World Cancer Research Fund

American Institute for Cancer Research

CUP Continuous Update Project

Analysing research on cancer prevention and survival

Preservation and processing of foods
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. Preservation and processing of foods and the risk of cancer is one of many parts that make up the CUP Third Expert Report: for a full list of contents, see dietandcancerreport.org

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

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Key

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

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

Executive summary

Background and context

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

Foods can be preserved and processed in a number of ways prior to consumption. These different methods affect the chemical composition of foods as well as their nutritional value and *carcinogenic* potential.

Processed meat generally refers to meats (usually red meats) that have been preserved by salting, curing, fermentation, smoking, or other processes to enhance flavour or improve preservation. Examples of processed meat include ham, salami, bacon, pastrami and some sausages. These include sausages, bratwursts, chorizo, frankfurters and 'hot dogs' to which nitrites or nitrates or other preservatives are added.

Salting is a traditional method of preserving raw fish throughout much of the world. Depending on the precise conditions, salt-preserved fish may also undergo fermentation. Cantonese-style salted fish is characterised by using less salt and a higher degree of fermentation during the drying process than fish preserved (or salted) by other means, because of the relatively high outdoor temperature and moisture levels.

Although the use of salt as a preservative has generally decreased as industrial and domestic use of refrigeration has increased, some traditional diets still include substantial amounts of salt-preserved foods, including salted meat, fish, vegetables and sometimes also fruit. The requirement for salt for human health has been estimated to be much lower than amounts currently consumed. World Health Organization pragmatically recommends restricting average salt consumption for populations to less than 5 grams per day (equivalent to less than 2 grams of sodium per day).

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.

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

Findings

There is **strong evidence** that consuming:

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

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

- **foods preserved by salting increases** the risk of stomach cancer.

For processed meat, Cantonese-style salted fish and foods preserved by salting, the evidence shows that, in general, the more people consume, the higher the risk of some cancers.

The Panel used the strong evidence on 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'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).

A global recommendation about consumption of foods preserved by salting has not been made as these types of food are mostly consumed only in Asia. Nevertheless, the Panel advises that it's best not to consume foods preserved by salting (see Recommendations and public health and policy implications, Section 3: Issues relevant only in specific parts of the world – Foods preserved by salting).

There is also other evidence on preservation and processing of foods that is limited (either in amount or by methodological flaws), but is suggestive of an increased 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 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. Preservation and processing of foods and the risk of cancer: a summary matrix

WCRF/AICR GRADING		DECREASES RISK		INCREASES RISK	
PRESERVATION AND PROCESSING OF FOODS AND THE RISK OF CANCER					
		Exposure	**Cancer site**	**Exposure**	**Cancer site**
STRONG EVIDENCE	**Convincing**			Processed meat[1]	Colorectum 2017
	Probable			Cantonese-style salted fish[2]	Nasopharynx 2017
				Foods preserved by salting[3]	Stomach 2016
LIMITED EVIDENCE	**Limited – suggestive**			Preserved non-starchy vegetables	Nasopharynx 2017
				Processed meat[1]	Nasopharynx 2017
					Oesophagus (squamous cell carcinoma) 2016
					Lung 2017
					Stomach (non-cardia) 2016
					Pancreas 2012
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 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 on 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.

3 The term 'foods preserved by salting' refers mainly to high-salt foods and salt-preserved foods, including pickled vegetables and salted or dried fish, as traditionally prepared in East Asia. Evidence for foods preserved by salting and stomach cancer comes from salt-preserved foods including vegetables and fish.

Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from 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 justifies 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 making recommendations designed to reduce the risk of cancer.

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

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

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

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

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

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

2. Summary of Panel judgements

The conclusions drawn by the Continuous Update Project (CUP) Panel are based on the evidence from both epidemiological and mechanistic studies relating specific methods of preservation and processing of foods to the risk of development of particular cancer types. Each conclusion on the likely causal relationship between preservation and processing of foods 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

- **Increased risk**
  - **Cantonese-style salted fish:**[2] Consumption of Cantonese-style salted fish is probably a cause of nasopharyngeal cancer.

  - **Foods preserved by salting:**[3] Consumption of foods preserved by salting is probably a cause of stomach cancer.

For processed meat, Cantonese-style salted fish and foods preserved by salting, the evidence shows that, in general, the more people consume, the higher the risk of some cancers.

The Panel used the strong evidence on 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 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).

A global recommendation about consumption of foods preserved by salting has not been made as these foods are consumed mostly in Asia. Nevertheless, the Panel advises that it's best not to consume foods preserved by salting (See Recommendations and public health and policy implications, Section 3: Issues relevant only in specific parts of the world – Foods preserved by salting).

LIMITED EVIDENCE

Limited – suggestive

- **Increased risk**
  - **Preserved non-starchy vegetables:** The evidence suggesting that consumption of preserved non-starchy vegetables increases the risk of nasopharyngeal cancer is limited.
  - **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.
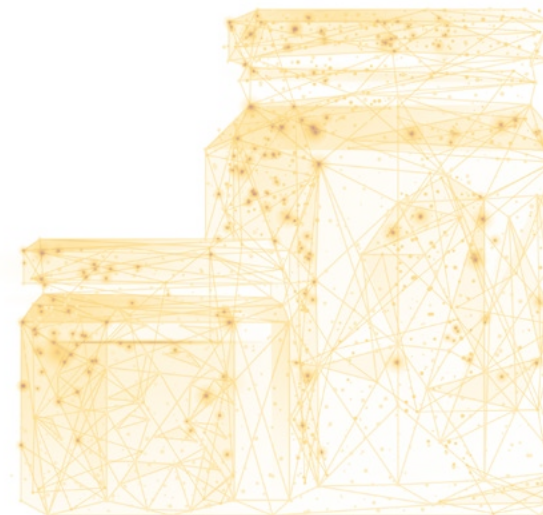
The Panel did not use the limited evidence when making Recommendations designed to reduce the risk of developing cancer. Further research is required into these possible effects on the risk of cancer.

