Other dietary exposures
and the risk of cancer

2018

Contents

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. Other dietary exposures 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 other dietary exposures affect 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].

The nature, quantity and proportion of different foods and drinks in diets, and the frequency with which they are consumed, constitute dietary patterns. The impact of diet and nutrition on health is generally determined by dietary patterns coupled with physical activity and other factors, in relation to people's particular nutritional needs, rather than individual foods and drinks or specific dietary constituents. However, dietary patterns are difficult to characterise and are rarely a focus of epidemiological and experimental investigations. Specific foods and dietary components are more commonly addressed. Where possible this Third Expert Report has focussed on food and drinks; evidence for individual *macronutrients* and *micronutrients* is also considered within this section.

Carbohydrates, fats and proteins are macronutrients that supply *energy* and are essential for tissue structure and function as well as physical and mental growth and development. These macronutrients can be subdivided into monosaccharides (such as glucose) and polysaccharides (such as starch) for carbohydrates; saturated, unsaturated and trans fatty acids for fats; and amino acids for proteins. These constituent parts have different metabolic, physiological and biochemical effects, alone or in combination. Glycaemic index and glycaemic load are terms used to characterise foods and diets based on their effects on blood glucose levels.

A series of substances that do not supply energy have been identified as also being vital to life, typically in small amounts: these are vitamins, minerals and trace elements. As well as being contained in foods, these micronutrients are also available as supplements (usually in pill or powder form), and some are consumed in doses far in excess of what could be absorbed from food in any typical diet.

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.

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[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.

Findings

There is **strong evidence** that consuming:

- **greater glycaemic load of the diet increases** the risk of endometrial cancer.

- **consuming high-dose beta-carotene supplements increases** the risk of lung cancer (in people who smoke or used to smoke tobacco).

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

- **consuming beta-carotene in supplements is unlikely** to have substantial effect on the risk of skin cancer (non-melanoma).

- **consuming calcium supplements decreases** the risk of colorectal cancer.

The evidence shows that, in general, the greater the glycaemic load in a person's diet, the higher the risk of endometrial cancer. For high-dose beta-carotene supplements and calcium supplements, conclusions can be drawn only for the doses that were investigated.

The Panel used the strong evidence on supplements and glycaemic load when making Recommendations (see below) designed to reduce the risk of developing cancer.

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

Recommendations

Our Cancer Prevention Recommendations – for preventing cancer in general – include maintaining a healthy weight, being physically active and eating a healthy diet. It is best to eat a healthy diet rather than rely on dietary supplements to protect against cancer. 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
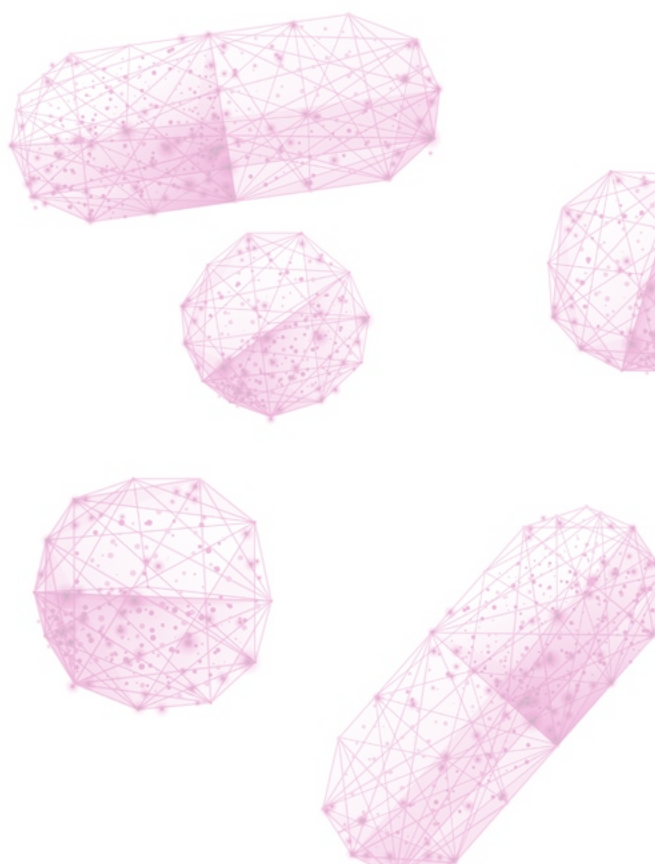
1. Other dietary exposures and the risk of cancer: a summary matrix

OTHER DIETARY EXPOSURES AND THE RISK OF CANCER					
WCRF/AICR GRADING		**DECREASES RISK**		**INCREASES RISK**	
		Exposure	**Cancer site**	**Exposure**	**Cancer site**
STRONG EVIDENCE	**Convincing**			High-dose beta-carotene supplements	Lung (in people who smoke or used to smoke tobacco) 2017[1]
	Probable	Calcium supplements	Colorectum 2017[2]	Glycaemic load[3]	Endometrium 2013
LIMITED EVIDENCE	**Limited – suggestive**	Healthy dietary patterns[4]	Mouth, pharynx and larynx 2018	Foods and drinks containing fructose[5]	Pancreas 2012
		Foods containing retinol	Lung 2017[6]	Foods containing saturated fatty acids	Pancreas 2012
		Vitamin D	Colorectum 2017[7]	Low plasma alpha-tocopherol concentrations	Prostate 2014
		Foods containing beta-carotene	Lung 2017[8]	Low plasma selenium concentrations	Prostate 2014
		Multivitamin supplements[9]	Colorectum 2017		
STRONG EVIDENCE	**Substantial effect on risk unlikely**	Beta-carotene: Prostate 2014[10] High-dose beta-carotene supplements: Skin (non-melanoma) 2017[11]			

1 The evidence for high-dose beta-carotene supplements and lung cancer (in people who smoke or used to smoke tobacco) is derived from studies using high-dose supplements (20 to 30 milligrams per day or 50 milligrams per day on alternate days for beta-carotene; 25,000 international units per day for retinol).

2 The evidence for calcium supplements and colorectal cancer is derived from studies using supplements at a dose >200 milligrams per day.

3 The glycaemic load of a food may be calculated by multiplying the glycaemic index of a food, expressed as a percentage, by the number of grams of carbohydrate in a serving of the food.

4 Judgements relate to healthy dietary patterns as marked by greater healthy dietary indices. These indices produce an integrated score to assess adherence to healthy eating or lifestyle recommendations or patterns. They are characterised by factors such as healthy weight management; engagement in physical activity; limiting intake of foods and drinks that promote weight gain; limiting intake of red and processed meat; limiting intake of alcoholic drinks; and a higher intake of wholegrains, vegetables and fruit.

5 The evidence for food and drinks containing fructose and pancreatic cancer includes both foods naturally containing fructose and foods that have had fructose added during preparation or processing.

6 The evidence for foods containing retinol and lung cancer is derived from studies on dietary intake and serum or plasma levels.

7 The evidence for vitamin D and colorectal cancer is derived from studies on dietary intake, supplements and serum or plasma levels.

8 The evidence for beta-carotene and lung cancer is derived from studies on dietary intake and serum levels.

9 Definitions and categorisation of multivitamin supplements are not standardised across studies.

10 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 high-dose supplement use (20, 30 and 50 milligrams per day).

11 The evidence for beta-carotene and non-melanoma skin cancer is derived from one study on plasma levels, as well as studies on high-dose supplement use (50 milligrams per day and 50 milligrams per day on alternate days).

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 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.
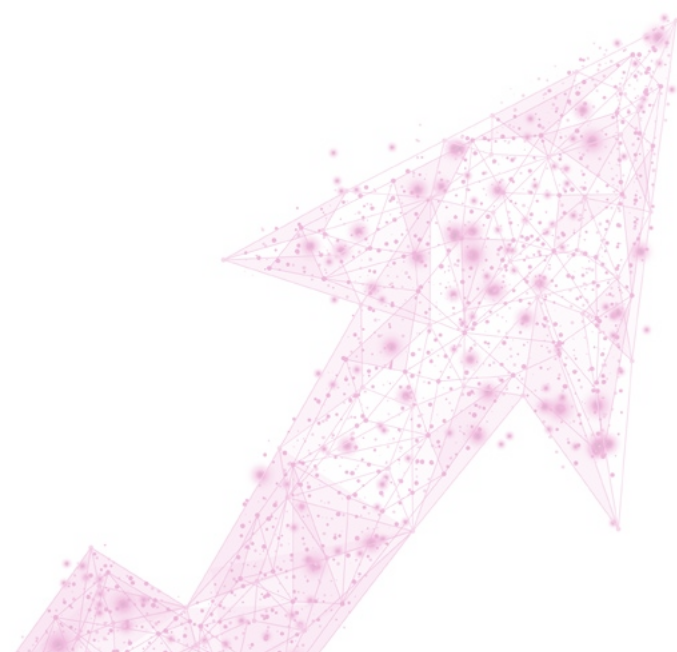
2. Summary of Panel judgements

The conclusions drawn by the CUP Panel are based on the evidence from both epidemiological and mechanistic studies relating specific other dietary exposures to the risk of development of particular cancer types. Each conclusion on the likely causal relationship between other dietary exposures and a cancer forms a part of the overall body of evidence that is considered during the process of making Cancer Prevention Recommendations. Any single conclusion does not represent a recommendation in its own right. The Cancer Prevention Recommendations are based on a synthesis of all these separate conclusions, as well as other relevant evidence, and can be found at the end of this Third Expert Report.

The CUP Panel concluded:

STRONG EVIDENCE

Convincing
- **Increased risk**
  - **High-dose beta-carotene supplements:** Consumption of high-dose beta-carotene supplements is a convincing cause of lung cancer (in people who smoke or used to smoke tobacco).[1]

Probable
- **Decreased risk**
  - **Calcium supplements:** Consumption of calcium supplements probably protects against colorectal cancer.[2]
- **Increased risk**
  - **Glycaemic load:**[3] Greater glycaemic load of the diet is probably a cause of endometrial cancer.

See page 10 for footnotes.

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]
- **High-dose beta-carotene supplements:** Consumption of high-dose beta-carotene supplements is unlikely to have a substantial effect on the risk of skin cancer (non-melanoma).[5]

The evidence shows that, in general, the greater the glycaemic load in a person's diet, the higher the risk of endometrial cancer. For high-dose beta-carotene supplements and calcium supplements, conclusions can be drawn only for the doses that were investigated.

The Panel used the strong evidence on supplements and glycaemic load 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).

LIMITED EVIDENCE

Limited – suggestive

- **Decreased risk**

  - **Healthy dietary patterns:**[6] The evidence suggesting that choosing healthy dietary patterns decreases the risk of cancers of the mouth, pharynx and larynx is limited.

  - **Foods containing retinol:** The evidence suggesting that consumption of foods containing retinol decreases the risk of lung cancer[7] is limited.

  - **Vitamin D:** The evidence suggesting that consumption of vitamin D decreases the risk of colorectal cancer[8] is limited.

  - **Beta-carotene:** The evidence suggesting that consumption of beta-carotene decreases the risk of lung cancer[9] is limited.

  - **Multivitamin supplements:**[10] The evidence suggesting that taking multivitamin supplements decreases the risk of colorectal cancer is limited.

- **Increased risk**

  - **Foods and drinks containing fructose:** The evidence suggesting that consumption of foods and drinks containing fructose increases the risk of pancreatic cancer[11] is limited.

  - **Foods containing saturated fatty acids:** The evidence suggesting that consumption of foods containing saturated fatty acids increases the risk of pancreatic cancer is limited.

  - **Low plasma alpha-tocopherol concentrations:** The evidence suggesting that low plasma alpha-tocopherol concentrations increase the risk of prostate cancer is limited.

  - **Low plasma selenium concentrations:** The evidence suggesting that low plasma selenium concentrations increase the risk of prostate cancer is limited.

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

See Definitions of WCRF/AICR grading criteria (**Section 1**: other dietary exposures 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'.
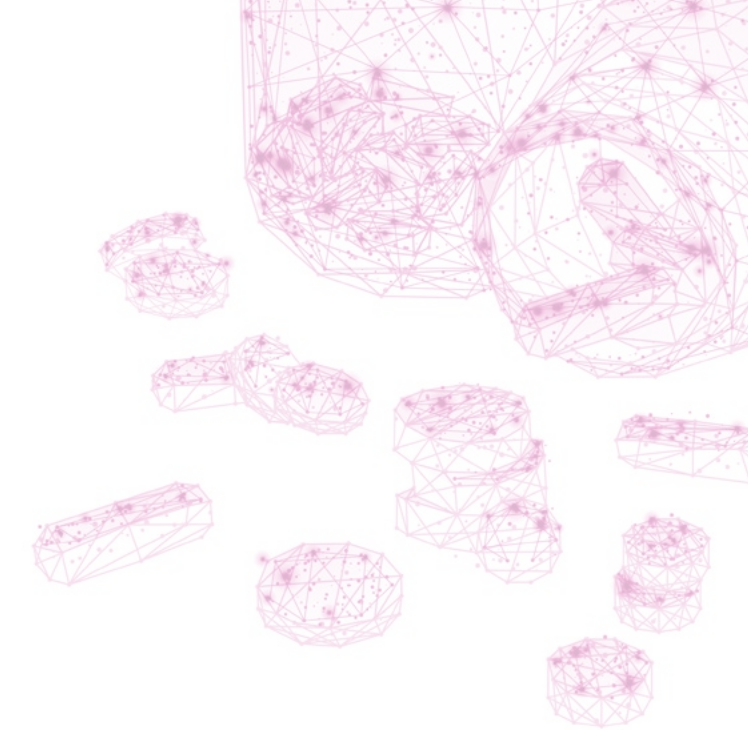
1   The evidence for high-dose beta-carotene supplements and lung cancer (people who smoke/used to smoke tobacco) is derived from studies using high-dose supplements (20 to 30 milligrams per day or 50 milligrams per day on alternate days for beta-carotene; 25,000 international units per day for retinol).

2   The evidence for calcium supplements and colorectal cancer is derived from studies using supplements at a dose >200 milligrams per day.

3   Glycaemic load is the glycaemic index of a food multiplied by the number of grams of carbohydrate in the serving of food.

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 high-dose supplement use (20, 30 and 50 milligrams per day).

5   The evidence for beta-carotene and non-melanoma skin cancer is derived from one study on plasma levels, as well as studies on high-dose supplement use (50 milligrams per day and 50 milligrams per day on alternate days).

