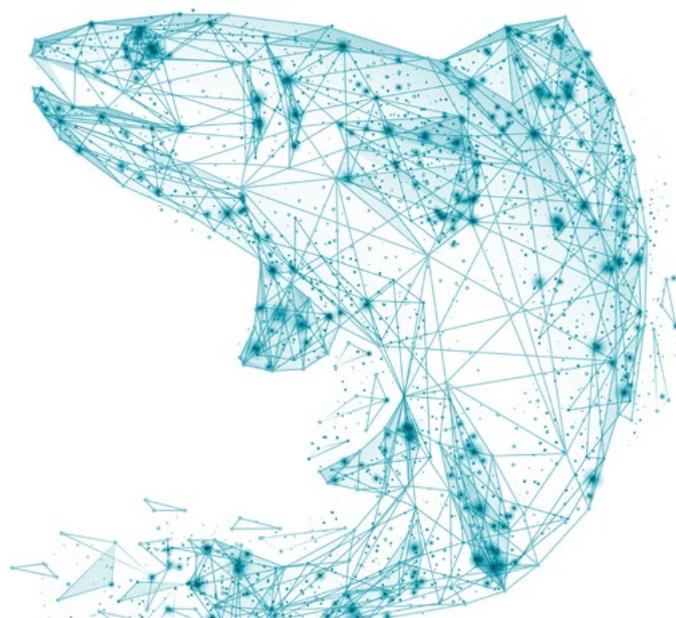World Cancer Research Fund
American Institute for Cancer Research

CUP Continuous Update Project

Analysing research on cancer prevention and survival

Meat, fish and dairy products
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. Meat, fish and dairy products 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.

How to cite the Third Expert Report

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

Key

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

References to other parts of the Third Expert Report are highlighted in purple.

Executive summary

Background and context

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

Meat, fish and dairy products are all animal foods. Animal foods is a term used to describe all foods of animal origin. These foods may be derived from the animal flesh itself (for example, meat, fish and poultry) or foods that are produced by animals (for example, eggs, as well as dairy products such as milk and products made from milk including cheese, butter, ghee and yoghurt).

Animal foods are generally a good source of protein, but the fat content varies according to the specific species from which they are derived. Dairy products are a good source of calcium. Consumption of foods such as red meat and fish generally increases with economic development, whereas consumption of dairy products is variable, particularly in Asia where many populations are *lactose intolerant*.

Animal foods such as meat and fish may be processed before consumption by smoking, curing, salting or by adding preservatives. Meat and fish are also often cooked using very high temperatures during frying, grilling (broiling) or barbecuing (charbroiling). These methods of processing and preparation may affect the chemical composition as well as the nutritional value of animal foods.

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

Findings

There is strong evidence that consuming:

- **red meat increases** the risk of colorectal cancer

- **processed meat increases** the risk of colorectal cancer

- **Cantonese-style salted fish increases** the risk of nasopharyngeal cancer

- **dairy products decrease** the risk of colorectal cancer

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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.

For red meat, processed meat and Cantonese-style salted fish the evidence shows that, in general, the more people consume, the higher the risk of some cancers. In contrast, the evidence shows that, in general, the more dairy products people consume, the lower the risk of colorectal cancer.

The Panel used the strong evidence on red meat and processed meat when making recommendations (see below) designed to reduce the risk of developing cancer.

A global recommendation about consumption of Cantonese-style salted fish has not been made as this type of fish is consumed only in specific parts of the world. Nevertheless, the Panel advises that it is best not to consume Cantonese-style salted fish (see Recommendations and public health and policy implications, Section 3: Issues relevant only in specific parts of the world – Cantonese-style salted fish).

The Panel did not base a recommendation on the strong evidence that the consumption of dairy products decreases the risk of colorectal cancer, as there is other evidence that is suggestive of an increased risk of prostate cancer; although, that evidence fell below the general threshold required for making a recommendation (See Recommendations and public health and policy implications, Section 3: Issues on which the evidence is divergent between cancer sites – Dairy products and calcium).

There is also other evidence on meat, fish and dairy products that is limited (either in amount or by methodological flaws) but 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. For people who eat meat this includes eating no more than moderate amounts of red meat, such as beef, pork and lamb, and eating little, if any, processed meat. 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. Meat, fish and dairy products and the risk of cancer: a summary matrix

MEAT, FISH AND DAIRY PRODUCTS AND THE RISK OF CANCER				
WCRF/AICR GRADING		**DECREASES RISK**		**INCREASES RISK**	
		Exposure	**Cancer site**	**Exposure**	**Cancer site**
STRONG EVIDENCE	**Convincing**			Processed meat[1]	Colorectum 2017
	Probable	Dairy products	Colorectum 2017[2]	Red meat[3] Cantonese-style salted fish[4]	Colorectum 2017 Nasopharynx 2017
LIMITED EVIDENCE	**Limited – suggestive**	Fish	Liver 2015 Colorectum 2017	Red meat[3]	Nasopharynx 2017 Lung 2017 Pancreas 2012
				Processed meat[1]	Nasopharynx 2017 Oesophagus (squamous cell carcinoma) 2016 Lung 2017 Stomach (non-cardia) 2016 Pancreas 2012
				Foods containing haem iron[6]	Colorectum 2017
				Grilled (broiled) or barbecued (charbroiled) meat and fish	Stomach 2016
		Dairy products	Breast (premenopause) 2017[5]	Dairy products	Prostate 2014[7]
		Diets high in calcium	Breast (premenopause) 2017 Breast (postmenopause) 2017	Diets high in calcium	Prostate 2014
STRONG EVIDENCE	**Substantial effect on risk unlikely**	None identified			

1 The term 'processed meat' in the CUP refers to meats transformed through salting, curing, fermentation, smoking or other processes to enhance flavour or improve preservation.

2 The evidence for dairy products and colorectal cancer includes total dairy, milk and cheese and dietary calcium intakes.

3 The term 'red meat' in the CUP refers to beef, veal, pork, lamb, mutton, horse and goat.

4 Cantonese-style salted fish is part of the traditional diet consumed by people living in the Pearl River Delta region in Southern China. This style of fish, which is prepared with less salt than is used in the northern part of China, is allowed to ferment, and so is eaten in a decomposed state. This conclusion does not apply to fish preserved (or salted) by other means. Evidence is primarily from case-control studies, there is only one cohort study.

5 The evidence for dairy products and premenopausal breast cancer includes total dairy and milk intakes.

6 The term 'haem iron' refers to iron attached to a haemoprotein, which is found only in foods of animal origin. Foods that contain haem iron include red and processed meat, fish and poultry.

7 The evidence for dairy products and prostate cancer includes total dairy, milk, cheese and yogurt intakes.

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

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

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

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

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

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

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

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

'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.
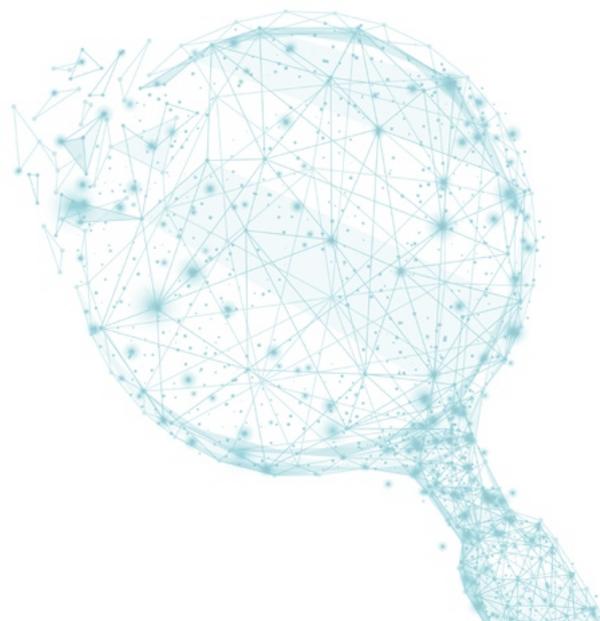
2. Summary of Panel judgements

The conclusions drawn by the CUP Panel are based on the evidence from both epidemiological and mechanistic studies relating meat, fish and dairy products to the risk of development of particular cancer types. Each conclusion on the likely causal relationship between meat, fish and dairy products 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**

  - **Processed meat:**[1] Consumption of processed meat is a convincing cause of colorectal cancer.

Probable

- **Decreased risk**

  - **Dairy products:** Consumption of dairy products probably protects against colorectal cancer.[2]

- **Increased risk**

  - **Red meat:**[3] Consumption of red meat is probably a cause of colorectal cancer.

  - **Cantonese-style salted fish:**[4] Consumption of Cantonese-style salted fish is probably a cause of nasopharyngeal cancer.

For red meat, processed meat and Cantonese-style salted fish the evidence shows that, in general, the more people consume, the higher the risk of some cancers. In contrast, the evidence shows that, in general, the more dairy products people consume, the lower the risk of colorectal cancer.

The Panel used the strong evidence on red meat and processed meat 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).

A global recommendation about consumption of Cantonese-style salted fish has not been made as this type of fish is consumed only in specific parts of the world. Nevertheless, the Panel advises that it's best not to consume Cantonese-style salted fish (see Recommendations and public health and policy implications, Section 3: Issues relevant only in specific parts of the world – Cantonese-style salted fish).

The Panel did not base a recommendation on the strong evidence that the consumption of dairy products decreases the risk of colorectal cancer as there is some other evidence that is suggestive of an increased risk of prostate cancer, although that evidence fell below the general threshold required for making a recommendation (see Recommendations and public health and policy implications, Section 3: Issues where the evidence is divergent between cancer sites – Dairy products and calcium).

LIMITED EVIDENCE

Limited – suggestive

- **Decreased risk**
    - **Fish:** The evidence suggesting that consumption of fish decreases the risk of liver cancer and colorectal cancer is limited.
    - **Dairy products:** The evidence suggesting that consumption of dairy products decreases the risk of premenopausal breast cancer[5] is limited.
    - **Diets high in calcium:** The evidence suggesting that diets high in calcium decrease the risk of pre and postmenopausal breast cancer is limited.

- **Increased risk**
    - **Red meat:[3]** The evidence suggesting that consumption of red meat increases the risk of cancers of the following types is limited: nasopharynx, lung and pancreas.
    - **Processed meat:[1]** The evidence suggesting that consumption of processed meat increases the risk of cancers of the following types is limited: nasopharynx, oesophagus (squamous cell carcinoma), lung, stomach (non-cardia) and pancreas.
    - **Foods containing haem iron:[6]** The evidence suggesting that consumption of foods containing haem iron increases the risk of colorectal cancer is limited.
    - **Grilled (broiled) or barbecued (charbroiled) meat and fish:** The evidence suggesting that consumption of grilled (broiled) or barbecued (charbroiled) meat and fish increases the risk of stomach cancer is limited.
    - **Dairy products:** The evidence suggesting that consumption of dairy products increases the risk of prostate cancer[7] is limited.
    - **Diets high in calcium:** The evidence suggesting that diets high in calcium 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**: Meat, fish and dairy products and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'strong, 'convincing', 'probable', 'limited and 'limited – suggestive'.

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1. The term 'processed meat' in the CUP refers to meats transformed through salting, curing, fermentation, smoking or other processes to enhance flavour or improve preservation.
2. The evidence for dairy products and colorectal cancer includes total dairy, milk and cheese and dietary calcium intakes.
3. The term 'red meat' in the CUP refers to beef, veal, pork, lamb, mutton, horse and goat.
4. Cantonese-style salted fish is part of the traditional diet consumed by people living in the Pearl River Delta region in Southern China. This style of fish, which is prepared with less salt than is used in the northern part of China, is allowed to ferment, and so is eaten in a decomposed state. This conclusion does not apply to fish preserved (or salted) by other means. Evidence is primarily from case-control studies, there is only one cohort study.
5. The evidence for dairy products and premenopausal breast cancer includes total dairy and milk intakes.
6. The term 'haem iron' refers to iron attached to a haemoprotein, which is found only in foods of animal origin. Foods that contain haem iron include red and processed meat, fish and poultry.
7. The evidence for dairy products and prostate cancer includes total dairy, milk, cheese and yogurt intakes.

3. Definitions and patterns

Meat, fish and dairy products are all animal foods. Animal foods is a term used to describe all foods of animal origin. These foods may be derived from the animal flesh itself (for example, red meat, fish and poultry) or foods which are produced by animals (for example, eggs, as well as dairy products such as milk and products made from milk including cheese, butter, ghee and yoghurt).

Animal foods are generally a good source of protein, but the fat content is variable according to the specific species from which they are derived. Dairy products are a good source of calcium. Consumption of foods such as red meat and fish generally increases with economic development, whereas consumption of dairy products is variable, particularly in Asia where many populations are *lactose intolerant*.

Animal foods such as meat and fish may be processed before consumption by smoking, curing, salting or by adding preservatives. Meat and fish are also often cooked using very high temperatures during frying, grilling (broiling) or barbecuing (charbroiling). These methods of processing and preparation may impact on the chemical composition as well as the nutritional value of animal foods.
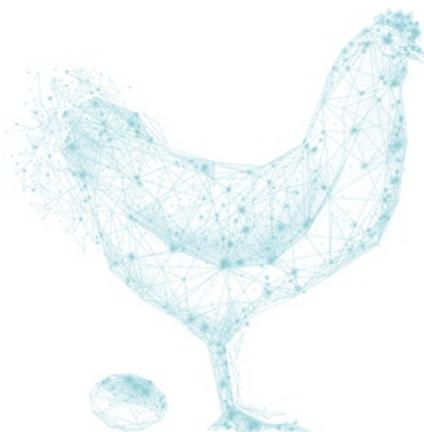
3.1 Red meat

In this Third Expert Report, the term 'meat' includes all animal flesh apart from fish and seafood. See **Box 1** for general information about meat composition and consumption patterns.

The term 'red meat' refers to all types of mammalian muscle meat. In this Third Expert Report this includes beef, veal, pork, lamb, mutton, horse and goat.

Meat can also be classified according to whether the animal was domesticated or wild. Most meats consumed around the world today are from domesticated animals and the evidence presented in this Third Expert Report reflects this; there are no separate analyses on domesticated and wild animals. Some meats are processed in various ways (see **Section 3.2**).

3.2 Processed meat

There is no generally agreed definition of 'processed meat'. The term is used inconsistently in epidemiological studies. The specificity of judgements and recommendations is therefore limited.

In the Third Expert Report the term 'processed meat' refers to meat that has been transformed through salting, curing, fermentation, smoking or other processes to enhance flavour or improve preservation. Depending on food preparation practices, processed meat can include ham, salami, bacon and pastrami and some sausages. These include sausages, bratwursts, chorizo, frankfurters and 'hot dogs', to which nitrites, nitrates or other preservatives are added. Most processed meats contain pork or beef but may also contain other red meats, poultry, offal or meat by-products such as blood. Minced meats such as hamburgers or fresh sausages may sometimes, though not always,

fall within the definition of processed meat. For general information about meat composition and consumption patterns, see **Box 1**.

3.2.1 Production of N-nitroso compounds

Nitrite is used to preserve processed meats (it is toxic to bacteria) and gives cured meats their recognisable colour and flavours. The addition of nitrite to food is regulated and monitored in most countries.

Nitrite can react with the degradation products of amino acids to form *N-nitroso compounds* (*nitrosamines* or nitrosamides). These may be formed in meat during the curing process or in the body (particularly in the stomach) following intake of dietary nitrite (or nitrate).

Processed meat is also a source of exogenously derived *N-nitroso compounds*, which may have carcinogenic potential [4].

3.3 Foods containing haem iron

Haem iron, which is iron attached to a haemoprotein, is found only in foods of animal origin, such as meat and meat products, fish and blood products. The iron in plant foods is non-haem iron. The amount of dietary iron needed to meet the body's requirements depends on its bioavailability from the diet. This varies with the type of iron, other aspects of the diet, as well as factors related to the consumer such as their iron status. Iron from animal sources is better absorbed than iron from plant sources, but non-haem iron *absorption* is enhanced when the body's iron status is low, or when iron-rich foods are eaten together with foods rich in vitamin C or with meat.

3.4 Fish

The definition of fish in this Third Expert Report includes any of various cold-blooded, aquatic vertebrates, having gills, commonly fins, and typically an elongated body covered with scales. It also includes shellfish. There are more than 27,000 species of salt and freshwater fish; many crustaceans, bivalves and cephalopods can also be eaten. Like meat, fish is also processed, for instance by drying, salting (see **Section 3.5**) and smoking. For general information about fish composition and consumption patterns, see **Box 2**.

3.5 Cantonese-style salted fish

Salting is a traditional method of preserving raw fish throughout much of the world. Salted fish is a component of diets typical of Asia, Africa and parts of the Mediterranean. The freshness of the fish and the salting and drying conditions vary considerably between regions, although fish are usually dried outside, in direct sunlight.

Depending on the precise conditions, salt-preserved fish may also undergo fermentation. The degree of fermentation that occurs depends on the freshness of the raw fish, the amount of salt used, the outdoor temperature and the duration of the drying process. In general, excluding the factor of freshness, salted fish is less likely to be fermented in the northern part of China than in the southern part of China (where nasopharyngeal cancer is more common).

Box 2: Fish – composition and consumption patterns

Composition
Fish contains about 6 to 25 per cent protein by weight. It has a fat content of between 0.7 per cent by weight in low-fat fish, such as cod or skate, and 19 per cent in oily fish such as Atlantic salmon [5].

Consumption patterns
Globally, about 19 kilograms per capita per year of fish is available for consumption, which supplies average daily intakes of 33 kilocalories, 5.2 grams of protein and 1.2 grams of fat. The quantity of fish available for consumption is highest in Oceania (27 kilograms per capita per year in 2013), followed by Europe (22 kilograms per capita per year in 2013) and Asia (21 kilograms per capita per year in 2013); it is lowest in the Americas (14 kilograms per capita per year in 2013) and Africa (11 kilograms per capita per year in 2013) [3].