See Definitions of WCRF/AICR grading criteria (**Section 1**: Preservation and processing of foods and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'strong evidence', 'convincing', 'probable', 'limited evidence' and 'limited – suggestive'.

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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] 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 on 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.

[3] The term 'foods preserved by salting' refers mainly to high-salt foods and salt-preserved foods, including pickled vegetables and salted or dried fish, as traditionally prepared in East Asia. Evidence for foods preserved by salting and stomach cancer comes from salt-preserved foods including vegetables and fish.

3. Definitions and patterns

Foods can be preserved and processed in a number of ways prior to consumption. These different methods affect the chemical composition of foods as well as their nutritional value and *carcinogenic* potential.

3.1 Preserved non-starchy vegetables

Preserved vegetables include those that are salted, dried, fermented or pickled. Pickling, broadly defined, is the use of brine (a concentrated salt solution), vinegar, soy sauce or a spicy solution to preserve and give a unique flavour to a food [2]. Numerous vegetables can be pickled, not only to preserve them but also to modify their flavour. Some vegetables may also be fermented during pickling.

The preserving processes of particular interest in this Third Expert Report are traditional methods used in some parts of China, Thailand, Singapore and Japan. For more general information on salting of foods as well as consumption of salt in the diet, see **Section 3.4**.

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 or 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.

3.3 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).

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 [3]. This style of fish, which is prepared with less salt than is used on the northern part of China, is allowed to ferment, and so is eaten in a decomposed state.

See **Section 3.4** for more general information on salting of foods as well as consumption of salt in the diet.

3.4 Foods preserved by salting

The use of sodium chloride (salt) as a preservative has generally decreased as industrial and domestic use of refrigeration has increased [4]. However, some traditional diets include substantial amounts of salt-preserved foods, including salted meat, fish, vegetables and sometimes also fruit. For more information on how salt may be used in the preservation and processing of different foods, see **Sections 3.1** and **3.3**.

The sodium found in sodium chloride is essential for the body to function normally. It is a major electrolyte in extracellular fluid. The body's sodium content and its concentration in body fluids are controlled *homeostatically* to very precise limits; excess sodium is excreted in the urine [5]. The requirement for sodium for human health has been estimated to be as little as 200 to 500 milligrams for adults [5]. On a pragmatic basis, World Health Organization recommends restricting average sodium consumption for populations to less than 2 grams per day (equivalent to less than 5 grams of sodium chloride per day) [5].

The average adult daily intake of sodium chloride worldwide varies from 4 grams in Kenya to 15 grams in Kazakhstan [6]. Very high levels of intake are found in Japan, some parts of China, Korea, Portugal, and Brazil and other Portuguese-speaking countries, where diets contain substantial amounts of salt-preserved, salt-pickled, salted or salty foods. The average adult intake of sodium chloride is about 9 to 12 grams per day in *high-income countries*, including those in Europe and North America [6].

4. Interpretation of the evidence

4.1 General

For general considerations that may affect interpretation of the evidence, 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

4.2.1 Exposures

4.2.1.1 Preserved non-starchy vegetables

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

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

Study design. For nasopharyngeal cancer, there was a lack of cohort studies so the evidence for that came from a published *meta-analysis* of *case-control studies* [7]. 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* [7]. 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 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 [3]. This style of fish, which is prepared with less salt than is used on 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).
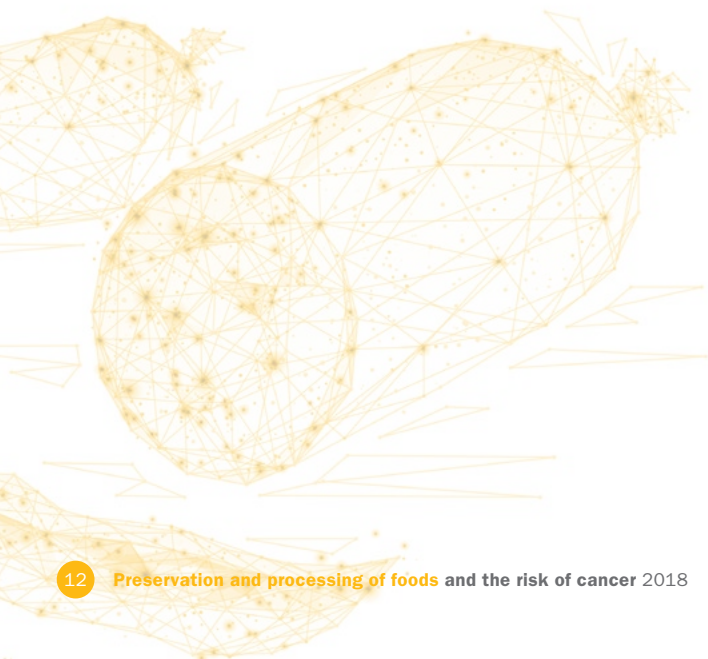
4.2.1.4 Foods preserved by salting

Definition. Evidence in the CUP comes from studies of salt-preserved foods, salt-preserved vegetables and salt-preserved fish, and refers mainly to high-salt foods and salt-preserved foods, including pickled

vegetables and salted or dried fish, as traditionally prepared in East Asia.

Evidence on salt-preserved vegetables came from studies in Asia, except for one study conducted in Europe [8]. The European study [8] examined pickles (vegetables pickled in vinegar). The other studies included salt-preserved vegetables (including cucumber, ginger and cabbage) as traditionally prepared in East Asia by pickling in brine or soy sauce. Some vegetables may have been fermented during pickling.

Salt-preserved fish was defined variously as salted, dried, smoked, salty or processed fish. Most studies were in Japanese or Korean populations, except for one conducted in Finland [9].

The category of salt-preserved foods was heterogeneous and included both high-salt foods and foods preserved by salting, some of which were also included in the categories of salt-preserved vegetables and salt-preserved fish. Studies were conducted in Asia, except for one study conducted in Norway [10]. The Norwegian study included salted meat and fish in its definition. The other studies included high-salt foods such as salt-preserved and pickled vegetables, dried fish and miso soup; salty confectionery; and undefined salted foods.

