetables and fruit 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.
- 3 The evidence for foods containing isoflavones and lung cancer in people who have never smoked tobacco is derived from studies on dietary intake.

There is biological plausibility to support a protective effect of vitamin C on colorectal cancer development. Vitamin C is a potent antioxidant, reducing levels of reactive oxygen species, inhibiting lipid peroxidation and reducing nitrates [187]. Vitamin C has also been shown to inhibit the formation of carcinogens in experimental models and to protect DNA from mutagenic insults [264].

5.9.2.4 CUP Panel’s conclusion

The evidence was limited but generally consistent, and the CUP dose–response-meta-analysis showed a statistically significant decreased risk of colon cancer per 40 milligrams increase in vitamin C consumed per day. There was evidence of moderate heterogeneity. One published pooled analysis reported no significant association. No analysis for colorectal or rectal cancer was possible. There is evidence of plausible mechanisms in humans.

The CUP Panel concluded:

- The evidence suggesting that greater consumption of foods containing vitamin C decreases the risk of colon cancer is limited.

5.10 Foods containing isoflavones

Table 5.28 summarises the main findings from the CUP highest versus lowest meta-analysis of cohort studies on consumption of foods containing isoflavones and the risk of lung cancer. A dose–response meta-analysis could not be conducted in the CUP, as most studies did not provide the required information.

Evidence for cancers of the following types was discussed in the CUP but was too limited to draw a conclusion:¹ lung (people who smoke or used to smoke; 2017); breast (pre and postmenopause; 2017); and endometrium (2013).

The evidence on eating foods containing isoflavones and the risk of cancer that was graded by the Panel as ‘limited – suggestive’ is described in the following subsections.

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.

¹ ‘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.

5.10.1 Lung (people who have never smoked tobacco)

(Also see CUP lung cancer report 2017: Section 7.8 and CUP lung cancer SLR 2015: Section 5.8.)

The evidence for dietary isoflavones and the risk of lung cancer, stratified by tobacco smoking, is presented in the following subsections. No studies on serum isoflavones were identified. For information on dietary isoflavones (not stratified by tobacco smoking), see CUP lung cancer SLR 2015, Section 5.8.

5.10.1.1 CUP highest versus lowest meta-analysis stratified by tobacco smoking

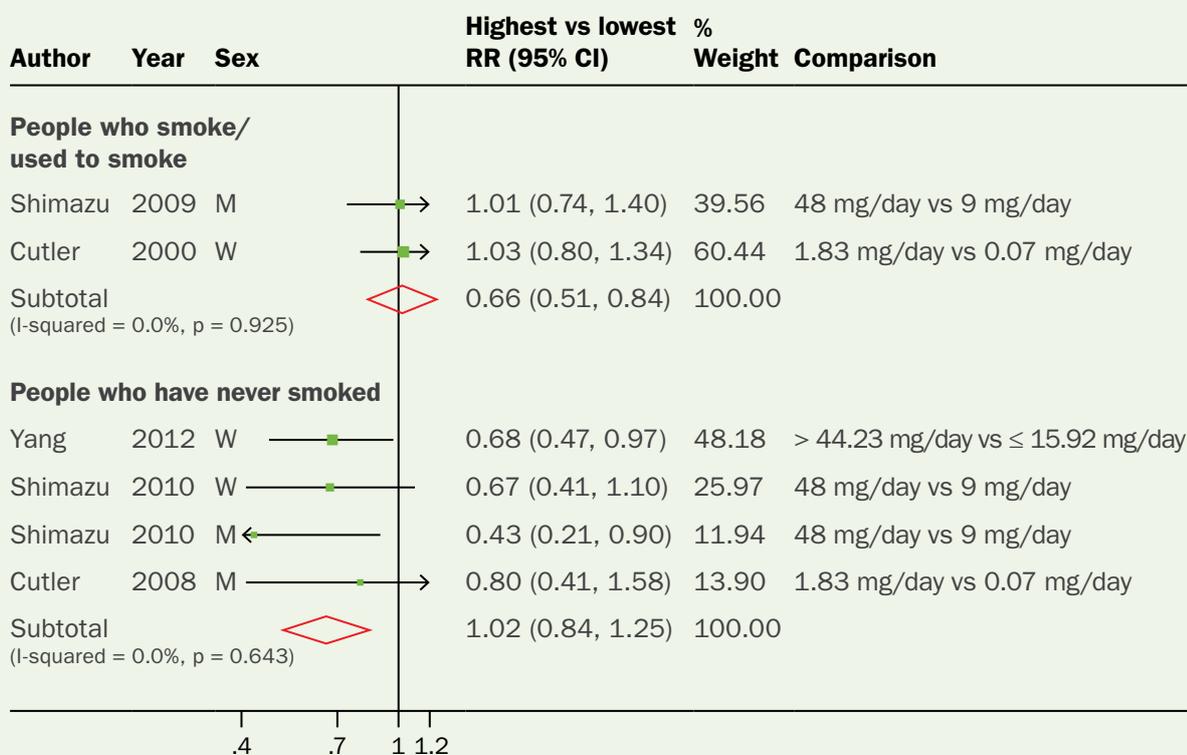
Three of four identified studies reporting results on people who have never smoked were included in a highest versus lowest meta-

