World Cancer Research Fund International

CUP Continuous Update Project

Analysing research on cancer prevention and survival

Diet, nutrition, physical activity and **stomach cancer**

2016

In partnership with

American Institute for Cancer Research

World Cancer Research Fund

Wereld Kanker Onderzoek Fonds

World Cancer Research Fund 世界癌症研究基金會

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WORLD CANCER RESEARCH FUND INTERNATIONAL

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)

World Cancer Research Fund International's Continuous Update Project (CUP) analyses global cancer prevention and survival research linked to diet, nutrition, physical activity and weight. Among experts worldwide it is a trusted, authoritative scientific resource which underpins current guidelines and policy for cancer prevention.

The CUP is produced in partnership with the American Institute for Cancer Research, World Cancer Research Fund UK, World Cancer Research Fund NL and World Cancer Research Fund HK.

The findings from the CUP are used to update our Cancer Prevention Recommendations, which were originally published in *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective* (our Second Expert Report) [1]. These ensure that everyone – from policymakers and health professionals to members of the public – has access to the most up-to-date information on how to reduce the risk of developing the disease.

As part of the CUP, scientific research from around the world is collated and added to a database of epidemiological studies on an ongoing basis and systematically reviewed by a team at Imperial College London. An independent panel of world-renowned experts then evaluates and interprets the evidence to make conclusions based on the body of scientific evidence. Their conclusions form the basis for reviewing and, where necessary, revising our Cancer Prevention Recommendations (see inside back cover).

A review of the Cancer Prevention Recommendations is expected to be published in 2017, once an analysis of all of the cancers being assessed has been conducted. So far, new CUP reports have been published with updated evidence on breast, colorectal, pancreatic, endometrial, ovarian, prostate, liver, gallbladder, kidney and bladder cancers. In addition, our first CUP report on breast cancer survivors was published in 2014.

This CUP report on stomach cancer updates the stomach cancer section of the Second Expert Report (Section 7.5) and is based on the findings of the CUP Stomach Cancer Systematic Literature Review (SLR) and the CUP Expert Panel discussion in June 2015. For further details please see the full CUP Stomach SLR 2015 **(wcrf.org/stomach-cancer-slr-2015)**.

HOW TO CITE THIS REPORT

World Cancer Research Fund International/American Institute for Cancer Research. Continuous Update Project Report: Diet, Nutrition, Physical Activity and Stomach Cancer. 2016. Available at: **wcrf.org/stomach-cancer-2016**.

All CUP reports are available at **wcrf.org/cupreports**.

[1] World Cancer Research Fund/American Institute for Cancer Research, *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*. wcrf.org/int/research-we-fund/continuous-update-project-cup/second-expert-report. 2007.

EXECUTIVE SUMMARY

Background and context

Stomach cancer – also known as gastric cancer – is the fifth most common cancer worldwide. Around 952,000 new cases of stomach cancer were recorded globally in 2012, accounting for seven per cent of all new cases of cancer [2].

Men are twice as likely as women to develop stomach cancer, and it is more common in older adults. For example, the average age at diagnosis in the United States (US) is 72 years.

Stomach cancer is the third most common cause of death from cancer. Symptoms often only appear at a late stage, which contributes to a poor prognosis. For example, in Europe and the US the five-year survival rate of stomach cancer is about 25 to 28 per cent, increasing to about 63 per cent if the cancer is diagnosed at an early stage. However, these survival rates are worse in less developed countries where stomach cancer is typically detected at a more advanced stage.

About 70 per cent of cases of stomach cancer occur in less developed countries with about half of all cases in Eastern Asia, particularly China [2].

Globally, overall incidence rates of stomach cancer are declining. This is attributed to a decrease in *Helicobacter pylori* infection and the use of refrigeration to preserve foods rather than using salt. Stomach cancer is classified into different types according to location of the tumour. Stomach cardia cancer occurs at the top part of the stomach closest to the oesophagus, and stomach non-cardia cancer occurs in all other areas of the stomach.

Stomach non-cardia cancer is more common than stomach cardia cancer, globally, and is most prevalent in Asia. Rates of stomach non-cardia cancer are declining. Stomach cardia cancer is more common than non-cardia cancer in more developed countries such as the UK and US, and is increasing in all countries.

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

In addition to the findings in this report, other established causes of stomach cancer include:

1. Smoking:

- Smoking is a cause of stomach cancer. It is estimated that 11 per cent of cases worldwide are attributable to tobacco use.