Fish consumption generally increases with economic development. Worldwide, between 1961 and 2013, the quantity of fish available for consumption per person per year has more than doubled, from 9 kilograms to 19 kilograms [3].

Cantonese-style salted fish is part of the traditional diet consumed by people living in the Pearl River Delta region in Southern China. It has even been given to children, as part of a weaning diet [6]. This style of fish, which is prepared with less salt than is used in the northern part of China, is allowed to ferment, and so is eaten in a decomposed state.

See **Box 2** for general information about fish composition and consumption patterns.

3.6 Grilled (broiled) or barbecued (charbroiled) meat and fish

Grilled (broiled) and barbecued (charbroiled) meat and fish are cooked using very high temperatures (up to 400°C).

If meat or fish is cooked over an open flame, at high temperatures, and becomes charred or 'well done', *heterocyclic amines or polycyclic aromatic hydrocarbons* can be formed.

Temperature is the most important factor in the formation of these chemicals. Frying, grilling (broiling) and barbecuing (charbroiling) produce the largest amounts because these cooking methods use very high temperatures.

Polycyclic aromatic hydrocarbons, which are formed when organic substances such as meat are burnt incompletely, may also have carcinogenic potential [7]. Grilling (broiling) and barbecuing (charbroiling) meat, fish or other foods with intense heat over a direct flame results in fat dropping on the hot fire, causing flames; these flames contain polycyclic aromatic hydrocarbons that stick to the surface of food [8].

3.7 Dairy products

Milk is produced by all mammalian species to suckle their young. It has evolved to meet the nutritional needs of mammalian infants of each species and so, in normal conditions, contains all the nutrients they need at that stage of their lives. Although all mammalian species produce milk, only a few are used to provide milk for human consumption, all of which are ruminants. Milk non-human species must be modified before feeding to human infants in order to provide an adequate source of nutrition.

Fresh milk can be consumed raw (untreated) or, as is common in many high-income countries, *pasteurised*. Milk is also commonly processed into a wide variety of foods including cream, concentrated milks, cheese, fats such as butter and ghee, and fermented foods such as yoghurt. For general information about the composition of dairy products and consumption patterns, see **Box 3**.
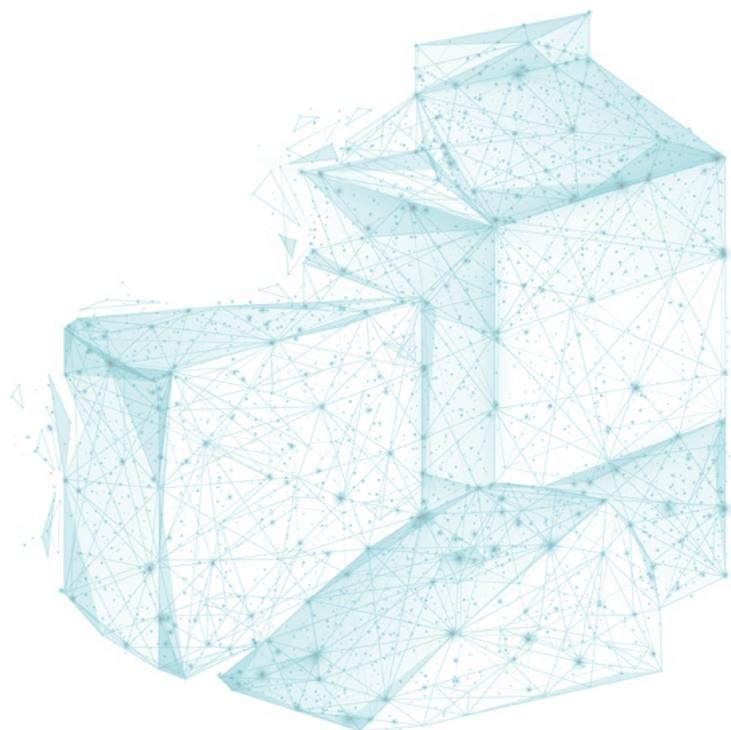
Composition

Dairy products in whole form have a high proportion of *energy* from fat and protein and contain some vitamins and minerals [9]. The precise composition varies between species and breeds and with the nature of their feed. Sheep and yak milks are particularly high in protein; buffalo, sheep and yak milks are high in fat. Typical whole cow milk contains 3.4 per cent protein and 3.6 per cent fat by weight [9]. Reduced fat (semi-skimmed or one per cent) and low-fat (skimmed) milks are produced from whole milk, and the foods made from these milks have a correspondingly lower fat and fat-soluble vitamin content than those made from whole milk.

Milk, cheese and yoghurt are valuable sources of calcium. Milk also contains several growth factors and *hormones*, though these are probably digested in the stomach. However, milk consumption has been shown to elevate circulating levels of *insulin-like growth factor* [143].

Consumption patterns

Data are available for milk and cream, which are consumed in the form of a range of dairy products. Globally, about 90 kilograms per capita per year of milk and cream are available for consumption, which supplies average daily intakes of 140 kilocalories, 8.3 grams of protein and 7.7 grams of fat. The quantity of milk and cream available for consumption is highest in Europe (218 kilograms per capita per year in 2013), followed by Oceania (205 kilograms per capita per year in 2013) and the Americas (169 kilograms per capita per year in 2013); it is lowest in Asia (60 kilograms per capita per year in 2013) and Africa (44 kilograms per capita per year in 2013).

Many populations are *lactose intolerant*, particularly in Asia, resulting in lower consumption of dairy produce in that region. Worldwide, between 1961 and 2013, milk and cream available for consumption per person each year have increased from 76 kilograms to 90 kilograms [3].

3.8 Diets high in calcium

Calcium is found in plant as well as in animal foods, but it is less easily absorbed from plant foods. Dairy products are particularly good sources. Other animal sources include fish (when eaten with their bones) and meat dishes (when rendered on the bone in stews). Plant sources include green vegetables, nuts and pulses (legumes) [9, 10].

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 proliferation [11].

Calcium metabolism is controlled by various factors – including parathyroid hormone, and vitamin D and related hormonal compounds formed by the liver and kidney – which are necessary for the *absorption* of calcium from foods and its regulation in the body.

In countries with high intakes of dairy products, these products are the main source of calcium.
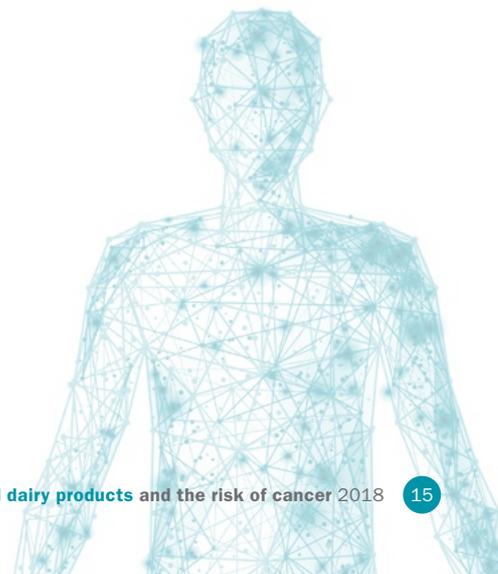
4. Interpretation of the evidence

4.1 General

For general considerations that may affect interpretation of the evidence in the CUP, see Judging the evidence.

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

4.2 Specific

Specific factors that the Panel bears in mind when interpreting evidence on whether consuming meat, fish and dairy products increases or decreases the risk of developing cancer are described in this section. Factors that are relevant to specific cancers are presented here too.

4.2.1 Exposures

Practically all the evidence on meat and fish relates to these foods being preserved, processed or prepared (cooked) in some way before consumption. Evidence on meat, and increasingly on fish, is nearly all from industrial production of these foods. Although the nutrient composition of wild animals and birds differs from their domesticated equivalents, in particular the quantity and nature of body fat, there is little evidence relating their consumption to the risk of cancer. Although some methods of preservation, processing and preparation or cooking of meat and fish are known to generate *carcinogens*, epidemiological evidence of any relation to cancer is generally lacking.

4.2.1.1 Red meat

Definition. Red meat in the CUP refers to all types of mammalian muscle meat, such as beef, veal, pork, lamb, mutton, horse and goat. Most meats consumed around the world today are from domesticated animals and the evidence presented in this Third Expert Report reflects this; there are no separate analyses on domesticated and wild animals.

Confounding. People who consume large amounts of red meat tend to consume less poultry, fish and vegetables, and vice versa. So an apparent effect of red meat could possibly be due, at least in part, to low intakes of these other foods. Some studies adjust for other dietary components such as *dietary fibre* and calcium, but few adjust for specific foods such as vegetables and fruit. Further analysis of *adjustment* factors was not performed in the CUP.

Study design. For most cancers, the evidence came from cohort studies. For nasopharyngeal cancer, there was a lack of cohort studies, so the evidence for that cancer came from a published meta-analysis of case-control studies [12]. Case-control studies are subject to recall bias, which can occur when participants recall past dietary intake or physical activity. It is differentially affected by whether they are cases or controls in the study. Participants may have different behaviours than non-participants, and such differences may vary between cases and controls (see Judging the evidence).

4.2.1.2 Processed meat

Definitions. There is no agreed definition for 'processed meat'. In the Third Expert Report the term 'processed meat' refers to meat that has been transformed through salting, curing, fermentation, smoking or other processes to enhance flavour or improve preservation. For further information, see **Section 3.2**. Some studies count minced meat, ham, bacon

and sausages as processed meats; others do not. Evidence on processed meat in the CUP came from diverse geographic locations, including the United States, Asia and Europe. Processed meat was defined variously as meat items having undergone salt-preservation, smoking or fermentation, and included sausages, bacon, ham, meatballs, burgers and cold meats. Processed meat was generally described as processed meat, preserved meat or cured meat, but items included in the group could vary between studies.

Confounding. People who consume large amounts of processed meat tend to consume less poultry, fish and vegetables, and vice versa. So an apparent effect of processed meat could possibly be due, at least in part, to low intakes of these other foods. Some studies adjust for other dietary components such as *dietary fibre* and calcium, but few adjust for specific foods like vegetables and fruit. Further analysis of *adjustment* factors was not performed in the CUP.

Study design. For most cancers, the evidence came from cohort studies. For nasopharyngeal cancer, there was a lack of cohort studies, so the evidence for that came from a published meta-analysis of case-control studies [12]. Case-control studies are subject to recall bias, which can occur when participants recall past dietary intake or physical activity. It is differentially affected by whether they are cases or controls in the study. Participants may have different behaviours than non-participants, and such differences may vary between cases and controls (see Judging the evidence).

4.2.1.3 Foods containing haem iron

Definition. Haem iron (which is iron attached to a haemoprotein) is found only in foods of animal origin, such as meat and meat products, fish and blood products. Studies in this Third Expert Report included red and

processed meat, fish and poultry. Studies included in the CUP under this group assessed haem iron as a nutrient. The term 'foods containing haem iron' is used by the CUP as the Panel's conclusions are based on foods and drinks rather than nutrients, because the nutrient intake is estimated from records of food consumption.

Confounding. A diet that is high in haem iron reflects a diet that contains a large amount of meat and fish. People who consume large amounts of meat tend to consume less vegetables, and vice versa. Some studies adjust for other dietary components such as *dietary fibre* and calcium, but few adjust for specific foods such as vegetables and fruit. Further analysis of *adjustment* factors was not performed in the CUP.

4.2.1.4 Fish

Definition. 'Fish' is a broad classification. Fish products have different nutritional profiles and biological effects, two obvious examples being white fish and oily fish. These are often not distinguished in epidemiological studies. The CUP definition of fish includes all types, including shellfish.

Confounding. People who consume large amounts of red meat and processed meat tend to consume less poultry, fish and vegetables, and vice versa. So an apparent effect of fish could possibly be due, at least in part, to low intakes of red meat and processed meat. Many of the studies in the CUP analyses adjusted for meat intakes, either as total meat, red meat or processed meat.

4.2.1.5 Cantonese-style salted fish

Definition. Cantonese-style salted fish is part of the traditional diet consumed by people living in the Pearl River Delta region in Southern China. It has even been given to children, as part of a weaning diet [6]. This style of fish, which is prepared with

less salt than is used in the northern part of China, is allowed to ferment, and so is eaten in a decomposed state.

Study design. For nasopharyngeal cancer, there was a lack of cohort studies, so case-control studies of salted fish (which included Cantonese-style salted fish) were reviewed. Case-control studies are subject to recall bias, which can occur when participants recall past dietary intake or physical activity. It is differentially affected by whether they are cases or controls in the study. Participants may have different behaviours than non-participants, and such differences may vary between cases and controls (see Judging the evidence).

4.2.1.6 Grilled (broiled) or barbecued (charbroiled) meat and fish

Definition. Grilled (broiled) and barbecued (charbroiled) meat and fish are cooked using very high temperatures (up to 400°C).

4.2.1.7 Dairy products

Definition. Studies may report on a combined intake of milk, cheese and yogurt, rather than the specific types of dairy products. The proportion of each type of dairy product may therefore not be known. Studies usually do not make any distinction between products, such as cheeses from different sources and with different compositions. Where possible, information on specific types of dairy foods is analysed by the CUP; however, the main analysis is based on total dairy products.

Most studies are carried out in high-income countries, where consumption of cow's milk and its products is high, and where the main dairy product consumed is milk. Most of the epidemiological studies reviewed in this Third Expert Report are from countries with high intakes of dairy products.

4.2.1.8 Diets high in calcium

Definition. This factor includes calcium from both plant and animal sources. In countries with high intakes of dairy products, these products are the main source of calcium. Studies included in the CUP under this group assessed dietary calcium as a nutrient. The term 'diets high in calcium' is used by the CUP, as the Panel's conclusions are based on foods and drinks rather than nutrients, because nutrient intake is estimated from records of foods consumed.

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) [13], 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 Nasopharynx

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

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

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

Smoking tobacco

Smoking tobacco is a cause of nasopharyngeal cancer. It is estimated that 23 per cent of cases of nasopharyngeal cancers are attributable to smoking tobacco [14].

Occupational exposure

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

Infectious agents

Epstein-Barr virus infection is a cause of nasopharyngeal cancer. Although it is a necessary cause, it is not sufficient [15] as only a fraction of the infected population develops nasopharyngeal cancer [15].

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

For more detailed information on adjustments made in CUP analyses on Cantonese-style salted fish, see **Section 5.5.1**.

4.2.2.2 Oesophagus

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

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

Globally, squamous cell carcinoma is the most common type and accounts for 87 per cent of cases [16]; however, the proportion of adenocarcinomas is increasing dramatically in affluent nations. Squamous cell carcinomas have different geographic and temporal trends from adenocarcinomas and follow a different disease path. Different approaches or definitions in different studies are potential sources of heterogeneity.

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

Smoking tobacco, chewing tobacco and snuff

Smoking tobacco (or use of smokeless tobacco, sometimes called 'chewing tobacco' or 'snuff') is a cause of oesophageal cancer. *Squamous cell carcinoma* is more strongly associated with smoking tobacco than *adenocarcinoma* [17]. It is estimated that 42 per cent of deaths of oesophageal cancer are attributable to tobacco use [18].

Infection

Between 12 and 39 per cent of oesophageal squamous cell carcinomas worldwide are related to carcinogenic types of human papilloma virus [19]. *Helicobacter pylori (H. pylori)* infection, an established risk factor for *non-cardia stomach cancer*, is associated with a 41 to 43 per cent decreased risk of oesophageal adenocarcinoma [20, 21].
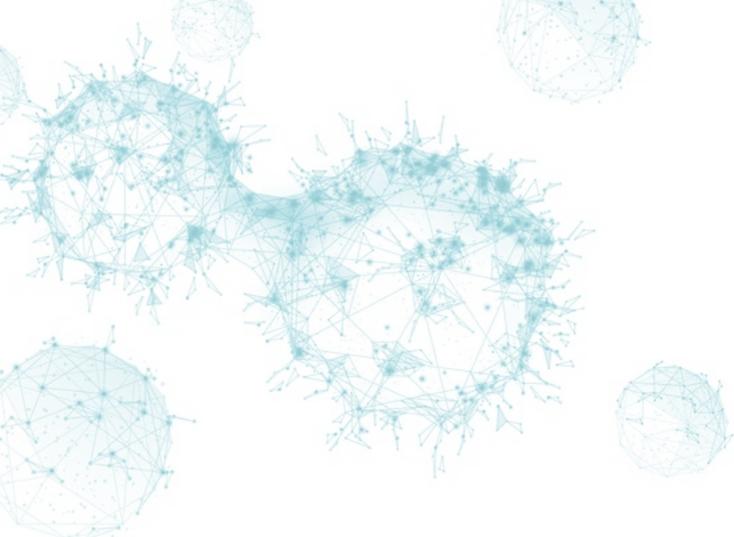
Other diseases

Risk of adenocarcinoma of the oesophagus is increased by gastro-oesophageal reflux disease, a common condition in which stomach acid damages the lining of the lower part of the oesophagus [17]. This type of oesophageal cancer is also increased by a rare condition, oesophageal achalasia (in which the valve at the end of the oesophagus called the 'cardia' fails to open and food gets stuck in the oesophagus) [17].

Family history

Tylosis A, a late-onset, inherited familial disease characterised by thickening of the skin of the palms and soles (hyperkeratosis), is associated with a 25 per cent lifetime incidence of oesophageal squamous cell carcinoma [22].

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

4.2.2.3 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 [23].

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 [24]. 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 [25].

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 [26], as is exposure to indoor air pollution from wood and coal burning for cooking and heating [27].

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.

4.2.2.4 Stomach

Infection with *H. pylori* is strongly implicated in the aetiology of intestinal *non-cardia stomach cancer*. The role of any other factor is to enhance risk of infection, integration and/or persistence.