analysis stratified by tobacco smoking, which showed a statistically significant decreased risk of lung cancer in people who have never smoked for the highest compared with the lowest level of dietary isoflavones consumed (RR 0.66 [95% CI 0.51–0.84]; n = 714 cases) (see **Figure 5.30**).

No significant association was observed between the risk of lung cancer and dietary isoflavone intake in people who have ever smoked (RR 1.02 [95% CI 0.84–1.25]; n = 1,054).

All studies included in the highest versus lowest meta-analysis adjusted for age and some adjusted for BMI, alcohol consumption and other dietary factors. For information on the *adjustments* made in individual studies, see CUP lung cancer SLR 2015, Table 219.

Figure 5.30: CUP highest versus lowest meta-analysis¹ for dietary isoflavone intake and the risk of lung cancer stratified by tobacco smoking



Source: Yang, 2012 [270]; Shimazu, 2010 [271]; Cutler, 2008 [272].

¹ A total of three studies reporting on people who have never smoked were analysed in the CUP highest versus lowest meta-analysis. In one study, the relative risk for men and women was reported separately.

5.10.1.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. Two other published meta-analyses of cohort and *case-control studies* on consumption of dietary isoflavones and the risk of lung cancer have been identified. Both analyses reported a statistically significant decreased risk when comparing the highest with the lowest levels of dietary isoflavone intake (RR 0.63 [95% CI 0.45–0.90] and RR 0.80 [95% CI 0.71–0.89], respectively) [270, 273]. However, the dose–response meta-analysis for one [273] was not significant.

5.10.1.3 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 are currently prevailing 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](#).

Isoflavones, including genistein and daidzein, are mainly found in soy and soy products and share structural similarity with the steroid *hormone* 17-beta oestradiol. They have a high affinity for the beta-isoform of the *oestrogen* receptor and act as both oestrogen agonists and antagonists. The role of oestrogen signalling in lung cancer is not understood, though there is evidence from observational studies and clinical trials supporting a link between use of exogenous oestrogens and higher risk of lung cancer [274]. Oestrogen receptors are expressed in healthy lung tissue and in lung tumours [275], and oestrogen induces proliferation of NSCLC cells [276].

In addition, genistein is reported to be a protein tyrosine kinase (PTK) inhibitor and has been shown to inhibit EGFR PTK activity *in vitro* and growth of NSCLC *cell lines*, particularly those with mutated EGFR [277, 278].

5.10.1.4 CUP Panel's conclusion

The evidence for consumption of foods containing isoflavones and the risk of lung cancer was limited but generally consistent. When stratified by tobacco smoking, a statistically significant decreased risk was observed for the highest compared with the lowest level of intake in people who have never smoked, but not in people who smoke or those who used to smoke. There is evidence of plausible mechanisms in humans.

The CUP Panel concluded:

- **The evidence suggesting that greater consumption of foods containing isoflavones decreases the risk of lung cancer in people who have never smoked tobacco is limited.**

5.11 Other

The effect of other foods of plant origin and their constituents on the risk of cancer was evaluated, as well as those that were graded by the Panel as ‘limited – suggestive’, ‘probable’, ‘convincing’ or ‘substantial effect on risk unlikely’. These included pulses (legumes), garlic and dietary and serum folate. However, data were either of too low quality or too inconsistent, or the number of studies too few, to allow conclusions to be reached.