2. Infection:

- *Helicobacter pylori* infection is a cause of stomach non-cardia cancer. Also, infection with Epstein-Barr virus is under investigation as a contributor to stomach cancer.

3. Industrial chemical exposure:

- Occupational exposure to dusty and high-temperature environments – such as wood-processing and food-machine operators – has been associated with an increased risk of stomach cancer. Other industries including rubber manufacturing, coal mining, metal processing and chromium production have also been associated with an elevated risk of this cancer.

How the research was conducted

The global scientific research on diet, weight, physical activity and the risk of stomach cancer was systematically gathered and analysed, and then independently assessed by a panel of leading international scientists in order to draw conclusions about which of these factors increase or decrease the risk of developing the disease.

More research has been conducted in this area since our 2007 Second Expert Report [1]. In total, this new report analyses 89 studies from around the world, comprising 17.5 million adults and nearly 77,000 cases of stomach cancer.

To ensure consistency, the methodology for the Continuous Update Project remains largely unchanged from that used for our 2007 Second Expert Report [1].

A summary of the mechanisms underpinning all the findings can be found in the Evidence and Judgements section of this report.

Findings

Strong evidence

- **There is strong evidence that consuming approximately three or more alcoholic drinks per day increases the risk of stomach cancer.**
- **There is strong evidence that consuming foods preserved by salting increases the risk of stomach cancer.** Research mainly relates to high-salt foods and salt-preserved foods, including pickled vegetables and salted or dried fish, as traditionally prepared in East Asia.
- **There is strong evidence that consuming processed meat increases the risk of stomach non-cardia cancer.** Processed meat is meat that has been preserved by smoking, curing or salting, or by the addition of preservatives. Examples include ham, bacon, pastrami and salami, as well as hot dogs and some sausages.

- **There is strong evidence that being overweight or obese increases the risk of stomach cardia cancer.** Being overweight or obese was assessed by body mass index (BMI).

Limited evidence

- **There is some evidence that suggests consuming grilled or barbecued meat and fish increases the risk of stomach cancer.**
- **There is some evidence that suggests consuming little or no fruit increases the risk of stomach cancer.**
- **There is some evidence that suggests consuming citrus fruit decreases the risk of stomach cardia cancer.**

Recommendations

Our Cancer Prevention Recommendations – for preventing cancer in general – include maintaining a healthy weight, being physically active, eating a healthy diet (this includes avoiding processed meat such as ham and bacon and limiting salt intake), and limiting alcohol consumption (if consumed at all). The Cancer Prevention Recommendations are listed on the inside back cover of this report, with full details available at **wcrf.org/recommendations**.

References

[1] World Cancer Research Fund/American Institute for Cancer Research, *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*. wcrf.org/int/research-we-fund/continuous-update-project-cup/second-expert-report. 2007.

[2] Ferlay J, Soerjomataram I, Ervik M, *et al*. GLOBOCAN 2012 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. 2015; Available from http://globocan.iarc.fr

2016	DIET, NUTRITION, PHYSICAL ACTIVITY AND STOMACH CANCER		
		DECREASES RISK	**INCREASES RISK**
STRONG EVIDENCE	**Convincing**		
	Probable		**Body fatness (cardia)[1]** **Alcoholic drinks[2]** **Foods preserved by salting[3]** **Processed meat (non-cardia)**
LIMITED EVIDENCE	**Limited – suggestive**	Citrus fruit (cardia)	Grilled (broiled) or barbecued (charbroiled) meat and fish Low fruit intake
	Limited – no conclusion	Cereals (grains) and their products; dietary fibre; vegetables; pulses (legumes); potatoes, starchy roots, tubers and plantains; citrus fruit (non-cardia); nuts and seeds; herbs, chilli; spices and condiments; meat (unprocessed); processed meat (cardia); poultry; fish (unprocessed); eggs; milk and dairy products; total salt; added salt; fruit juices; coffee; tea; green tea; frying; drying or dried food; dietary nitrate and nitrite; N-nitrosodimethylamine; protein; fats and oils; total fat; fatty acid composition; cholesterol; sugars; beta-carotene; retinol; thiamin; riboflavin; vitamin C; vitamin D; multivitamin/mineral supplements; calcium; iron; selenium; body fatness (non-cardia); physical activity; sedentary behaviour; adult attained height; energy intake	
STRONG EVIDENCE	**Substantial effect on risk unlikely**		

1 Body fatness is marked by body mass index (BMI).
2 Based on evidence for alcohol intakes above approximately 45 grams per day (about 3 drinks a day).
3 Evidence comes from 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.