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

Classification. Stomach cancer is usually differentiated by the anatomical site of origin: *cardia stomach cancer* (cardia cancer), which occurs near the gastro-oesophageal junction, and *non-cardia stomach cancer* (non-cardia cancer), which occurs outside this area, in the lower portion of the stomach. Cardia and non-cardia stomach cancer have distinct pathogeneses and aetiologies, but not all studies distinguish between them, particularly older studies. For these studies, there is a greater likelihood that the general term 'stomach cancer' may reflect a combination of the two subtypes, and therefore results may be less informative. Furthermore, definitions of cardia cancer classifications sometimes vary according to distance from the gastro-oesophageal junction, raising concerns about misclassification [28].

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

Smoking tobacco

Smoking tobacco is a cause of stomach cancer. It is estimated that 13 per cent of deaths worldwide are attributable to smoking tobacco [18].

Infection

Persistent colonisation of the stomach with *H. pylori* is a risk factor for non-cardia stomach cancer, but in some studies has been found to be inversely associated with the risk of cardia stomach cancer [29, 30].

Industrial chemical exposure

Occupational exposure to dusty and high-temperature environments – as experienced by wood-processing and food-machine operators – has been associated with an increased risk of stomach cancer [31]. Working in other industries, including rubber manufacturing, coal mining, metal processing and chromium production, has also been associated with an elevated risk of this cancer [32, 33].

Family history and ethnicity

Inherited mutations of certain genes, particularly the glutathione S-transferase (GSTM1)-null phenotype, are associated with an increased risk of stomach cancer [34]. Certain *polymorphisms* of interleukin genes (IL-17 and IL-10) have also been associated with increased risk of stomach cancer, particularly in Asian populations. These polymorphisms may interact with *H. pylori* infection [35] and smoking tobacco [36] to affect cancer risk.

Pernicious anaemia

People with the autoimmune form of pernicious anaemia have an increased risk of stomach cancer [37, 38]. This form of pernicious anaemia involves the autoimmune destruction of parietal cells in the gastric mucosa [38, 39]. These cells produce intrinsic factor, a protein that is needed to absorb vitamin B12 from foods, so the resultant vitamin B12 deficiency hinders the production of fully functioning red blood cells.

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

4.2.2.5 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 [18].

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 [40].

Confounding. Smoking tobacco is a possible *confounder*.

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

4.2.2.6 Liver

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

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

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

Disease

Cirrhosis of the liver increases the risk of liver cancer [41].

Medication

Long-term use of oral contraceptives containing high doses of oestrogen and progesterone increases the risk of liver cancer [42].

Infection

Chronic infection with the hepatitis B or C virus is a cause of liver cancer [43].

Smoking tobacco

Smoking tobacco increases the risk of liver cancer generally, but there is a further increase in risk among people who smoke and have the hepatitis B or hepatitis C virus infection and also among people who smoke and consume large amounts of alcohol [44,

45]. It is estimated that 14 per cent of deaths worldwide from liver cancer are attributable to smoking tobacco [18].

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

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

4.2.2.7 Colorectum

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 that 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 [46].

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 [47].

Family history

Based on twin studies, up to 45 per cent of colorectal cancer cases may involve a heritable component [48]. Between five and 10 per cent of colorectal cancers are consequences of recognised hereditary conditions [49]. 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 red meat, processed meat and dairy products, see **Sections 5.1.1**, **5.2.1** and **5.7.1** respectively.

4.2.2.8 Breast

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

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

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

Most data come from high-income countries. Breast cancer is hormone related, and factors that modify risk may have different effects on cancers diagnosed in the pre and postmenopausal periods.
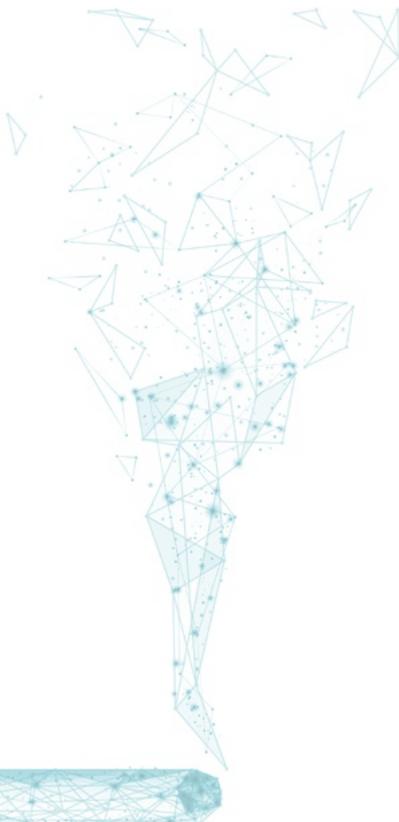
Due to the importance of menopausal status as an *effect modifier*, studies should stratify for menopause status, but many do not. Breast cancer is now recognised as a heterogeneous disease, with several subtypes according to hormone receptor status or molecular intrinsic markers. Although there is growing evidence that these subtypes have different causes, most studies have limited statistical power to evaluate effects by subtype.

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

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

Life events

Early *menarche* (before the age of 12), late natural *menopause* (after the age of 55), not bearing children and first pregnancy over the age of 30 all increase lifetime exposure to oestrogen and progesterone and the risk of breast cancer [50–52]. The reverse also applies: late menarche, early menopause, bearing children and pregnancy before the age of 30 all reduce the risk of breast cancer [50, 51].

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

Radiation

Exposure to ionising radiation from medical treatment such as X-rays, particularly during puberty, increases the risk of breast cancer [53, 54].

Medication

MHT (containing oestrogen or progesterone) increases the risk of breast cancer [55]. Oral contraceptives containing both oestrogen and progesterone also cause a small increased risk of breast cancer in young women, among current and recent users only [56].

Family history

Some inherited mutations, particularly in BRCA1, BRCA2 and p53, result in a very high risk of breast cancer. However, germline mutations in these genes are infrequent and account for only two to five per cent of all cases of breast cancer [57].

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

4.2.2.9 Prostate

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

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

There are several ways of characterising prostate cancers according to grade (aggression) or stage. The term 'advanced' prostate cancer is sometimes employed in epidemiologic studies and is variably defined as higher grade, later stage, presence of metastatic disease or death.

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 [58]. Genetic susceptibility has been linked to African heritage and familial disease [59]. 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 [60].

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

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.

5. Evidence and judgements

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

Full systematic literature reviews (SLRs) for each cancer are available online. For most cancer sites considered in the CUP,[1] there is also a CUP cancer report. CUP cancer reports summarise findings from the SLRs, again focusing on a specific cancer site. This section also presents findings from the SLRs, but from a different perspective: it brings together all of the key findings on meat, fish and dairy products 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 Red meat

Table 5.1 summarises the main findings from the CUP dose–response meta-analyses of cohort studies on consumption of red meat and the risk of cancer.

Table 5.1: Summary of CUP dose–response meta-analyses of red meat intake[1] and the risk of cancer

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment / contrast	I² (%)	Conclusion[2]	Date of CUP cancer report[3]
Colorectum	14	8	6,662	1.12 (1.00–1.25)	100 g/day	24	Probable: Increases risk	2017
Nasopharynx[4]	7	6	1,858	1.35 (1.21–1.51)	<100 vs 0 g/week	–	Limited – suggestive: Increases risk	2017
Lung	7	7	9,765	1.22 (1.02–1.46)	100 g/day	66	Limited – suggestive: Increases risk	2017
Pancreas	10	8	2,761	1.19 (0.98–1.45)	100 g/day	52	Limited – suggestive: Increases risk	2012

1 The term 'red meat' in the CUP refers to beef, veal, pork, lamb, mutton, horse and goat.

2 See Definitions of WCRF/AICR grading criteria (**Section 1**: Meat, fish and dairy products and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'probable' and 'limited – suggestive'.

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

4 A dose–response meta-analysis of cohort studies could not be conducted in the CUP as none were identified. Evidence is from a published highest versus lowest meta-analysis of case-control studies [12].

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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. CUP cancer reports not are currently available for nasopharynx, cervix and skin.

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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); liver (2015); breast (pre and postmenopause; 2017); ovary (2014); endometrium (2013); prostate (2014); kidney (2015); bladder (2015); and skin (2017).

The strong evidence on the effects of eating red meat 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 eating red meat and the risk of cancer that was graded by the Panel as 'limited – suggestive' and suggests a direction of effect, see the following CUP documents:

- CUP nasopharyngeal cancer SLR 2017: Section 2.5.1.3.

- CUP lung cancer report 2017: Section 7.9 and CUP lung cancer SLR 2015: Section 2.5.1.3.

- CUP pancreatic cancer report 2012: Section 7.1 and CUP pancreatic cancer SLR 2011: Section 2.5.1.3.

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

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

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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 by any combination of these.

5.1.1 Colorectum

(Also see CUP colorectal cancer report 2017: Sections 7.5.1 and 7.5.2 and CUP colorectal cancer SLR 2016: Sections 2.5.1 and 2.5.1.3.)

5.1.1.1 CUP dose–response meta-analyses

Eight of 14 identified studies were included in the dose–response meta-analysis, which showed no statistically significant association between the risk of colorectal cancer and consumption of red meat (RR 1.12 [95% CI 1.00–1.25], per 100 grams increase per day; n = 6,662 cases) (see **Figure 5.1**). Low *heterogeneity* was observed (I^2 = 24%) and there was no evidence of small study bias with *Egger's test* (p = 0.48).

In sensitivity analyses, summary RRs ranged from 1.09 (95% CI 0.96–1.25) when one study with 25 per cent of the weight [61] was omitted to 1.19 (95% CI 1.06–1.34) when one study with 35 per cent of the weight [62] was omitted.

Stratified analyses for the risk of colorectal cancer per 100 grams increase in red meat consumed per day were conducted for sex, geographic location and cancer type.

When stratified by sex, no statistically significant association was observed for men (RR 1.28 [95% CI 0.49–3.34]) and women (RR 1.02 [95% CI 0.78–1.33]; see CUP colorectal cancer SLR 2016, Figure 127). When stratified by geographic location, a significant increased risk was observed in Europe (RR 1.23 [95% CI 1.08–1.41], but not North America or Asia; see CUP colorectal cancer SLR 2016, Figure 128). When stratified by cancer type, a significant increased risk was observed for colon cancer (RR 1.22 [95% CI 1.06–1.39]; see CUP colorectal cancer SLR 2016, Figure 132), but not rectal cancer.

Figure 5.1: CUP dose–response meta-analysis[1] for the risk of colorectal cancer, per 100 grams increase in red meat consumed per day

Author	Year	Sex	Per 100 g RR (95% CI)	% Weight
Ollberding	2012	M/W	1.01 (0.90, 1.14)	35.10
Lee	2009	W	0.81 (0.50, 1.29)	5.17
Larsson	2005	W	1.23 (0.90, 1.67)	10.56
Norat	2005	M/W	1.21 (1.02, 1.43)	24.84
English	2004	M/W	1.19 (0.89, 1.58)	12.02
Tiemersma	2002	M/W	1.69 (0.88, 3.23)	2.82
Jarvinen	2001	M/W	1.37 (0.92, 2.06)	6.75
Pietinen	1999	M	0.83 (0.43, 1.61)	2.75
Overall (I-squared = 0.0%, p = 0.996)			1.12 (1.00, 1.25)	100.00

NOTE: Weights are from random effects analysis

.3   1 1.5 3
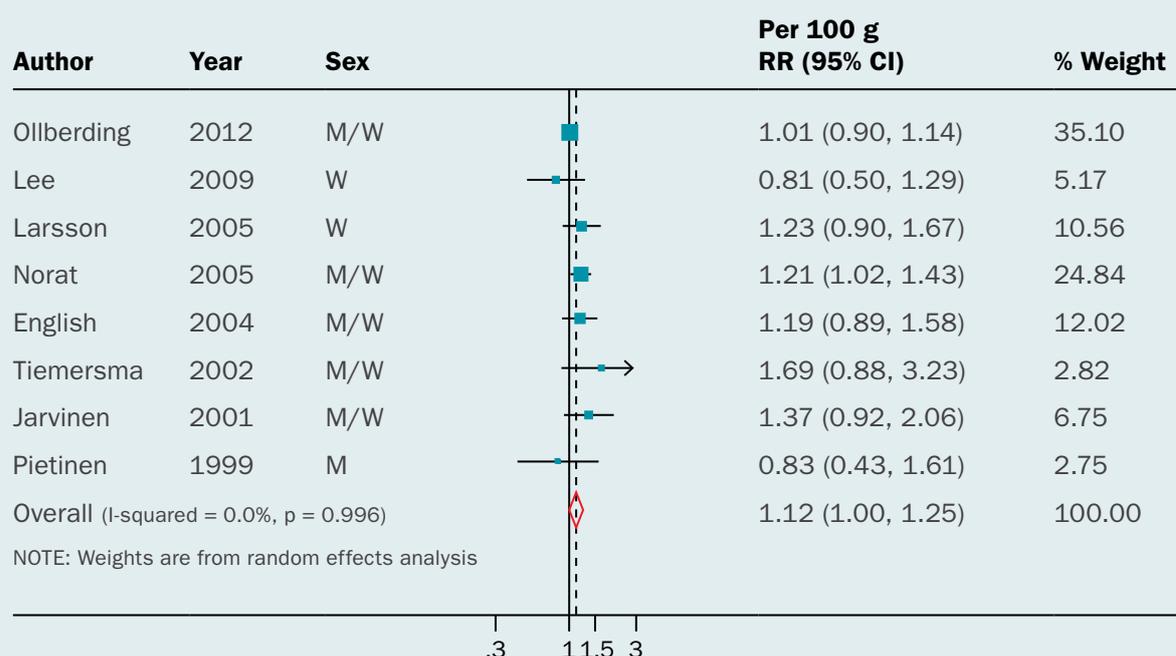
Source: Ollberding, 2012 [62]; Lee, 2009 [63]; Larsson, 2005 [64]; Norat, 2005 [61]; English, 2004 [65]; Tiemersma, 2002 [66]; Jarvinen, 2001 [67]; Pietinen, 1999 [68].

There was no evidence of a non-linear dose response relationship (p = 0.88).

All studies included in the dose–response meta-analysis adjusted for multiple factors. Most studies adjusted for alcohol consumption and some adjusted for tobacco smoking. Only one study adjusted for *menopausal hormone therapy* (MHT) in women [62]. For information on the *adjustments* made in individual studies, see CUP colorectal cancer SLR 2016, Table 79.

A separate dose–response meta-analysis of 15 studies showed a statistically significant 12 per cent increased risk of colorectal cancer per 100 grams increase in red and processed meat consumed per day (RR 1.12 [95% CI 1.04–1.21]; n = 31,551 cases; see CUP colorectal cancer SLR 2016, Figure 83).

5.1.1.2 Published pooled analyses and meta-analyses

Three published pooled analyses (see **Table 5.2**) and two other published meta-analyses on consumption of red meat and the risk of colorectal cancer were identified.

All three published pooled analyses reported no statistically significant association [69–71] and were not included in the CUP dose–response meta-analysis.

One of the published meta-analyses combined nine studies with different outcomes (colorectal, colon and rectal cancers) and reported no significant association (RR 1.05 [95% CI 0.98–1.12]) for the highest compared with the lowest level of red meat consumed [72]. The other meta-analysis reported previous results from CUP [73].

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[1] Six studies could not be included in the dose–response meta-analysis; one reported on mortality and five did not provide sufficient information. For further details, see CUP colorectal cancer SLR 2016, Table 80.

Table 5.2: Summary of published pooled analyses of red meat intake and the risk of colorectal cancer

Publication	Increment/contrast	RR (95% CI)	No. of studies	No. of cases
Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) and Colon Cancer Family Registry (CCFR) [69]	1 serving/day	1.05 (0.94–1.18)	7 nested case-control studies	3,488
Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) and Colon Cancer Family Registry (CCFR) [70]	Highest vs lowest	1.06 (0.90–1.24)[1]	5 nested case-control studies	2,564
UK Dietary Cohort Consortium [71][2]	50 g/day	1.01 (0.84–1.22)	7 cohort studies	579

1 Relationship was not modified by NAT2 enzyme activity (based on *polymorphism* at rs1495741).
2 The average intake of red meat was low (38.2 grams per day in men and 28.7 grams per day in women controls), and there were a high number of vegetarians in the cases.

5.1.1.3 Mechanisms

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

For further information on general processes involved in the development of cancer see The cancer process.

Cooking meats at high temperatures, prolonged exposure to heat and cooking by various types of grilling results in the formation of *heterocyclic amines and polycyclic aromatic hydrocarbons,* both of which have been linked to colorectal cancer development in experimental studies [8]. In addition, haem iron, which is present at high levels in red meat, has been shown to promote colorectal *tumorigenesis* by stimulating the endogenous formation of carcinogenic *N-nitroso compounds* [74]. There is moderate mechanistic evidence to support a relationship between high consumption of red meat and colorectal cancer.

Polycyclic aromatic hydrocarbons, which are formed when organic substances like meat are burnt incompletely, may also have carcinogenic potential [7]. Grilling (broiling) and barbecuing (charbroiling) meat, fish, or other foods with intense heat over a direct flame results in fat dropping on the hot fire, causing flames; these flames contain polycyclic aromatic hydrocarbons that stick to the surface of food [8].
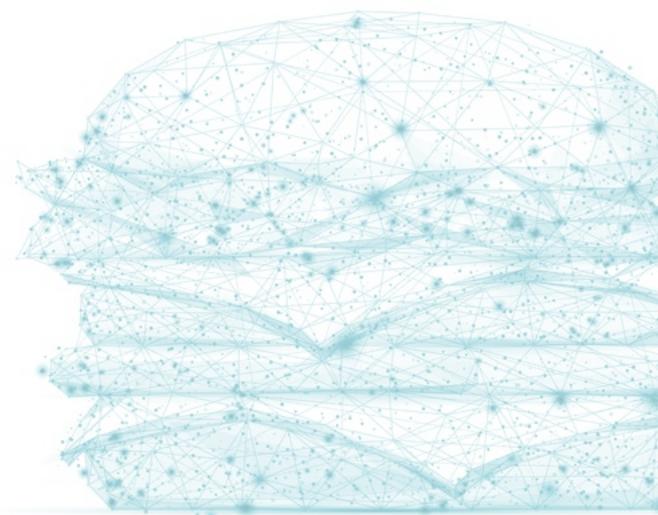
5.1.1.4 CUP Panel's conclusions

The evidence for red meat intake was generally consistent and showed an increased risk in the dose–response meta-analyses for colorectal, colon and rectal cancers. The result was statistically significant for colon cancer but not for colorectal and rectal cancers. For colorectal cancer, stratified analyses by geographic location showed a significant increased risk in studies conducted in Europe. Three published pooled analyses reported no significant association but were consistent in the direction of effect. There is evidence of plausible mechanisms operating in humans.