6. Comparison with the 2007 Second Expert Report

In 2007, there was strong evidence that consuming foods containing dietary fibre is protective against colorectal cancer. This evidence has stayed strong and there is now also strong evidence that consuming wholegrains also protects against this cancer. The evidence that consuming foods contaminated with aflatoxins is a cause of liver cancer has remained strong.

In 2007 there was strong evidence that consuming non-starchy vegetables, fruit and some of their constituents reduces the risk of several cancers. This evidence has weakened for specific cancers due to more evidence from cohort studies being available and also more analyses of tobacco smoking. The Panel gave more weight to evidence in people who had never smoked and considered that the decreased risk observed in people who smoke may be due to residual confounding. However, the pattern of association and the direction of effect across cancers are consistent, and overall the evidence of a protective effect is more persuasive than for specific cancers. Overall the Panel judged that greater consumption of non-starchy vegetables and/or fruit probably protects against a number of aerodigestive cancers and some other cancers. There is also new evidence emerging that the greatest risk is for people who consume no or low amounts of non-starchy vegetables or fruit.



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Abbreviations

AFB₁	Aflatoxin B ₁
AFM₁	Aflatoxin M ₁
AICR	American Institute for Cancer Research
CCNFSDU	Codex Committee on Nutrition and Foods for Special Dietary Uses
CI	Confidence interval
CUP	Continuous Update Project
DNA	Deoxyribonucleic acid
EGFR	Epidermal growth factor receptor
EPIC	European Prospective Investigation into Cancer and Nutrition
ER-negative	Oestrogen-receptor-negative
ER-positive	Oestrogen-receptor-positive
<i>H. pylori</i>	<i>Helicobacter pylori</i>
HBsAg	Hepatitis B surface antigen
HPV	Human papilloma viruses
MHT	Menopausal hormone therapy
NSCLC	Non-small-cell lung cancer
PR-negative	Progesterone-receptor-negative
PR-positive	Progesterone-receptor-positive
PTK	Protein tyrosine kinase
RR	Relative risk
SCLC	Small-cell lung cancer
SLR	Systematic literature review
WCRF	World Cancer Research Fund

Glossary

Absorption

The movement of nutrients and other food constituents from the gut into the blood.

Adenocarcinoma

Cancer of glandular epithelial cells.

Adenosquamous carcinoma

A type of cancer that contains two types of cells: squamous cells (thin, flat cells that line certain organs) and gland-like cells.

Adipose tissue

Body fat. Tissue comprising mainly cells containing triglyceride (adipocytes). It acts as an energy reserve, provides insulation and protection, and secretes metabolically active hormones.

Adjustment

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

Aflatoxins

Naturally occurring mycotoxins that are produced by many species of *Aspergillus*, a fungus, most notably *Aspergillus flavus* and *Aspergillus parasiticus*. Aflatoxins are toxic and carcinogenic to animals, including humans.

Alpha-tocopherol

A form of vitamin E.

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.

Bias

In epidemiology, consistent deviation of an observed result from the true value in a particular direction (systematic error) due to factors pertaining to the observer or to the study type or analysis (see **selection bias**).

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.

Biomarker

A naturally occurring molecule, gene or characteristic by which a particular pathological or physiological process can be identified.

Body mass index (BMI)

Body weight expressed in kilograms divided by the square of height expressed in metres (BMI = kg/m²). Provides an indirect measure of body fatness.

Caecum

A pouch connected to the junction of the small and large intestines.

Carbohydrate polymer

Macromolecules comprised of two or more monomeric sugar units bound together by glycosidic linkages.

Carcinogen

Any substance or agent capable of causing cancer.

Carcinogenesis

The process by which a malignant tumour is formed.

Cardia stomach cancer

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

Carotenoids

A diverse class of compounds providing colour to many plants. Carotenoids are often classified in two groups: as those providing the host with vitamin A, such as beta-carotene, and the non-pro-vitamin A carotenoids, such as lycopene, which provides the familiar red colour of tomatoes.

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.

Cell line

A cell culture developed from a single cell and therefore consisting of cells with a uniform genetic make-up.

Cell proliferation

An increase in the number of cells as a result of increased cell division.