For an explanation of stomach cancer subtypes (cardia and non-cardia), see Section 2 on page 8 and the **Glossary** on page 45.

CUP Continuous Update Project

1. Summary of Panel judgements

Stomach cancer is divided into two subtypes based on anatomical site of origin. Throughout this report, cancer of the gastric cardia, which occurs near the gastro-oesophageal junction, is referred to as cardia cancer, and non-cardia gastric cancer, which occurs elsewhere, is referred to as non-cardia cancer. For some exposures, evidence was consistent for both subtypes and a conclusion was drawn for overall stomach cancer.

Overall, the Panel notes the strength of the evidence that consumption of alcoholic drinks and foods preserved by salting are causes of stomach cancer; that consumption of processed meat is a cause of non-cardia cancer; and that body fatness is a cause of cardia cancer.

The Continuous Update Project (CUP) Panel judges as follows:

- **Alcoholic drinks: Consumption of alcoholic drinks is probably a cause of stomach cancer. This is based on evidence for intakes greater than 45 grams per day (about 3 drinks a day).**
- **Foods preserved by salting: Consumption of foods preserved by salting is probably a cause of stomach cancer.**
- **Processed meat: Consumption of processed meat is probably a cause of non-cardia cancer.**
- **Body fatness: Greater body fatness (as marked by BMI) is probably a cause of cardia cancer.**
- **Grilled (broiled) or barbecued (charbroiled) meat and fish: The evidence suggesting that consumption of grilled (broiled) or barbecued (charbroiled) meat and fish increases the risk of stomach cancer is limited.**
- **Low fruit intake: The evidence suggesting that low intake of fruit increases the risk of stomach cancer is limited.**
- **Citrus fruit: The evidence suggesting that consumption of citrus fruit decreases the risk of cardia cancer is limited.**

For a full description of the definitions of, and criteria for, the terminology of ‘convincing’, ‘probable’, ‘limited – suggestive’, ‘limited – no conclusion’ and ‘substantial effect on risk unlikely’, see the **Appendix**.

The Panel judgements for stomach cancer are shown in the matrix on page 6.

2. Trends, incidence and survival

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, as well as the intrinsic factor necessary for absorption of vitamin B12, and acts as a receptacle for masticated food, which is sent to the small intestines though muscular contractions. The body of the stomach is lined with a mucous membrane consisting of columnar epithelial cells and glands, surrounded by muscle.

Stomach cancer (also known as gastric cancer) is the fifth most common cancer in the world. Approximately 952,000 cases were diagnosed globally in 2012, accounting for 6.8 per cent of all cancers. It is the third most common cause of death from cancer [2].

Stomach cancer is more prevalent in less developing countries than in more developed countries, with about 70 per cent of cases occurring in less developed countries [2]. About half of all cases occur in Eastern Asia, notably China [3]. The highest incidence of stomach cancer is seen in Asia, and the lowest in Africa [2], although incidence rates of stomach cancer subtypes are subject to geographical variation (see below for details). Age-standardised rates are about twice as high in men as in women, and stomach cancer is more common in older adults (over the age of 50). In the United States, the median age at diagnosis is 72 years [4].

Global rates of stomach cancer are declining. This decline has been attributed to a reduction in *Helicobacter pylori* infection (*H. pylori*; see **Box 2** on page 11). The decline has also been attributed to improved food preservation practices such as refrigeration, which also enables increased consumption of fresh fruit and vegetables and reduced consumption of salt-preserved foods [3].

Stomach cancer is usually differentiated according to the anatomical site of origin: gastric cardia cancer (cardia cancer), which occurs near the gastro-oesophageal junction, and non-cardia gastric cancer (non-cardia cancer), which occurs outside this area, in the lower portion of the stomach.

Non-cardia cancer is sometimes referred to as distal stomach cancer. Many earlier studies did not distinguish between the cancer sites and reported on total stomach cancer. Non-cardia cancer is more prevalent globally than cardia cancer, with most countries reporting an incidence ratio of two to one [5]. It is most prevalent in Asia, although rates are declining.

Conversely, rates of cardia cancer are increasing globally. It is more prevalent in high-income countries with lower incidence rates, which may have a higher proportion of cardia than non-cardia cancer, particularly the United States and the United Kingdom [6, 7]. However, the increase in cardia cancer is seen in all countries, regardless of overall stomach cancer incidence [3]. Cardia cancer is three times more prevalent in men than in women [5].