The CUP Panel concluded:

- **Consumption of red meat is probably a cause of colorectal cancer.**

5.2 Processed meat

Table 5.3 summarises the main findings from the CUP dose–response meta-analyses of cohort studies on consumption of processed meat and the risk of cancer.

Table 5.3: Summary of CUP dose–response meta-analyses of processed meat[1] intake and the risk of cancer

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment / contrast	I² (%)	Conclusion[2]	Date of CUP cancer report[3]
Colorectum	13	10	10,738	1.16 (1.08–1.26)	50 g/day	20	Convincing: Increases risk	2017
Nasopharynx[4]	13	10	5,434	1.46 (1.31–1.64)	<30 vs 0 g/week	–	Limited – suggestive: Increases risk	2017
Oesophagus (squamous cell carcinoma)	2	2	322	1.34 (1.00–1.81)	50 g/day	0	Limited – suggestive: Increases risk	2016
Lung	9	7	10,292	1.14 (1.05–1.24)	50 g/day	0	Limited – suggestive: Increases risk	2017
Stomach (non-cardia)	3	3	1,149	1.18 (1.01–1.38)	50 g/day	3	Limited – suggestive: Increases risk	2016
Pancreas	8	7	2,748	1.17 (1.01–1.34)	50 g/day	0	Limited – suggestive: Increases risk	2012

1 The term 'processed meat' in the CUP refers to meats transformed through salting, curing, fermentation, smoking or other processes to enhance flavour or improve preservation.

2 See Definitions of WCRF/AICR grading criteria (**Section 1**: Meat, fish and dairy products and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'convincing' and 'limited – suggestive'.

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

4 A dose–response meta-analysis of cohort studies could not be conducted in the CUP as none were identified. Evidence is from a published highest versus lowest meta-analysis of case-control studies [12].

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; 2016); stomach (cardia; 2016); liver (2015); breast (pre and postmenopause; 2017); ovary (2014); endometrium (2013); prostate (2014); kidney (2015); bladder (2015); and skin (2017).

The strong evidence on the effects of eating processed meat 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 eating processed meat and the risk of cancer that was graded by the Panel as 'limited – suggestive' and suggests a direction of effect, see the following CUP documents:

- CUP nasopharyngeal cancer SLR 2017: Section 2.5.1.2.

- CUP oesophageal cancer report 2016: Section 7.3 and CUP oesophageal cancer SLR 2015: Section 2.5.1.2.

- CUP lung cancer report 2017: Section 7.10 and CUP lung cancer SLR 2015: Section 2.5.1.2.

- CUP stomach cancer report 2016: Section 7.4 and CUP stomach cancer SLR 2015: Section 2.5.1.2.

- CUP pancreatic cancer report 2012: Section 7.2 and CUP pancreatic cancer SLR 2011: Section 2.5.1.2.

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

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

5.2.1 Colorectum

(Also see CUP colorectal cancer report 2017: Sections 7.5.1 and 7.5.3 and CUP colorectal cancer SLR 2016: Sections 2.5.1 and 2.5.1.2.)

5.2.1.1 CUP dose–response meta-analyses

Ten of 13 identified studies were included in the dose–response meta-analysis, which showed a statistically significant 16 per cent increased risk of colorectal cancer per 50 grams increase in processed meat consumed per day (RR 1.16 [95% CI 1.08–1.26]; n = 10,738 cases) (see **Figure 5.2**). Low *heterogeneity* was observed ($I^2 = 20\%$) and there was no evidence of small study bias with *Egger's test* (p = 0.29).
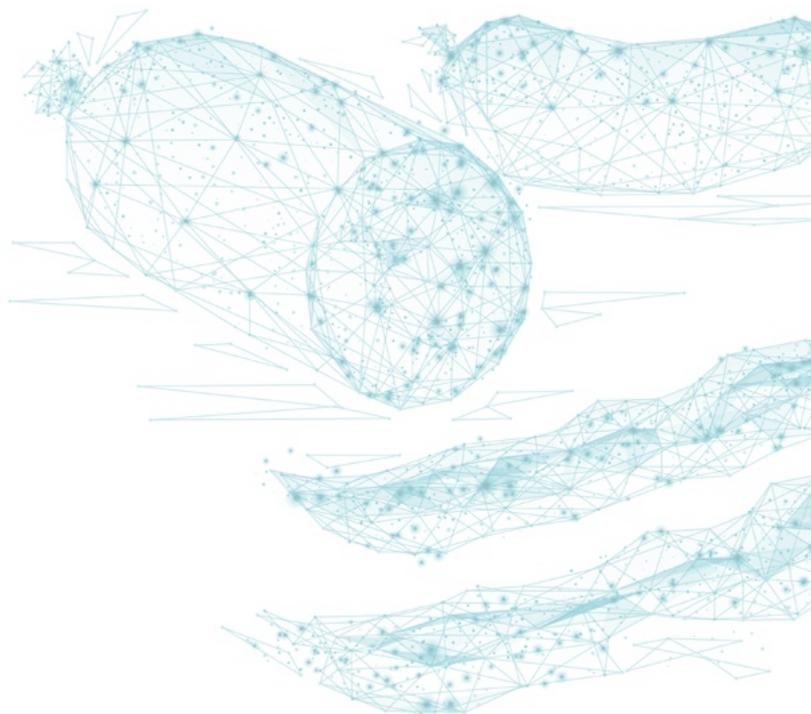
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[1] **'Limited – no conclusion'**: There is enough evidence to warrant Panel consideration, but it is so limited that no conclusion can be made. The evidence may be limited in amount, by inconsistency in the direction of effect, by methodological flaws, or by any combination of these.

Figure 5.2: CUP dose–response meta-analysis for the risk of colorectal cancer, per 50 grams increase in processed meat consumed per day

Author	Year	Sex		Per 50 g RR (95% CI)	% Weight
Ollberding	2012	M/W		1.09 (0.94, 1.26)	18.77
Cross	2010	M/W		1.26 (1.13, 1.40)	26.51
Balder	2006	M/W		1.21 (0.91, 1.61)	6.44
Sato	2006	M/W		0.77 (0.24, 2.42)	0.45
Larsson	2005	W		1.13 (0.85, 1.51)	6.39
Norat	2005	M/W		1.15 (1.02, 1.29)	24.21
English	2004	M/W		1.61 (1.12, 2.30)	4.24
Lin	2004	W		0.56 (0.24, 1.23)	0.88
Flood	2003	W		1.17 (0.76, 1.81)	2.99
Pietinen	1999	M		1.01 (0.80, 1.27)	9.13
Overall (I-squared 20.1%, p = 0.258)				1.16 (1.08, 1.26)	100.00
NOTE: Weights are from random effects analysis					

.5   1   1.5   3
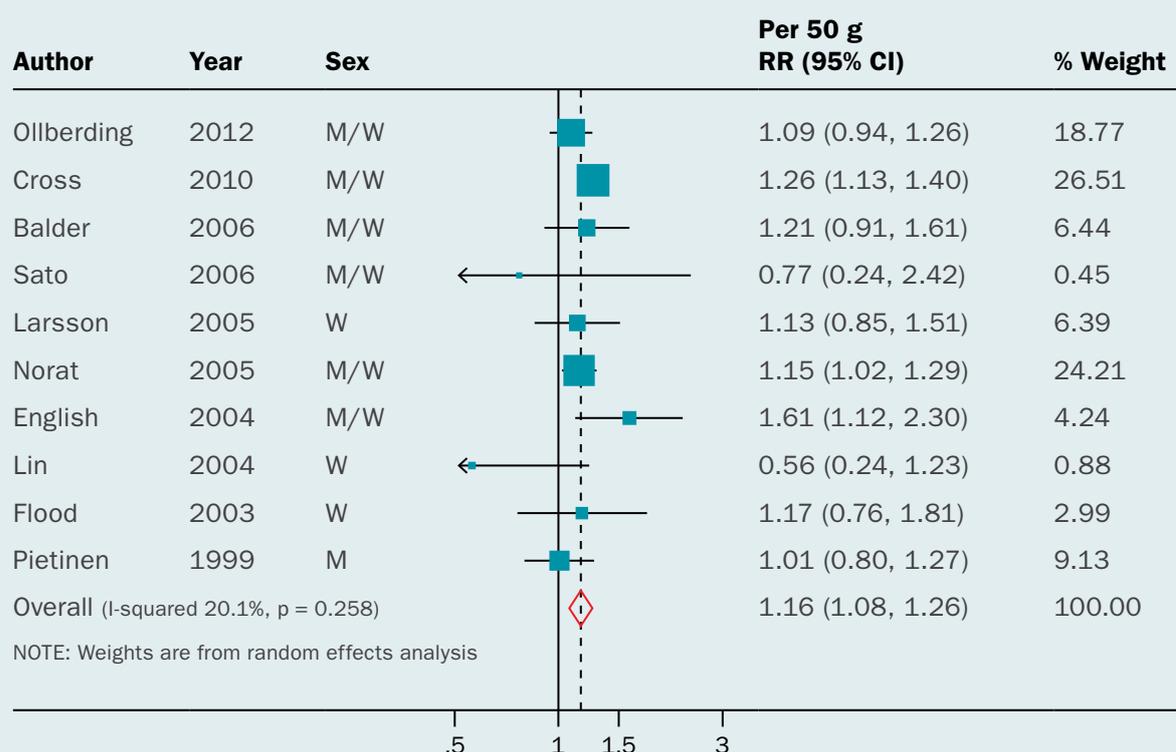
Source: Ollberding, 2012 [62]; Cross, 2010 [75]; Balder, 2006 [76]; Sato, 2006 [77]; Larsson, 2005 [64]; Norat, 2005 [61]; English, 2004 [65]; Lin, 2004 [78]; Flood, 2003 [79]; Pietinen, 1999 [68].

Stratified analyses for the risk of colorectal cancer per 50 grams increase in processed meat consumed per day were conducted for sex, geographic location and cancer type.

When stratified by sex, no statistically significant increase or decrease in risk was observed for men (RR 1.11 [95% CI 0.86–1.43]) and women (RR 1.18 [95% CI 0.99–1.41]; see CUP colorectal cancer SLR 2016, Figure 106). When stratified by geographic location, a significant increased risk was observed in Europe (RR 1.13 [95% CI 1.03–1.24]), but not Asia or North America (see CUP colorectal cancer SLR 2016, Figure 107). When stratified by cancer type, a significant increased risk was observed for colon cancer (RR 1.23 [95% CI 1.11–1.35]; see CUP colorectal cancer SLR 2016, Figure 111), but not rectal cancer.

There was no evidence of a non-linear dose response relationship (p = 0.93).

Most studies included in the dose–response meta-analysis adjusted for tobacco smoking, alcohol consumption and multiple factors. Only two studies adjusted for MHT in women [62, 78]. For information on the *adjustments* made in individual studies, see CUP colorectal cancer SLR 2016, Table 67.

A separate dose–response meta-analysis of 15 studies showed a statistically significant 12 per cent increased risk of colorectal cancer per 100 grams increase in red and processed meat consumed per day (RR 1.12 [95% CI 1.04–1.21]; n = 31,551 cases; see CUP colorectal cancer SLR 2016, Figure 83).

5.2.1.2 Published pooled analyses and meta-analyses

Two published pooled analyses (see **Table 5.4**) and two other published meta-analyses on consumption of processed meat and the risk of colorectal cancer were identified.

One of the pooled analyses reported a statistically significant increased risk [69] and one reported no significant increase or decrease in risk [71]; neither study was included in the CUP dose–response meta-analysis.

One meta-analysis [80] reported that consumption of processed meat significantly increased the risk of colorectal cancer (RR 1.10 [95% CI 1.05–1.15] per 30 grams per day) and the other meta-analysis reported previous results from CUP [73].

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.

Overall it is likely that a combination of mechanisms contribute to higher risk of colorectal cancer among people consuming high quantities of processed meat. Similar to red meat, processed meat is rich in fat, protein and haem iron, which can promote *tumorigenesis* through the mechanisms described in **Section 5.1.1.3** [8]. Processed meats, such as sausages, are often cooked at high temperatures, which can lead to increased exposure to *heterocyclic amines and polycyclic aromatic hydrocarbons*. Processed meat is invariably higher in fat content than red meat, which may promote *carcinogenesis* through synthesis of secondary bile acids; however, human data supporting this hypothesis are weak. Processed meat is also a source of exogenously derived *N-nitroso compounds*, which may have carcinogenic potential [4].

Table 5.4: Summary of published pooled analyses of processed meat intake and the risk of colorectal cancer

Publication	Increment/ contrast	RR (95% CI)	p value	No. of studies	No. of cases
Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) and Colon Cancer Family Registry (CCFR) [69]	1 serving/ day	1.48 (1.30–1.70)	–	7 nested case-control studies	3,488
UK Dietary Cohort Consortium [71]	50 g/day	0.88 (0.68–1.15)	0.36	7 cohort studies	579

5.2.1.4 CUP Panel's conclusion

There is generally consistent evidence showing that consumption of processed meat increases the risk of colorectal cancer. The dose–response meta-analysis showed a statistically significant increased risk per 50 grams increase in consumption per day. Low *heterogeneity* was observed. Stratified analyses showed a significant increased risk for studies conducted in Europe and for colon cancer. One *pooled analysis* reported a statistically significant increased risk; the other reported no significant association. There is robust evidence for mechanisms operating in humans.

> **The CUP Panel concluded:**
>
> • **Consumption of processed meat is a convincing cause of colorectal cancer.**

5.3 Foods containing haem iron

Table 5.5 summarises the main findings from the CUP dose–response meta-analysis of cohort studies on consumption of foods containing haem iron and the risk of colorectal cancer.

There was no discussion on foods containing haem iron and any other cancer considered in the CUP as there were too few studies.

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

• CUP colorectal cancer report 2017: Section 7.6 and CUP colorectal cancer SLR 2016: Section 5.6.2.

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

Table 5.5: CUP dose–response meta-analysis for consumption of foods containing haem iron[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)	Increment	I[2] (%)	Conclusion[2]	Date of CUP cancer report[3]
Colorectum	8	6	6,070	1.04 (0.98–1.10)	1 mg/day	0	Limited – suggestive: Increases risk	2017

1 The term 'haem iron' refers to iron attached to a haemoprotein, which is found only in foods of animal origin. Foods that contain haem iron include red and processed meat, fish and poultry.

2 See Definitions of WCRF/AICR grading criteria (**Section 1**: Meat, fish and dairy products 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.

5.4 Fish

Table 5.6 summarises the main findings from the CUP dose–response meta-analyses of cohort studies on consumption of fish 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); nasopharynx (2017); oesophagus (adenocarcinoma and squamous cell carcinoma; 2016); lung (2017); stomach (2016); pancreas (2012); gallbladder (2015); breast (pre and postmenopause; 2017); ovary (2014); endometrium (2013); prostate (2014); kidney (2015); bladder (2015); and skin (2017).

For more information on the evidence for eating fish and the risk of cancer that was graded by the Panel as 'limited – suggestive' and suggests a direction of effect, see the following CUP documents:
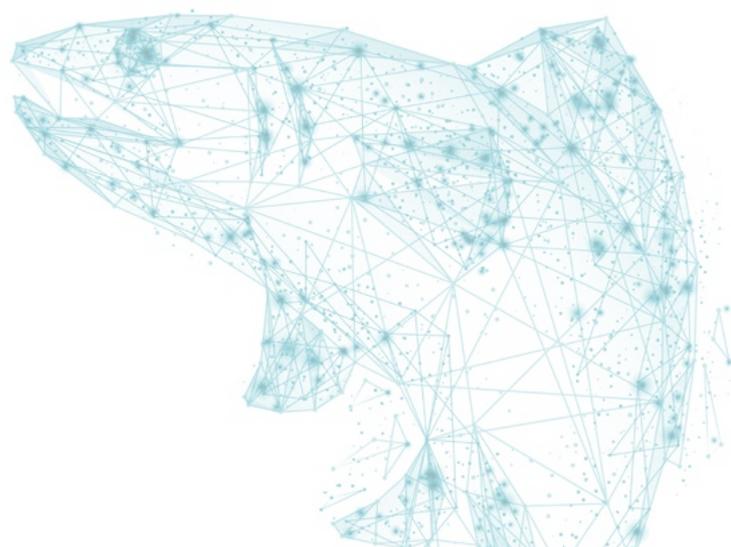
- CUP liver cancer report 2015: Section 7.2 and CUP liver cancer SLR 2014: Section 2.5.2.
- CUP colorectal cancer report 2017: Section 7.7 and CUP colorectal cancer SLR 2016: Section 2.5.2.

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

Table 5.6: Summary of CUP dose–response meta-analyses of fish intake and the risk of cancer

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I[2] (%)	Conclusion[1]	Date of CUP cancer report[2]
Liver	6	4	1,812	0.94 (0.89–0.99)	20 g/day	53	Limited – suggestive: Decreases risk	2015
Colorectum	11	18	10,356	0.89 (0.80–0.99)	100 g/day	0	Limited – suggestive: Decreases risk	2017

1   See Definitions of WCRF/AICR grading criteria (**Section 1**: Meat, fish and dairy products 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.

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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.