6   Judgements relate to healthy dietary patterns as marked by greater healthy dietary indices. These indices produce an integrated score to assess adherence to healthy eating or lifestyle recommendations or patterns. They are characterised by factors such as healthy weight management; engagement in physical activity; limiting intake of foods and drinks that promote weight gain; limiting intake of red and processed meat; limiting intake of alcoholic drinks; and a higher intake of wholegrains, vegetables and fruit.

7   The evidence for foods containing retinol and lung cancer includes evidence from dietary intake and serum or plasma levels.

8   The evidence for vitamin D and colorectal cancer includes evidence from dietary intake, supplements and serum or plasma levels.

9   The evidence for beta-carotene and lung cancer is derived from studies on dietary intake and serum levels.

10   Definitions and categorisation of multivitamin supplements are not standardised across studies.

11   The evidence for food and drinks containing fructose and pancreatic cancer includes both foods naturally containing fructose and foods that have had fructose added during preparation or processing.

3. Definitions and patterns

The nature, quantity and proportion of different foods and drinks in diets, and the frequency with which they are consumed, constitute dietary patterns. The impact of diet and nutrition on health is generally determined by dietary patterns coupled with physical activity and other factors, in relation to people's particular nutritional needs, rather than individual foods and drinks or specific dietary constituents. However, dietary patterns are difficult to characterise and are rarely a focus of epidemiological and experimental investigations. Specific foods and dietary components are more commonly addressed. Where possible this Third Expert Report has focussed on food and drinks, but evidence for individual *macronutrients* and *micronutrients* is also considered within this section.

Carbohydrates, fats and proteins are macronutrients that supply *energy* and are essential for tissue structure and function as well as physical and mental growth and development. These macronutrients can be subdivided into monosaccharides (such as glucose) and polysaccharides (such as starch) for carbohydrates; saturated, unsaturated and trans fatty acids for fats; and amino acids for proteins. These constituent parts have different metabolic, physiological and biochemical effects, alone or in combination. Glycaemic index and glycaemic load are terms used to characterise foods and diets based on their effects on blood glucose levels.

A series of substances that do not supply energy have been identified as also being vital to life, typically in small amounts: these are vitamins, minerals and trace elements. As well as being contained in foods, these micronutrients are also available as supplements (usually in pill or powder form), and some are consumed in doses far in excess of what could be absorbed from food in any typical diet.

3.1 Healthy dietary patterns

People who are conscious of the effects of diet and nutrition on health and well-being, and on the risk of disease, may choose to consume 'healthy' diets. For many people a 'healthy' diet is seen simply as a diet regime designed to reduce excess body fat. However, there are many possible combinations of foods and drinks that combine to make a 'healthy' dietary pattern. There are common characteristics of healthy diets, and different components are often correlated. It can be difficult to unravel the contributions of individual dietary components, but integrating them into a dietary pattern helps to mitigate this problem.

This Third Expert Report covers healthy dietary patterns as described by specific healthy dietary indices. These include the American Cancer Society (ACS) Cancer Prevention Guidelines score [2], the Healthy Eating Index-2005 (HEI-2005) [3], the alternate Mediterranean (aMED) score [4] and the World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) score [5].

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

The HEI-2005 score assesses concordance with 2005 Dietary Guidelines for Americans and includes intakes of plant foods, milk, meat, saturated fat, sodium, *energy* from solid fats,[1] alcohol and added sugar.

The aMed score is a modified Mediterranean Diet score that includes consumption of vegetables (excluding potatoes), pulses (legumes), fruit, nuts, wholegrains, fish, red and processed meat, and alcohol, as well as the ratio of monounsaturated to saturated fat in the diet.

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

3.2 Glycaemic load

The degree to which different foods and meals raise blood glucose depends not only on the nature of the carbohydrate, but also on the characteristics of the foods consumed and the other foods they are consumed with. For general information about carbohydrates, see **Box 1**.

Glycaemic index is a measure of the increase in blood glucose (and *insulin*) after consumption of a standard amount of a food under controlled conditions. The test food must contain the same amount of available carbohydrate (usually 50 grams) as the standard. Glycaemic index was originally used as an aid to food choice for people with diabetes and has more recently been applied for people without diabetes. The rise in blood glucose after consuming a food depends not only on the glycaemic index but also on the amount of food eaten. A related measure, glycaemic load of a food, takes into account

the amount of that food consumed; that of the diet takes into account the calculated aggregate of the glycaemic loads of the foods constituting that diet. The glycaemic load of a food may be measured directly or calculated by multiplying the glycaemic index of a food, expressed as a percentage, by the number of grams of carbohydrate in a serving of the food.

Factors that influence the glycaemic index of a food include the type of carbohydrate, how the food is processed or cooked, and the other *macronutrients* present in the food or meal. In general, low glycaemic index foods tend to be high in fibre, although some foods high in fibre have a high glycaemic index and vice versa. Other factors can affect glycaemic index by influencing speed of *absorption*; for instance, higher fat foods tend to have a low glycaemic index, because fat can slow down absorption. The calculated glycaemic index of a mixed meal or whole diet has been shown in some studies to correlate with the actual glycaemic index obtained by feeding a mixed meal, though this is not a universal finding. Although the concept of glycaemic index has been controversial, the glycaemic index and glycaemic load of diets have predicted risks of type 2 diabetes and coronary heart disease and related *biomarkers*, independently of dietary fibre, in prospective epidemiological studies.

3.3 Food and drinks containing fructose

Fructose is found in food as a single sugar molecule (monosaccharide), or bound with glucose, another monosaccharide, to form sucrose, a disaccharide commonly known as sugar.

Sugars in typical diets in high-income countries are typically added to food during processing and preparation (cooking) as well as at the table. This added sugar is defined as 'free sugars' by the World Health Organization together with sugar naturally present in honey,

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[1] In the HEI-2005 guidelines, the term 'solid fats' includes meat and poultry fats, milk fat, 'shortenings' used in baking and hard margarine.

syrups, fruit juices and fruit juice concentrates. Intrinsic sugars are those found in whole fresh foods such as fruit and vegetables [6].

Sucrose is refined from sugar beet or sugar cane. High-fructose corn syrup contains glucose and fructose, usually in close to equal amounts, and is increasingly used in food and drink manufacture, particularly in the USA. For general information about carbohydrates, including fructose, see **Box 1**.

3.4 Foods containing saturated fatty acids

Fats in diets are mostly made up from triglycerides – three fatty acid molecules attached to a glycerol backbone. The body stores excess *energy* as lipids in the form of body fat (also known as *adipose tissue*).

Dietary fats include solid fats and liquid oils. Fats with a high proportion of 'saturated' fatty acids are solid or semisolid at ambient temperatures; those with a higher amount of 'unsaturated' fatty acids are more likely to be oils. The different degrees of saturation produce various effects in the body. Diets high in saturated fatty acids increase circulating blood concentrations of *cholesterol* and the risk of cardiovascular disease. Fats from animal sources usually have a high proportion of saturated fatty acids, and these are common in processed foods.

Box 1: Carbohydrates

Carbohydrates consist of monosaccharide sugars, or larger molecules of these units joined together: disaccharides (two units), *oligosaccharides* (a few units) or polysaccharides (also known as polymers; many units). For instance, glucose and fructose are monosaccharides, sucrose is a disaccharide formed of glucose and fructose, and starch is a polymer of glucose units. Polysaccharides are sometimes called 'complex' carbohydrates and monosaccharides 'simple' carbohydrates.

Carbohydrates are generally the main source of *energy* in diets. They supply about 4 kilocalories per gram. They form part of important structural components in the body and, in the form of glucose, are the principal and preferred energy source for metabolism. They also play major roles in several essential cellular and physiological processes. Non-starch polysaccharides are another type of complex carbohydrate but unlike starch, they cannot be digested by the body. Non-starch polysaccharides therefore do not provide energy, but they are the major component of dietary fibre.

Glycaemic index and glycaemic load are terms used to characterise foods and diets based on their effects on blood glucose levels (see **Section 3.2**).

Cereals (grains) and products made from them (such as breads, pastas and breakfast cereals), as well as starchy roots and tubers, are all high in carbohydrates. These foods contain a mixture of complex and simple carbohydrates and other *nutrients*. Until recently, starches have been the main source of carbohydrate in human diets. With industrialisation and urbanisation, sugars have been added in increasing quantities in food preparation and as an ingredient in processed foods. Diets consumed in some *high-income* countries now may contain roughly as much carbohydrate in the form of sugars as they do starches.

The quantity of sugars in manufactured foods and drinks varies. Sugared drinks are generally about 10 per cent by volume added sugars, and up to 100 per cent of their energy comes from sugars. Sugars are often added to fruit juices. Jams and other preserves are about 60 per cent sugars. Cakes, biscuits (cookies) and other baked goods contain starches, fats and sugars in varying proportions. Confectionery, including chocolate, is generally high in sugars.

3.5 Foods containing retinol

Retinol is also known as vitamin A. Retinol is found in animal products, of which liver is a particularly rich source, but not in plant-based foods. Other sources include eggs and dairy products. Retinol may also be synthesised in the body from certain *carotenoids* that occur in plant foods, such as beta-carotene. For general information about vitamins, see **Box 2**.

3.6 Vitamin D

Vitamin D plays a critical role in calcium and bone metabolism and in controlling *cell differentiation*. Vitamin D may be derived from the action of sunlight on the skin or may be consumed in the diet. Natural sources include sardines and other oily fish, meat and eggs; foods such as milk or fat spreads may be fortified with vitamin D. For general information about vitamins, see **Box 2**.

3.7 Alpha-tocopherol

Alpha-tocopherol is a form of vitamin E. Vitamin E occurs in eight forms, with alpha- and gamma-tocopherol being the most commonly available. The main dietary sources of vitamin E are vegetable oils such as palm, sunflower, corn, soya bean and olive oils. Nuts, peanut butter, sunflower seeds and wheatgerm are also sources. Wholegrains, fish, green, leafy vegetables and fortified breakfast cereals also contain this vitamin. For general information about vitamins, see **Box 2**.

3.8 Selenium

Selenium is a mineral element that occurs in different chemical forms. It is toxic in large amounts but is essential in the diet at trace levels. It is present at varying concentrations in different soils, and since plants take up selenium from the soil, these concentrations determine the amount present in vegetables.

Box 2: Vitamins

Vitamins are organic molecules, which may be fat or water soluble, that are needed for metabolism but cannot be made in the body and so must be supplied in the diet. They each have specific functions in the body.

Vitamins A (retinol), D, E and K are fat soluble and can only be digested, absorbed and transported in conjunction with fats. They are found in liver, egg yolk and oily fish, and in the fat in milk and dairy products, animal fats and vegetable oils. Fat-soluble vitamins are stored in the liver and in body fat stores. For this reason, they do not need to be consumed every day. Partly for the same reason, continuous high intakes, especially of retinol and vitamin D, can lead to excess accumulation and toxicity.

Vitamin C and the B vitamins are water soluble. The B group includes thiamin (vitamin B_1), riboflavin (B_2), niacin (B_3), pantothenic acid (B_5), pyridoxine (B_6), biotin (B_7), folate (B_9) and cobalamin (B_{12}). Excess amounts of water-soluble vitamins are generally not toxic because they are excreted in the urine rather than stored in the body. This also means that they generally have to be consumed more frequently than fat-soluble vitamins. Foods of plant origin are important sources of water-soluble vitamins: for example, grains, vegetables, fruit, some roots and tubers and pulses. They can be destroyed by heat or exposure to the air, or lost by leaching during cooking, for instance when vegetables are boiled. For further information on foods of plant origin and their constituents, see Exposures: Wholegrains, vegetables and fruit.

Thus, selenium deficiency is more prevalent in regions where the selenium content of the soil is low. Selenium is a component of the amino acids *selenocysteine* and *selenomethionine*, which are integrated into proteins to form *selenoproteins*. Selenoproteins are important in contributing to antioxidant functions, for example, through glutathione peroxidase. The best dietary sources of selenium are nuts, offal, fish, eggs and poultry, with bread, meat products, fish, poultry and eggs contributing the most to overall selenium intake in the diet [7].

3.9 Beta-carotene

Beta-carotene is a *carotenoid* that can be converted to retinol by the body. Although retinol can be obtained directly from animal products, it may also be synthesised from carotenoids in foods of plant origin containing carotenoids. Carotenoids are a family of more than 600 fat-soluble red or orange pigments that comprise xanthophylls (such as lutein) and carotenes (such as alpha- and beta-carotene and lycopene). Beta-carotene is found naturally in yellow, orange and green fruit and green, leafy vegetables, such as cantaloupe melon, oranges, carrots, spinach, lettuce, tomatoes, sweet potatoes, broccoli and winter squash (pumpkin).

Beta-carotene is also available as a supplement in a wide range of doses. For more information about *micronutrient* supplements, see **Box 3**. For further information on foods containing carotenoids and beta-carotene, see Exposures: Wholegrains, vegetables and fruit.

3.10 Calcium

Calcium is the most abundant mineral in the body and is the major mineral constituent of bones. It is central to a variety of functions in the body, such as bone metabolism, nerve and muscle activity, and the control of *cell differentiation* and *cell proliferation*. Calcium
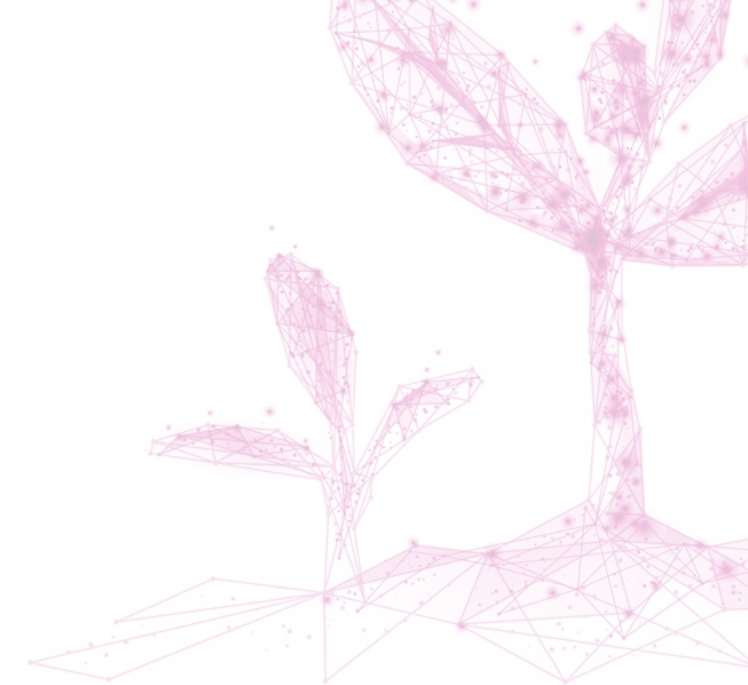
metabolism and *absorption* are controlled by various factors – including parathyroid hormone and vitamin D and related hormonal compounds formed by the liver and kidney.