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.

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.

Colon

Part of the large intestine extending from the caecum to the rectum.

Confidence interval (CI)

A measure of the uncertainty in an estimate, usually reported as 95% confidence interval (CI), which is the range of values within which there is a 95% chance that the true value lies. For example, the association of tobacco smoking and relative risk of lung cancer may be expressed as 10 (95% CI 5–15). This means that the estimate of the relative risk was calculated as 10 and that there is a 95% chance that the true value lies between 5 and 15.

Confounder/confounding factors

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

Deoxyribonucleic acid (DNA)

The double-stranded, helical molecular chain found within the nucleus of each cell, which carries the genetic information.

Diet, nutrition and physical activity

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

Dietary fibre

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

Dose–response

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

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.

Endogenous

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

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.

Fatty acid

A carboxylic acid with a carbon chain of varying length, which may be saturated (no double bonds) or unsaturated (one or more double bonds). Three fatty acids attached to a glycerol backbone make up a triglyceride, the usual form of fat in food and adipose tissue.

Flavonoids

Flavonoids are bioactive compounds that are found naturally in fruits and vegetables, as well as other dietary sources such as tea (*Camellia sinensis*).

Free radicals

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

Genotoxic

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

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 I² test.

High-income countries

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

Hormone

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

Hormone receptor status

Hormone receptors are proteins found in and on breast or other cells that respond to circulating hormones and influence cell structure or function. A cancer is called oestrogen-receptor-positive (ER+) if it has receptors for oestrogen, and oestrogen-receptor-negative (ER-) if it does not have the receptors for oestrogen.

Hyperplasia

An increase in the number of cells in a tissue.

In vitro

Processes that occur outside the body, in a laboratory apparatus.

Insulin

A protein hormone secreted by the pancreas that promotes the uptake and utilisation of glucose, particularly in the liver and muscles. Inadequate secretion of, or tissue response to, insulin leads to diabetes mellitus.

Insulin resistance

A pathological condition in which cells fail to respond normally to the hormone insulin.

Isoflavones

Constituent of plants with oestrogen-like properties.

Lipid peroxidation

The oxidative degradation of lipids. It is the process in which free radicals 'steal' electrons from the lipids in cell membranes, resulting in cell damage.

Low-income countries

As defined by the World Bank, countries with an average annual gross national income per capita of US\$1,005 or less in 2016. This term is more precise than and used in preference to 'economically developing countries'.

Menarche

The start of menstruation.

Menopausal hormone therapy (MHT)

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

Menopause

The cessation of menstruation.

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.

Monomeric unit

A molecule that can combine with others of the same kind to form a polymer. Glucose molecules, for example, are monomeric units that can combine to form the polymer cellulose.

Mucinous carcinoma

A type of cancer that begins in cells that line certain internal organs and produce mucin (the main component of mucus).

Mutation

A permanent change in the nucleotide sequence of the genome (an organism's complete set of DNA).

Mycotoxins

Naturally occurring toxins produced by fungi, which grow on a variety of crops and foods, often under warm and humid conditions. They can cause a number of acute and chronic illnesses in humans and other animals.

N-nitroso compound

A substance that may be present in foods treated with sodium nitrate, particularly processed meat and fish. It may also be formed endogenously, for example, from haem and dietary sources of nitrate and nitrite. N-nitroso compounds are known carcinogens.

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.

Nutrient

A substance present in food and required by the body for maintenance of normal structure and function, and for growth and development.

Obesity

Excess body fat to a degree that increases the risk of various diseases. Conventionally defined as a BMI of 30 kg/m² or more. Different cut-off points have been proposed for specific populations.

Oestrogen

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

Oligosaccharide

A compound comprising between 3 and 10 simple sugar molecules (monosaccharides).

p53

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

Phenotype

The observable characteristics displayed by an organism; depends on both the genotype (the genetic makeup of a cell) and environmental factors.

Phytochemicals

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

Polymorphisms

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

Pooled analysis

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

Prevalence

The total number of individuals who have a characteristic, disease or health condition at a specific time, related to the size of the population, for example, expressed as a percentage of the population.