Confounding. Preserved foods may be eaten more by people who do not have access to refrigeration. The use of pickled vegetables may therefore be associated with poor socio-economic status, and thus with a high prevalence of *Helicobacter pylori (H. pylori)* infection, leading to the possibility of association by *confounding factors* (see CUP stomach cancer report 2016).

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) [11], 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 [12].

Occupational exposure

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

Infectious agents

Epstein-Barr virus (EBV) infection is a cause of nasopharyngeal cancer. Although it is a necessary cause, it is not sufficient [13] as only a fraction of the infected population develops nasopharyngeal cancer [13].

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 Evidence and judgements, **Section 5.3.1**.

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 [14]; 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* [15]. It is estimated that 42 per cent of deaths of oesophageal cancer are attributable to tobacco use [16].

Infection

Between 12 and 39 per cent of oesophageal squamous cell *carcinomas* worldwide are related to carcinogenic types of human papilloma virus [17]. *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 [18, 19].

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 [15]. 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) [15].

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 [20].

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 [21].

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 [22]. 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 [23].

⚛ 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 [24], as is exposure to indoor air pollution from wood and coal burning for cooking and heating [25].

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 [26].

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 [16].

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 [27, 28].

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 [29]. 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 [30, 31].

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 [32]. 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 [33] and smoking tobacco [34] to affect cancer risk.

Pernicious anaemia

People with the autoimmune form of pernicious anaemia have an increased risk of stomach cancer [35, 36]. This form of pernicious anaemia involves the autoimmune destruction of parietal cells in the gastric mucosa [36, 37]. These cells produce intrinsic factor, a protein that is needed to absorb vitamin B_{12} from foods, so the resultant vitamin B_{12} deficiency hinders the production of fully functioning red blood cells.

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

For more detailed information on *adjustments* made in CUP analyses on foods preserved by salting, see Evidence and judgements, **Section 5.4.1**.

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 [16].

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 [38].

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 Colon and rectum

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

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

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

Other diseases

Inflammatory bowel disease (Crohn's disease and ulcerative colitis) increases the risk of, and so may be seen as a cause of, colon cancer [39].

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 [40].

Family history

Based on twin studies, up to 45 per cent of colorectal cancer cases may involve a heritable component [41]. Between five and 10 per cent of colorectal cancers are consequences of recognised hereditary conditions [42]. 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 processed meat, see Evidence and judgements, **Section 5.2.1**.

5. Evidence and judgements

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

Full systematic literature reviews (SLRs) for each cancer are available online. For most cancer sites considered in the CUP,[1] there is also a CUP cancer report. CUP cancer reports summarise findings from the SLRs, again focusing on a specific cancer site. The section below also presents findings from the SLRs, but from a different perspective: it brings together all of the key findings on specific methods of preservation and processing of foods 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 Preserved non-starchy vegetables

Evidence for salt-preserved vegetables and risk of stomach cancer can be found in **Section 5.4.1**.

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

There was no discussion of preserved vegetables and any other cancer considered in the CUP as there were too few studies. For information on eating salt-preserved foods, which may include preserved vegetables, see **Section 5.4**.

Table 5.1: Summary of CUP dose–response meta-analyses of preserved vegetable intake and the risk of cancer

Cancer	Type	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I² (%)	Conclusion[1]	Date of CUP cancer report[2]
Nasopharynx[3]	Preserved vegetables	14	5	3,924	1.42 (1.04–1.93)	once/week	76	Limited – suggestive: Increases risk	2017

1   See Definitions of WCRF/AICR grading criteria (**Section 1**: Preservation and processing of foods 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   A dose–response meta-analysis of cohort studies could not be conducted in the CUP. Evidence is from a WCRF/AICR Second Expert Report published meta-analysis of *case-control studies* on preserved vegetable intake and nasopharyngeal cancer [43].

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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.

For more information on the evidence for eating preserved vegetables and the risk of cancer that was graded by the Panel as 'limited – suggestive' and suggests a direction of effect, see CUP nasopharyngeal cancer SLR 2017: Section 2.2.1.5.

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

5.2 Processed meat

Table 5.2 summarises the main findings from the CUP dose–response meta-analyses of cohort studies on consumption of processed meat 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; 2016); stomach (cardia; 2016); liver (2015); breast (pre and postmenopause; 2017); ovary (2014); endometrium (2013); prostate (2014); kidney (2015); bladder (2015); and skin (2017).

Table 5.2: 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	I[2] (%)	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**: Preservation and processing of foods 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* [7].

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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.

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 5.1**). Low *heterogeneity* was observed (I^2 = 20%) and there was no evidence of small study bias with *Egger's test* (p = 0.29).