Dairy products such as milk, cheese and yoghurt are valuable sources of calcium. In countries with high intakes of dairy products, they are the main source of calcium. Other animal sources include fish (when eaten with their bones) and meat dishes (when the bones are included in the preparation of broths or stews). Calcium is found in plant as well as animal foods, but it is less easily absorbed from plant foods. Plant sources include green vegetables, nuts and pulses [8, 9].

Calcium is also available as a supplement in a wide range of doses. For more information about micronutrient supplements, see **Box 3**.

3.11 Multivitamin supplements

A multivitamin supplement contains a combination of vitamins, minerals, trace elements and other *bioactive constituents*, usually in pill or powder form. However, the definitions and categorisation of multivitamin supplements are not standardised. For more information about micronutrient supplements, see **Box 3**.

Box 3: Micronutrient supplements

Supplements

Vitamins, minerals, trace elements and other *bioactive constituents* are available as supplements, usually in pill or powder form. These began to be manufactured and marketed after their functions were identified, and claims were soon made for general benefits in prevention of disease and promotion of well-being, though evidence for effects beyond preventing or treating micronutrient deficiencies is generally not compelling.

Many dietary supplements are classed as foods, although some may be regulated medicinal products. Manufacturers of food supplements may market their products using health claims, which may be regulated, though this varies between countries. It is usually not permitted to market a product classed as a food with specific claims that it can prevent, treat or cure disease.

Many people in *high-income* countries take dietary supplements. In the UK, 35 per cent of respondents reported taking dietary supplements. About 50 per cent of people in the USA take supplements in some form.

Levels of supplementation

The effects of bioactive constituents vary with the type of substance and quantities consumed. The amounts of *nutrients* and other substances in diets depend on the nature and quantity of the foods and drinks consumed, as well as any supplements.

The quantity of nutrients and other substances contained in dietary supplements, in this context usually referred to as doses, may be at levels that can be found in normal diets or at higher levels. Amounts at levels about the same as those that can be consumed in diets are known as 'physiological doses'. Higher amounts, at levels above any that can be readily consumed from foods, are known as 'high dose', 'pharmacological dose', or sometimes as 'mega-doses'.

Some nutrients, such as water-soluble vitamins, have been thought to be harmless at pharmacological doses, but there is now evidence that this is not always the case. Other nutrients, including fat-soluble vitamins and all minerals and trace elements, are known to be toxic at pharmacological doses; some of these, selenium being one example, are known to be toxic at intakes not far above the dose needed to meet nutritional need.

Randomised controlled trials using various doses of micronutrients have shown that supplements may influence the risk of cancers at some sites.

Expert reports issued by United Nations agencies and national governments set out intakes of nutrients estimated to be required by population groups to prevent deficiency and also sometimes an upper level of intake deemed to be safe.

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 other dietary exposures increase or decrease the risk of developing cancer are described in the following subsections. Factors that are relevant to specific cancers are presented here too.

4.2.1 Exposures

4.2.1.1 Healthy dietary patterns

Definitions. In this Third Expert Report, healthy dietary patterns were assessed by measuring specific healthy dietary indices including the American Cancer Society (ACS) Cancer Prevention Guidelines score [2], the Healthy Eating Index-2005 [3], the alternate Mediterranean score [4] and the World Cancer Research Fund/American Institute for Cancer Research score [5] (for further details, see **Section 3.1**).

Confounding. Patterns of diet are interrelated with other habitual behaviours that may affect the risk of cancer, such as smoking tobacco or participating in physical activity; people who habitually consume any type of diet for the sake of their health or for reasons of belief may also modify other aspects of their way of life.

These behaviours are likely to confound results that appear to show associations with the risk of cancer.

Reporting bias. In studies that rely on self-reporting, people who habitually consume or who try to follow types of diets in the belief that these are healthy may provide inaccurate records. They may overestimate their consumption of foods such as vegetables, fruit and other foods they believe to be healthy, and underestimate or fail to report consumption of foods and drinks they believe to be unhealthy. This type of reporting bias is a general issue with studies that rely on self-reporting but may be a special issue in the context of dietary exposures. Studies of specific dietary patterns undertaken by scientists who themselves follow these patterns may be seen as biased for this reason.

4.2.1.2 Glycaemic load

Definition. Glycaemic load takes into account the glycaemic index (a measure of the degree to which a food raises blood glucose compared with a standard food, under standard conditions) as well as the actual amount of carbohydrate consumed (for further details, see **Section 3.2**).

4.2.1.3 Macronutrients and micronutrients in foods

Definition. Macronutrients and their constituent parts are either carbohydrates (monosaccharides and polysaccharides), fats (saturated and unsaturated fatty acids) or proteins (amino acids). Macronutrients provide *energy* and are essential for normal growth and development. Vitamins, minerals and trace elements are micronutrients vital for life that are typically found in small amounts in food. For further information on the various macronutrients and micronutrients included in this Third Expert Report, see **Section 3**.

Dietary intake. Dietary assessment of selenium is problematic as the content of selenium in foods depends to a large extent on the soil selenium content of the area in which the foods are grown. Blood and toenail concentrations of selenium are sometimes used as an indicator of intake.

Reporting bias. The food sources of many micronutrients may be subject to reporting bias which will also be reflected in micronutrient intakes. Over-reporting of vegetables and fruit will lead to higher estimates of dietary beta-carotene and *carotenoids*.

4.2.1.4 Micronutrient supplements

Definitions. Vitamins, minerals, trace elements and other *bioactive constituents* are available as micronutrient supplements, usually in pill or powder form (for further details, see **Box 3**). Definitions and categorisation of multivitamin supplements are not standardised.

Confounding. In trials using supplements given in combinations, it is not possible to attribute any effect to an individual *nutrient*.

Dietary intake. The results of supplement trials can be assumed only to apply to doses and forms of the micronutrient present in the supplement.

Study design. *Randomised controlled trials* using micronutrient supplements provide strong evidence, under the specific experimental conditions. The doses used in trials are often pharmacological, in which case they cannot be taken as directly relevant to the *nutrients* as contained in foods and diets. Supplements in synthetic forms are sometimes but not always chemically identical to the nutrient as found in food, and so may have different biochemical effects. This may also be because of the level of the dose, because the nutrient is given in isolation or separated from the nutritional matrix as found in foods, or for other reasons.

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) [10], 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 [11].

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 [12].

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 diet and cancers of the mouth, pharynx and larynx have not included data on HPV infection.

4.2.2.2 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 [13].

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 [14]. 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 [15].

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 [16], as is exposure to indoor air pollution from wood and coal burning for cooking and heating [17].

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 CUP analyses on high-dose beta-carotene supplements, see Evidence and judgements (**Section 5.10.1**).

4.2.2.3 Pancreas

Definition. The pancreas is an elongated gland located behind the stomach. It contains two types of tissue, *exocrine* and *endocrine*. The exocrine pancreas produces digestive enzymes that are secreted into the small intestine. Cells in the endocrine pancreas produce *hormones* including *insulin* and glucagon, which influence glucose metabolism.

Classification. Over 95 per cent of pancreatic cancers are *adenocarcinomas* of the exocrine pancreas, the type included in the CUP.

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

Smoking tobacco, chewing tobacco and snuff

Smoking tobacco (or use of smokeless tobacco, sometimes called 'chewing tobacco' or 'snuff') is an established cause

of pancreatic cancer, and approximately 22 per cent of deaths from pancreatic cancer are attributable to smoking tobacco [11].

👪 Family history

More than 90 per cent of pancreatic cancer cases are sporadic (due to spontaneous rather than inherited *mutations*), although a family history increases risk, particularly where more than one family member is involved [18].

Confounding. Smoking tobacco is a possible *confounder*.

Measurement. Owing to very low survival rates, both incidence and mortality can be assessed.

4.2.2.4 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 [19].

🚬 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 [20].

👪 Family history

Based on twin studies, up to 45 per cent of colorectal cancer cases may involve a heritable component [21]. Between five and 10 per cent of colorectal cancers are consequences of recognised hereditary conditions [22]. 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 on calcium supplements, see Evidence and judgements (**Section 5.11.1**).
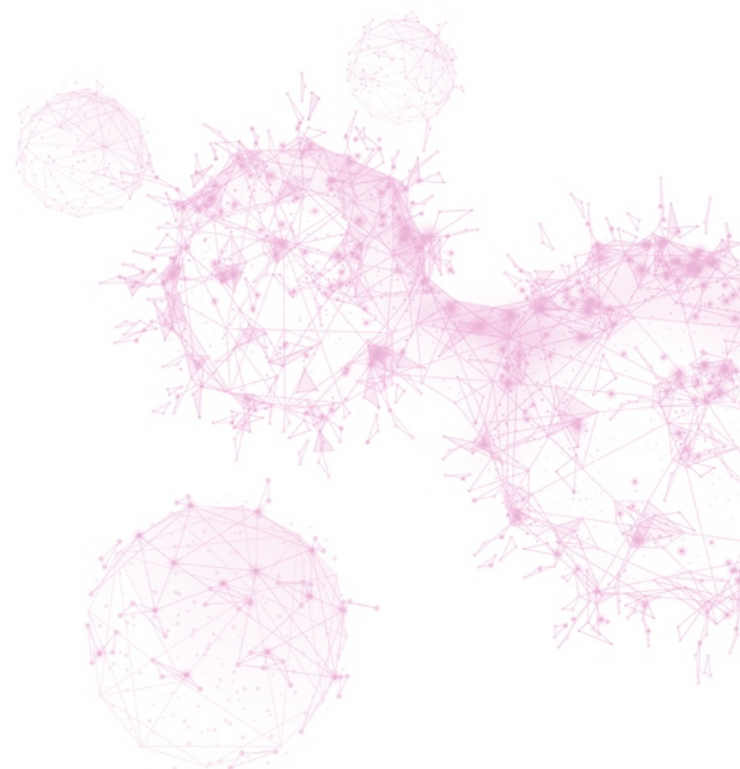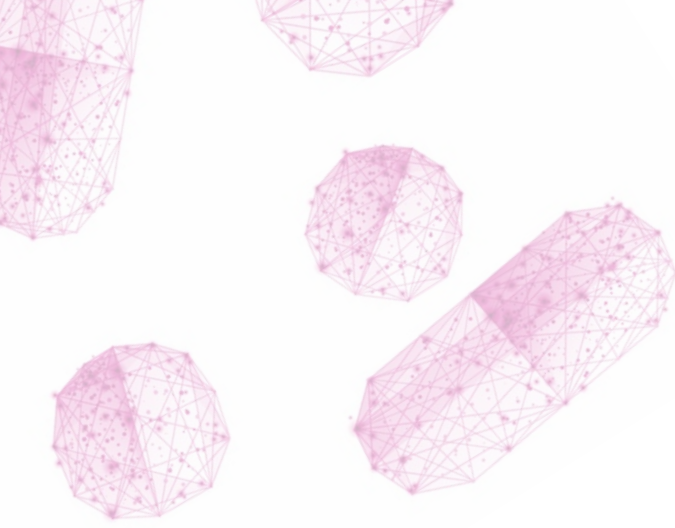
4.2.2.5 Endometrium

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

Classification. The majority of cancers that occur in the body of the uterus are endometrial cancers, mostly *adenocarcinomas* [23]. Because endometrial cancer is *hormone* related, factors that modify risk might have different effects at different times of life.

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

📅 Life events

Not bearing children and late natural *menopause* (after the age of 55) both increase the risk of endometrial cancer [24]. The reverse also applies: bearing children and early menopause both reduce the risk of endometrial cancer [25–29].

💊 Medication

Oral contraceptives, which contain either a combination of *oestrogen* and *progesterone*, or progesterone only, protect against endometrial cancer [28, 30]. *Menopausal oestrogen hormone therapy* unaccompanied by progesterone is a cause of this cancer. Menopausal oestrogen-only hormone therapy is normally prescribed only to women who have had a hysterectomy [28, 30]. Tamoxifen, a hormonal therapy used for breast cancer, can also increase the risk of endometrial cancer.

👨‍👩 Family history

Women with a family history of endometrial or colorectal cancer have a higher risk of endometrial cancer [31]. Lifetime risk of endometrial cancer in women with Lynch syndrome *mutations* MLH1 or MSH2 is approximately 40 per cent, with a median age of 49. Women with MSH6 mutations have a similar risk of endometrial cancer but a later age of diagnosis [32].

Confounding. Including data on women who were at high risk of endometrial cancer who have had hysterectomies may have influenced the results. MHT is an *effect modifier*; in women who have never used MHT there is a stronger association between *body mass index (BMI)* and endometrial cancer than in women who have ever used it [33].

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

4.2.2.6 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. The evidence included in the CUP for beta-carotene does not specify whether disease was advanced or not.

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 [34]. Genetic susceptibility has been linked to African heritage and *familial* disease [35]. 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 [36].

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

For more detailed information on *adjustments* made in CUP analyses on beta-carotene, see Evidence and judgements (**Section 5.9.1**).

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.

4.2.2.7 Skin

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

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

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

Radiation

Over-exposure to ultraviolet radiation (mainly from sunlight, but also from ultraviolet-emitting tanning devices) is the chief cause of melanoma and non-melanoma skin cancers [37, 38].

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[1] Kufe D *et al*. Holland Frei Cancer Medicine. 6 ed. Hamilton, Ontario: BC Decker, 2003.

Medication

Immune suppression medication following organ transplantation is associated with an increased risk of skin cancers, especially squamous cell carcinoma [39].

Infection and infestation

HPV can cause squamous cell carcinomas of the skin, especially in immunocompromised people [39]. Patients with AIDS, who are immunocompromised, are also at increased risk of squamous cell carcinoma, but development of Kaposi's sarcoma, which is otherwise rare, is a characteristic complication.

Occupational exposure

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

Genetics and family history

There are some rare, high-penetrance genetic mutations known to cause melanoma, such as mutations in the CDKN2A gene, but these do not make a large contribution to the total number of melanoma cases[1]. People who have a family history of melanoma are predisposed to this cancer [40][2,3].