5.5 Cantonese-style salted fish

Due to a lack of cohort studies, case-control studies were reviewed for nasopharyngeal cancer. **Table 5.7** summarises the main findings from the CUP dose–response meta-analyses of case-control studies on consumption of salted fish (including Cantonese-style salted fish) and the risk of nasopharyngeal cancer.

Table 5.7: Summary of CUP dose–response meta-analyses of case-control studies for consumption of salted fish (including Cantonese-style salted fish)[1] and the risk of nasopharyngeal cancer

Cancer	Adult/childhood consumption	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]
Nasopharynx	Adult	28	12	5,391	1.31 (1.16–1.47)	1 time/week	78	**Probable: Increases risk**	2017
	Childhood	16	9	1,673	1.35 (1.14–1.60)	1 time/week	83		

1 Cantonese-style salted fish is part of the traditional diet consumed by people living in the Pearl River Delta region in Southern China. This style of fish, which is prepared with less salt than is used in the northern part of China, is allowed to ferment, and so is eaten in a decomposed state. This conclusion does not apply to fish preserved (or salted) by other means. Evidence is primarily from case-control studies, there is only one cohort study.

2 See Definitions of WCRF/AICR grading criteria (**Section 1**: Meat, fish and dairy products 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.

There was no discussion specifically on Cantonese-style salted fish and any other cancer considered in the CUP as there were too few studies. Evidence for salted fish and liver cancer (2015) was discussed in the CUP but was too limited to draw a conclusion.[1] The evidence for salt-preserved fish was included in the conclusion for foods preserved by salting and stomach cancer (see CUP stomach cancer report 2016).

The strong evidence on the effects of eating salted fish (including Cantonese-style salted fish) on the risk of cancer is described below. 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 section below and in the appendix (see **Appendix 2**) 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.

5.5.1 Nasopharynx

(Also see CUP nasopharyngeal cancer SLR 2017: Section 2.5.2.1.)

The evidence for adult consumption and childhood consumption of salted fish (including Cantonese-style salted fish) is presented in the sections below.

5.5.1.1 Cohort studies

One cohort study was identified during the 2007 Second Expert Report [81] from Sihui County, Guangdong Province, China, where populations are at high risk of developing nasopharyngeal cancer (17 incident cases from 505 men and women, followed for 9 years). A statistically significant increased risk of nasopharyngeal cancer was observed when one or more portions of salted fish were consumed per week in adulthood during the 1960s and 1970s (p < 0.001 and p = 0.014, respectively) but not in the 1980s (p = 0.21), when compared with less frequent consumption. A significant increased risk of nasopharyngeal cancer was also observed when one or more portions of salted fish were consumed per week during childhood (p = 0.038) compared with less frequent consumption. There was no *adjustment* for other factors.

5.5.1.2 Case-control studies

5.5.1.2.1 CUP dose–response meta-analysis for adult consumption

Due to a lack of cohort studies, case-control studies were reviewed for nasopharyngeal cancer. Twelve of 28 identified case-control studies were included in the dose–response meta-analysis, which showed a statistically significant 31 per cent increased risk of nasopharyngeal cancer per one portion increase in salted fish consumed per week (1.31 [95% CI 1.16–1.47]; n = 5,391 cases) (see **Figure 5.3**).

High *heterogeneity* was observed (I^2 = 78%). There was evidence of small study bias with

Egger's test (p = 0.01). Inspection of the funnel plot suggested that smaller-sized studies reported an increased risk rather than a decreased risk of nasopharyngeal cancer (see CUP nasopharyngeal cancer SLR 2017, Figure 10).

Stratified analyses for the risk of nasopharyngeal cancer per one portion increase in salted fish consumed per week were conducted for geographic location. A significant increased risk was observed in China (RR 1.38 [95% CI 1.19–1.59]), but not in other countries; see CUP nasopharyngeal cancer SLR 2017, Figure 11).

All studies apart from one [84] included in the dose–response meta-analysis adjusted for age and sex. Some studies adjusted for area of residence and tobacco smoking. No study was adjusted for EBV status. For information on the *adjustments* made in individual studies, see CUP nasopharyngeal cancer SLR 2017, Table 12.

5.5.1.2.2 CUP dose–response meta-analysis for childhood consumption

Nine of 16 identified case-control studies were included in the dose–response meta-analysis for the 2007 Second Expert Report, which showed a statistically significant 35 per cent increased risk of nasopharyngeal cancer per one portion increase in salted fish consumed per week for children age 10 years (1.35 [95% CI 1.14–1.60]; n = 1,840 cases). High *heterogeneity* was observed (I^2 = 83%). Seven studies could not be included in the dose–response meta-analysis mainly because sufficient information was not provided. For further details see CUP nasopharyngeal cancer SLR 2017, Appendix 2.

Since the dose–response meta-analysis from the 2007 Second Expert Report, one new case-control study has been identified in the CUP which showed a significant increased risk of nasopharyngeal cancer for the highest

(one portion or more weekly) compared with the lowest (less than monthly) level of salted fish consumed prior to age 12 years (RR 1.57 [95% CI 1.16–2.13]; n = 1,387 cases) [83].

5.5.1.3 Published pooled analyses and meta-analyses

No published pooled analyses and no other published meta-analyses on salted fish and the risk of nasopharyngeal cancer were identified.
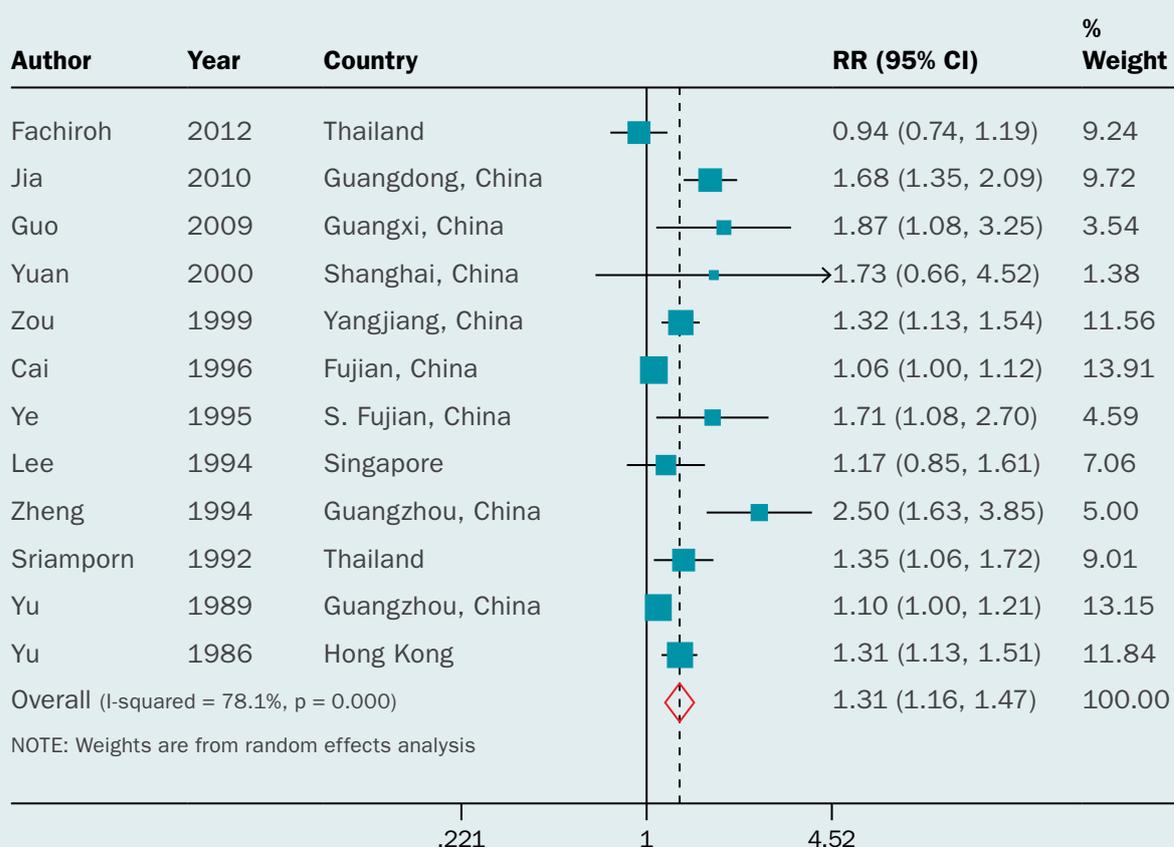
5.5.1.4 Mechanisms

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

For further information on general processes involved in the development of cancer see The cancer process.

Cantonese-style salted fish contains *nitrosamines* and nitrosamine precursors. High levels of one such nitrosamine, *N*-nitrosodimethylamine, found in some samples of Cantonese-style salted fish, has been shown to induce cancer development in experimental models in animals [94].

Figure 5.3: CUP dose–response meta-analysis[1] of case-control studies for the risk of nasopharyngeal cancer, per one portion increase in salted fish consumed per week

Author	Year	Country	RR (95% CI)	% Weight
Fachiroh	2012	Thailand	0.94 (0.74, 1.19)	9.24
Jia	2010	Guangdong, China	1.68 (1.35, 2.09)	9.72
Guo	2009	Guangxi, China	1.87 (1.08, 3.25)	3.54
Yuan	2000	Shanghai, China	1.73 (0.66, 4.52)	1.38
Zou	1999	Yangjiang, China	1.32 (1.13, 1.54)	11.56
Cai	1996	Fujian, China	1.06 (1.00, 1.12)	13.91
Ye	1995	S. Fujian, China	1.71 (1.08, 2.70)	4.59
Lee	1994	Singapore	1.17 (0.85, 1.61)	7.06
Zheng	1994	Guangzhou, China	2.50 (1.63, 3.85)	5.00
Sriamporn	1992	Thailand	1.35 (1.06, 1.72)	9.01
Yu	1989	Guangzhou, China	1.10 (1.00, 1.21)	13.15
Yu	1986	Hong Kong	1.31 (1.13, 1.51)	11.84
Overall (I-squared = 78.1%, p = 0.000)			1.31 (1.16, 1.47)	100.00

NOTE: Weights are from random effects analysis

.221   1   4.52

Source: Fachiroh, 2012 [82]; Jia, 2010 [83]; Guo, 2009 [84]; Yuan, 2000 [85]; Zou, 1999 [86]; Cai, 1996 [87]; Ye, 1995 [88]; Lee, 1994 [89]; Zheng, 1994 [90]; Sriamporn, 1992 [91]; Yu, 1989 [92]; Yu, 1986 [93].

[1] Sixteen studies could not be included in the dose–response meta-analysis, mainly because sufficient information was not provided. For further details, see CUP nasopharyngeal cancer SLR 2017, Table 13.

5.5.1.5 CUP Panel's conclusion

The evidence from case-control studies was generally consistent and showed an increased risk of nasopharyngeal cancer with increased consumption of salted fish (including Cantonese-style salted fish). The dose–response meta-analysis showed a significant increased risk of nasopharyngeal cancer per portion per week consumed in adulthood. There is high *heterogeneity* but this is largely related to size of the effect. The significant increased risk was observed for China but not for other countries. A previous dose–response meta-analysis for the 2007 Second Expert Report reported a significant increased risk for salted fish (including Cantonese-style salted fish) consumed in childhood and nasopharyngeal cancer. The International Agency for Research on Cancer (IARC) has judged that salted fish (Chinese style) is carcinogenic to humans. There is robust evidence for mechanisms operating in humans.

> **The CUP Panel concluded:**
>
> - **Consumption of Cantonese-style salted fish is probably a cause of nasopharyngeal cancer.**

5.6 Grilled (broiled) or barbecued (charbroiled) meat and fish

Table 5.8 summarises the main findings from published highest versus lowest meta-analyses of cohort studies identified on consumption of grilled (broiled) or barbecued (charbroiled) meat and fish and the risk of stomach cancer. Highest versus lowest and dose–response meta-analyses 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]: mouth, pharynx and larynx (2018); and oesophagus (adenocarcinoma and squamous cell carcinoma; 2016).

Table 5.8: Summary of highest versus lowest analyses from individual published studies for consumption of grilled (broiled) or barbecued (charboiled) meat and fish and the risk of stomach cancer

Cancer	Exposure	No. of cases	Risk estimate (95% CI)/p value	Conclusion[1]	Date of CUP cancer report[2]
Stomach[3]	Grilled fish [95]	79 deaths	1.7 p < 0.05	Limited – suggestive: Increases risk	2016
	Grilled fish [96]	1,270 diagnoses	0.84 (0.55–1.29)		
	Grilled meat [97]	57 deaths	2.27 (1.06–4.85)		

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

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

3   A dose–response meta-analysis of cohort studies could not be conducted in the CUP. Evidence is from three published highest versus lowest meta-analyses [95–97].

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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.

For more information on the evidence for eating grilled (broiled) or barbecued (charbroiled) meat and fish 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 below:

- CUP stomach cancer report 2016: Section 7.6 and CUP stomach cancer SLR 2015: Section 4.4.2.6.

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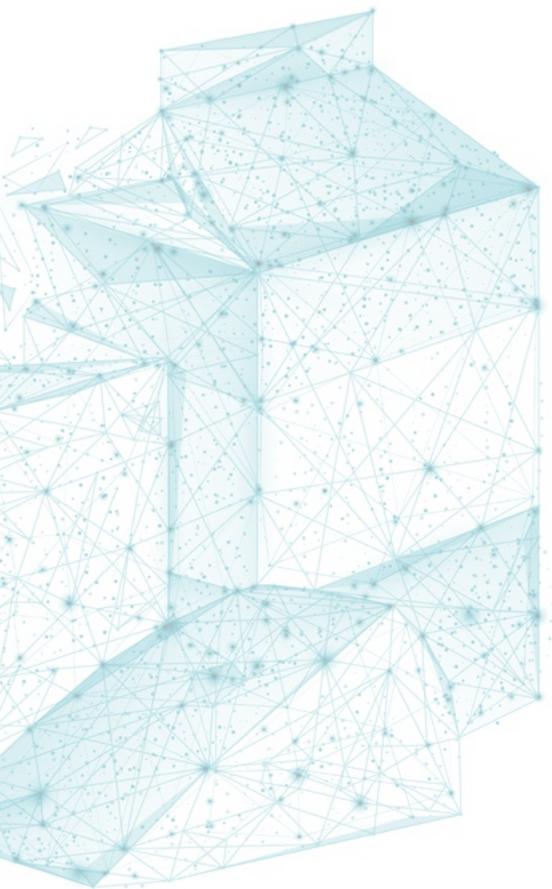
5.7 Dairy products

Table 5.9 summarises the main findings from the CUP dose–response meta-analyses of cohort studies on consumption of dairy products and the risk of cancer.

Table 5.9: Summary of CUP dose–response meta-analyses for consumption of dairy products and the risk of cancer

Cancer	Type of evidence	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	Dairy products	14	10	14,859	0.87 (0.83–0.90)	400 g/day	18	Probable: Decreases risk	2017
	Milk	13	9	10,738	0.94 (0.92–0.96)	200 g/day	0		
	Cheese	9	7	6,462	0.94 (0.87–1.02)	50 g/day	10		
	Dietary calcium	20	13	11,519	0.94 (0.93–0.96)	200 mg/day	0		
Breast (premeno-pause)[3]	Dairy products	13	7	2,862	0.95 (0.92–0.99)	200 g/day	0	Limited – suggestive: Decreases risk	2017
Prostate[4]	Dairy products	21	15	38,107	1.07 (1.02–1.12)	400 g/day	0	Limited – suggestive: Increases risk	2014

1   See Definitions of WCRF/AICR grading criteria (**Section 1**: Meat, fish and dairy products and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'probable' and 'limited – suggestive'.

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

3   The evidence for dairy products and premenopausal breast cancer includes total dairy shown in the table and also milk intakes see CUP breast cancer report 2017 for further information.

4   The evidence for dairy products and prostate cancer includes total dairy shown in the table and also milk, cheese and yogurt intakes see CUP prostate cancer report 2014 for further information.

For more information on the evidence for consuming dairy products 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 below:

- CUP breast cancer report 2017: Section 7.3 and CUP breast cancer SLR 2017: Section 2.7.

- CUP prostate cancer report 2014: Section 7.1 and CUP prostate cancer SLR 2014: Section 2.7.

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

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

5.7.1 Colorectum

(Also see CUP colorectal cancer report 2017: Section 7.8 and CUP colorectal cancer SLR 2016: Sections 2.7, 2.7.1, 2.7.2, 5.6.3 and Appendix 4.)

The evidence for dairy products, milk, cheese and dietary calcium is presented in the sections below.

5.7.1.1 Dairy products

5.7.1.1.1 CUP dose–response meta-analyses

Ten of fourteen identified studies were included in the dose–response meta-analysis, which showed a statistically significant 13 per cent decreased risk of colorectal cancer per 400 grams increase in dairy products consumed per day (RR 0.87 [95% CI 0.83–0.90]; n = 14,859 cases) (see **Figure 5.4**). Low *heterogeneity* was observed (I^2 = 18%) and there was no evidence of small study bias with *Egger's test* (p = 0.63).

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

The strong evidence on the effects of consuming dairy products on the risk of cancer is described below. 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.