Histologically, stomach cancer demonstrates marked heterogeneity, but most stomach cancers are adenocarcinomas (tubular, papillary, mucinous) or various types of carcinomas (i.e., signet cells).

Symptoms of stomach cancer include reflux, manifested as heartburn or indigestion, and reduced appetite. Symptoms of more advanced stomach cancer may include pain in the abdomen, vomiting, difficulty swallowing, anaemia, weight loss and tarry or sticky blood in the stool. However, symptoms often only appear at a late stage, which contributes to the poor overall prognosis. The five-year survival rate of stomach cancer is 25 per cent in Europe and 28 per cent in the United States, but increases to 63 per cent if diagnosed at an early stage [8, 9]. See **Box 1** for further information.

Box 1: Cancer incidence and survival

The cancer incidence rates and figures given here are those reported by cancer registries, now established in many countries. These registries record cases of cancer that have been diagnosed. However, many cases of cancer are not identified or recorded: some countries do not have cancer registries, regions of some countries have few or no records, records in countries suffering war or other disruption are bound to be incomplete, and some people with cancer do not consult a physician. Altogether, this means that the actual incidence of cancer is probably higher than the figures given here.

The information on cancer survival shown here is for the United States and Europe. Survival rates are generally higher in high-income countries and other parts of the world where there are established services for screening and early detection of cancer as well as well-established treatment facilities. Survival is often a function of the stage at which a cancer is detected and diagnosed.

3. Pathogenesis

The lining of the stomach is exposed to carcinogens present in foods, which are held in the stomach for a period of up to five hours during digestion.

More than 95 per cent of stomach cancers are adenocarcinomas, with primary gastric lymphoma being the second most common malignancy. Pathogenesis and aetiology differ between cardia and non-cardia cancers [10].

Chronic gastritis, inflammation brought about by a variety of environmental factors and ageing can eventually lead to changes in the characteristics of the stomach mucosal cells. These changes appear to be precursor conditions to the development of non-cardia cancer [1].

Non-cardia cancers may be either intestinal (well-differentiated) or diffuse (undifferentiated, from mucus-producing cells). Intestinal types commonly undergo a cascade from normal mucosa through chronic gastritis to atrophic gastritis, intestinal dysplasia, and then adenocarcinoma. This progression may take several years [10]. Intestinal types are more common in males and older adults, whereas diffuse types may occur in all age groups with equal sex distribution and show more rapid progression and poorer prognosis.

H. pylori infection is strongly implicated in the aetiology of intestinal non-cardia cancer. Infection appears to interact with dietary factors (see **Box 2**). One pooled analysis reported an increased stomach cancer risk with *H. pylori* infection (RR = 2.9), increasing to RR = 5.9 when the analysis was restricted to cases occurring at least 10 years after infection diagnosis [11]. A rare, genetically inherited form of diffuse stomach cancer also exists, which is unrelated to *H. pylori* infection. Rare hereditary variants contribute to about 1–3 per cent of stomach cancers [10].

The pathogenesis of cardia cancer is less well established, although it is associated with inflammation of the cardia [12]. There are similarities between cardia cancer and oesophageal adenocarcinoma, which is inversely associated with *H. pylori* infection and positively with Barrett's oesophagus. However, evidence for Barrett's oesophagus as a causal factor in cardia cancer is not conclusive [13]. Cardia cancer may, in some populations, be inversely associated with *H. pylori* infection, but cardia cancer in the presence of *H. pylori* infection shows an association with gastric atrophy [14]. A dual aetiology, with some tumours linked to *H. pylori* infection and some to reflux injury, is emerging [15, 16].

Inherited mutations of certain genes, particularly the GSTM1-null phenotype, are associated with elevated risk of stomach cancer [17]. 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 [18] and smoking [19] to affect cancer risk.

Box 2: *Helicobacter pylori*

Helicobacter pylori (H. pylori) **is a gram-negative bacterium that lives in the human stomach. It colonises the gastric mucosa and elicits both inflammatory and lifelong immune responses, including the release of various bacterial and host-dependent cytotoxic substances [20]. Infection does not usually produce symptoms, and spreads through saliva and faecal material.**

Globally, *H. pylori* infection affects 50 per cent of the population, and prevalence increases with age. However, there is wide geographical variation [21]. Average *H. pylori* prevalence is 35 per cent in high-income countries and 85 per cent in low-income countries [3]. The highest prevalence is in Asia; in South Korea, infection reaches 90 per cent at age 20 years [22].