Skin pigmentation

There is an inverse relationship between risk of skin cancer and skin pigmentation, with highest risks observed in populations with the fairest skin. This is likely due to lower production of the protective skin pigment melanin [37].

Confounding. Sun exposure is an important *confounder*.

For more detailed information on CUP analyses on beta-carotene, see Evidence and judgements (**Section 5.10.2**).

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[4], there is also a CUP cancer report. CUP cancer reports summarise findings from the SLRs, again focusing on a specific cancer site. The following subsections also present findings from the SLRs, but from a different perspective: they bring together all of the key findings on other dietary exposures and the risk of cancer.

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

5.1 Healthy dietary patterns

Table 5.1 summarises the main findings from two published *cohort studies* on healthy dietary patterns and the risk of cancers of the mouth, pharynx and larynx. Highest versus lowest and *dose–response meta-analyses* could not be conducted in the CUP as there were too few studies.

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1 Berwick M *et al. Cancer Epidemiol Biomarkers Prev* 2006; 15: 1520–5
2 Ward SV *et al. Cancer Epidemiol* 2015; 39: 346–5r
3 Chen T *et al. Eur J Cancer* 2014; 50: 2659–67
4 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 are not currently available for nasopharynx, cervix and skin.

Table 5.1: Summary of published cohort studies of healthy dietary patterns and the risk of cancers of the mouth, pharynx and larynx

Cancer	Subtype	Study	Diet index	No. of cases	Risk estimate (95% CI)	Contrast	P trend	Conclusion[1]	Date of CUP cancer report[2]
Mouth, pharynx and larynx	Oral cavity	NIH-AARP [41]	ACS	862 men, 292 women	0.79 (0.64–0.97) 0.71 (0.48–1.06)	Quintile 5 vs quintile 1	0.06 0.03	Limited – suggestive: Decreases risk	2018
	Laryngeal			620	0.82 (0.64–1.05)		0.06		
	Head and neck	NIH-AARP [42]	HEI-2005	1466 men, 402 women	0.74 (0.61–0.89) 0.48 (0.33–0.70)	Quintile 5 vs quintile 1	0.0008 < 0.0001		
			aMED		0.80 (0.64–1.01) 0.42 (0.24–0.74)	7–9 vs 0–2	0.002 < 0.0001		
	Upper aer-odigestive tract	EPIC [43]	WCRF/AICR	602	0.69 (0.50–0.95)	Quintile 5 vs quintile 1	< 0.0001		

1 See Definitions of WCRF/AICR grading criteria (**Section 1**: Other dietary exposures and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'limited – suggestive'.

2 Throughout this 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 Judgements relate to healthy dietary patterns as marked by greater healthy dietary indices. These indices produce an integrated score to assess adherence to healthy eating or lifestyle recommendations or patterns. They are characterised by factors such as healthy weight management; engagement in physical activity; limiting intake of foods and drinks that promote weight gain; limiting intake of red and processed meat; limiting intake of alcoholic drinks; and a higher intake of wholegrains, vegetables and fruit.

Abbreviations: aMED, alternate Mediterranean score [44]; EPIC, European Prospective Investigation into Cancer and Nutrition; HEI-2005, Healthy Eating Index-2005 [5]; NIH-AARP, National Institutes of Health-American Association of Retired Persons; ACS, American Cancer Society; WCRF/AICR, World Cancer Research Fund and the American Institute for Cancer Research Score [43].

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), lung (2017), stomach (2016), gallbladder (2015), liver (2015), colorectum (2017), breast (pre and postmenopause; 2017), ovary (2014), endometrium (2013), prostate (2014), kidney (2015) and skin (2017).

For more information on the evidence for healthy dietary patterns and the risk of cancer that was graded by the Panel as 'limited – suggestive' and suggests a direction of effect, see the CUP documents listed:

- CUP mouth, pharynx and larynx cancer report 2018: Section 7.2 and CUP mouth, pharynx and larynx cancer SLR 2016: Section 1.

Also, for information on mechanisms that could plausibly influence the risk of cancer, see **Appendix 2**. Please note that the information supersedes that in CUP cancer reports published before this Third Expert Report.

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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.

5.2 Glycaemic load

Table 5.2 summarises the main findings from the CUP dose–response meta-analysis of cohort studies on glycaemic load and the risk of endometrial cancer.

Evidence for cancers of the following types was discussed in the CUP but was too limited to draw a conclusion:[1] pancreas (2012), liver (2015), colorectum (2017) and breast (pre and postmenopause; 2017).

The strong evidence on the effects of glycaemic load 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.

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 Endometrium

(Also see CUP endometrial cancer report 2013: Section 7.1 and CUP endometrial cancer SLR 2012: Sections 5.1 and 5.1.6.)

The evidence for glycaemic load and carbohydrate are presented in the following subsections. For information on glycaemic index, see CUP endometrial cancer SLR 2012, Section 5.1.5.

5.2.1.1 Glycaemic load

5.2.1.1.1 CUP dose–response meta-analysis

All six identified studies were included in the dose–response meta-analysis, which showed a statistically significant 15 per cent increased risk of endometrial cancer per 50 units increase in glycaemic load per day (RR 1.15 [95% CI 1.06–1.25]; n = 3,869 cases) (see **Figure 5.1**). No *heterogeneity* was observed, and there was no evidence of small study bias with *Egger's test* (p = 0.13).

Table 5.2: CUP dose–response meta-analysis of glycaemic load[1] and the risk of endometrial cancer

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I² (%)	Conclusion[2]	Date of CUP cancer report[3]
Endometrium	6	6	3,869	1.15 (1.06–1.25)	50 units/ day	0	Probable: Increases risk	2013

1 The glycaemic load of a food may be calculated by multiplying the glycaemic index of a food, expressed as a percentage, by the number of grams of carbohydrate in a serving of the food.

2 See Definitions of WCRF/AICR grading criteria (**Section 1**: Other dietary exposures and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'probable'.

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

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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 5.1: CUP dose–response meta-analysis for the risk of endometrial cancer, per 50 units increase in glycaemic load per day

Author	Year		Per 50 units/day RR (95% CI)	% Weight
Cui	2011		1.26 (0.97, 1.65)	9.89
George	2009		1.07 (0.89, 1.27)	22.68
Cust	2007		1.14 (0.96, 1.34)	25.31
Larsson	2007		1.10 (0.88, 1.37)	14.06
Silvera	2005		1.21 (0.98, 1.50)	15.28
Folsom	2003		1.23 (0.98, 1.56)	12.77
Overall (I-squared = 0.0%, p = 0.857)			1.15 (1.06, 1.25)	100.00
NOTE: Weights are from random effects analysis				

.75 1 1.5 2
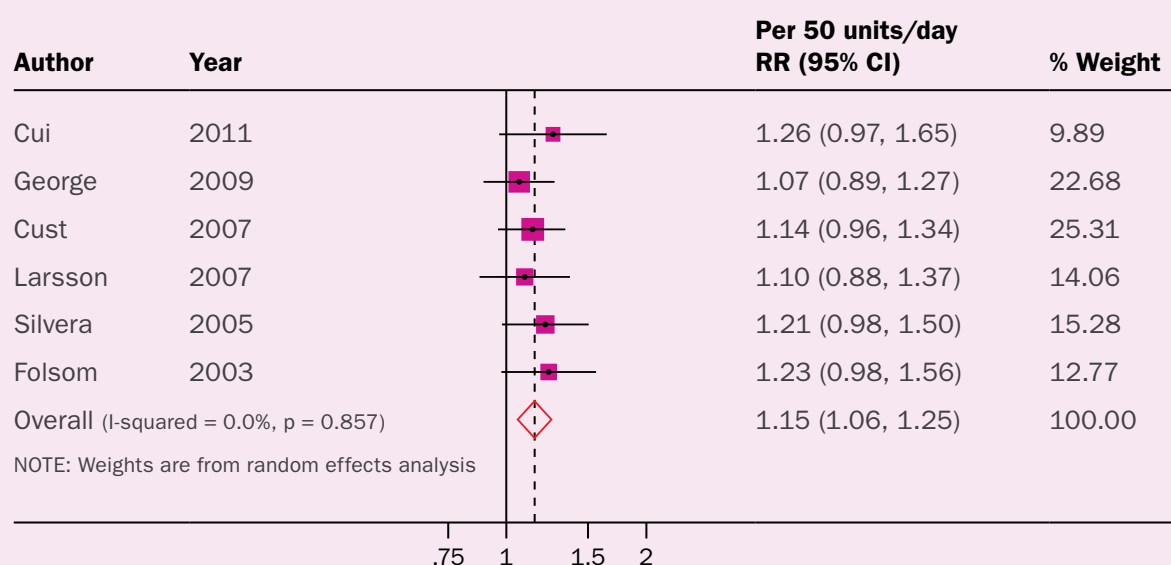
Source: Cui, 2011 [45]; George, 2009 [46]; Cust, 2007 [47]; Larsson, 2007 [48]; Silvera, 2005 [49]; Folsom, 2003 [50].

One published study that was included in the CUP dose–response meta-analysis reported a statistically significant increased risk when comparing the highest with the lowest glycaemic load for obese women (RR 1.88 [95% CI 1.08–3.29]) and premenopausal women (RR 1.55 [95% CI 1.05–2.29]) [49]. Another published study that was also included in the CUP dose–response meta-analysis reported a significant increased risk for the highest compared with the lowest glycaemic load in women who were both physically inactive and overweight (RR 2.99 [1.17–7.67]) [48].

All studies included in the dose–response meta-analysis *adjusted* for age and BMI, most studies adjusted for tobacco smoking and hormone use, and some studies adjusted also for reproductive factors, physical activity and alcohol consumption.

5.2.1.1.2 Published pooled analyses and meta-analyses

No published *pooled analyses* were identified. Three other published meta-analyses on glycaemic load and the risk of endometrial cancer have been identified. Two of the meta-analyses found a statistically significant increased risk when comparing the highest with the lowest glycaemic load (RR 1.22 [95% CI 1.09–1.37] [51] and RR 1.21 [95% CI 1.07–1.36] [52]. The other meta-analysis (which included mainly *cohort studies* and one *case-control study*) found a significant increased risk for the highest compared with the lowest glycaemic load (RR 1.36 [95% CI 1.14–1.62]) [53].

5.2.1.2 Carbohydrate

5.2.1.2.1 CUP dose–response meta-analysis

All five identified studies were included in the dose–response meta-analysis, which showed a statistically significant 18 per cent increased risk of endometrial cancer per 100 grams increase in carbohydrate consumed per day (RR 1.18 [95% CI 1.02–1.37]; n = 2,629 cases) (see CUP endometrial cancer SLR 2012, Figure 27). No *heterogeneity* was observed, and there was no evidence of small study bias with *Egger's test* (p = 0.73).

All studies included in the dose–response meta-analysis *adjusted* for both energy intake and body mass index (BMI) as potential *confounding factor*s, except one study that adjusted only for energy intake and not BMI [54].

5.2.1.2.2 Published pooled analyses and meta-analyses

No published pooled analyses and no other published meta-analyses on carbohydrate intake and the risk of endometrial cancer were identified.

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.

The major proposed mechanisms by which the intake of foods with higher glycaemic load could affect endometrial cancer risk relate to elevated postprandial glucose and *insulin* levels, and subsequent development of *insulin resistance*, diabetes and *obesity* – all factors that are associated with endometrial cancer development [55–57].

5.2.1.4 CUP Panel's conclusion

The Panel noted issues with regard to characterising carbohydrate-related exposures and, given their complex nature, the difficulty in interpreting these exposures. The Panel considered the primary exposure with an observed effect to be 'glycaemic load', with the evidence for carbohydrate as supporting evidence for this effect. The Panel also noted that the evidence for carbohydrate is derived largely from developed countries where a large proportion of carbohydrate is in the form of sugars and highly processed foods.

The evidence was generally consistent, and the CUP dose–response meta-analysis showed a statistically significant increased risk of endometrial cancer with increased glycaemic load. No *heterogeneity* was observed. Three published meta-analyses also reported a significant increased risk. There is also evidence of plausible mechanisms operating in humans.

> **The CUP Panel concluded:**
>
> - **Greater glycaemic load of the diet is probably a cause of endometrial cancer.**

5.3 Foods and drinks containing fructose

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

Evidence for colorectal cancer (2017) was discussed in the CUP but was too limited to draw a conclusion.[1]

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[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.

Table 5.3: CUP dose–response meta-analysis for consumption of foods and drinks containing fructose[1] and the risk of pancreatic cancer

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I[2] (%)	Conclusion[2]	Date of CUP cancer report[3]
Pancreas[4]	7	6	2,831	1.22 (1.08–1.37)	25 g/day	0	Limited – suggestive: Increases risk	2012

1 Fructose comes from many sources (for example, soft drinks, fruit juices and sucrose), which may differ between population groups, and makes the evidence difficult to interpret. It is also unclear whether fructose may be acting as a marker for other linked exposures.

2 See Definitions of WCRF/AICR grading criteria (**Section 1**: Other dietary exposures and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'limited – suggestive'.

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

4 The evidence for foods and drinks containing fructose and pancreatic cancer includes both foods naturally containing fructose and foods that have had fructose added during preparation or processing.

For more information on the evidence for consuming foods and drinks containing fructose and the risk of cancer that was graded by the Panel as 'limited – suggestive' and suggests a direction of effect, see the CUP documents listed:

- CUP pancreatic cancer report 2012: Section 7.6 and CUP pancreatic cancer SLR 2011: Section 5.1.4.

Also, for information on mechanisms that could plausibly influence the risk of cancer, see

Appendix 2. Please note that the information supersedes that in CUP cancer reports published before this Third Expert Report.

5.4 Foods containing saturated fatty acids

Table 5.4 summarises the main findings from the CUP dose–response meta-analysis of cohort studies on consumption of foods containing saturated fatty acids and the risk of pancreatic cancer.

Table 5.4: CUP dose–response meta-analysis of consumption of foods containing saturated fatty acids[1] and the risk of pancreatic cancer

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I[2] (%)	Conclusion[2]	Date of CUP cancer report[3]
Pancreas	6	5	2,740	1.11 (1.01–1.21)	10 g/day	43	Limited – suggestive: Increases risk	2012

1 It is not clear whether total fat intake has any effect independent of the association with saturated fatty acids. See CUP pancreatic cancer report 2012, Section 7.3, and CUP pancreatic cancer SLR 2011, Section 5.2.1, for further details.

2 See Definitions of WCRF/AICR grading criteria (**Section 1**: Other dietary exposures and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'limited – suggestive'.