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.
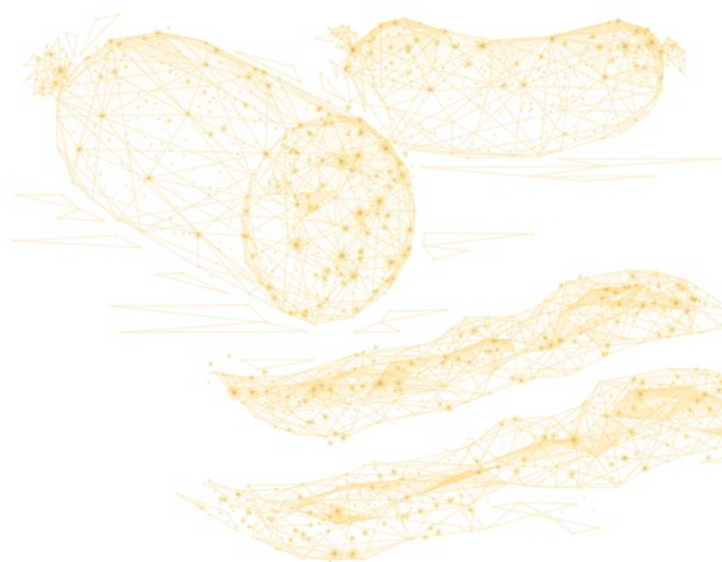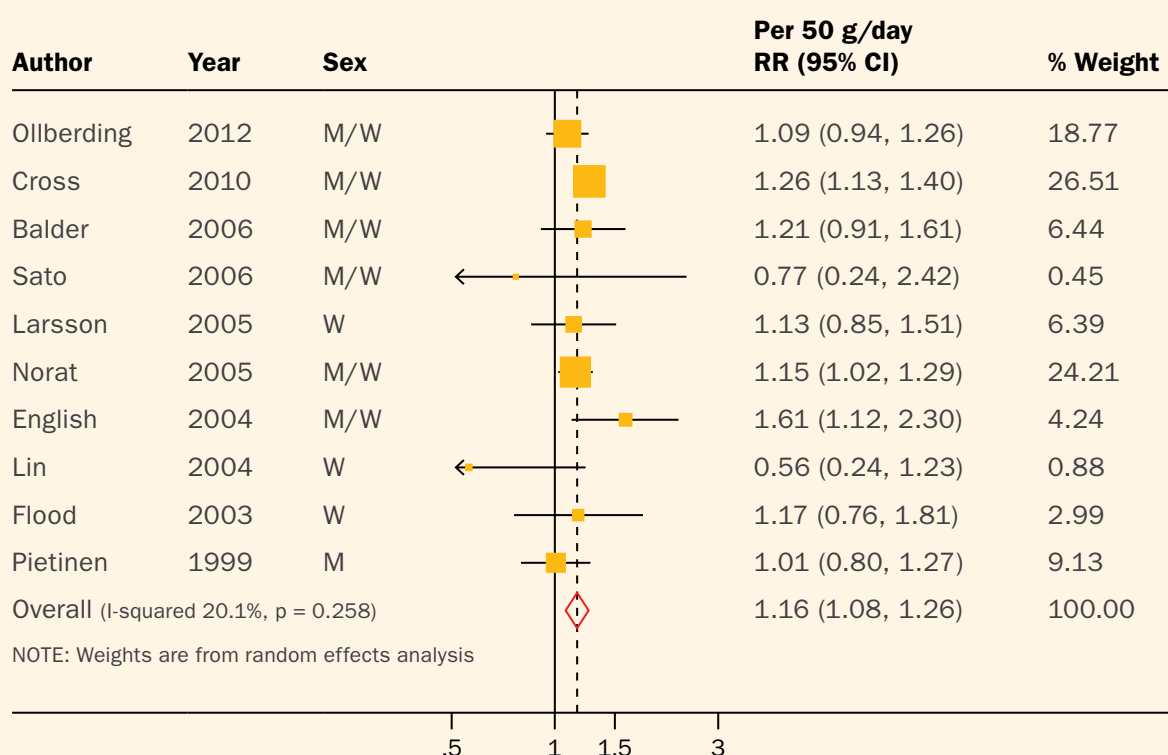
Figure 5.1: CUP dose–response meta-analysis for the risk of colorectal cancer, per 50 grams increase in processed meat consumed per day

Author	Year	Sex	Per 50 g/day 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

Source: Ollberding, 2012 [44]; Cross, 2010 [45]; Balder, 2006 [46]; Sato, 2006 [47]; Larsson, 2005 [48]; Norat, 2005 [49]; English, 2004 [50]; Lin, 2004 [51]; Flood, 2003 [52]; Pietinen, 1999 [53].

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 [44, 51]. 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 5.3**) 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 [54] and one reported no significant increase or decrease in risk [55]; neither study was included in the CUP dose–response meta-analysis.

One meta-analysis [56] 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 [57].

Table 5.3: Summary of published pooled analyses of processed meat intake and the risk of colorectal cancer

Publication	Increment	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) [54]	1 serving/day	1.48 (1.30–1.70)	–	7 *nested case-control studies*	3,488
UK Dietary Cohort Consortium [55]	50 g/day	0.88 (0.68–1.15)	0.36	7 cohort studies	579

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 contributes 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* [58]. 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 [59].

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 Cantonese-style salted fish

Due to a lack of cohort studies, *case-control studies* were reviewed for nasopharyngeal cancer. **Table 5.4** 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 5.4: 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	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]
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 on 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**: Preservation and processing of foods 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 following section and in the appendix (see **Appendix 2**) supersedes that in CUP cancer reports published before this Third Expert Report.

5.3.1 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 following subsections.

5.3.1.1 Cohort studies

One cohort study was identified during the 2007 Second Expert Report [60] 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

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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.