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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 5.4: CUP dose–response meta-analysis[1] for the risk of colorectal cancer, per 400 grams increase in dairy products consumed per day

Author	Year	Sex		Per 400 g/day RR (95% CI)	% Weight
Murphy	2013	M/W		0.88 (0.83, 0.93)	25.96
Park	2009	M		0.84 (0.78, 0.91)	19.31
Park	2007	M		0.81 (0.71, 0.92)	7.85
Larsson	2006	M		0.80 (0.72, 0.89)	11.60
McCarl	2006	W		0.85 (0.77, 0.95)	11.45
Lin	2005	W		0.88 (0.65, 1.18)	1.71
McCullough	2003	M/W		0.93 (0.73, 1.17)	2.65
Terry	2002	W		0.98 (0.88, 1.10)	9.95
Jarvinen	2001	M/W		1.01 (0.79, 1.28)	2.50
Pietinen	1999	M		0.84 (0.73, 0.97)	7.02
Overall (I-squared = 18.4%, p = 0.274)				0.87 (0.83, 0.90)	100.00
NOTE: Weights are from random effects analysis					

.5   .75   1   1.5
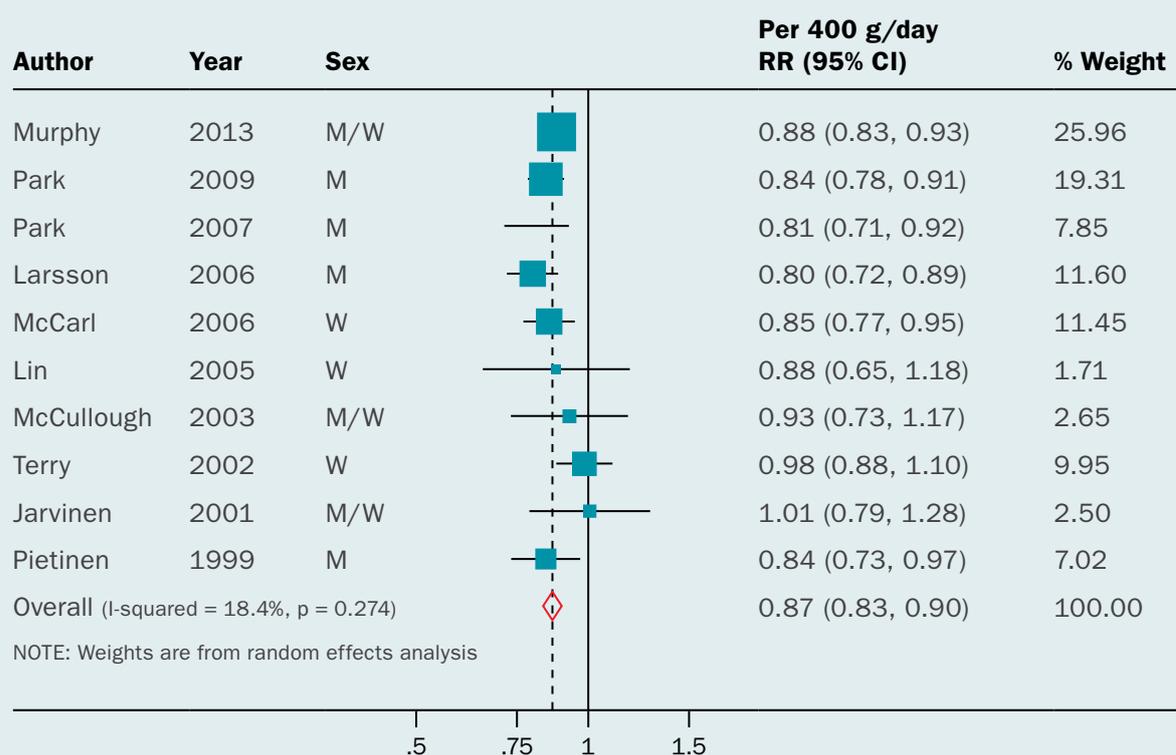
Source: Murphy, 2013 [98]; Park, 2009 [99]; Park, 2007 [100]; Larsson, 2006 [101]; McCarl, 2006 [102]; Lin, 2005 [103]; McCullough, 2003 [104]; Terry, 2002 [105]; Jarvinen, 2001 [106]; Pietinen, 1999 [68].

Stratified analyses for the risk of colorectal cancer per 400 grams increase in dairy products consumed per day were conducted for sex, geographic location and cancer type.

When stratified by sex, a statistically significant decreased risk was observed for men (RR 0.84 [95% CI 0.80–0.89]) and women (RR 0.86 [95% CI 0.78–0.96]; see CUP colorectal cancer SLR 2016, Figure 186). When stratified by geographic location, a significant decreased risk was observed in North America (RR 0.85 [95% CI 0.80–0.89]) and Europe (RR 0.88 [95% CI 0.82–0.95]; see CUP colorectal cancer SLR 2016, Figure 187). When stratified by cancer type, a significant decreased risk was observed for colon cancer (RR 0.87 [95% CI 0.81–0.94]; see CUP colorectal cancer SLR 2016, Figure 192), but not rectal cancer.

There was evidence of a non-linear dose response relationship (p = 0.003; see **Figure 5.5**); the association was slightly stronger at lower intakes.

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[1] Four studies could not be included in the dose–response meta-analysis: one reported on mortality, one on household intake and two did not provide sufficient information. For further details see CUP colorectal cancer SLR 2016, Table 107.

Figure 5.5: CUP non-linear dose–response association of dairy products intake and the risk of colorectal cancer
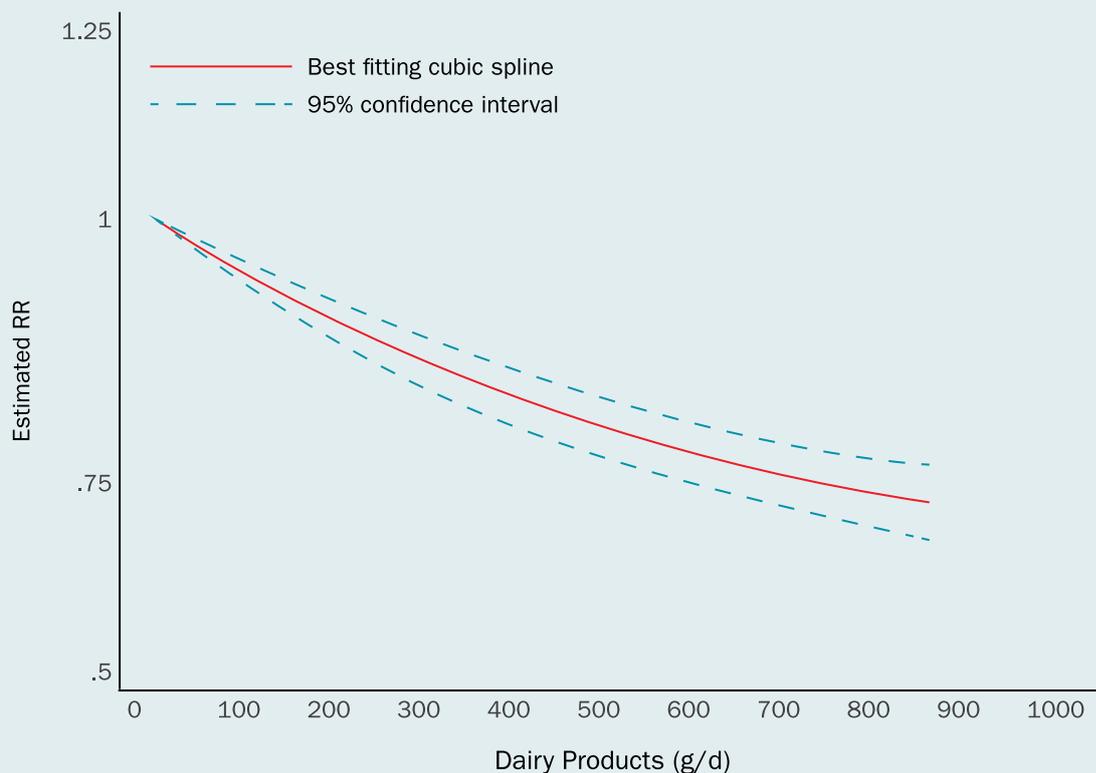
Most studies included in the dose–response meta-analysis adjusted for the majority of colorectal cancer risk factors, including physical activity, *body mass index* (BMI), alcohol consumption, tobacco smoking, red meat and MHT in women. For information on the *adjustments* made in individual studies, see CUP colorectal cancer SLR 2016, Table 106.

5.7.1.1.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. Two other published meta-analyses on consumption of dairy products and the risk of colorectal cancer have been identified. One analysis [107] reported a statistically s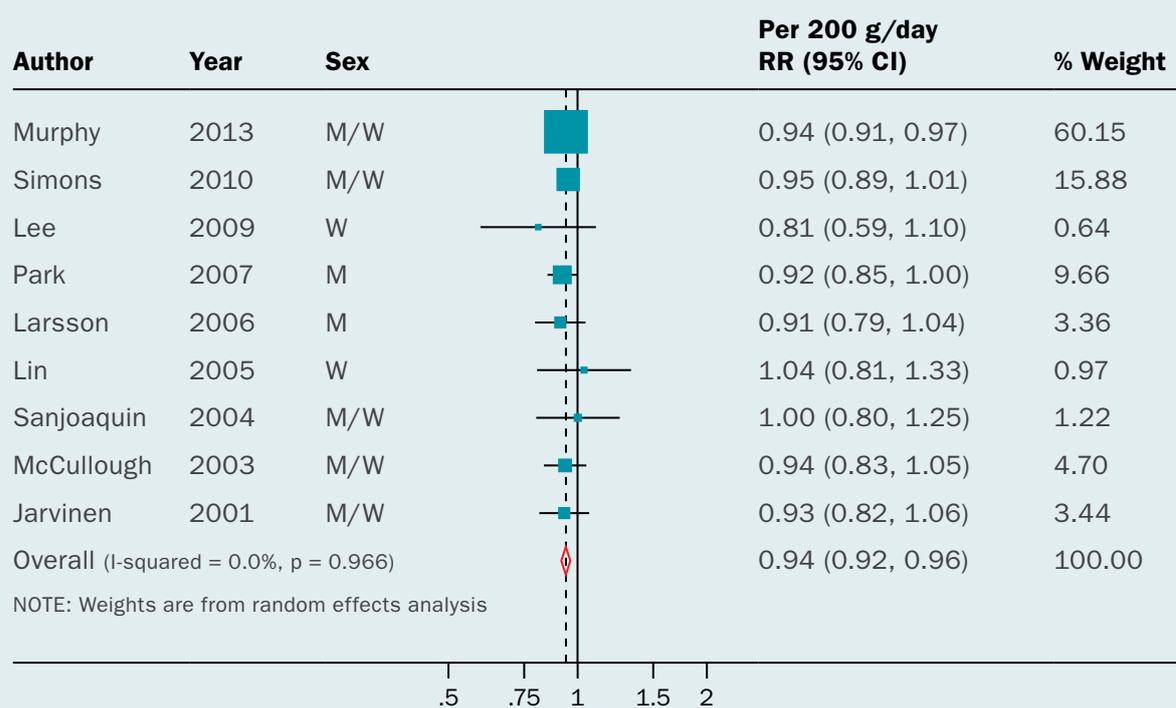ignificant decreased risk for the highest compared with the lowest level of dairy products consumed (RR 0.84 [95% CI 0.75–0.95]). The other meta-analysis reported previous results from the CUP [108].

5.7.1.2 Milk

5.7.1.2.1 CUP dose–response meta-analyses

Nine of 13 identified studies were included in the dose–response meta-analysis, which showed a statistically significant six per cent decreased risk of colorectal cancer per 200 grams of milk consumed per day (RR 0.94 [95% CI 0.92–0.96]; n = 10,738 cases) (see **Figure 5.6**). No *heterogeneity* was observed and there was no evidence of small study bias with *Egger's test* (p = 0.63).

Figure 5.6: CUP dose–response meta-analysis[1] for the risk of colorectal cancer, per 200 grams increase in milk consumed per day

Author	Year	Sex		Per 200 g/day RR (95% CI)	% Weight
Murphy	2013	M/W		0.94 (0.91, 0.97)	60.15
Simons	2010	M/W		0.95 (0.89, 1.01)	15.88
Lee	2009	W		0.81 (0.59, 1.10)	0.64
Park	2007	M		0.92 (0.85, 1.00)	9.66
Larsson	2006	M		0.91 (0.79, 1.04)	3.36
Lin	2005	W		1.04 (0.81, 1.33)	0.97
Sanjoaquin	2004	M/W		1.00 (0.80, 1.25)	1.22
McCullough	2003	M/W		0.94 (0.83, 1.05)	4.70
Jarvinen	2001	M/W		0.93 (0.82, 1.06)	3.44
Overall (I-squared = 0.0%, p = 0.966)				0.94 (0.92, 0.96)	100.00
NOTE: Weights are from random effects analysis					

.5 .75 1 1.5 2

Source: Murphy, 2013 [98]; Simons, 2010 [109]; Lee, 2009 [63]; Park, 2007 [100]; Larsson, 2006 [101]; Lin, 2005 [110]; Sanjoaquin, 2004 [111]; McCullough, 2003 [104]; Jarvinen, 2001 [106].

Stratified analyses for the risk of colorectal cancer per 200 grams increase in milk consumed per day were conducted for sex, geographic location and cancer type.

When stratified by sex, a statistically significant decreased risk was observed for men (RR 0.92 [95% CI 0.87–0.98]) but not women (RR 0.96 [95% CI 0.89–1.03]; see CUP colorectal cancer SLR 2016, Figure 202). When stratified by geographic location, a significant decreased risk was observed in Europe (RR 0.94 [95% CI 0.91–0.96]) and North America (RR 0.93 [95% CI 0.88–0.99]; see CUP colorectal cancer SLR 2016, Figure 203), but not Asia. When stratified by cancer type, a significant decreased risk was observed for colon cancer (RR 0.93 [95% CI 0.91–0.96]) and rectal cancer (RR 0.94 [95% CI 0.91–0.97]; see CUP colorectal cancer SLR 2016, Figures 208 and 213, respectively).

There was no evidence of a non-linear dose response relationship (p = 0.95).

Most studies included in the dose–response meta-analysis adjusted for the majority of colorectal cancer risk factors, including physical activity, BMI, alcohol consumption, tobacco smoking, red meat and MHT in women. For information on the *adjustments* made in individual studies, see CUP colorectal cancer SLR 2016, Table 114.

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[1] Four studies could not be included in the dose–response meta-analysis: two reported on mortality, one on household intake and one did not provide sufficient information. For further details, see CUP colorectal cancer SLR 2016, Table 115.

5.7.1.2.2 Published pooled analyses and meta-analyses

One published *pooled analysis* (see **Table 5.10**) and three other published meta-analyses on consumption of milk and the risk of colorectal cancer were identified. The pooled analysis reported a statistically significant decreased risk for the highest compared with the lowest level of milk consumed [112].

Two meta-analyses [107, 113] reported a significant decreased risk of colorectal cancer for the highest compared with the lowest level of milk consumed (RR 0.90 [95% CI 0.83–0.97] and RR 0.85 [95% CI 0.77–0.93] respectively). The other meta-analysis reported previous results from the CUP [108].

An additional CUP meta-analysis of the pooled analysis [112] combined with non-overlapping studies from the CUP showed a significant decreased risk of colorectal cancer per 200 grams of milk consumed per day (RR 0.94 [95% CI 0.93–0.96]).
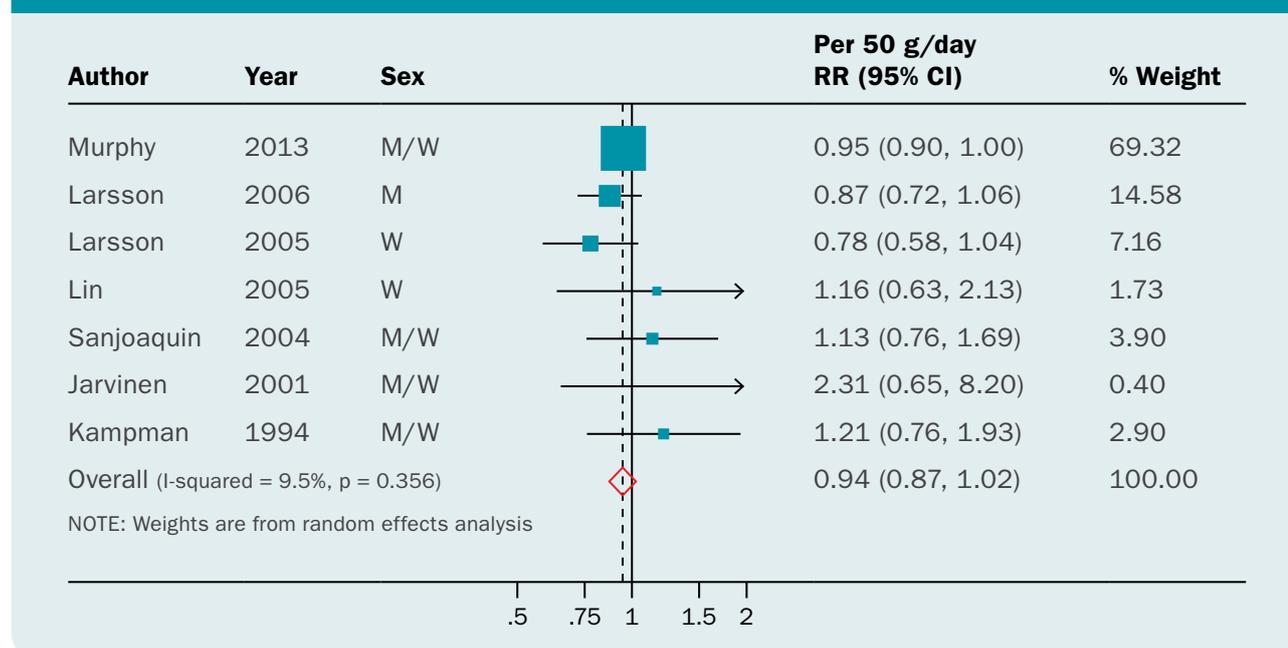
5.7.1.3 Cheese

5.7.1.3.1 CUP dose–response meta-analyses

Seven of nine identified studies were included in the dose–response meta-analysis, which showed no statistically significant association between the risk of colorectal cancer and consumption of cheese (RR 0.94 [95% CI 0.87–1.02], per 50 grams increase per day; n = 6,462 cases) (see **Figure 5.7**). Low *heterogeneity* was observed (I^2 = 10%) and there was no evidence of small study bias with *Egger's test* (p = 0.42).