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

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), breast (pre and postmenopause; 2017), ovary (2014), endometrium (2013) and prostate (2014).

For more information on the evidence for eating foods containing saturated fatty acids and the risk of cancer that was graded by the Panel as 'limited – suggestive' and suggests a direction of effect, see the CUP documents listed:

- CUP pancreatic cancer report 2012: Section 7.3 and CUP pancreatic cancer SLR 2011: Section 5.2.2.

Also, for information on mechanisms that could plausibly influence the risk of cancer, see **Appendix 2**. Please note that the information supersedes that in CUP cancer reports published before this Third Expert Report.

5.5 Foods containing retinol

Table 5.5 summarises the main findings from the CUP dose–response meta-analysis of cohort studies on consumption of foods containing retinol and the risk of lung 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); stomach (2016); colorectum (2017); endometrium (2013); cervix (2017); prostate (2014); kidney (2015); and skin (2017).

For more information on the evidence for eating foods containing retinol and the risk of cancer that was graded by the Panel as 'limited – suggestive' and suggests a direction of effect, see the CUP documents listed:

- CUP lung cancer report 2017: Section 7.11 and CUP lung cancer SLR 2015: Section 5.5.1.1.

Table 5.5: CUP dose–response meta-analysis for consumption of foods containing retinol and the risk of lung cancer

Cancer	Type	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I² (%)	Conclusion[1]	Date of CUP cancer report[2]
Lung[3]	Dietary[4]	7	3	1,925	1.00 (1.00–1.00)	100 IU/day	97	Limited – suggestive: Decreases risk	2017
	Serum	15	8	2,855	0.97 (0.95–0.98)	10 µg/ 100 ml	0		

1. See Definitions of WCRF/AICR grading criteria (**Section 1**: Other dietary exposures 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 retinol and lung cancer is derived from studies on dietary intake and serum or plasma levels.
4. The dose–response meta-analysis for dietary retinol and the risk of lung cancer has not been updated, the result from 2007 Second Expert Report is presented.

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[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.

Also, for information on mechanisms that could plausibly influence the risk of cancer, see **Appendix 2**. Please note that the information supersedes that in CUP cancer reports published before this Third Expert Report.

5.6 Vitamin D

Table 5.6 summarises the main findings from the CUP dose–response meta-analysis of cohort studies on vitamin D intake 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); lung (2017); stomach (2016);

gallbladder (2015); liver (2015); breast (pre and postmenopause; 2017); ovary (2014); prostate (2014); bladder (2015); and skin (2017).

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

- CUP colorectal cancer report 2017: Section 7.10 and CUP colorectal cancer SLR 2016: Section 5.5.10 and Appendix 6.

Also, for information on mechanisms that could plausibly influence the risk of cancer, see **Appendix 2**. Please note that the information supersedes that in CUP cancer reports published before this Third Expert Report.

Table 5.6: CUP dose–response meta-analysis of vitamin D intake and the risk of colorectal cancer

Cancer	Type	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I² (%)	Conclusion[1]	Date of CUP cancer report[2]
Colorectum[3]	Dietary[4]	15	10	5,171	0.95 (0.93–0.98)	100 IU/day	11	Limited – suggestive: Decreases risk	2017
	Serum or plasma	12	11	4,801	0.92 (0.85–1.00)	30 nmol/L	54		
	Supplements[4,5]	3	2	415	0.93 (0.88–0.98)	100 IU/day	0		

1   See Definitions of WCRF/AICR grading criteria (**Section 1**: Other dietary exposures 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 vitamin D and colorectal cancer is derived from studies on dietary intake, supplements and serum or plasma levels.

4   Dose–response meta-analyses for dietary vitamin D and vitamin D supplements and the risk of colorectal cancer have not been not updated. Results from the 2010 CUP colorectal cancer SLR are presented; see CUP colorectal cancer SLR 2016, Appendix 6.

5   The evidence for vitamin D supplements is for the risk of colon cancer only; no conclusion was drawn for rectal 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 any combination of these.

Table 5.7: CUP dose–response meta-analysis for low plasma alpha-tocopherol concentrations and the risk of prostate cancer

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I² (%)	Conclusion[1]	Date of CUP cancer report[2]
Prostate	12	9	4,989	0.99 (0.98–1.00)	1 mg/L	0	Limited – suggestive: Increases risk for low levels[3]	2014

1 See Definitions of WCRF/AICR grading criteria (**Section 1**: Other dietary exposures 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 Panel's interpretation of the available evidence was that there is an increased risk of prostate cancer at low levels of plasma alpha-tocopherol.

5.7 Low plasma alpha-tocopherol concentrations

Table 5.7 summarises the main findings from the CUP dose–response meta-analysis of cohort studies on *low* plasma alpha-tocopherol concentrations and the risk of prostate cancer.

There was no discussion on low plasma alpha-tocopherol concentrations and any other cancer considered in the CUP as there were too few studies.

For more information on the evidence for low plasma alpha-tocopherol concentrations and the risk of cancer that was graded by the Panel as 'limited – suggestive' and suggests a direction of effect, see the CUP documents listed:

- CUP prostate cancer report 2014: Section 7.4 and CUP prostate cancer SLR 2014: Section 5.5.11.

Also, for information on mechanisms that could plausibly influence the risk of cancer, see **Appendix 2**. Please note that the information supersedes that in CUP cancer reports published before this Third Expert Report.

5.8 Low plasma selenium concentrations

Table 5.8 summarises the main findings from the CUP dose–response meta-analysis of cohort studies on *low* plasma selenium concentrations and the risk of prostate 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); lung (2017); stomach (2016); colorectum (2017); breast (2017) and skin (2017).

For more information on the evidence for low plasma selenium concentrations and the risk of cancer that was graded by the Panel as 'limited – suggestive' and suggests a direction of effect, see the CUP documents listed:

- CUP prostate cancer report 2014: Section 7.5 and CUP prostate cancer SLR 2014: Section 5.6.4.

Also, for information on mechanisms that could plausibly influence the risk of cancer, see **Appendix 2**. Please note that the information 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 any combination of these.

Table 5.8: CUP dose–response meta-analysis of low plasma selenium concentrations and the risk of prostate cancer

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I² (%)	Conclusion[1]	Date of CUP cancer report[2]
Prostate	17	9	3,559	0.95 (0.91–1.00)	10 µg/l	29	Limited – suggestive: Increases risk for low levels[3]	2014

1 See Definitions of WCRF/AICR grading criteria (**Section 1**: Other dietary exposures 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 Panel's interpretation of the available evidence was that there is an increased risk of prostate cancer at low levels of plasma selenium.

5.9 Foods containing beta-carotene

Table 5.9 summarises the main findings from the CUP dose–response meta-analyses of cohort studies on consumption of beta-carotene (including dietary, serum or plasma measures) 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); stomach (2016); colorectum (2017); ovary (2014); endometrium (2013); cervix (2017); kidney (2015); bladder (2015) and skin (2017).

The strong evidence on the effects of consuming 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.

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

● CUP lung cancer report 2017: Section 7.6 and CUP lung cancer SLR 2015: Section 5.5.1.2.

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.

5.9.1 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 or 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.

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.

Table 5.9: 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)	Incre-ment	I² (%)	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	13	2,958	0.92 (0.87–0.97)	10 µg/ 100 ml	40		
Pros-tate[4]	Dietary	11	10	12,219	1.00 (0.99–1.00)	700 µg/day	0	Substantial effect on risk unlikely	2014
	Serum or plasma	14	9	3,449	0.99 (0.95–1.04)	10 µg/ 100 ml	38		
	Supple-ments[5]	8	0	–	No statistically significant association in 8 studies	–	–		

1   See Definitions of WCRF/AICR grading criteria (**Section 1**: Other dietary exposures 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 'beta-carotene', which is based on evidence on dietary intake and serum levels, and another on 'high-dose beta-carotene supplements'. The evidence for beta-carotene is presented here. For information on high-dose beta-carotene supplements, see **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 or plasma levels, as well as studies on high-dose supplement use (20, 30 and 50 milligrams per day).

5   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 (RCTs) which all reported no statistically significant association.

5.9.1.1 Dietary beta-carotene

5.9.1.1.1 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 5.2**). In general, most of the risk estimates were close to 1.0.

5.9.1.1.2 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 5.3**). 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.

Figure 5.2: CUP highest versus lowest meta-analysis for dietary beta-carotene intake and the risk of prostate cancer
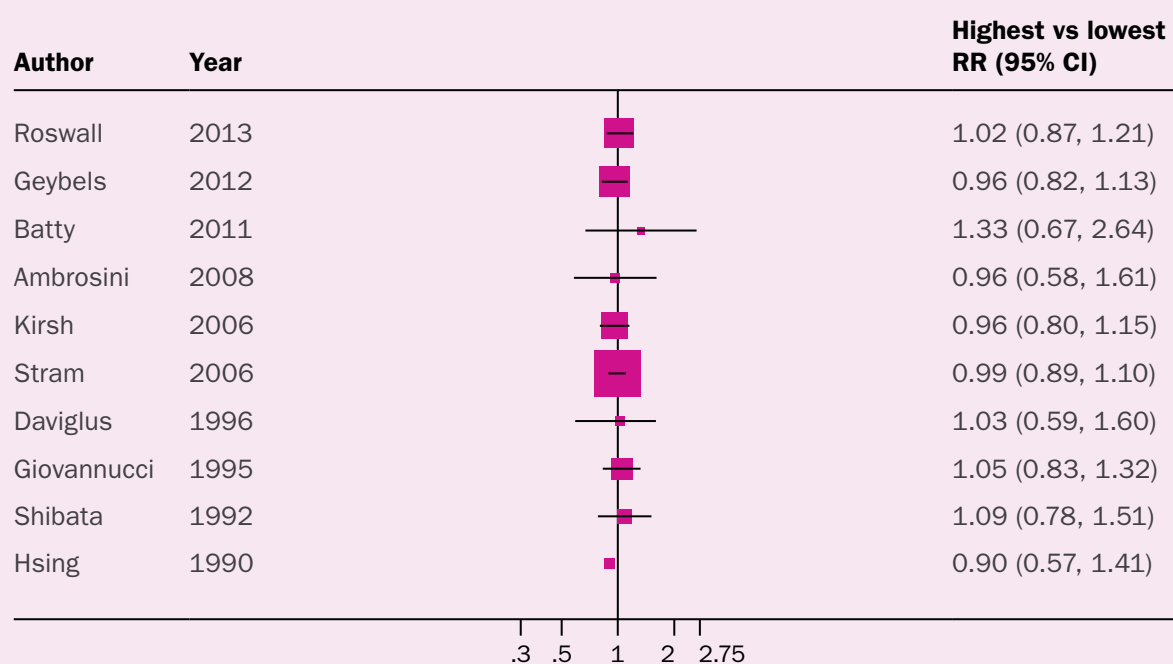
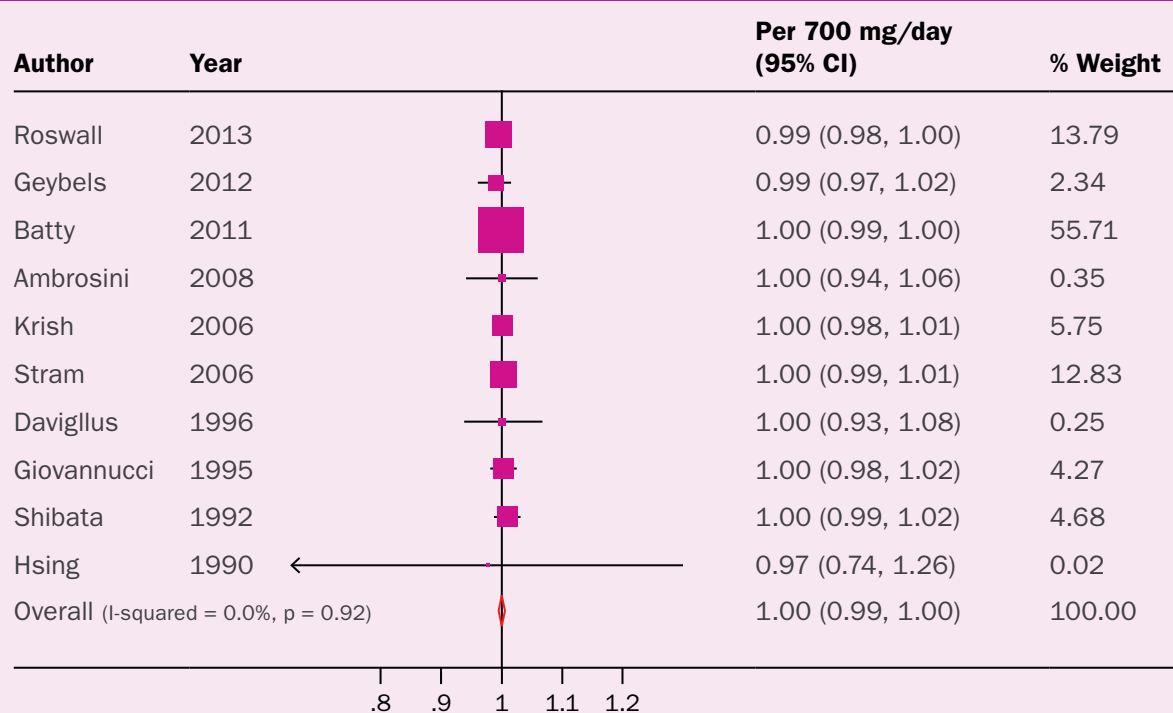| Author	Year		Highest vs lowest RR (95% CI)
Roswall	2013		1.02 (0.87, 1.21)
Geybels	2012		0.96 (0.82, 1.13)
Batty	2011		1.33 (0.67, 2.64)
Ambrosini	2008		0.96 (0.58, 1.61)
Kirsh	2006		0.96 (0.80, 1.15)
Stram	2006		0.99 (0.89, 1.10)
Daviglus	1996		1.03 (0.59, 1.60)
Giovannucci	1995		1.05 (0.83, 1.32)
Shibata	1992		1.09 (0.78, 1.51)
Hsing	1990		0.90 (0.57, 1.41)

.3   .5   1   2   2.75

Source: Roswall, 2013 [58]; Geybels, 2012 [59]; Batty, 2011 [60]; Ambrosini, 2008 [61]; Kirsh, 2006 [62]; Stram, 2006 [63]; Daviglus, 1996 [64]; Giovannucci, 1995 [65]; Shibata, 1992 [66]; Hsing, 1990 [67].