of salted fish were consumed per week during childhood (p = 0.038) compared with less frequent consumption. There was no *adjustment* for other factors.
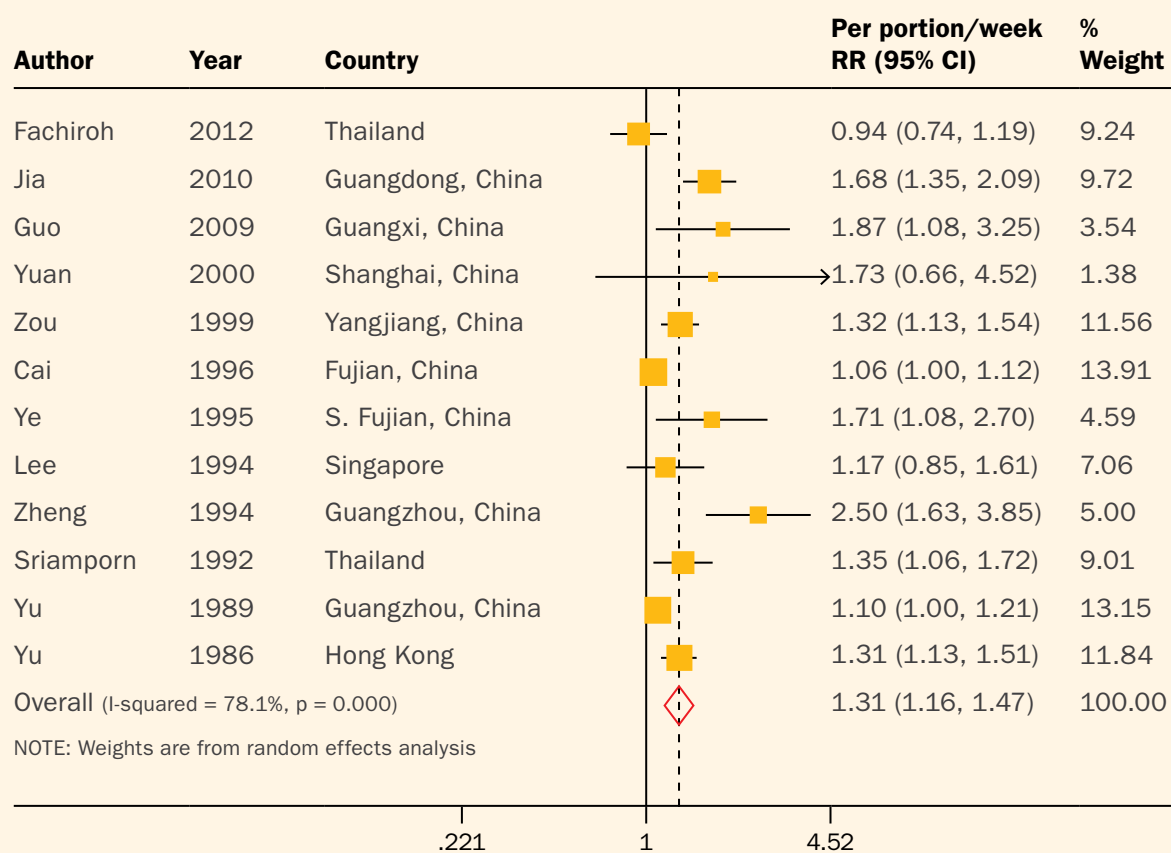
5.3.1.2 Case-control studies

5.3.1.2.1 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 5.2**).

Figure 5.2: 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		Per portion/week 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 [61]; Jia, 2010 [62]; Guo, 2009 [63]; Yuan, 2000 [64]; Zou, 1999 [65]; Cai, 1996 [66]; Ye, 1995 [67]; Lee, 1994 [68]; Zheng, 1994 [69]; Sriamporn, 1992 [70]; Yu, 1989 [71]; Yu, 1986 [72].

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[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.

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 [63] 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.

5.3.1.2.2 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) [62].

5.3.1.3 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.

5.3.1.4 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 [73].

5.3.1.5 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.**

5.4 Foods preserved by salting

Table 5.5 summarises the main findings from CUP meta-analyses of cohort studies on consumption of foods preserved by salting and the risk of stomach cancer. Dose–response meta-analyses were performed for salt-preserved vegetables and salt-preserved fish. A highest versus lowest meta-analysis was performed for salt-preserved foods as there were too few studies to conduct a dose–response meta-analysis.

Evidence for cancers of the following types was discussed in the CUP but was too limited to draw a conclusion[1]: oesophageal cancer (adenocarcinoma and squamous cell carcinoma; 2016); and lung cancer (2017).

Table 5.5: Summary of CUP meta-analyses for consumption of foods preserved by salting[1] and the risk of stomach cancer

Cancer	Salt-preserved exposure	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]
Stomach	Vegetables	14	9	3,932	1.09 (1.05–1.13)	20 g/day	0	**Probable: Increases risk**	2016
	Fish	11	4	2,110	1.06 (0.98–1.15)	20 g/day	0		
	Foods	6	5	635	1.70 (1.18–2.45)	Highest vs lowest	–		

1 The term 'foods preserved by salting' refers mainly to high-salt foods and salt-preserved foods, including pickled vegetables and salted or dried fish, as traditionally prepared in East Asia. Evidence for foods preserved by salting and stomach cancer comes from salt-preserved foods including vegetables and fish.

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

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

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

The strong evidence on the effects of eating foods preserved by salting on the risk of cancer is described in the following sections. This strong evidence includes analyses performed in the CUP and/or other published analyses and information on mechanisms that could plausibly influence the risk of cancer.

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

5.4.1 Stomach

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

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

5.4.1.1 Salt-preserved vegetables

5.4.1.1.1 CUP dose–response meta-analyses

Nine of 14 identified studies were included in the dose–response meta-analysis, which showed a statistically significant nine per cent increased risk of stomach cancer per 20 grams increase in salt-preserved vegetables consumed per day (RR 1.09 [95% CI 1.05–1.13]; n = 3,932 cases) (see **Figure 5.3**). No *heterogeneity* was observed and there was no evidence of small study bias with *Egger's test* (p = 0.14).

A stratified analysis for the risk of stomach cancer per 20 grams increase in salt-preserved vegetables consumed per day was conducted for outcome; a statistically significant increased risk was observed for incidence (RR 1.09 [95% CI 1.02–1.16]), but not mortality (see CUP stomach cancer SLR 2015, Figure 38). For details of other stratified analyses that have been conducted, please see CUP stomach cancer SLR 2015, Section 2.2.1.5.