Progesterone

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

Randomised controlled trial (RCT)

A study in which a comparison is made between one intervention (often a treatment or prevention strategy) and another (control). Sometimes the control group receives an inactive agent (a placebo). Groups are randomised to one intervention or the other, so that any difference in outcome between the two groups can be ascribed with confidence to the intervention. Sometimes, neither investigators nor subjects know to which intervention they have been randomised; this is called 'double-blinding'.

Reactive oxygen species (ROS)

Oxygen-containing radical species or reactive ions that can oxidise DNA (remove electrons), for example, hydroxyl radical (OH⁻), hydrogen peroxide (H₂O₂) or superoxide radical (O²⁻).

Relative risk (RR)

The ratio of the rate of an outcome (for example, disease (incidence) or death (mortality)) among people exposed to a factor, to the rate among the unexposed, usually used in cohort studies.

Selection bias

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

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.

Tumorigenesis

The process of tumour development.

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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). 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.

Wholegrains

Colorectum

Wholegrains provide various nutrients including vitamin E, selenium, copper, zinc and bioactive non-nutrient compounds such as lignans, phytoestrogens and phenolic compounds as well as dietary fibre. Many of these compounds, which are largely found in the bran and germ of the grain, have plausible anti-carcinogenic properties. For instance, several phenolic acids have been shown in experimental studies to stimulate anti-oxidative activity [91, 92]. Alkylresorcinols, which are *biomarkers* of wholegrain wheat and rye intake, were shown to be inversely related to colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) [93]. Wholegrains may also protect against colorectal cancer by binding *carcinogens* and regulating glycaemic response.

Foods containing dietary fibre

Colorectum

In humans, different types of fibre can, to varying degrees, be fermented or metabolised by the colonic microflora, and this can influence the types and patterns of bacterial populations found in the *colon*. Microbial fermentation within the large bowel forms short-chain *fatty acids*, such as butyrate, that have been shown in experimental studies to have anti-proliferative effects for colon cancer cells [91, 107]. Other mechanisms by which greater dietary fibre intake may lower colorectal cancer risk include the reduction of intestinal transit time and increased faecal bulk, which would lessen the potential for faecal mutagens to interact with the colon mucosa, and a reduction of secondary bile acid production [91, 107]. High-fibre diets may also reduce *insulin resistance*, which is a risk factor for colorectal cancer [108]. Overall there is moderate mechanistic evidence linking dietary fibre intake with a reduced risk of colorectal cancer.

Aflatoxins

Liver

Aflatoxin, and specifically aflatoxin B₁, is a *mycotoxin* produced by moulds of the *Aspergillus* species, which contaminates many food crops stored in warm and moist conditions, a problem most evident in areas of Africa and Asia. Aflatoxin B₁ is metabolised in the liver by members of the cytochrome P450 family, specifically CYP3A4 and CYP3A5, to its reactive intermediate, 8,9-exo-epoxide, which can form aflatoxin-N⁷-guanine adducts. The products of aflatoxin biotransformation in the liver are known to be highly *genotoxic* to the organ [120], and *hepatocellular carcinomas* from regions with high exposure to aflatoxin tend to bear a high *mutation* load in TP53 characteristic of aflatoxin adduct formation [121–123].

Non-starchy vegetables

Greater intake

Mouth, pharynx and larynx

Vegetables comprise a diverse group of foods, and their consumption provides exposure to a wide array of *nutrients* and *phytochemicals*. Although there is a substantial body of evidence demonstrating potential anti-tumorigenic effects of many components found in vegetables, including *carotenoids*; vitamins A, C, and E; selenium; phenolic acids; *flavonoids*; and glucosinolates, in a range of different tissue types, experimental models of *de novo carcinogenesis* of the oral, oropharyngeal, pharyngeal and laryngeal mucosa are limited. Thus, the number of studies of the effects of vegetables or extracts or specific phytochemicals on these tissues remains modest. This approach is complemented by studies of *tumorigenesis* using transplantable models that employ human *squamous cell carcinoma* cells in immune-deficient mice. In parallel, *in vitro* studies examine how specific substances affect various aspects of carcinogenesis and cancer cell growth [128]. Human *randomised controlled trials* of vegetable intake or components from vegetables are few and limited in size and often focus on *biomarkers* or premalignant oral conditions, such as leukoplakia [129]. It is likely that the epidemiological relationships between vegetables and reduced risk of cancers of the mouth, pharynx and larynx are mediated by multiple components that are themselves mediated by a range of mechanisms [130]. Future studies focusing on how diets rich in vegetables or specific vegetables and their unique phytochemicals may affect cancers of the mouth, pharynx and larynx are necessary.