Table 5.10: Summary of published pooled analyses for consumption of milk and the risk of colorectal cancer

Publication	Increment	RR (95% CI)	No. of studies	No. of cases
Pooling Project of Prospective Studies on Diet and Cancer [112]	200 g/day	0.95 (0.92–0.97)	10 cohort studies	4,992

Figure 5.7: CUP dose–response meta-analysis for the risk of colorectal cancer, per 50 grams increase in cheese consumed per day

Author	Year	Sex		Per 50 g/day RR (95% CI)	% Weight
Murphy	2013	M/W		0.95 (0.90, 1.00)	69.32
Larsson	2006	M		0.87 (0.72, 1.06)	14.58
Larsson	2005	W		0.78 (0.58, 1.04)	7.16
Lin	2005	W		1.16 (0.63, 2.13)	1.73
Sanjoaquin	2004	M/W		1.13 (0.76, 1.69)	3.90
Jarvinen	2001	M/W		2.31 (0.65, 8.20)	0.40
Kampman	1994	M/W		1.21 (0.76, 1.93)	2.90
Overall (I-squared = 9.5%, p = 0.356)				0.94 (0.87, 1.02)	100.00

NOTE: Weights are from random effects analysis

.5   .75   1   1.5   2

Source: Murphy, 2013 [98]; Larsson, 2006 [101]; Larsson, 2005 [64]; Lin, 2005 [110]; Sanjoaquin, 2004 [111]; Jarvinen, 2001 [106]; Kampman, 1994 [114]

Stratified analyses for the risk of colorectal cancer per 50 grams increase in cheese consumed per day were conducted for sex, geographic location and cancer type.

When stratified by sex, no statistically significant association was observed for men (RR 0.87 [95% CI 0.72–1.06]) or women (RR 0.87 [95% CI 0.61–1.23]). When stratified by geographic location, no significant association was observed in Europe or North America. When stratified by cancer site, no significant association was observed for colon or rectal cancer.

There was evidence of a non-linear dose response relationship (p = 0.047; see **Figure 5.8** and CUP colorectal cancer report 2017, Table 24), showing a trend towards increased risk at low levels and a decreased risk of colorectal cancer at higher levels, although the risk estimates never reached statistical significance.
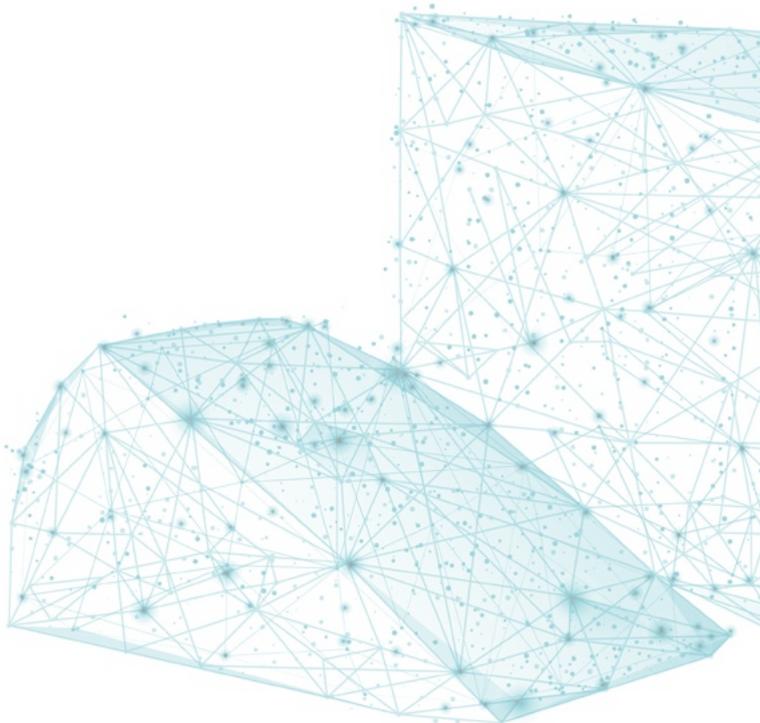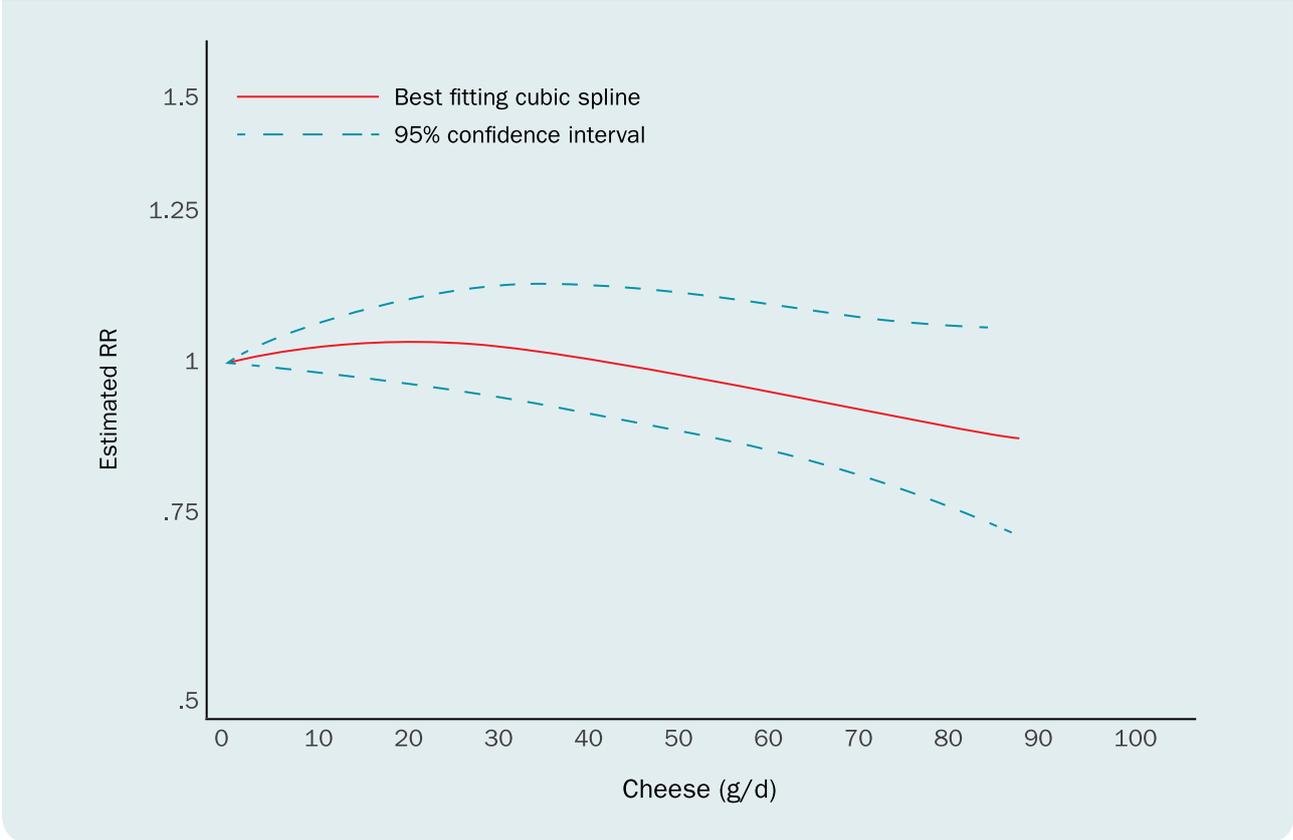
Figure 5.8: CUP non-linear dose–response association of cheese intake and the risk of colorectal cancer

5.7.1.4 Dietary calcium

5.7.1.2.1 CUP dose–response meta-analyses

Thirteen of 20 identified studies were included in the dose–response meta-analysis, which showed a statistically significant six per cent decreased risk of colorectal cancer per 200 milligrams increase in dietary calcium intake per day (RR 0.94 [95% CI 0.93–0.96]; n = 11,519 cases) (see **Figure 5.9**).

No *heterogeneity* was observed and there was no evidence of small study bias with *Egger's test* (p = 0.91).

Most studies in the dose–response meta-analysis adjusted for the majority of colorectal cancer risk factors, including physical activity, BMI, alcohol consumption, tobacco smoking, red meat and MHT in women. For information on the *adjustments* made in individual studies, see CUP colorectal cancer SLR 2016, Table 121.

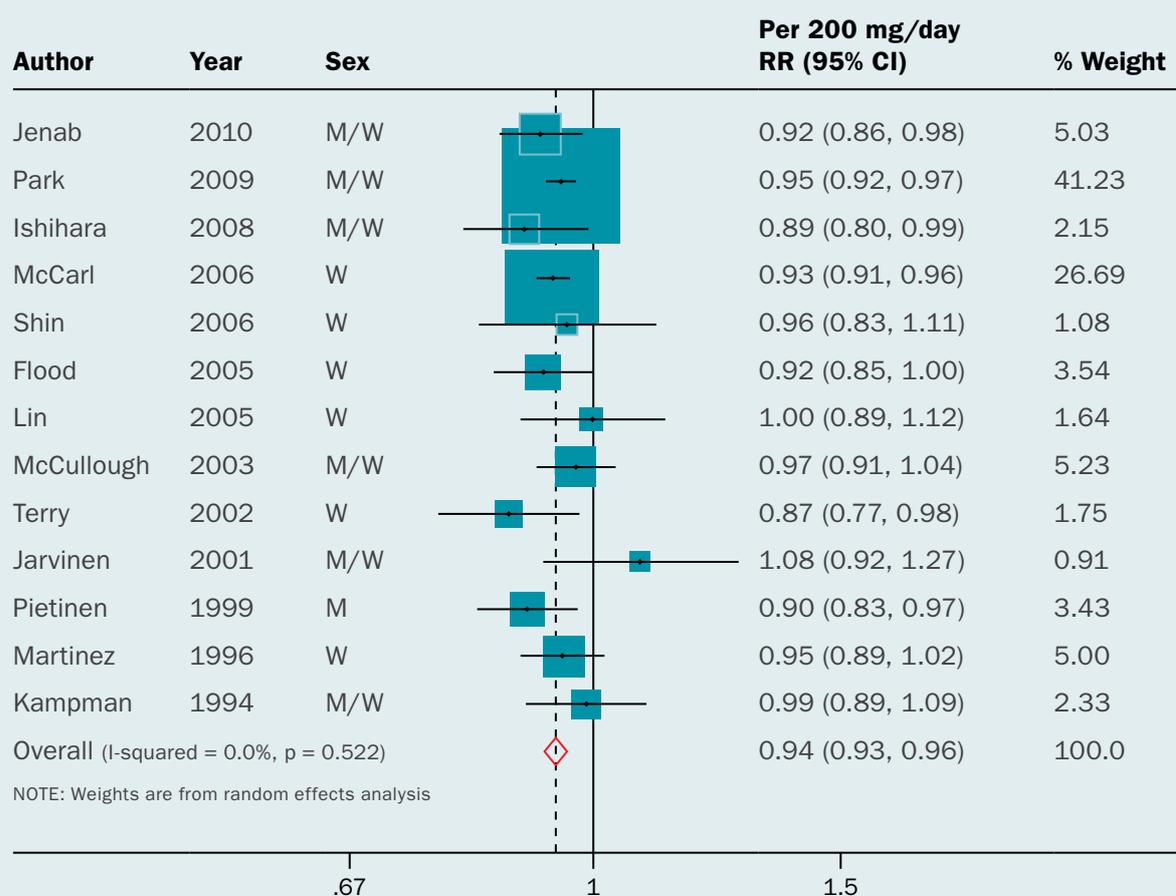#### 5.7.1.3.2 Published pooled analyses and meta-analyses

One published *pooled analysis* (see **Table 5.11**) and two other published meta-analyses on consumption of cheese and the risk of colorectal cancer were identified. The pooled analysis (not included in the CUP dose–response meta-analysis) reported no statistically significant association for the highest compared with the lowest levels of cheese consumed [112].

One highest versus lowest meta-analysis [113] reported no significant association between the risk of colorectal cancer and consumption of cheese (RR 1.11 [95% CI 0.90–1.36]). The other meta-analysis reported previous results from the CUP [108].

Table 5.11: Summary of published pooled analyses of cheese intake and the risk of colorectal cancer

Publication	Contrast	RR (95% CI)	p value	No. of studies	No. of cases
Pooling Project of Prospective Studies on Diet and Cancer [112]	≥ 25 vs < 5 g/day	1.10 (0.98–1.24)	0.37	10 cohort studies	7,157

Figure 5.9: CUP dose–response meta-analysis[1] for the risk of colorectal cancer, per 200 milligrams increase in dietary calcium intake per day

Author	Year	Sex		Per 200 mg/day RR (95% CI)	% Weight
Jenab	2010	M/W		0.92 (0.86, 0.98)	5.03
Park	2009	M/W		0.95 (0.92, 0.97)	41.23
Ishihara	2008	M/W		0.89 (0.80, 0.99)	2.15
McCarl	2006	W		0.93 (0.91, 0.96)	26.69
Shin	2006	W		0.96 (0.83, 1.11)	1.08
Flood	2005	W		0.92 (0.85, 1.00)	3.54
Lin	2005	W		1.00 (0.89, 1.12)	1.64
McCullough	2003	M/W		0.97 (0.91, 1.04)	5.23
Terry	2002	W		0.87 (0.77, 0.98)	1.75
Jarvinen	2001	M/W		1.08 (0.92, 1.27)	0.91
Pietinen	1999	M		0.90 (0.83, 0.97)	3.43
Martinez	1996	W		0.95 (0.89, 1.02)	5.00
Kampman	1994	M/W		0.99 (0.89, 1.09)	2.33
Overall (I-squared = 0.0%, p = 0.522)				0.94 (0.93, 0.96)	100.0
NOTE: Weights are from random effects analysis					

.67   1   1.5

Source: Jenab, 2010 [115]; Park, 2009 [99]; Ishihara, 2008 [116]; McCarl, 2006 [102]; Shin, 2006 [117]; Flood, 2005 [118]; Lin, 2005 [110]; McCullough, 2003 [104]; Terry, 2002 [105]; Jarvinen, 2001 [106]; Pietinen, 1999 [68]; Martinez, 1996 [119]; Kampman, 1994 [114].

Stratified analyses for the risk of colorectal cancer per 200 milligrams increase in dietary calcium intake per day were conducted for sex and cancer type.

When stratified by sex, a statistically significant decreased risk was observed for men (RR 0.93 [95% CI 0.88–0.99]) and women (RR 0.93 [95% CI 0.91–0.95]; see CUP colorectal cancer SLR 2016, Appendix 4. When stratified by cancer type, a significant decreased risk was observed for colon cancer (RR 0.93 [95% CI 0.89–0.97]; see CUP colorectal cancer SLR 2016, Appendix 4, but not rectal cancer.

Most studies in the dose–response meta-analysis adjusted for the majority of colorectal cancer risk factors, including physical activity, BMI, alcohol consumption, tobacco smoking, red meat and MHT in women.

5.7.1.4.2 Published pooled analyses and meta-analyses

One published pooled analysis (see **Table 5.12**) on dietary calcium intake and the risk of colorectal cancer was identified. No other published meta-analyses have been identified.

The pooled analysis (not included in the CUP dose–response meta-analysis) reported a statistically significant decreased risk for the highest compared with the lowest level of dietary calcium intake [109].

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[1] Seven studies could not be included in the dose–response meta-analysis because sufficient information was not provided. For further details see CUP colorectal cancer SLR 2016, Appendix 4.

Table 5.12: Summary of published pooled analyses of dietary calcium intake and the risk of colorectal cancer

Publication	Contrast	RR (95% CI)	drinking milk p value	No. of studies	No. of cases
Pooling Project of Prospective Studies on Diet and Cancer [112]	Highest vs lowest	0.86 (0.78–0.95)	0.02	10 cohort studies	4,992

5.7.1.5 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.

Observed inverse associations between intake of dairy products and colorectal cancer development have been largely attributed to their high calcium content. In addition to calcium, lactic acid-producing bacteria may also protect against colorectal cancer [120], while the casein and lactose in milk may increase calcium bioavailability [121]. Other *nutrients* or *bioactive constituents* in dairy products, such as lactoferrin, vitamin D (from fortified dairy products) or the short-chain fatty acid butyrate may also impart some protective functions against colorectal cancer [120], but these require better elucidation.

5.7.1.6 CUP Panel's conclusion

The evidence was generally consistent for dairy products, milk, cheese and dietary calcium, and showed a decreased risk of colorectal cancer with higher consumption. The dose–response meta-analyses for dairy products, milk and dietary calcium were statistically significant with no or little *heterogeneity*. The decreased risk observed for cheese

was smaller than for the other exposures. A non-linear relationship was observed for dairy products and cheese. Analyses for colon cancer and those stratified by sex or geographic location generally showed a significant decreased risk. One published *pooled analysis* reported a significant decreased risk for the highest compared with the lowest level of intake of milk and dietary calcium. There is evidence of plausible mechanisms in humans.