Figure 5.3: CUP dose–response meta-analysis[1] for the risk of stomach cancer, per 20 grams increase in salt-preserved vegetables consumed per day

Author	Year	Per 20g per day RR (95% CI)	% Weight
Takachi	2010	1.11 (1.05, 1.17)	52.16
Iso	2007	1.09 (0.95, 1.24)	7.57
Sauvaget	2005	1.07 (1.00, 1.15)	25.59
Ngoan	2002	1.07 (0.93, 1.25)	6.02
Botterweck	1998	0.38 (0.15, 0.96)	0.15
Galanis	1998	1.02 (0.86, 1.20)	4.69
Kato	1992a	1.29 (0.89, 1.88)	0.95
Kato	1992b	0.84 (0.50, 1.42)	0.49
Nomura	1990	1.13 (0.89, 1.44)	2.36
Overall (I-squared = 0.0%, p = 0.436)		1.09 (1.05, 1.13)	100.00

NOTE: Weights are from random effects analysis

.3 .6 1 1.3 1.6
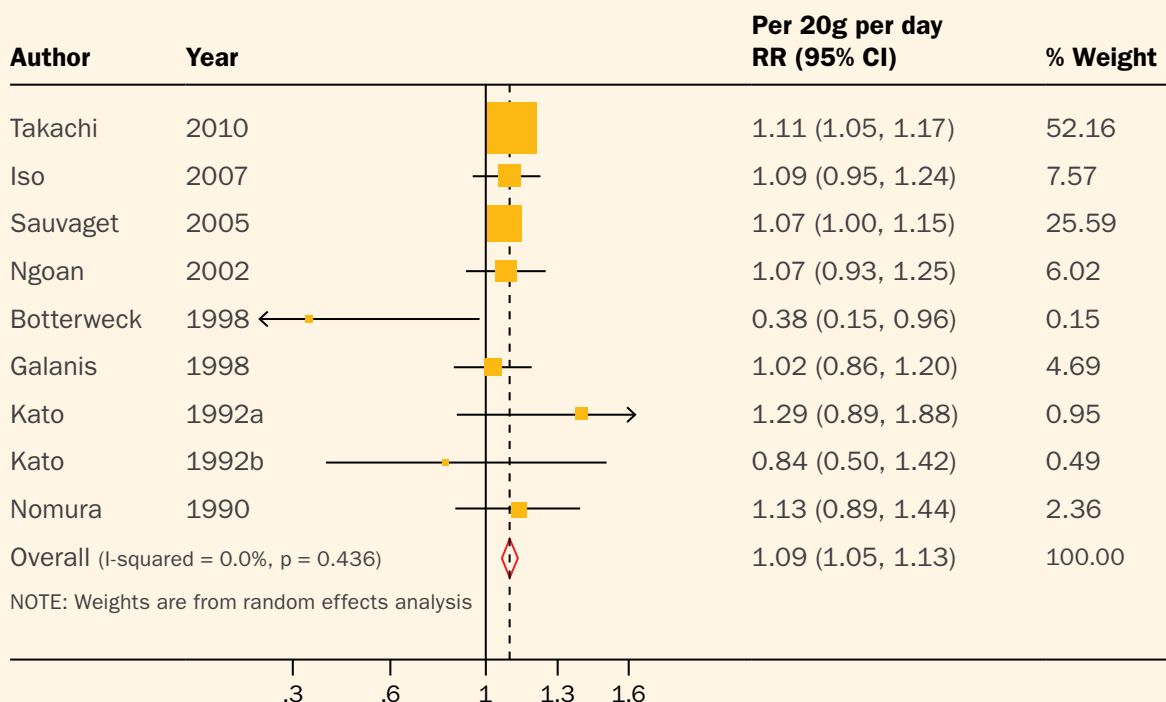
Source: Takachi, 2010 [74]; Iso, 2007 [75]; Sauvaget, 2005 [76]; Ngoan, 2002 [77]; Botterweck, 1998 [8]; Galanis, 1998 [78]; Kato, 1992 [79]; Kato, 1992 [80]; Nomura, 1990 [81].

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

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

5.4.1.1.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. Two other published meta-analyses on consumption of salt-preserved and pickled vegetables and the risk of stomach cancer have been identified, both of which reported a statistically significant increased risk for the highest compared with the lowest level consumed (RR 1.27 [95% CI 1.09–1.49] [82] and RR 1.32 [95% CI 1.10–1.59] [83]).

5.4.1.2 Salt-preserved fish

5.4.1.2.1 CUP dose–response meta-analyses

Although meta-analyses are only updated in the CUP when there are at least five studies with the required data, this section has been included because the evidence that salted and salty foods are causally related to stomach cancer risk was judged as probable in the 2007 Second Expert Report.

Four of 11 identified studies were included in the dose–response meta-analysis, which showed no statistically significant association between the risk of stomach cancer and consumption of salt-preserved fish (RR 1.06 [95% CI 0.98–1.15]; per 20 grams increase per day, n = 2,110 cases) (see **Figure 5.4**). No *heterogeneity* was observed.

As many studies could not be included in the dose–response meta-analysis, an analysis comparing the highest with the lowest level of consumption was conducted on eight studies, which showed a significant increased risk of stomach cancer (RR 1.15 [95% CI 1.01–1.31]). When one study [74] was removed from the analysis, the risk estimate was no longer significant.

All studies included in the dose–response meta-analysis adjusted for tobacco smoking and alcohol, except for one study that adjusted only for age and residence area [75]. None of the studies adjusted for *H. pylori* status. For information on the *adjustments* made in individual studies, see CUP stomach cancer SLR 2015, Table 88.