Nasopharynx

Fruit and non-starchy vegetables contain a large number of potential anti-tumorigenic agents, such as dietary fibre, *carotenoids*, vitamins C and E, selenium, dithiolthiones, glucosinolates and indoles, isothiocyanates, *flavonoids*, phenols, protease inhibitors, plant sterols, allium compounds and limonene [131]. It is likely that a combination of these *nutrients* is responsible for the lower risk of nasopharyngeal cancer that has been observed among high consumers of fruit and non-starchy vegetables.

Oesophagus (adenocarcinoma/squamous cell carcinoma)

Fruit and non-starchy vegetables contain a large number of potential anti-tumorigenic agents, such as dietary fibre, *carotenoids*, vitamins C and E, selenium, dithiolthiones, glucosinolates and indoles, isothiocyanates, *flavonoids*, phenols, protease inhibitors, plant sterols, allium compounds and limonene [131]. It is likely that a combination of these *nutrients* is responsible for the lower risk of oesophageal cancer that has been observed among high consumers of fruit and non-starchy vegetables.

Lung (people who smoke/used to smoke tobacco)

Vegetables comprise a diverse group of foods, and their consumption provides exposure to a wide array of *phytochemicals*. Although there is a substantial body of evidence demonstrating potential anti-tumorigenic effects of many agents found in vegetables, including *carotenoids*; vitamins A, C, and E; selenium; phenolic acids; *flavonoids*; and glucosinolates, among others, in a range of different tissue types, experimental models of de novo *carcinogenesis* of the lung are limited. Thus, the number of studies of the effects of vegetables or extracts or specific phytochemicals on lung tissue remain modest. It is likely that the epidemiological relationships between vegetables and reduced risk of lung cancer are mediated by multiple components and through a range of mechanisms. Vegetables are a source of carotenoids, and there are suggestive epidemiologic and mechanistic data linking their intake to lower risk of lung cancer, see **Section 5.7.1**. Future studies focusing on how diets rich in vegetables or specific vegetables and their unique phytochemicals may affect lung cancer development are warranted.

Breast (oestrogen receptor-negative)

Vegetables are a source of many *nutrients* and thus may increase levels of pro-vitamin A *carotenoids*, vitamins C and E, folate, selenium, and other nutrients that are hypothesised to affect the risk of certain cancers. Plants also provide a source of fibre in the diet, which may affect the colonic microbiota and host metabolism to alter cancer risk. Plants are also a rich source of chemical substances collectively referred to as *phytochemicals*. Many of these compounds are used by the plants as part of their hormonal environment and protect the plant from stress due to heat, cold, sunlight, infections and predators in addition to playing a role in reproduction. We now appreciate that many phytochemicals have potential anti-carcinogenic and anti-tumorigenic properties. These include many classes of compounds, such as dithiolthiones, glucosinolates and indoles, isothiocyanates, *flavonoids*, phenols, protease inhibitors, plant sterols, allium compounds and limonene [131]. A possible protective effect of *bioactive constituents* in vegetables may be more detectable in the less hormonally dependent ER-negative tumours than in ER-positive tumours, where a dominant effect of oestrogens might obscure a smaller effect on risk from vegetables. EGFR tends to be overexpressed in ER-negative breast tumours, and some phytochemicals found in vegetables have been suggested to reduce the level of EGFR, which may, in turn, reduce the risk of developing ER-negative breast cancer [149].

Greater intake (vegetables and fruit combined)

Bladder

Fruit and vegetables contain a large number of potential anti-tumorigenic agents, such as dietary fibre, *carotenoids*, vitamins C and E, selenium, dithiolthiones, glucosinolates and indoles, isothiocyanates, *flavonoids*, phenols, protease inhibitors, plant sterols, allium compounds and limonene [131]. It is likely that a combination of these *nutrients* is responsible for a lower risk of bladder cancer being associated with greater consumption of fruit and vegetables. A better understanding of the exact mechanisms is required.