Figure 5.3: CUP dose–response meta-analysis for the risk of prostate cancer, per 700 micrograms increase in dietary beta-carotene consumed per day

Author	Year		Per 700 mg/day (95% CI)	% Weight
Roswall	2013		0.99 (0.98, 1.00)	13.79
Geybels	2012		0.99 (0.97, 1.02)	2.34
Batty	2011		1.00 (0.99, 1.00)	55.71
Ambrosini	2008		1.00 (0.94, 1.06)	0.35
Krish	2006		1.00 (0.98, 1.01)	5.75
Stram	2006		1.00 (0.99, 1.01)	12.83
Davigllus	1996		1.00 (0.93, 1.08)	0.25
Giovannucci	1995		1.00 (0.98, 1.02)	4.27
Shibata	1992		1.00 (0.99, 1.02)	4.68
Hsing	1990		0.97 (0.74, 1.26)	0.02
Overall (I-squared = 0.0%, p = 0.92)			1.00 (0.99, 1.00)	100.00

.8   .9   1   1.1   1.2

Source: Roswall, 2013 [58]; Geybels, 2012 [59]; Batty, 2011 [60]; Ambrosini, 2008 [61]; Kirsh, 2006 [62]; Stram, 2006 [63]; Daviglus, 1996 [64]; Giovannucci, 1995 [65]; Shibata, 1992 [66]; Hsing, 1990 [67].

5.9.1.1.3 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.

5.9.1.2 Serum or plasma beta-carotene

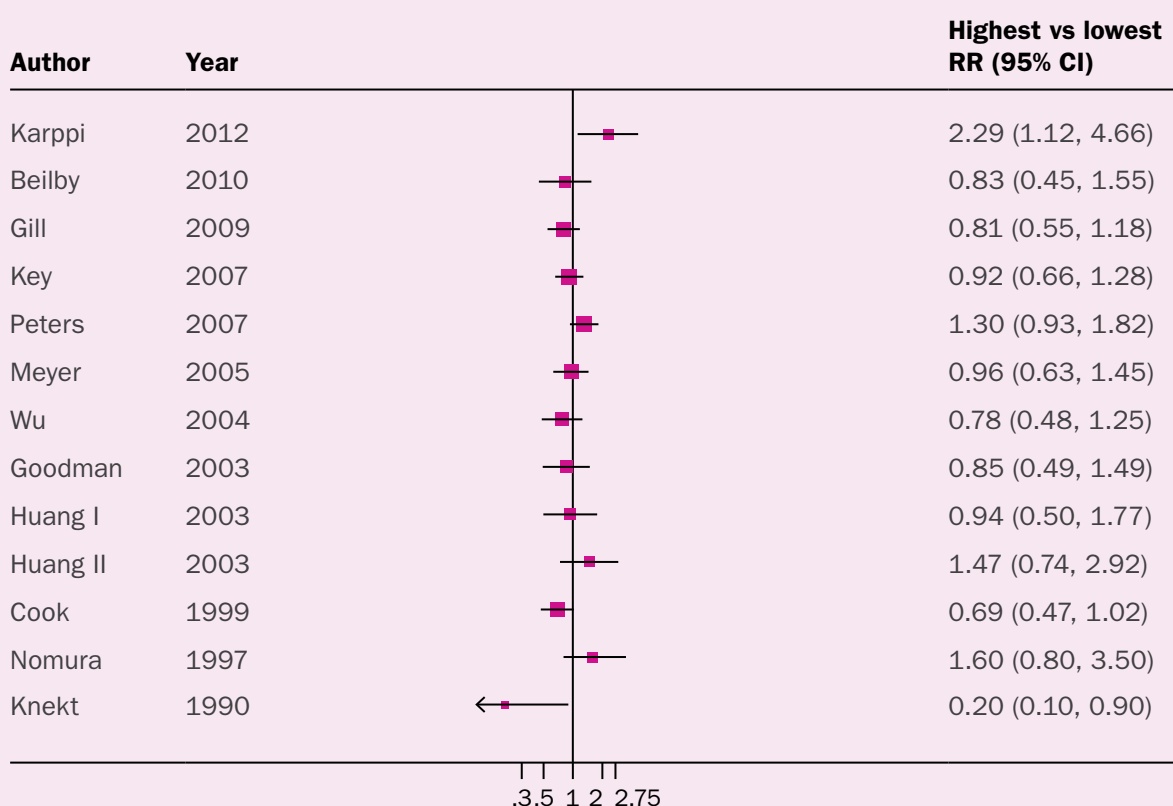#### 5.9.1.2.1 CUP highest versus lowest meta-analyses

Thirteen of 14 identified studies on serum or plasma beta-carotene levels and the risk of prostate cancer were included in a highest versus lowest meta-analysis (see **Figure 5.4**). No apparent pattern of increased or decreased risk was observed.

5.9.1.2.2 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 or plasma.

In Cook and colleagues 1999, the RRs were recalculated using Hamling method (Hamling *et al*, 2008). beta-carotene levels (RR 0.99 [95% CI 0.95–1.04], per 10 micrograms increase per 100 millilitres of serum or plasma; n = 3,449 cases) (see **Figure 5.5**). Moderate *heterogeneity* was observed (I^2 = 38%) and there was no evidence of small study bias with *Egger's test* (p = 0.47).
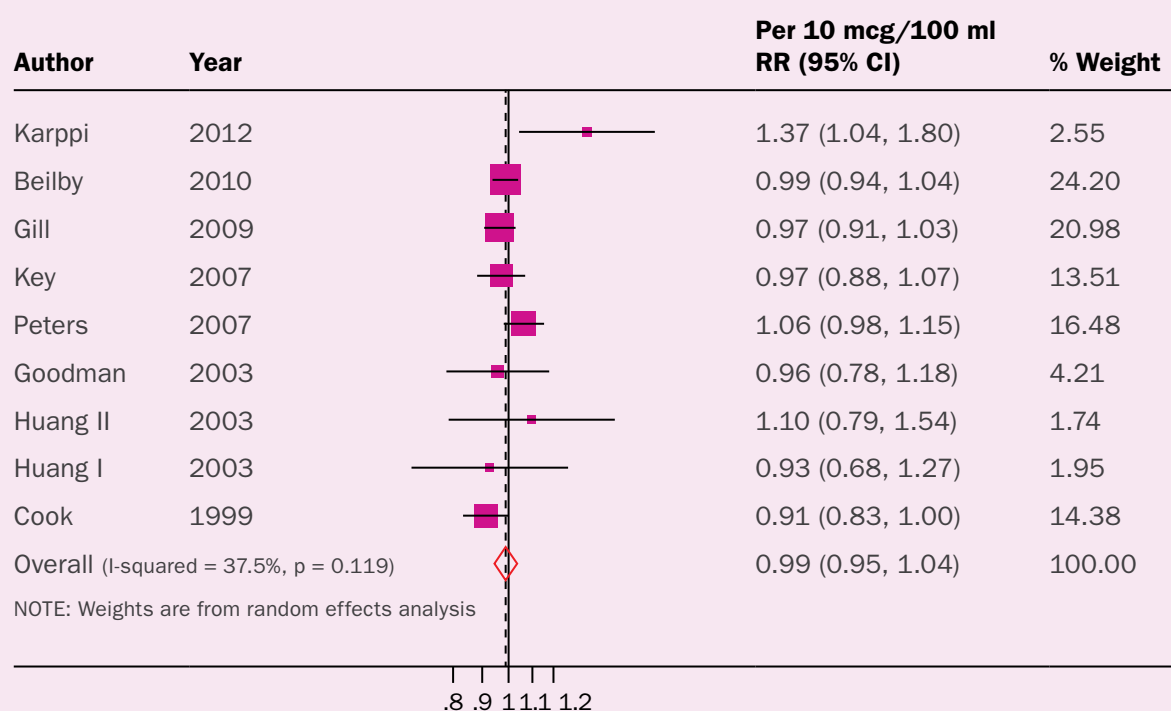

Figure 5.4: CUP highest versus lowest meta-analysis[1] for serum or plasma levels of beta-carotene and the risk of prostate cancer

Author	Year		Highest vs lowest RR (95% CI)
Karppi	2012		2.29 (1.12, 4.66)
Beilby	2010		0.83 (0.45, 1.55)
Gill	2009		0.81 (0.55, 1.18)
Key	2007		0.92 (0.66, 1.28)
Peters	2007		1.30 (0.93, 1.82)
Meyer	2005		0.96 (0.63, 1.45)
Wu	2004		0.78 (0.48, 1.25)
Goodman	2003		0.85 (0.49, 1.49)
Huang I	2003		0.94 (0.50, 1.77)
Huang II	2003		1.47 (0.74, 2.92)
Cook	1999		0.69 (0.47, 1.02)
Nomura	1997		1.60 (0.80, 3.50)
Knekt	1990		0.20 (0.10, 0.90)

.3.5 1 2 2.75

Source: Karppi, 2012 [68]; Beilby, 2010 [69]; Gill, 2009 [70]; Key, 2007 [71]; Peters, 2007 [72]; Meyer, 2005 [73]; Wu, 2004 [74]; Goodman, 2003 [75]; Huang, 2003 [76]; Cook, 1999 [77]; Nomura, 1997 [78]; Knekt, 1990 [79].

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[1] In Cook *et al*, 1999, the RRs were recalculated using Hamling method (Hamling *et al*, 2008).

Figure 5.5: 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 or plasma

Author	Year		Per 10 mcg/100 ml RR (95% CI)	% Weight
Karppi	2012		1.37 (1.04, 1.80)	2.55
Beilby	2010		0.99 (0.94, 1.04)	24.20
Gill	2009		0.97 (0.91, 1.03)	20.98
Key	2007		0.97 (0.88, 1.07)	13.51
Peters	2007		1.06 (0.98, 1.15)	16.48
Goodman	2003		0.96 (0.78, 1.18)	4.21
Huang II	2003		1.10 (0.79, 1.54)	1.74
Huang I	2003		0.93 (0.68, 1.27)	1.95
Cook	1999		0.91 (0.83, 1.00)	14.38
Overall (I-squared = 37.5%, p = 0.119)			0.99 (0.95, 1.04)	100.00

NOTE: Weights are from random effects analysis

Source: Karppi, 2012 [68]; Beilby, 2010 [69]; Gill, 2009 [70]; Key, 2007 [71]; Peters, 2007 [72]; Goodman, 2003 [75]; Huang, 2003 [76]; Cook, 1999 [77].

A stratified analysis for the risk of prostate cancer per 10 micrograms increase in beta-carotene per 100 millilitres of serum or 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.

5.9.1.2.3 Published pooled analyses and meta-analyses

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

5.9.1.3 High-dose beta-carotene supplements

5.9.1.3.1 Published cohort studies and randomised controlled trials

Overall, five published cohort studies and three randomised controlled trials (RCTs) 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 [58, 62, 74, 77, 80] reported no statistically significant association between consumption of high-dose beta-carotene supplements and the risk of prostate cancer. In addition, the three RCTs all reported no significant association (see **Table 5.10**).

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[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 [76], included two studies.

Table 5.10: 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) [81, 82]	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) [83]	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) [84, 85]	29,133	20 mg of beta-carotene only or with 50 mg of *alpha-tocopherol*	5–8	6–8	1.26 (0.98–1.62) for the 1985–1993 follow-up period

5.9.1.3.2 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 has been identified that included an RCT, a *case-control* and a *cohort study* and reported no statistically significant association [86].

5.9.1.4 Mechanisms

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

5.9.1.5 CUP Panel's conclusion

There is strong evidence from good quality cohort studies on dietary intake, serum levels and supplement use, which 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.

5.10 High-dose beta-carotene supplements

For evidence on high-dose beta-carotene supplements and prostate, see **Section 5.9**.

Table 5.11 summarises the number of published studies on high-dose beta-carotene supplements and the risk of cancer. Highest versus lowest and dose–response meta-analyses could not be conducted in the CUP due to heterogeneity between the studies and no continuous measure of supplement use in cohort studies.

Evidence for cancers of the following types was discussed in the CUP but was too limited to draw a conclusion:[1] mouth, pharynx, larynx (2018); oesophagus (adenocarcinoma and squamous cell carcinoma; 2016); lung (people who have never smoked; 2017) and skin (melanoma; 2017).

The strong evidence on the effects of taking high-dose beta-carotene supplements on the risk of lung cancer and skin (non-melanoma) cancer is described in the following subsections. This strong evidence includes analyses performed in the CUP and/or other published analyses, and information on mechanisms that could plausibly influence the risk of cancer. For evidence on high-dose beta-carotene supplements related to prostate cancer, see **Section 5.9**).

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.

Table 5.11: Summary of published studies of high-dose beta-carotene supplements and the risk of cancer

Cancer	Total no. of studies	RCT	Cohort studies	Conclusion[1]	Date of CUP cancer report[2]
Lung (people who smoke/ used to smoke tobacco)[3]	11	6	5	**Convincing: Increases risk[4]**	2017
Skin cancer (non-melanoma)[5]	3	2	1	**Substantial effect on risk unlikely**	2017

1 See Definitions of WCRF/AICR grading criteria (**Section 1**: Other dietary exposures 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 high-dose beta-carotene supplements and lung cancer (people who smoke or used to smoke tobacco) is derived from studies using high-dose supplements (20 to 30 milligrams per day or 50 milligrams per day on alternate days for beta-carotene; 25,000 international units per day for retinol).

4 The Panel made two separate conclusions on lung cancer and beta-carotene: one based on evidence on dietary intake and serum levels, and another on high-dose beta-carotene supplements. The evidence based on high-dose beta-carotene supplements is presented here. For information on dietary intake and serum levels, see **Section 5.9**.

5 The evidence for beta-carotene and non-melanoma skin cancer is derived from one study on plasma levels, as well as studies on high-dose supplement use (50 milligrams per day and 50 milligrams per day on alternate days).

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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.

5.10.1 Lung

(Also see CUP lung cancer report 2017: Section 7.2 and CUP lung cancer SLR 2015: Section 5.5.1.2.)

The evidence for high-dose beta-carotene supplements is presented in the following subsections. For evidence specifically on dietary intake and serum levels of beta-carotene and the risk of lung cancer, see **Section 5.9**.

5.10.1.1 Published randomised controlled trials

Six published RCTs on high-dose beta-carotene supplements and the risk of lung cancer were identified. A summary of the results from these published trials is presented in **Table 5.12**.