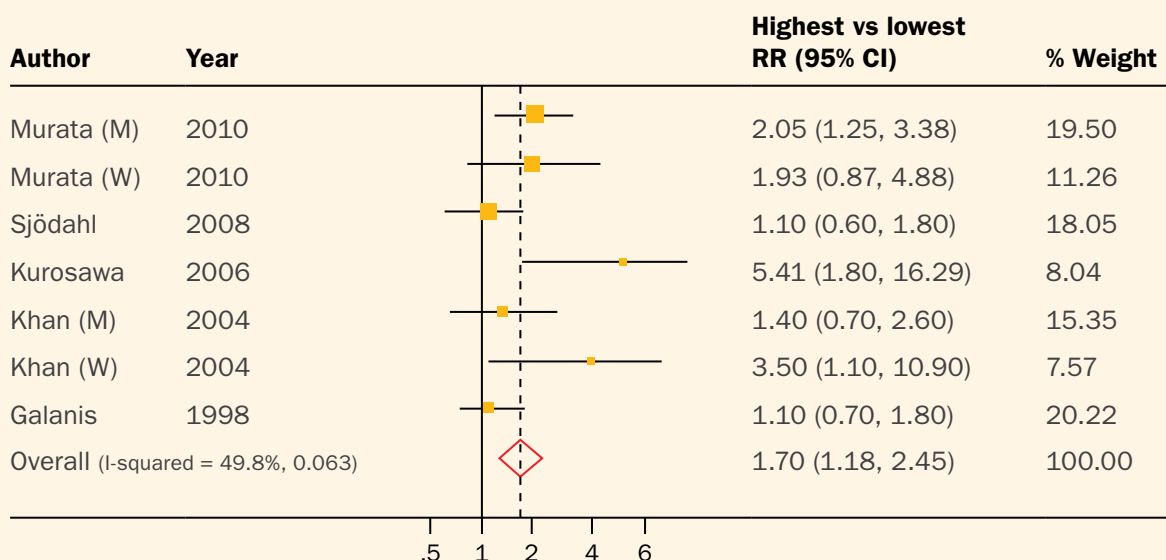**Figure 5.4: CUP dose–response meta-analysis[1] for the risk of stomach cancer, per 20 grams increase in salt-preserved fish consumed per day**

Author	Year	Sex		Per 20 g/day RR (95% CI)	% Weight
Ko	2013	M/W		1.06 (0.85, 1.34)	11.70
Takachi	2010	M/W		1.07 (0.96, 1.18)	61.87
Iso	2007	M/W		1.04 (0.88, 1.24)	20.77
Ngoan	2002	M/W		1.04 (0.75, 1.44)	5.65
Overall (I-squared = 0.0%, p = 0.996)				1.06 (0.98, 1.15)	100.00
NOTE: Weights are from random effects analysis					

.692   1   1.44
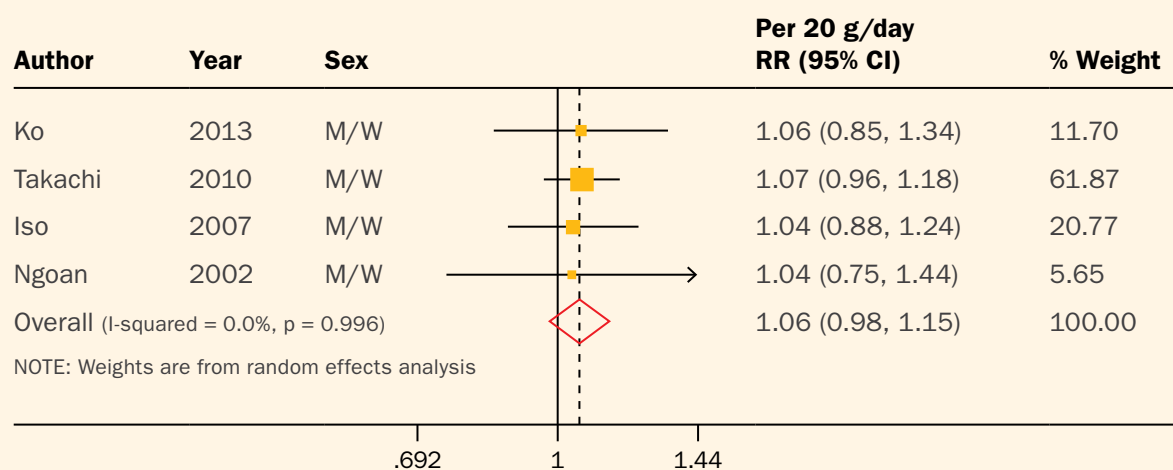
Source: Ko, 2013 [84]; Takachi, 2010 [74]; Iso, 2007 [75]; Ngoan, 2002 [77].

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

5.4.1.2.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. One other published *meta-analysis* on consumption of salt-preserved fish and the risk of stomach cancer has been identified, which reported a significant increased risk for the highest compared with the lowest level consumed (RR 1.24 [95% CI 1.03–1.50]) [82].

5.4.1.3 Salt-preserved foods

5.4.1.3.1 CUP highest versus lowest meta-analysis

Dose–response meta-analysis could not be conducted in the CUP as there were too few studies. Five of six identified studies were included in the highest versus lowest meta-analysis, which showed a statistically significant increased risk of stomach cancer for the highest compared with the lowest level of salt-preserved foods consumed (RR 1.70 [95% CI 1.18–2.45]; n = 635 cases) (see **Figure 5.5**).

All studies included in the highest versus lowest meta-analysis except one [78] adjusted for tobacco smoking. None of the studies adjusted for *H. pylori* status. For information on the *adjustments* made in individual studies, see CUP stomach cancer SLR 2015, Table 139.

5.4.1.3.2 Published pooled analyses and meta-analyses

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

5.4.1.4 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.

Figure 5.5: CUP highest versus lowest meta-analysis[1] for consumption of salt-preserved foods and the risk of stomach cancer

Author	Year	Highest vs lowest RR (95% CI)	% Weight
Murata (M)	2010	2.05 (1.25, 3.38)	19.50
Murata (W)	2010	1.93 (0.87, 4.88)	11.26
Sjödahl	2008	1.10 (0.60, 1.80)	18.05
Kurosawa	2006	5.41 (1.80, 16.29)	8.04
Khan (M)	2004	1.40 (0.70, 2.60)	15.35
Khan (W)	2004	3.50 (1.10, 10.90)	7.57
Galanis	1998	1.10 (0.70, 1.80)	20.22
Overall (I-squared = 49.8%, 0.063)		1.70 (1.18, 2.45)	100.00

Source: Murata, 2010 [85]; Sjödahl, 2008 [10], Kurosawa, 2006 [86], Khan, 2004 [87], Galanis, 1998 [78].