Low intake

Colorectum

Vegetables are a diverse group of foods, and consumption of vegetables provides a large number of potential anti-carcinogenic *nutrients* and bioactive *phytochemicals*, such as dietary fibre, *carotenoids*, vitamins C and E, selenium, folate, dithiolthiones, glucosinolates and indoles, isothiocyanates, *flavonoids*, phenols, protease inhibitors, plant sterols, allium compounds and limonene [131]. A substantial body of experimental data exists linking many of these compounds with anticancer activity in colorectal cancer cells in both animal and *in vitro* models [159]. However, robust evidence from human studies supporting a relationship between specific vegetables and compounds found within vegetables and colorectal cancer is currently lacking. It is possible that a combination of these nutrients is responsible for the lower risk of colorectal cancer associated with vegetable consumption. Mechanistic evidence supporting the inverse relationship between vegetables and colorectal cancer is moderate in strength.

Foods preserved by salting (including preserved non-starchy vegetables)

Stomach

Animal models have shown that high salt levels alter the viscosity of the mucus protecting the stomach and enhance the formation of *N-nitroso compounds* [176]. In addition, high salt intake may stimulate the colonization of *H. pylori*, the strongest known risk factor for stomach cancer [177]. Finally, in animal models, high salt levels have been shown to be responsible for the primary cellular damage that results in the promotion of stomach cancer development [178].

Preserved non-starchy vegetables

Nasopharynx

Preserved vegetables contain high levels of salt, which has been shown in animal models to alter the mucus viscosity and enhance the formation of *carcinogenic nitrosamines* and related *N-nitroso compounds* [176]. The role of nitrosamines and/or nitrosamine metabolism in the development of nasopharynx cancer has been demonstrated in a small tissue-level gene expression study [279].

Fruit

Greater intake

Oesophagus (squamous cell carcinoma)

Fruit and non-starchy vegetables contain a large number of potential anti-tumorigenic agents, such as dietary fibre, *carotenoids*, vitamins C and E, selenium, dithiolthiones, glucosinolates and indoles, isothiocyanates, *flavonoids*, phenols, protease inhibitors, plant sterols, allium compounds and limonene [131]. It is likely that a combination of these *nutrients* is responsible for the lower risk of oesophageal cancer that has been observed among high consumers of fruit and non-starchy vegetables.

Lung (people who smoke/used to smoke tobacco)

Fruit are a source of vitamins C and E as well as numerous *bioactive compounds* that may have anti-tumorigenic potential, including *carotenoids*, *flavonoids* and polyphenols. Many of these compounds have anti-oxidative properties that could inhibit cellular damage and exposure to *reactive oxygen species*. Some fruit are a source of carotenoids, and there are suggestive epidemiologic and mechanistic data linking their intake to lower risk of lung cancer, see **Section 5.7.1**. Future studies focusing on how diets rich in fruit or specific fruits and their unique *phytochemicals* may affect lung cancer development are warranted.

Greater intake (citrus fruit)

Stomach (cardia)

Citrus fruit contain a large number of potential anti-tumorigenic agents, such as dietary fibre, *carotenoids*, vitamin C, *flavonoids* and folate [131]. It is likely that a combination of these *nutrients* is responsible for a lower *cardia stomach cancer* being associated with greater consumption of citrus fruit. A better understanding of the exact mechanisms is required.

Low intake

Stomach

Fruit contains a multiple potential anti-tumorigenic agents, such as dietary fibre, folate, *carotenoids*, vitamins C and E, selenium, *flavonoids*, phenols and limonene [131]. For example, vitamins C and E can act as *antioxidants* by donating electrons to *free radicals*, which can block their damaging activity. Several other plant-derived compounds (*phytochemicals*) display antioxidant activity in laboratory experiments. It is likely that a combination of these *nutrients* is responsible for any relationship between low fruit intake and stomach cancer.

Colorectum

In addition to their fibre content, fruit are a source of vitamins C and E as well as numerous *bioactive compounds* that may have anti-tumorigenic potential. These include folate, *flavonoids*, polyphenols and limonene. Many of these compounds have anti-oxidative properties that could inhibit cellular damage and exposure to *reactive oxygen species* [187].