Regions with high stomach cancer incidence rates tend to have high seroprevalence rates for *H. pylori* infection. However, in some regions of Africa and South Asia, particularly India, *H. pylori* infection rates are high but stomach cancer incidence rates remain low [23].

Evidence from preclinical studies suggests that *H. pylori* interacts with dietary factors such as salt to affect cancer risk [24]. *H. pylori* infection also appears to reduce the bioavailability of vitamin C and iron [25, 26].

The longer the time of infection and the greater the impact on the gastric mucosa, the more likely it is that stomach cancer will develop. The site of the cancer is most likely to be where the mucosa is most affected [27]. Those who develop extensive gastritis and gastric atrophy are at increased risk of developing cancer.

In studies of precancerous lesions or gastric atrophy, eradication of *H. pylori* promoted regression of these cancer precursors [28]. Early eradication of *H. pylori* infection is associated with decreased cancer risk in affected individuals [29], prompting interest in infection eradication as a cancer prevention strategy.

Stomach cancer may develop without apparent infection with *H. pylori*. An average of 86 per cent of non-cardia cancers are reported to test positive for *H. pylori* [11]. However, cases of non-cardia cancer that test negative for *H. pylori* may have undergone a loss of infection associated with the atrophic gastritis, and consequently a decline in antibody titre. *H. pylori* infection is regarded as critical to intestinal type non-cardia cancer development [30, 31].

The relationship between *H. pylori* infection and cardia cancer is less clear, possibly due to discrepancies in classification or interaction between factors. Some studies have reported an inverse association [32], and others a positive association [33] or no effect [11]. The global decline in *H. pylori* rates has coincided with a decrease in incidence of non-cardia cancer, but increased incidence of cardia cancer.

4. Other established causes

Tobacco use

Smoking is a cause of stomach cancer (subtype non-specific) [34]. Both current and former smokers have an increased risk of stomach cancer compared with people who have never smoked, with estimates of increased risk ranging from 1.5–2.5 times that of never-smokers [35]. The risk increase is larger in men than in women, but a dose-response relationship is apparent in both [36, 37]. Risk increases are also seen for tobacco used orally. Studies of smokeless tobacco ('snus') use in Scandinavia have reported an increased risk of non-cardia cancer among snus users who had never smoked compared with non-users [38]. It is estimated that 11 per cent of stomach cancer cases worldwide and over 17 per cent of cases in Europe are attributable to tobacco use [35, 39].

Infection and infestation

H. pylori infection is a cause of non-cardia cancer (see **Box 2**). The International Agency for Research on Cancer (IARC) has classified chronic infection with *H. pylori* as carcinogenic to humans (Class I) [30]. Infection with Epstein-Barr virus is also associated with increased risk of stomach cancer and is implicated in about 10 per cent of stomach cancers [40].

Industrial chemical exposure

Occupational exposure to dusty and high-temperature environments, such as in wood-processing and food machine-operating occupations, has been associated with increased risk of stomach cancer, particularly diffuse type non-cardia cancer [41]. Exposure to other dusty environments, such as in rubber manufacturing, coal mining and metal processing, has also been implicated [42]. Industrial exposure to chromium VI during chromium production or plating work has also been associated with increased risk of stomach cancer [43].

5. Interpretation of the evidence

5.1 General

For general considerations that may affect interpretation of the evidence, see Sections 3.3 and 3.5, and Boxes 3.1, 3.2, 3.6 and 3.7 in the Second Expert Report [1].

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

5.2 Specific

Considerations specific to stomach cancer include:

Classification

The two subtypes of stomach cancer according to cancer site (cardia and non-cardia cancers) 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, cardia cancer classification definitions sometimes vary according to distance from the gastro-oesophageal junction, raising concerns of misclassification [6]. Cardia cancer shares some risk factors with oesophageal adenocarcinoma, in particular body fatness and smoking, and may have a common aetiology. Some studies examine cases of cardia cancer concurrently with oesophageal adenocarcinoma.

Confounding

Smoking and *H. pylori* infection are possible confounders or effect modifiers. Most studies in the analyses adjusted for smoking. Few studies adjusted for *H. pylori* infection. One study provided evidence of an interaction between dietary factors (meat intake) and *H. pylori* infection [44], although another study on vegetable and fruit intake in a subset of participants with known *H. pylori* status did not show a clear pattern [45].