> **The CUP Panel concluded:**
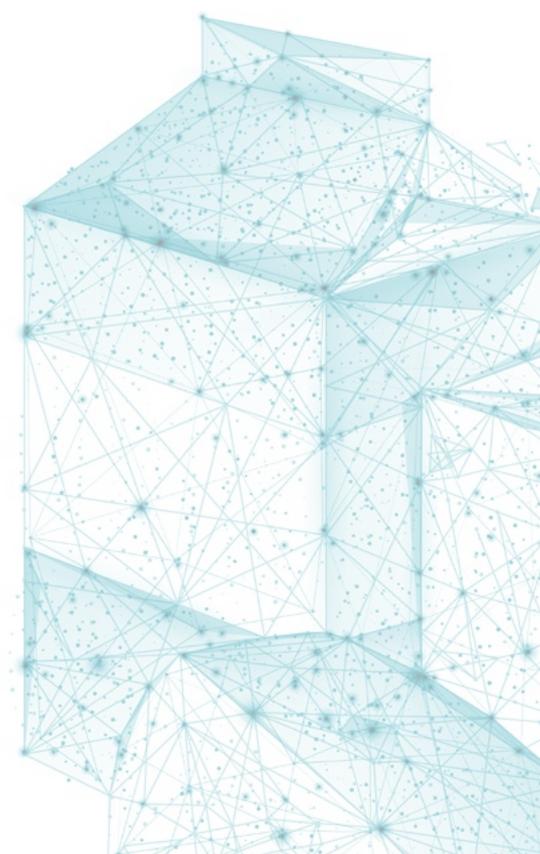> - **Consumption of dairy products probably protects against colorectal cancer.**

Table 5.13: Summary of CUP dose–response meta-analyses of diets high in calcium and the risk of 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]
Breast (premenopause)	6	5	2,980	0.87 (0.76–0.99)	300 mg/day	67	Limited – suggestive: Decreases risk	2017
Breast (postmenopause)	7	6	10,137	0.96 (0.94–0.99)	300 mg/day	0	Limited – suggestive: Decreases risk	2017
Prostate	16	15	38,749	1.05 (1.02–1.09)	400 mg/day	49	Limited – suggestive: Increases risk	2014

1   See Definitions of WCRF/AICR grading criteria (**Section 1**: Meat, fish and dairy products 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.

5.8 Diets high in calcium

Table 5.13 summarises the main findings from the CUP dose–response meta-analyses of cohort studies on diets high in calcium and the risk of cancer.

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

For more information on the evidence for diets high in calcium 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 below:

- CUP breast cancer report 2017: Section 7.4 and CUP breast cancer SLR 2017: Section 5.6.3.

- CUP prostate cancer report 2014: Section 7.2 and CUP prostate cancer SLR 2014: Section 5.6.3.

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

5.9 Other

The effect of other meat, fish and dairy products on the risk of cancer was evaluated, as well as those that were graded by the Panel as 'limited – suggestive', 'probable' or 'convincing'. These included poultry and eggs. However, data were either of too low quality or too inconsistent, or the number of studies too few, to allow conclusions to be reached.

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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 by any combination of these.

6. Comparison with the 2007 Second Expert Report

In the 2007 Second Expert Report, there was strong evidence that red meat and processed meat increased the risk of colorectal cancer, and this evidence has remained strong. The evidence that Cantonese-style salted fish is probably a cause of nasopharyngeal cancer and that milk (Third Expert Report conclusion is for dairy products) probably protects against colorectal cancer has also remained strong.

In addition, more studies were included to assess the association between diets high in calcium and prostate cancer, leading to the strength of evidence and the judgement being downgraded from 'probable' to 'limited – suggestive' increases risk.

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Abbreviations

AICR American Institute for Cancer Research

BMI Body mass index

CI Confidence interval

CUP Continuous Update Project

H. pylori *Helicobacter pylori*

IGF Insulin-like growth factor

MHT Menopausal hormone therapy

NSCLC Non-small-cell lung cancer

PSA Prostate-specific antigen

RR Relative risk

SCLC Small-cell lung cancer

SLR Systematic literature review

WCRF World Cancer Research Fund

Glossary

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

Adenocarcinoma
Cancer of glandular epithelial cells.

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

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

Advanced glycation endproducts (AGEs)
Proteins or lipids that become glycated following exposure to sugars.

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

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

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

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

Carcinogen
Any substance or agent capable of causing cancer.

Carcinogenesis
The process by which a malignant tumour is formed.

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

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.

Cirrhosis

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

Cohort study

A study of a (usually large) group of people whose characteristics are recorded at recruitment (and sometimes later) and followed up for a period of time during which outcomes of interest are noted. Differences in the frequency of outcomes (such as disease) within the cohort are calculated in relation to different levels of exposure to factors of interest – for example, tobacco smoking, alcohol consumption, diet and exercise. Differences in the likelihood of a particular outcome are presented as the relative risk, comparing one level of exposure with another.

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.

Conjugated linoleic acids

Specific fatty acids typically found in lipids derived from foods, such as milk or meats, from ruminant animals such as cows, goats or sheep.

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

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

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

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

Eicosanoids
Compounds formed in the body from long-chain polyunsaturated fatty acids formed by cyclooxygenase or lipoxygenase, which act as local hormones and are involved in inflammation, regulating cell growth, and a variety of other functions.

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.

Epithelial (see **epithelium**)

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

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.

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

Hepatocellular carcinoma
Primary malignant tumour of the liver.

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

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.

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

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

Lactose intolerance
The inability to digest lactose, a component of milk and some other dairy products. The basis for lactose intolerance is the lack of an enzyme called lactase in the small intestine.

Large cell carcinoma
A term used to describe a microscopically identified variant of certain cancers, for example, lung cancers, in which the abnormal cells are particularly large.

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

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

Menarche
The start of menstruation.

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

Menopause
The cessation of menstruation.

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

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

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

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

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

Non-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.

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.

Pasteurisation
Partial sterilisation of foods at a temperature that destroys microorganisms such as bacteria, viruses, moulds, yeast and protozoa without major changes in the chemistry of the food.

Physical activity
Any movement using skeletal muscles that requires more energy than resting.

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

Polyunsaturated fatty acids (PUFAs)
Fatty acids containing two or more double bonds.

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.

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–).

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

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

Squamous cell carcinoma
A malignant cancer derived from squamous epithelial cells.

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

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.

Tumorigenesis

The process of tumour development.

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Appendix 1: Criteria for grading evidence for cancer prevention

Adapted from Chapter 3 of the 2007 Second Expert Report [1]. Listed here are the criteria agreed by the Panel that were necessary to support the judgements shown in the matrices. The grades shown here are 'convincing', 'probable', 'limited – suggestive', 'limited – no conclusion', and 'substantial effect on risk unlikely'. In effect, the criteria define these terms.

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

CONVINCING (STRONG EVIDENCE)

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

All of the following are generally required:

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

PROBABLE (STRONG EVIDENCE)

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

All of the following are generally required:

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

LIMITED – SUGGESTIVE

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

All of the following are generally required:

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

LIMITED – NO CONCLUSION

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

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

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

SUBSTANTIAL EFFECT ON RISK UNLIKELY (STRONG EVIDENCE)

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

All of the following are generally required:

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

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

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

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

SPECIAL UPGRADING FACTORS

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

Factors may include the following:

- Presence of a plausible biological gradient ('dose–response') in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.

- A particularly large summary effect size (an *odds ratio* or *relative risk* of 2.0 or more, depending on the unit of exposure) after appropriate control for confounders.

- Evidence from randomised trials in humans.

- Evidence from appropriately controlled experiments demonstrating one or more plausible and specific mechanisms actually operating in humans.

- Robust and reproducible evidence from experimental studies in appropriate animal models showing that typical human exposures can lead to relevant cancer outcomes.

Appendix 2: Mechanisms

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

Red meat
Colorectum

Cooking meats at high temperatures, prolonged exposure to heat and cooking by various types of grilling results in the formation of *heterocyclic amines and polycyclic aromatic hydrocarbons*, both of which have been linked to colorectal cancer development in experimental studies [8]. In addition, haem iron, which is present at high levels in red meat, has been shown to promote colorectal *tumorigenesis* by stimulating the endogenous formation of carcinogenic *N-nitroso compounds* [74]. There is moderate mechanistic evidence to support a relationship between high consumption of red meat and colorectal cancer.

Nasopharynx

Cooking meats at high temperatures results in the formation of *heterocyclic amines and polycyclic aromatic hydrocarbons*, both of which have been linked to cancer development in experimental studies [122]. In addition, haem iron, which is present at high levels in red meat, has been shown to promote *tumorigenesis* by stimulating the endogenous formation of carcinogenic *N-nitroso compounds* [123]. However, experimental studies have not been undertaken into whether these mechanisms are applicable for nasopharynx cancer.

Lung

Tobacco smoking is by far the most important risk factor for lung cancer and tobacco smoking-derived compounds such as polycyclic aromatic hydrocarbons and *nitrosamines* are *carcinogens* in the lung [124, 125]. Red and processed meat may also be a source of these compounds – cooking meats at high temperatures, prolonged exposure to heat and cooking by various types of grilling results in the formation of *heterocyclic amines and polycyclic aromatic hydrocarbons*, both of which have been linked to the development of lung cancer in animal model studies. For example, the HCA MeIQx – a compound formed in meat cooked at high temperatures – has been shown to be a *genotoxic* carcinogen in a rodent model of lung cancer [126].

Pancreas

A number of mechanisms have been postulated linking red and processed meats with cancer development though mechanisms specific for pancreatic cancer are currently lacking. These include high content of haem iron, which can enhance oxidative stress, and *polycyclic aromatic hydrocarbons*, *heterocyclic amines* and *N-nitroso compounds*, which may be directly carcinogenic and pro-inflammatory [127]. In addition, high-temperature cooking of red and processed meats may enhance production of *advanced glycation endproducts (AGEs)*, which may have a variety of cancer-promoting effects [128]. Consumption of red and processed meats may lead to insulin resistance and *hyperinsulinemia*, promoting growth of cancer cells [129].

Processed meat
Colorectum

Overall it is likely that a combination of mechanisms contribute to higher risk of colorectal cancer among individuals consuming high quantities of processed meat. Similar to red meat, processed meat is rich in fat, protein and haem iron, which can promote *tumorigenesis* through the mechanisms described under red meat and colorectum [8]. Processed meats, such as sausages, are often cooked at high temperatures, which can lead to increased exposure to *heterocyclic amines and polycyclic aromatic hydrocarbons*. Processed meat is invariably higher in fat content than red meat, which may promote *carcinogenesis* through synthesis of secondary bile acids; however, human data supporting this hypothesis are weak. Processed meat is also a source of exogenously derived *N-nitroso compounds*, which may have carcinogenic potential [4].

Nasopharynx

Cooking meats at high temperatures results in the formation of *heterocyclic amines and polycyclic aromatic hydrocarbons*, both of which have been linked to cancer development in experimental studies [122]. In addition, *haem* iron, which is present at high levels in red meat, has been shown to promote *tumorigenesis* by stimulating the endogenous formation of carcinogenic *N-nitroso compounds* [123]. Processed meats are a source of nitrate and nitrite, both associated with N-nitroso compounds, which in animal models have been shown to induce cancer development [123, 130]. In addition, cooking processed meats at high temperatures results in the formation of heterocyclic amines and polycyclic aromatic hydrocarbons, both of which have been linked to cancer development in experimental studies [122]. However, experimental studies have not been undertaken into whether these mechanisms are applicable to nasopharyngeal cancer.

Oesophagus (squamous cell carcinoma)

Processed meats are a source of nitrate and nitrite, both associated with *N-nitroso compounds*, shown in animal models to induce cancer development [123, 130]. In addition, cooking processed meats at high temperatures results in the formation of *heterocyclic amines and polycyclic aromatic hydrocarbons*, both of which have been linked to cancer development in experimental studies [122].

Lung

Overall it is likely that a combination of mechanisms contribute to higher risk of lung cancer among people consuming high quantities of processed meat. Similar to red meat, processed meat is rich in fat, protein and haem iron, which can promote *tumorigenesis* through the mechanisms described under red meat and colorectum [8]. Processed meats, such as sausages, are often cooked at high temperatures, which can lead to increased exposure to *heterocyclic amines and polycyclic aromatic hydrocarbons*, which are lung *carcinogens* [126]. Processed meat may also be a source of exogenously derived *N-nitroso compounds*, which have carcinogenic potential in the lung.

Stomach (non-cardia)

Processed meats are a source of nitrate and nitrite, both associated with *N-nitroso compounds*, which in animal models have been shown to induce cancer development [123, 130]. In addition, cooking processed meats at high temperatures results in the formation of *heterocyclic amines and polycyclic aromatic hydrocarbons*, both of which have been linked to cancer development in experimental studies [122].

Pancreas

A number of mechanisms have been postulated linking red and processed meats with cancer development, though mechanisms specific for pancreatic cancer are currently lacking. These include high content of haem iron, which can enhance oxidative stress, and *polycyclic aromatic hydrocarbons, heterocyclic amines* and *N-nitroso compounds*, which may be directly carcinogenic and pro-inflammatory [127]. In addition, high-temperature cooking of red and processed meats may enhance production of *advanced glycation endproducts (AGEs)*, which may have a variety of cancer-promoting effects [128]. Consumption of red and processed meats may lead to insulin resistance and *hyperinsulinemia*, promoting the growth of cancer cells [129].

Foods containing haem iron
Colorectum

Higher consumption of meat and meat products may increase exposure to greater quantities of bioavailable haem iron among those not at risk of iron deficiency. Iron is involved in processes of oxygen transport, oxidative phosphorylation, DNA synthesis and cell growth. However, increased intake of iron is thought to augment synthesis of *reactive oxygen species* by acting as a catalyst in free radical-generating pathways in the *colon*. In turn, reactive oxygen species can induce *lipid peroxidatio*n and cellular and DNA damage [131].

Fish
Liver

Fish, particularly fatty fish, contain high concentrations of the long-chain omega-3 fatty acids docosahexaenoic acid and eicosapentaenoic acid. The biological effects of these fatty acids include modulating the production of inflammatory *eicosanoid*s and reducing tumour cell growth [132, 133]. Additional purported mechanisms of omega-3 fatty acids include modulation of transcription factor activity and signal transduction as well as alteration of oestrogen metabolism [132]. Supporting evidence of direct relevance to liver cancers is rare, but in an animal study, fish oil supplementation has been shown to slow the growth of chemically induced *hepatocellular carcinoma* [134]. Other animal studies have demonstrated that diets rich in omega-3 fatty acids can attenuate the hepatic injury oxidative stress and *inflammation* caused by non-alcoholic steatohepatitis, a condition that is causally linked to hepatocellular carcinoma development [135]. Fish may also contain high amounts of vitamin D and selenium, which may protect against the development of liver cancers [136, 137].

Colorectum

Experimental studies suggest that long-chain n-3 *polyunsaturated fatty acids* found in fish, such as eicosapentaenoic acid and docosahexaenoic acid, suppress the development of colorectal cancer [132, 138]. Long-chain n-3 PUFAs have been shown to influence inflammatory pathways by the suppression of synthesis of n-6 PUFA derived *eicosanoids*. There are limited mechanistic data for a link between fish consumption and colorectal cancer risk in humans.

Cantonese-style salted fish
Nasopharynx

Cantonese-style salted fish contains *nitrosamines* and nitrosamine precursors. High levels of one such nitrosamine, N-nitrosodimethylamine, found in some samples of Cantonese-style salted fish, have been shown to induce cancer development in experimental models in animals [94].

Grilled (broiled) or barbecued (charbroiled) meat and fish
Stomach

When meat and fish are cooked on a grill or barbecue, the mutagenic chemicals *heterocyclic amines and polycyclic aromatic hydrocarbons* may be formed, both of which have been linked to cancer development in experimental studies [122]. However, current experimental evidence linking these chemicals directly to stomach cancer is limited.

Dairy products
Colorectum

Observed inverse associations between intake of dairy products and colorectal cancer development have been largely attributed to their high calcium content. In addition to calcium, *lactic acid-producing* bacteria may also protect against colorectal cancer [120], and the casein and lactose in milk may increase calcium bioavailability [121]. Other nutrients or *bioactive constituents* in dairy products, such as lactoferrin, vitamin D (from fortified dairy products) or the short-chain fatty acid butyrate, may also impart some protection against colorectal cancer [120], but these require much better elucidation.

Breast (premenopause)

Dairy products are a major source of dietary calcium but are also rich in vitamin D and *conjugated linoleic acids*, which may have a protective effect on breast cancer development. Conjugated linoleic acids have been shown in experimental studies to inhibit mammary tumour development [139]. Results from epidemiological studies on dietary intakes or biomarkers of linoleic acid, however, have been inconsistent [140].

Prostate

Dairy products are an important source of calcium. High levels of calcium have been shown to downregulate the formation of the biologically active form of vitamin D, 1,25-dihydroxyvitamin D, thereby increasing cellular proliferation in the prostate [141]. However, pre-diagnostic circulating levels of vitamin D are not related to prostate cancer risk in epidemiological studies [142]. Greater consumption of milk has been associated with a modest increase in blood levels of *IGF*-1 [143]. Higher circulating concentrations of IGF-1 have been associated with an elevated risk for prostate cancer [144].

Diets high in calcium
Breast (premenopause)

Calcium has a potentially important role in *carcinogenesis* by regulating cell proliferation, differentiation and *apoptosis* [11, 145–147]. Calcium has been shown to reduce fat-induced mammary cell proliferation in rats by maintaining intracellular calcium concentrations [146, 148]. Vitamin D and calcium are metabolically linked, and there is evidence that calcium might, at least partially, exert anticarcinogenic effects through vitamin D [149]. For example, calcium is one of the key mediators of apoptosis induced by vitamin D compounds in breast cancer cells [150]. The intake of calcium and vitamin D supplements has also been associated with a decrease in mammographic density in premenopausal women and women not using *menopausal hormone therapy*, indicating a possible interaction with oestrogens [151, 152].

Breast (postmenopause)

Calcium has a potentially important role in *carcinogenesis* by regulating cell proliferation, differentiation and *apoptosis* [11, 145–147]. Calcium has been shown to reduce fat-induced mammary cell proliferation in rats by maintaining intracellular calcium concentrations [146, 148]. Vitamin D and calcium are metabolically linked and there is evidence that calcium might, at least partially, exert anticarcinogenic effects through vitamin D [149]. For example, calcium is one of the key mediators of apoptosis induced by vitamin D compounds in breast cancer cells [150] and postmenopausal women not using *menopausal hormone therapy*, indicating a possible interaction with oestrogens [151, 152].

Prostate

High levels of calcium have been shown to downregulate the formation of the biologically active form of vitamin D, 1,25-dihydroxyvitamin D, thereby increasing cellular proliferation in the prostate [141]. However, pre-diagnostic circulating levels of vitamin D are not related to prostate cancer risk in epidemiological studies [142]. Therefore, more mechanistic evidence is required to explain how higher circulating calcium levels are related to greater prostate cancer risk.

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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