Foods containing carotenoids

Lung

A number of human studies and *meta-analyses* have shown that higher circulating levels of *carotenoids*, including beta-carotene, lycopene and beta-cryptoxanthin, are associated with lower risk of lung cancer [202]. Further, evidence from both animal and laboratory studies has shown that *carotenoids* can block certain carcinogenic processes and inhibit tumour cell growth [203, 204]. Some proposed mechanisms for these actions include (1) functioning as an *antioxidant* [203, 205]; (2) acting as a precursor for retinoic acid [206, 207]; (3) enhancing immunologic function [208, 209]; (4) inducing *carcinogen*-metabolising enzymes [210]; (5) inhibiting *cell proliferation*; and (6) inducing *apoptosis*.

Breast

Carotenoids may act as *antioxidants* by quenching *free radicals* and protecting against macromolecular damage, including DNA damage [219, 220]. Carotenoids such as beta-carotene may have direct effects on cell signaling as well, such as reducing *cell proliferation* and inducing *apoptosis* [221, 222]. Circulating concentrations of carotenoids are also used in epidemiologic and clinical studies as *biomarkers* of intake of fruit and vegetables, which contain an array of *bioactive compounds*, including fibre, *flavonoids* and other antioxidants, and these may act synergistically to reduce breast cancer risk [215]. Alpha-carotene, beta-carotene and beta-cryptoxanthin may decrease cancer risk indirectly through their metabolism to vitamin A (retinol), which in turn regulates cell growth, differentiation and apoptosis through direct and indirect effects on gene expression [188]. Carotenoids may also be directly anticarcinogenic by several other mechanisms, including enhanced immune system functioning. Experimental evidence has also shown some carotenoids can inhibit the growth of both ER-positive and ER-negative breast cancer *cell lines*, and it is possible that an effect of carotenoids on ER-positive tumours is masked by the *hormone-related* associations that dominate as risk factors for ER-positive tumours [188].

Foods containing beta-carotene

Lung

A number of human studies and *meta-analyses* have shown that higher circulating levels of *carotenoids*, including beta-carotene, lycopene, and beta-cryptoxanthin, are associated with lower risk of lung cancer [202]. A number of human studies and *meta-analyses* have shown that higher circulating levels of beta-carotene are associated with a lower risk of lung cancer [202]. Further, evidence from both animal and laboratory studies has shown that carotenoids can block certain carcinogenic processes and inhibit tumour cell growth [203, 204]. Some proposed mechanisms for these actions include (1) functioning as an *antioxidant* [205, 233]; (2) acting as a precursor for retinoic acid [206, 207]; (3) enhancing immunologic function [208, 209]; (4) inducing *carcinogen-metabolising* enzymes [210]; (5) inhibiting *cell proliferation*; and (6) inducing *apoptosis*.

Prostate

No mechanisms are presented.

Foods containing vitamin C

Lung (people who smoke tobacco)

Vitamin C is a potent antioxidant, reducing levels of *reactive oxygen species*, inhibiting *lipid peroxidation* and reducing nitrates [187]. Vitamin C has also been shown to inhibit the formation of *carcinogens* in experimental models and to protect DNA from mutagenic insults [264].

Colorectum (colon)

There is biological plausibility to support a protective effect of vitamin C on colorectal cancer development. Vitamin C is a potent antioxidant, reducing levels of *reactive oxygen species*, inhibiting *lipid peroxidation* and reducing nitrates [187]. Vitamin C has also been shown to inhibit the formation of *carcinogens* in experimental models and to protect DNA from mutagenic insults [264].

Foods containing isoflavones

Lung (people who have never smoked)

Isoflavones, including genistein and daidzein, are mainly found in soy and soy products and share structural similarity with the steroid *hormone* 17-beta oestradiol. They have a high affinity for the beta-isoform of the *oestrogen* receptor and act as both *oestrogen* agonists and antagonists. The role of *oestrogen* signaling in lung cancer is not understood, though there is evidence from observational studies and clinical trials supporting a link between use of exogenous *oestrogens* and higher risk of lung cancer [274]. *Oestrogen* receptors are expressed in healthy lung tissue and in lung tumours [275], and *oestrogen* induces proliferation of NSCLC cells [276]. In addition, genistein is reported to be a PTK inhibitor and has been shown to inhibit EGFR PTK activity *in vitro* and the growth of NSCLC *cell lines*, particularly those with mutated EGFR [277], [278].

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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