6. Methodology

To ensure consistency with evidence collected and analysed for the Second Expert Report [1], the methodology for reviewing the epidemiological evidence in the Continuous Update Project (CUP) remains largely unchanged. However, on the basis of the experience of conducting the systematic literature reviews (SLRs) for the Second Expert Report, some modifications to the methodology were made. The updated literature search was restricted to Medline and included only randomised controlled trials, cohort and nested case-control studies. Due to their methodological limitations, case-control studies were not analysed in the CUP Stomach SLR 2015, unlike in the 2005 SLR used for the Second Expert Report.

Where possible for this update, meta-analyses for incidence and mortality were conducted separately. However, analyses combining studies on stomach cancer incidence and mortality were also conducted to explore whether this outcome could explain any heterogeneity in the results. Separate meta-analyses were also conducted for men and women, and by geographical location, where possible.

Studies reporting mean difference as a measure of association were not included in the CUP Stomach SLR 2015, as relative risks estimated from mean differences are not adjusted for confounders, and thus are not comparable with adjusted relative risks from other studies.

Non-linear meta-analysis was applied when the data suggested that the dose-response curve was non-linear, and when detecting a threshold of exposure might be of interest. Details on the non-linear meta-analyses can be found in the CUP Stomach SLR 2015.

Where possible, separate estimates were provided for cardia and non-cardia cancer. However, not all studies reported the site of stomach cancer. In the 2005 SLR, a distinction was made between distal and proximal stomach cancer, which roughly equate to non-cardia and cardia sites, respectively.

The CUP Stomach SLR 2015 included studies published up to 28 February 2014. For more information on methodology see the full CUP Stomach SLR 2015 at **wcrf.org/stomach-cancer-slr-2015.**

6.1 Mechanistic evidence

Where relevant, mechanistic reviews previously conducted for the Second Expert Report [1] are included in this report (more details can be found in chapters 2 and 4 of the Second Expert Report). These reviews have not been updated here, but will be updated in the future as part of a systematic literature review for the CUP of the mechanistic evidence (see below). A brief summary is given of possible mechanisms linking stomach cancer with: alcoholic drinks, salt-preserved foods, salt-preserved vegetables, processed or salt-preserved fish, grilled (broiled) or barbecued (charbroiled) meat and fish, and low fruit intake; cardia cancer with body fatness and citrus fruit; and non-cardia cancer with processed meat. Plausible mechanisms identified by CUP Panel members and published reviews are included in this report.

Work is under way to develop a method for systematically reviewing animal, human and other experimental studies. In future this will be used to conduct reviews of mechanisms for all cancer sites (see **wcrf.org** for further information). A full review of the mechanistic evidence for stomach cancer will form part of this larger review.

7. Evidence and judgements

The following sections summarise the evidence identified in the CUP Stomach SLR 2015 and provide a comparison with the findings from the Second Expert Report [1] and the Panel's conclusions. They also include a brief description of potential biological mechanisms for each exposure.

For information on the criteria for grading the epidemiological evidence, see the **Appendix** in this report. References to studies added as part of the CUP have been included; for details of references to other studies from the Second Expert Report, see the CUP Stomach SLR 2015.

7.1 Low fruit intake

(Also see CUP Stomach SLR 2015: Section 2.2.2)

The CUP identified eight new or updated studies (10 publications) [45-53] on fruit and stomach cancer risk, giving a total of 24 studies (34 publications; see CUP Stomach SLR 2015 Tables 37 and 38 for a full list of references). Of 11 studies (14 estimates) reporting on stomach cancer incidence, eight reported an inverse association, of which one was significant; one study reported a non-significant positive association; one study reported a non-significant inverse association for non-cardia cancer and no effect for cardia cancer; and one reported a positive association for non-cardia cancer and an inverse association for cardia cancer, both non-significant, when comparing the highest and lowest categories of intake (see CUP Stomach SLR 2015 Figure 40). Of seven studies (eight estimates) reporting on stomach cancer mortality, four reported a positive association, of which one was significant; and four reported a non-significant inverse association comparing the highest and lowest intake categories.

Thirteen of the 24 studies were included in the dose-response meta-analysis (n = 4,905), which showed no significant association per 100 grams of fruit consumed per day (RR = 0.98 (95% CI 0.94–1.02); see CUP Stomach SLR 2015 Figure 41). Low heterogeneity was observed (I^2 = 8%). However, there was evidence of a non-linear relationship (p < 0.001). Non-linear analysis showed that low fruit intake (below approximately 45 grams per day) was associated with a significant increased risk of stomach cancer, while higher fruit intake was associated with a significant decreased risk (see **Figure 1**, CUP Stomach SLR 2015 Figure 50; and **Table 1**, CUP Stomach SLR 2015 Table 39).