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

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

Animal models have shown that high salt levels alter the viscosity of the mucus protecting the stomach and enhance the formation of *N-nitroso compounds* [88]. In addition, high salt intake may stimulate the colonization of *H. pylori*, the strongest known risk factor for stomach cancer [89]. Finally, in animal models, high salt levels have been shown to be responsible for the primary cellular damage that results in the promotion of stomach cancer development [90].

5.4.1.5 CUP Panel's conclusions

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

The CUP Panel concluded:

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

5.5 Other

The effect of other types of preserved or processed foods on the risk of cancer was evaluated, as well as those that were graded by the Panel as 'limited – suggestive', 'probable', 'convincing' or 'substantial effect on risk unlikely'. These included total salt, added salt and frying as a method of cooking. However, data were either of too low quality or too inconsistent, or the number of studies too few to allow conclusions to be reached.

6. Comparison with the 2007 Second Expert Report

In 2007, there was strong evidence that 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 foods preserved by salting are probably a cause of stomach cancer has also remained strong. In 2007, there was strong evidence that salt, meaning total salt consumption, from processed foods, including salty and salted foods, and also salt added in cooking and at table, increased the risk of stomach cancer. This evidence is now less strong and no conclusion could be drawn.

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Abbreviations

AICR	American Institute for Cancer Research
CI	Confidence interval
CUP	Continuous Update Project
EBV	Epstein-Barr virus
H. pylori	*Helicobacter pylori*
MHT	Menopausal hormone therapy
NSCLC	Non-small-cell lung cancer
RR	Relative risk
SCLC	Small-cell lung cancer
SLR	Systematic literature review
WCRF	World Cancer Research Fund

Glossary

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.

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

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

Carcinogen
Any substance or agent capable of causing cancer.

Carcinogenesis
The process by which a malignant tumour is formed.

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.

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

Cohort study

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

Colon

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

Confidence interval (CI)

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

Confounder/confounding factors

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

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.

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

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

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

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

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.

Familial
Relating to or occurring in a family or its members.

Haem
The part of the organic molecule haemoglobin in red blood cells containing iron to which oxygen binds for transport around the body.

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

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.

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

Homeostatically
The tendency of the body to maintain a condition of balance or equilibrium within its internal environment, even when faced with external changes.

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.

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

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

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

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

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

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

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

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

Nitrosamine

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

Non-cardia stomach cancer

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

Non-communicable diseases (NCDs)

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

Non-linear analysis

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

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.

Phenotype

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

Polymorphisms

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

Pooled analysis

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

Rectum

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

Relative risk (RR)

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

Selection bias

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

Squamous cell carcinoma

A malignant cancer derived from squamous epithelial cells.

Statistical power

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

Systematic literature review (SLR)

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

Tumorigenesis

The process of tumour development.

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Appendix 1: Criteria for grading evidence for cancer prevention

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

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

CONVINCING (STRONG EVIDENCE)

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

All of the following are generally required:

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

PROBABLE (STRONG EVIDENCE)

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

All of the following are generally required:

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

LIMITED – SUGGESTIVE

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

All of the following are generally required:

- Evidence from at least two independent cohort studies or at least five case-control studies.

- The direction of effect is generally consistent though some unexplained heterogeneity may be present.

- Evidence for biological plausibility.

LIMITED – NO CONCLUSION

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

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

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

SUBSTANTIAL EFFECT ON RISK UNLIKELY (STRONG EVIDENCE)

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

All of the following are generally required:

- Evidence from more than one study type.

- Evidence from at least two independent cohort studies.

- Summary estimate of effect close to 1.0 for comparison of high- versus low-exposure categories.

- No substantial unexplained heterogeneity within or between study types or in different populations.

- Good-quality studies to exclude, with confidence, the possibility that the absence of an observed association results from random or systematic error, including inadequate power, imprecision or error in exposure measurement, inadequate range of exposure, confounding and selection bias.

- Absence of a demonstrable biological gradient ('dose–response').

- Absence of strong and plausible experimental evidence, from either human studies or relevant animal models, that typical human exposure levels lead to relevant cancer outcomes.

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

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

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

SPECIAL UPGRADING FACTORS

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

Factors may include the following:

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

Appendix 2: Mechanisms

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

Preserved non-starchy vegetables
Nasopharynx

Preserved vegetables contain high levels of salt, which has been shown in animal models to alter the mucus viscosity and enhance the formation of *carcinogenic nitrosamines* and related *N-nitroso compounds* [88]. The role of nitrosamines and/or nitrosamine metabolism in the development of nasopharynx cancer has been demonstrated in a small tissue level gene expression study [91].

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* [58]. 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 [59].

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 [92]. 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* [93]. 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 [93, 94]. 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 [92]. 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 [93, 94]. 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 [92].

Lung

Overall it is likely that a combination of mechanisms contribute to higher risk of lung 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 above for red meat [58]. Processed meats, such as sausages, are often cooked at high temperatures, which can lead to increased exposure to *heterocyclic amines and polycyclic aromatic hydrocarbon*s, which are lung *carcinogens* [95]. 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 [93, 94]. In addition, cooking processed meats at high temperatures results in the formation of *heterocyclic amines and polycyclic aromatic hydrocarbon*s, both of which have been linked to cancer development in experimental studies [92].

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 hydrocarbon*s, *heterocyclic amines* and *N-nitroso compounds*, which may be directly *carcinogenic* and pro-inflammatory [96]. 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 [97]. Consumption of red and processed meats may lead to *insulin resistance* and *hyperinsulinemia*, promoting growth of cancer cells [98].

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, has been shown to induce cancer development in experimental models in animals [73].

Foods preserved by salting
Stomach

Animal models have shown that high salt levels alter the viscosity of the mucus protecting the stomach and enhance the formation of *N-nitroso compounds* [88]. In addition, high salt intake may stimulate the colonization of *H. pylori*, the strongest known risk factor for stomach cancer [89]. Finally, in animal models, high salt levels have been shown to be responsible for the primary cellular damage which results in the promotion of stomach cancer development [90].

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.