The Women's Antioxidant Cardiovascular Study reported no statistically significant association between taking 50 milligrams of beta-carotene every other day and the risk of lung cancer during an average of 9.4 years of treatment [87].

Both the ATBC and CARET studies reported a significant increased risk of lung cancer during the supplementation period, but at follow-up the effect was reduced and no longer statistically significant [81, 84].

In the ATBC study, beta-carotene supplementation in people smoking more than 20 cigarettes daily was associated with a 25 per cent increased risk of lung cancer (RR 1.25 [95% CI, 1.07–1.46]) compared with those

Table 5.12: Summary of published randomised controlled trials for high-dose beta-carotene supplements and the risk of lung cancer

Study name and intervention	No. of cases		Trial period RR (95% CI)	Post-trial period
	Intervention	Control		
Women's Antioxidant Cardiovascular Study [87] **Beta-carotene 50 mg every other day vs placebo**	41	33	June 1995– January 2005	
			1.26 (0.80–1.99)	
ATBC study, lung cancer incidence [84] **Daily 20 mg beta-carotene vs no beta-carotene in men who smoke**	242	209	April 1985– April 1993	May 1993– April 2011
			1.17 (1.02–1.33)	1.04 (0.96–1.11)
CARET study, lung cancer incidence [81] **Daily beta-carotene (30 mg) and retinyl palmitate (25,000 IU) in people who smoke or used to smoke**	5.92/ 1,000 person years	4.62/ 1,000 person years	1985– January 1996	February 1996– December 2001
			1.28 (1.04–1.57)	1.12 (0.97–1.31)
Australian cohort of asbestos workers [88] **30 mg/day beta-carotene vs 25,000 IU/day retinol**	6	4	June 1990– May 1995	
			1.50 (0.43–5.28)	
Physicians Health Study (PHS) [83] **50 mg beta-carotene on alternate days vs placebo group**	85	93	June 1982– December 1995	
			0.9 (0.7–1.2)	
Women's Health Study [89] **50 mg of beta-carotene every other day for 2 years (women)**	30	21	April 1993– January 1996	February 1998
				1.43 (0.82–2.49)

smoking 5 to 19 cigarettes daily, in whom no significant association was observed. Similarly, beta-carotene supplementation in people who consumed 11 grams of ethanol or more per day was associated with a significant increased risk of lung cancer (RR 1.35 [95% CI, 1.01–1.81]) compared with the effect of supplementation in people who consumed less alcohol.

In the CARET study, the increased risk of lung cancer was higher in those who consumed high-dose beta-carotene supplements and also were exposed to either asbestos or smoked tobacco (at least 20 pack-years), although neither subgroup was statistically significant.

In the PHS, the risk related to beta-carotene consumption was similar for each tobacco smoking category in subgroup analyses [83].

5.10.1.2 Published cohort studies

Five published cohort studies on high-dose beta-carotene supplements and the risk of lung cancer were identified. Four of them reported no statistically significant association. The fifth study [90], a Danish prospective study in men and women, showed a significant increase in the risk of lung cancer per 5,000 micrograms increase in beta-carotene supplementation

per day (the comparison of > 13,500 vs 0 micrograms per day was not significant). A summary of the results from the published cohort studies is presented in **Table 5.13**.

5.10.1.3 Genotype and beta-carotene

As reported in the 2007 Second Expert Report [1], there is an interaction between beta-carotene, tobacco smoking and genotype. Glutathione-S transferase 1 and 2 are *carcinogen*-detoxifying enzymes. People without or with less active forms of these enzymes are less able to metabolise certain toxins than others and have a higher risk of some cancers, particularly if they smoke tobacco.

In the ATBC study, among those not supplemented with beta-carotene, there was no statistically significant increase or decrease in the risk of lung cancer in people with the glutathione-S-transferase variant GSTM1 who smoked more than 42 cigarettes per day compared with those who smoked fewer than 37 cigarettes per day, but there was a significant increased risk for higher compared with lower tobacco smoking in those without the GSTM1 variant (RR 8.2 [95% CI 2.2–29.8]).

Table 5.13: Summary of published cohort studies for high-dose beta-carotene supplements and the risk of lung cancer

Study	Increment/contrast	RR (95% CI)	No. of cases
Virtamo, 2014 ATBC [91]	Use vs no use	1.04 (0.96–1.11)	2,881
Roswall, 2009 Denmark Cohort [90]	Per 5,000 µg/day	1.64 (1.20–2.23)	721
	> 13,500 vs 0 µg/day	1.56 (0.58–4.25)	
Satia, 2009 Vitamins And Lifestyle (VITAL) Cohort Study [92]	> 1,200 µg/day vs no use men	1.10 (0.71–1.70)	297
	> 1,200 µg/day vs no use women	1.49 (0.76–2.58)	224
Michaud, 2000 Health Professionals Follow-up Study [93]	Use vs no use	0.82 (0.36–1.85)	275
Michaud, 2000 Nurses' Health Study [93]		1.23 (0.55–2.76)	519

In those who received beta-carotene supplements, there was a significant increased risk of lung cancer in people who smoke more than 42 cigarettes per day compared with less than 37 cigarettes per day in those with (RR 3.6 [95% CI 1.1–11.1]) or without (RR 6.0 [95% CI 1.9–19.1]) the GSTM1 variant.

In another study of Chinese tin miners at high risk of lung cancer, after adjusting for age and tobacco smoking, those with the wild-type Arg/Arg genotype in the XRCC1 gene (which is involved in DNA repair) had a statistically significant increased risk of lung cancer for the highest compared with the lowest tertiles of serum beta-carotene (RR 3.0 [95% CI 1.3–7.1], 190 to 900 micrograms per litre compared with < 90 micrograms per litre). No significant increase or decrease in risk was observed in people with the heterozygous or homozygous Arg/Trp or Trp/Trp variants [94].

5.10.1.4 Published pooled analyses and meta-analyses

No published pooled analyses and no published meta-analyses on beta-carotene supplements and the risk of lung cancer were identified.

5.10.1.5 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 two out of three intervention trials, high-dose beta-carotene supplements in humans were shown to increase the risk of lung cancer among people who smoke. These findings contrast with epidemiologic studies on dietary-derived beta-carotene and circulating beta-carotene levels, which generally report a decreased risk of lung cancer. The mechanisms underlying the effect of beta-carotene supplementation on lung cancer risk are likely complex and not fully understood. It has been hypothesised that carotenoids can also display pro-oxidant activity, and animal model studies have demonstrated that administration of high-dose beta-carotene leads to the initiation of lung neoplasia in the presence of tobacco smoke [95, 96]. High-dose beta-carotene in smoke-exposed animals was also found to yield a number of transient oxidative metabolites and upregulation of cytochrome P450 enzymes that may result in the destruction of retinoic acid, diminished retinoid signalling and enhanced cell proliferation [97, 98]. In addition, specific beta-carotene metabolites facilitate the binding of smoke-derived carcinogens to DNA. Overall, it appears that with respect to the risk of lung cancer the dose of beta-carotene is critical and likely explains the apparent paradoxical elevation of lung cancer incidence among people who smoke and who take high-dose beta-carotene supplements.

5.10.1.6 CUP Panel's conclusion

There is strong evidence from good-quality RCTs, which is consistent in terms of direction of effect with cohort studies. An interaction between tobacco smoking, genetics and beta-carotene is apparent; the adverse effect of high-dose beta-carotene supplements is seen mainly among people who smoke a lot of tobacco and in particular a subgroup characterised by genetic variation in GSTM. The evidence that high-dose beta-carotene supplements cause lung cancer in people who smoke or used to smoke tobacco is convincing.

The CUP Panel concluded:

- **High-dose beta-carotene supplements are a convincing cause of lung cancer in people who smoke or used to smoke tobacco.**

Table 5.14: Summary of published randomised controlled trials for beta-carotene supplements and the risk of non-melanoma skin cancer

Study	Length of intervention (years)	Total no. participants	Cases treatment/ placebo	Gender	Contrast	RR (95% CI)
PHS [100]	12	22,071	1,786/ 1,821	M	50 mg every other day vs placebo	0.98 (0.92–1.05)
Beta Carotene Trial 1983–89 [101]	5	1,805	362/340	M/W	50 mg/day vs placebo	1.04 (0.89–1.21)

5.10.2 Skin (non-melanoma)

(Also see CUP skin cancer SLR 2017: Section 5.5.1.2.)

The evidence for plasma levels and supplement use are presented in the following subsections. Highest versus lowest and dose–response meta-analyses could not be conducted as there were too few studies.

5.10.2.1 Plasma beta-carotene

5.10.2.1.1 Published nested case-control study

One published *nested case-control study* was identified, in which there was no statistically significant association between plasma beta-carotene concentration and the risk of non-melanoma skin cancer (RR 0.97 [95% CI 0.69–1.37] for ≥ 23.29 versus ≤ 7.28 micrograms per 100 millilitres of plasma beta-carotene among subjects assigned to placebo) [99].

5.10.2.1.2 Published pooled analyses and meta-analyses

No published pooled analyses and no published meta-analyses on plasma beta-carotene and the risk of non-melanoma skin cancer were identified.

5.10.2.2 High-dose beta-carotene supplements

5.10.2.2.1 Published randomised controlled trials

Two RCTs on beta-carotene supplements and the risk of non-melanoma skin cancer were identified. A summary of the results from these trials is presented in **Table 5.14**.

In both RCTs, analyses stratified by smoking did not show any significant effects regarding increase or decrease in risk of lung cancer [100, 101].

5.10.2.2.2 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 non-melanoma skin cancer has been identified, which included four RCTs and reported no statistically significant effect [102].

5.10.2.3 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.

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

5.10.2.4 CUP Panel's conclusion

There is strong evidence on beta-carotene from two good-quality RCTs on supplements and one nested case-control study on plasma levels, which all fail to demonstrate an association with the risk of non-melanoma skin cancer. There was no evidence of an adverse or protective effect for non-melanoma cancer using supplements at doses of 50 milligrams either daily or on alternate days.

The CUP Panel concluded:

- **Consuming high-dose beta-carotene supplements is unlikely to have a substantial effect on the risk of non-melanoma skin cancer.**

5.11 Calcium supplements

Table 5.15 summarises the main findings from the CUP highest versus lowest meta-analysis on calcium supplements and the risk of colorectal cancer. A dose–response meta-analysis could not be conducted in the CUP as there were too few studies.

Evidence for cancers of the following types was discussed but was too limited to draw a conclusion:[1] mouth, pharynx and larynx (2018); gallbladder (2015); liver (2015); breast (pre and postmenopause; 2017); prostate (2014); kidney (2015); bladder (2015) and skin (2017).

The strong evidence on the effects of taking calcium supplements on the risk of cancer is described in the following subsections.

Table 5.15: CUP highest versus lowest meta-analysis of calcium supplements and the risk of colorectal cancer

Cancer	Total no. of studies	No. of studies in highest vs lowest plot	No. of cases	Risk estimate (95% CI)	Contrast	I² (%)	Conclusion[1]	Date of CUP cancer report[2]
Colorectum[3]	10	7	9,115	6 studies reported decreased risk, which was significant in 2 studies[4]	Highest vs lowest[5]	–	**Probable: Decreases risk**	2017
	1	–	–	No significant effect in one RCT[6]	–	–		

1 See Definitions of WCRF/AICR grading criteria (**Section 1**: Other dietary exposures 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 calcium supplements and colorectal cancer is derived from studies using supplements at a dose >200 milligrams per day.

4 No summary estimate is provided as the dose of calcium supplement varied between the studies.

5 The highest versus lowest meta-analysis for calcium supplements and the risk of colorectal cancer has not been not updated; results from the 2010 CUP colorectal cancer SLR are presented (see CUP colorectal cancer SLR 2016, Appendix 5).

6 Evidence is from an RCT of calcium and vitamin supplements with a dose of 1,000 milligrams elemental calcium carbonate plus 400 international units of vitamin D_3 daily in 36,282 postmenopausal women in the USA [103]. No significant effect was observed compared with placebo (RR 1.06 [95% CI 0.85–1.32]).

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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.

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.

5.11.1 Colorectum

(Also see CUP colorectal cancer report 2017: Section 7.9 and CUP colorectal cancer SLR 2016: Section 5.5.10 and Appendix 5.)

5.11.1.1 Published randomised control trial

One published RCT on calcium supplements and the risk of colorectal cancer was identified. The Women's Health Initiative [103] was a double-blind, placebo-controlled clinical trial of 1,000 milligrams elemental calcium carbonate plus 400 international units of vitamin D$_3$ daily, with an average intervention period of seven years, in 36,282 postmenopausal women in the USA. The primary outcome measure was hip fracture, with total fractures and colorectal cancer as secondary outcome measures. No significant effects on the risk of colorectal cancer were observed for calcium and vitamin D supplementation compared with placebo use in all trial participants (RR 1.06 [95% CI 0.85–1.32]) and after excluding women using personal calcium or vitamin D supplements at baseline (RR 0.81 [95% CI 0.58–1.13]).

5.11.1.2 CUP highest versus lowest meta-analysis

A dose–response meta-analysis could not be conducted in the CUP. Seven of ten identified studies were included in the highest versus lowest meta-analysis; six studies reported a decreased risk, two of which were statistically significant [104, 105]. In another there was a significant decreased risk in men but not women [106]. One reported non-significant increased risk [107] (see **Figure 5.6**).

Figure 5.6: CUP highest versus lowest meta-analysis[1] for consumption of calcium supplements and the risk of colorectal cancer

Author	Year	Sex		Highest vs lowest supplemental calcium RR (95% CI)	Contrast
Park	2009	M		0.74 (0.58, 0.94)	>1000 vs 0 mg/d
Park	2009	W		0.86 (0.72, 1.02)	>1000 vs 0 mg/d
Park	2007	M		0.74 (0.60, 0.91)	>200 vs 0 mg/d
Park	2007	W		0.82 (0.69, 0.98)	>200 vs 0 mg/d
Flood	2005	W		0.76 (0.57, 1.01)	>801 (median 1130) vs 0 mg/d
Lin	2005	W		1.30 (0.90, 1.87)	≥500 vs 0 mg/d
Feskanich	2004	W		0.87 (0.69, 1.10)	users vs non users
McCullough	2003	M/W		0.69 (0.49, 0.97)	>500 (median 730) vs 0 mg/d
Kampman	1994	M/W		0.95 (0.50, 1.79)	users vs non users

.493   1   2.03

Source: Park, 2009 [106]; Park, 2007 [104]; Flood, 2005 [108]; Lin, 2005 [107]; Feskanich, 2004 [109]; McCullough, 2003 [105], Kampman, 1994 [110].