Figure 1: Non-linear dose-response association of fruit intake and stomach cancer

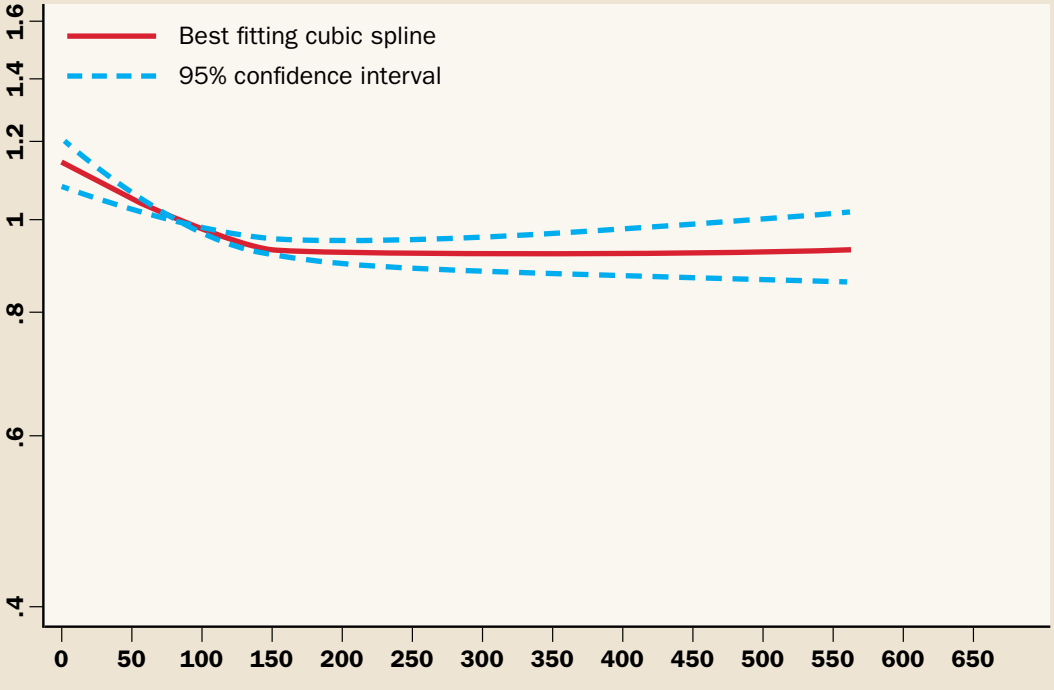


Table 1: Non-linear dose-response estimates of fruit intake and stomach cancer

FRUIT INTAKE (GRAMS PER DAY)	RR (95% CI)
0	1.18 (1.11–1.26)
43	1.08 (1.05–1.11)
86	1.00
137	0.95 (0.93–0.97)
196	0.94 (0.92–0.97)
236	0.95 (0.92–0.98)

When stratified by cancer subtype, the dose-response meta-analysis showed no significant association for both cardia and non-cardia cancers (see CUP Stomach SLR 2015 Figure 45). When stratified by smoking status, the dose-response meta-analysis showed a significant decreased risk per 100 grams of fruit consumed per day in current smokers only (RR = 0.89 (95% CI 0.81–0.97) for three studies; see CUP Stomach SLR 2015 Figure 49).

All studies included in the dose-response meta-analysis were adjusted for age. The majority were also adjusted for sex and smoking. None of the studies was adjusted for *H. pylori* status.

Four studies were not included in any of the CUP analysis, three due to not reporting sufficient data [54-56] and one for reporting extremely low fruit intakes that were not comparable with other studies [57]. None of the excluded studies reported a significant association.

The findings from the CUP Stomach SLR 2015 were similar to those in the overall dose-response meta-analysis from the 2005 SLR, which included eight studies and did not show a significant association between fruit intake and stomach cancer risk per 100 grams of fruit consumed per day (RR = 0.95 (95% CI 0.89–1.02)). The CUP Stomach SLR 2015 included more cohort studies and cases than presented in the 2005 SLR and additional non-linear analyses.

Published pooled analyses and meta-analyses

No pooled analysis was identified. One published meta-analysis on fruit intake and stomach cancer risk was identified in the CUP Stomach SLR 2015 [58]. It reported a significant 5 per cent decreased risk of stomach cancer per 100 grams of fruit consumed per day (RR = 0.95 (95% CI 0.91–0.99), I^2 = 38%).