[1] Seven studies were analysed in the CUP highest versus lowest meta-analysis. In two studies [104, 106], the relative risk for men and women was reported separately.

5.11.1.3 Published pooled analyses and meta-analyses

No published pooled analyses were identified. One other published meta-analysis on consumption of calcium supplements and the risk of colorectal cancer has been identified, which reported a statistically significant decreased risk of colorectal cancer when comparing the highest with the lowest levels of intake (RR 0.76 [95% CI 0.65–0.89]) [111].

5.11.1.4 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.

A long-standing mechanism proposed for calcium and its potential activity against colorectal cancer development is the ability of calcium to bind unconjugated bile acids and free fatty acids, diminishing their toxic effects on the colorectum [112]. More recent cell culture studies suggest that calcium may also reduce cancer *cell proliferation* and promote *cell differentiation*, likely by influencing different cell-signalling pathways [113].

5.11.1.5 CUP Panel's conclusion

The evidence was generally consistent and showed a decreased risk of colorectal cancer with consumption of calcium supplements (> 200 mg per day). The RCT reported a non-significant decreased risk for calcium and vitamin D supplementation compared with placebo use after excluding women who were using personal calcium or vitamin D

supplements at baseline. Six of the seven cohort studies in the highest versus lowest meta-analysis reported a decreased risk. One published meta-analysis reported a statistically significant decreased risk for colorectal cancer. There is evidence of plausible mechanisms in humans.

> **The CUP Panel concluded:**
>
> - **Calcium supplements probably protect against colorectal cancer.**

5.12 Multivitamin supplements

Table 5.16 summarises the main findings from the CUP highest versus lowest meta-analysis of cohort studies on consumption of multivitamin supplements and the risk of colorectal cancer. A dose–response meta-analysis could not be conducted in the CUP.

Evidence for cancers of the following types was discussed in the CUP but was too limited to draw a conclusion:[1] lung (2017), stomach (2016), pancreas (2012), endometrium (2013), prostate (2014), bladder (2015) and skin (2017).

For more information on the evidence for taking multivitamin supplements and the risk of cancer that was graded by the Panel as 'limited – suggestive' and suggests a direction of effect, see the CUP documents listed:

- CUP colorectal cancer report 2017: Section 7.11 and CUP colorectal cancer SLR 2016: Section 5.5.13.

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[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.

Table 5.16: CUP highest versus lowest meta-analysis of users versus non-users of multivitamin supplements[1] and the risk of colorectal cancer

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Contrast	Conclusion[2]	Date of CUP cancer report[3]
Colorectum	11	11	8,072	0.88 (0.79–0.98)	Users vs non-users	Limited – suggestive: Decreases risk	2017
	1	–	–	No significant effect in one RCT[4]	–		

1   Definitions and categorisation of multivitamin supplements are not standardised across studies.

2   See Definitions of WCRF/AICR grading criteria (**Section 1**: Other dietary exposures and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'limited – suggestive'.

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

4   Evidence is from an RCT of multivitamin supplementation with vitamin E (400 international units of synthetic tocopherol), vitamin C (500 milligrams of synthetic ascorbic acid) and beta-carotene (50 milligrams of lurotin) in 14,641 male physicians in the USA [114]. No significant effect was observed compared with placebo (RR 0.89 [95% CI 0.68–1.17]).

Also, for information on mechanisms that could plausibly influence the risk of cancer, see **Appendix 2**. Please note that the information supersedes that in CUP cancer reports published before this Third Expert Report.

5.13 Other

The effect of other dietary exposures 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 selenium supplements, vitamin E supplements and acrylamide. 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 taking high-dose beta-carotene supplements is a cause of lung cancer in people who smoke and that high beta-carotene supplements characterised by supplements and serum levels (and also dietary intake for prostate) are unlikely to have a substantial effect on the risk of prostate cancer and non-melanoma skin cancer. In addition, there was strong evidence that calcium supplements are protective against colorectal cancer and that selenium supplements are protective against prostate cancer. In general, this evidence from 2007 has stayed strong, and the strong evidence for beta-carotene supplements being a cause of lung cancer has been expanded to include people who used to smoke. However, more studies were included to assess the association between selenium supplements and prostate cancer leading to the strength of evidence and the judgement being downgraded from a probable cause to limited – no conclusion.

In this Third Expert Report, there is new strong evidence that glycaemic load is a cause of endometrial cancer.

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Abbreviations

AICR   American Institute for Cancer Research

aMED   alternate Mediterranean

ATBC   Alpha-Tocopherol Beta-Carotene Cancer Prevention Study

BMI   Body mass index

CARET   Beta-carotene and Retinol Efficacy Trial

CI   Confidence interval

CUP   Continuous Update Project

DNA   Deoxyribonucleic acid

GSTM   Glutathione-S-transferase

HEI-2005   Healthy Eating Index-2005

HPV   Human papilloma virus

MHT   Menopausal hormone therapy

NSCLC   Non-small-cell lung cancer

PHS   Physicians' Health Study

PSA   Prostate-specific antigen

RR   Relative risk

RCT   Randomised control trial

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**).

Angiogenesis

The process of generating new blood vessels.

Apoptosis

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

Basal cell carcinoma

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

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

Type of organic compound of sugars and an essential intermediate in the conversion of food to energy. A dietary micronutrient that releases energy when metabolised in the body.

Carcinogen

Any substance or agent capable of causing cancer.

Carcinogenesis

The process by which a malignant tumour is formed.

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 differentiation

The process of development of cells to take on the structural and functional characteristics specific to a particular tissue. Also, the degree to which tumour cells have the structure or function of the tissue from which the tumour arose. Tumours can be described as well, moderately or poorly differentiated: well-differentiated tumours appear similar to the cells of the tissue in which they arose; poorly differentiated tumours do not. The degree of differentiation may have prognostic significance.

Cell proliferation

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

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.

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.

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.

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.

Endocrine
Referring to organs or glands that secrete hormones into the blood.

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.

Exocrine
Relating to or denoting glands that secrete their products through ducts opening on to an epithelium rather than directly into the blood.

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.

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.

Glycaemic index

A measure of the increase in blood glucose (and insulin) after consumption of a standard amount of a food under controlled conditions.

Glycaemic load

The product of multiplying the glycaemic index by the amount of carbohydrate in a food as consumed. The glycaemic load of a diet takes into account the calculated aggregate of the glycaemic loads of the foods constituting that diet.

Head and neck cancer

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

Heterogeneity

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

High-income countries

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

Hormone

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

Hyperinsulinaemia

High blood concentrations of insulin.

Inflammation

The immunologic response of tissues to injury or infection. Inflammation is characterised by accumulation of white blood cells that produce several bioactive chemicals (cytokines), causing redness, pain, heat and swelling. Inflammation may be acute (such as in response to infection or injury) or chronic (as part of several conditions, including obesity).

Insulin

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.

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.

Macronutrient

The components of the diet that provide energy: protein, carbohydrate and fat.

Malignancy

A tumour with the capacity to spread to surrounding tissue or to other sites in the body.

Melanoma

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

Menopausal hormone therapy (MHT)

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

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

Mutation

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

Nested case-control study

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

Non-communicable diseases (NCDs)

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

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.

Odds ratio
A measure of the risk of an outcome such as cancer, associated with an exposure of interest, used in case-control studies; approximately equivalent to relative risk.

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

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

Polycyclic aromatic hydrocarbons (PAHs)
Potentially carcinogenic chemicals formed when muscle meat, including beef, pork, fish or poultry, is cooked using high-temperature methods.

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.

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

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 (H_2O_2) or superoxide radical (O^2–).

Rectum
The final section of the large intestine, terminating at the anus.

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.

Selenoproteins
Any protein which includes a selenocysteine residue, a selenium-containing amino acid.

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.

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

Systematic literature review (SLR)
A means of compiling and assessing published evidence that addresses a scientific question with a predefined protocol and transparent methods.

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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.

Healthy dietary patterns
Mouth, pharynx and larynx

Healthy dietary patterns characterised by higher consumption of fruit and vegetables and reflecting lower consumption of alcohol as well as red and *processed meats* have been shown to be protective for cancers of the mouth, pharynx and larynx [115]. It is likely that multiple individual components of healthy dietary patterns contribute to a potential impact on development of cancers of the mouth, pharynx and larynx, either with additive or interactive effects on pathways involved in oral *carcinogenesis*. Further development of statistical and bioinformatics approaches to examining dietary patterns in prospective cohort studies and oral cancer risk, particularly in those at higher risk due to tobacco smoking and infections, will provide greater insight into key relationships. There are currently no human clinical intervention trials evaluating healthy dietary patterns and the risk of cancers of the mouth, pharynx and larynx.

Glycaemic load
Endometrium

The major proposed mechanisms by which the intake of foods with higher glycaemic load could affect endometrial cancer risk relate to elevated postprandial glucose and *insulin* levels, and subsequent development of *insulin resistance*, diabetes and *obesity* – all factors that are associated with endometrial cancer development [55–57].

Foods and drinks containing fructose
Pancreas

Fructose is metabolised largely in the liver. Higher fructose intake may promote the development of non-alcoholic fatty liver disease and a cancer-promotive environment [116]. Fructose has also been shown to enhance *insulin resistance*, *inflammation* and production of *reactive oxygen species* [117].

Foods containing saturated fatty acids
Pancreas

Higher consumption of saturated fatty acids may be pro-inflammatory and promote the development of *insulin resistance*, both of which are proposed mechanisms for pancreatic cancer development [118]. An *in vitro* study on the HPAF line of pancreatic cancer cells shows a growth-promoting effect of saturated fatty acids [119], but there is little additional supporting data.

Foods containing retinol
Lung

Retinoid molecules possess an antiproliferative effect at the cellular level via growth arrest signalling, promotion of differentiation and induction of *apoptosis* [120]. Retinoic acid has also been shown to downregulate markers of *cell proliferation* such as hTERT (human telomerase reverse transcriptase) and cyclins D1 and 3, markers of DNA damage such as 8-oxo dGuo [121–123], and growth factors such as epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF), potentially inhibiting tumour growth, *angiogenesis* and *metastasis* [124, 125]. Retinoids are also hypothesised to modulate additional targets such as *reactive oxygen species*, mitochondrial permeability, lipoxygenase, cyclooxygenase-2 (Cox-2), nuclear factor-kB, ubiquitination, tumor necrosis factor-α, c-Myc, Ap-1 and cell surface death receptors [126].

Vitamin D
Colorectum

Underlying mechanisms for an association of vitamin D with colorectal cancer risk have been mostly studied in *in vitro* and experimental models, and there are limited data in humans. These studies suggest a role for circulating vitamin D, through its active form $1\alpha,25$-dihydroxyvitamin D3[1,25(OH)2D3], in control of cell growth, by reducing *cell proliferation* and promoting differentiation and *apoptosis* [127]. Other purported mechanisms of vitamin D action pertain to improved innate and adaptive immune function, inhibition of *angiogenesis*, reduced *inflammation* and regulation of microRNA expression with higher vitamin D status [127–129].

Low plasma alpha-tocopherol concentrations
Prostate

Alpha-tocopherol is believed to be the most biologically active isomer of vitamin E, with anti-oxidative properties. Alpha-tocopherol has also been shown to favourably modulate immune function, induce cellular *apoptosis* and lower concentrations of circulating testosterone [130].

Low plasma selenium concentrations
Prostate

Experimental evidence suggests selenium induces *apoptosis* and inhibits *cell proliferation* in tumour cell lines [131, 132]. In addition, selenium availability has been shown to regulate the activity of glutathione peroxidase, an enzyme which protects the cell from peroxide damage [132].

Beta-carotene
Lung

A number of human studies and meta-analyses have shown that higher circulating levels of *carotenoids* including β-carotene, lycopene and β-cryptoxanthin are associated with lower risk of lung cancer [133]. A number of human studies and meta-analyses have shown that higher circulating levels of β-carotene are associated with a lower risk of lung cancer [133]. Further, evidence from both animal and laboratory studies have shown that carotenoids can block certain carcinogenic processes and inhibit tumor cell growth [134, 135]. Some proposed mechanisms for these actions include (1) functioning as an antioxidant [136, 137]; (2) acting as a precursor for retinoic acid [138, 139]; (3) enhancing immunologic function [140, 141]; (4) inducing of *carcinogen*-metabolising enzymes [142]; and (5) inhibiting of *cell proliferation* and inducing of *apoptosis*.

Prostate

No mechanisms are presented.

High-dose beta-carotene supplements
Lung (people who smoke/used to smoke tobacco)

High-dose beta-carotene supplements in humans were shown to increase the risk of lung cancer among people who smoke in two out of three intervention trials. These findings contrast with epidemiologic studies on dietary-derived beta-carotene and circulating beta-carotene levels which generally report a decreased risk of lung cancer. The mechanisms underlying the effect of beta-carotene supplementation on lung cancer risk are likely complex and not fully understood. It has been hypothesised that *carotenoids* can also display pro-oxidant activity, and animal model studies have demonstrated that administration of high-dose beta-carotene leads to the initiation of lung neoplasia in the presence of tobacco smoke [95, 96]. High-dose beta-carotene in the smoke-exposed animals was also found to yield a number of transient oxidative metabolites and upregulation of cytochrome P450 enzymes that may result in the destruction of retinoic acid, diminished retinoid signalling and enhanced *cell proliferation* [97, 98]. In addition, specific beta-carotene metabolites facilitate the binding of smoke-derived *carcinogens* to DNA. Overall, it appears that the dose of beta-carotene is critical with respect to the risk of lung cancer and likely explains the apparent paradoxical elevation of lung cancer incidence among people who smoke and who take high-dose beta-carotene supplements.

Skin (non-melanoma)

No mechanisms are presented.

Calcium supplements
Colorectum

A long-standing mechanism proposed for calcium and its potential activity against colorectal cancer development is the ability of calcium to bind unconjugated bile acids and free fatty acids, diminishing their toxic effects on the colorectum [112]. More recent cell culture studies suggest that it may also reduce cancer *cell proliferation* and promote *cell differentiation*, likely by influencing different cell-signalling pathways [113].

Multivitamin supplements
Colorectum

Multivitamin supplements consist of a combination of several or in some instances many vitamins, making it challenging to determine the specific active ingredient. Numerous vitamins contained in multivitamin supplements have been shown to capture *free radicals and reactive oxygen species* and to prevent *lipid peroxidation* [143].

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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