Mechanisms

Note: A full review of mechanisms for this exposure will form part of a larger review of mechanisms (see Section 6.1 in this report).

The stomach is a particularly unusual chemical environment, and it is possible that, in addition to the general mechanisms described below, specific mechanisms apply; for instance, in relation to nitrosamine formation. It is also plausible that bioactive constituents in fruit would protect against *H. pylori*-induced damage and inflammation, which is implicated in the development of stomach cancer.

Some fruits contain high levels of flavonoids, including apples (quercetin) and grapefruit (naringin). Flavonoids have antioxidant effects and can also inhibit carcinogen-activating enzymes. Flavonoids can also alter the metabolism of other dietary agents. For instance, quercetin directly inhibits expression of CYP1A1 (a cytochrome P450 enzyme that helps to metabolise toxins into carcinogens), resulting in decreased DNA damage. The phytochemical antioxidants contained in fruit could reduce free-radical damage generated by inflammation, including that caused by *H. pylori*.

CUP Panel's conclusion:

The overall evidence was reasonably consistent, although no significant association was observed. Results were consistent for cardia and non-cardia cancers. There was evidence of a non-linear relationship. A significant increased risk was observed for intake of fruit below approximately 45 grams (about 0.5 portion) per day; and a significant decreased risk was observed at higher intakes, which appeared to plateau at about 140 grams (about 1.75 portions) per day. The CUP Panel concluded:

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

7.2 Citrus fruit

(Also see CUP Stomach SLR 2015: Section 2.2.2.1)

Analyses were performed for citrus fruit and overall stomach cancer, cardia and non-cardia cancers, but conclusions could be drawn only for cardia cancer. The CUP identified 11 studies (14 publications) on citrus fruit and overall stomach cancer risk (see CUP Stomach SLR 2015 Tables 43 and 44 for a full list of references).

For cardia cancer, three new studies (three publications) were identified on citrus fruit and cardia cancer incidence [48, 49, 51]. All reported an inverse association when comparing the highest and lowest categories of intake, of which one was significant (see CUP Stomach SLR 2015 Figure 52).

All three studies were included in the dose-response meta-analysis (n = 555), which showed a significant 24 per cent decreased risk of cardia cancer per 100 grams of citrus fruit consumed per day, with moderate heterogeneity (see **Table 2** and CUP Stomach SLR 2015 Figure 57).

The risk estimate for non-cardia cancer is shown for comparison.

Table 2: Summary of CUP 2015 stratified dose-response meta-analysis – citrus fruit and stomach cancer

ANALYSIS	INCREMENT	RR (95% CI)	I^2	NO. STUDIES	NO. CASES
CARDIA CANCER	Per 100g/day	0.76 (0.58-0.99)	53%	3	555
NON-CARDIA CANCER	Per 100g/day	1.04 (0.94-1.16)	1%	5	1,317

All studies included in the dose-response meta-analysis were adjusted for age, sex and smoking. None of the studies was adjusted for *H. pylori* status.

There was no analysis by cancer site in the 2005 SLR.

Published pooled analyses and meta-analyses

No pooled analyses or published meta-analyses were identified on citrus fruit intake and cardia cancer risk.

Mechanisms

Note: A full review of mechanisms for this exposure will form part of a larger review of mechanisms (see Section 6.1 in this report).

Citrus fruit is a good source of vitamin C, among other antioxidants. Vitamin C traps free radicals and oxygen radical species, protecting against oxidative damage. It also regenerates other antioxidant vitamins such as vitamin E. Vitamin C may also inhibit the formation of carcinogens and protect DNA from mutagenic attack. Beta-carotene and other carotenoid antioxidants are also found in citrus fruit, together with other antioxidants such as phenols and flavonoids, and potentially bioactive phytochemicals.

CUP Panel's conclusion:

All studies on cardia cancer were consistent in the direction of an inverse association, and the dose-response meta-analysis showed a statistically significant decreased risk, although with a limited number of cases. Moderate heterogeneity was identified. No published or pooled analysis was available.

For non-cardia cancer, evidence was limited and conclusions could not be drawn.

The CUP Panel concluded:

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

7.3. Foods preserved by salting

This category includes evidence on the following exposures: salt-preserved vegetables, salt-preserved fish and salt-preserved foods.

7.3.1 Salt-preserved vegetables

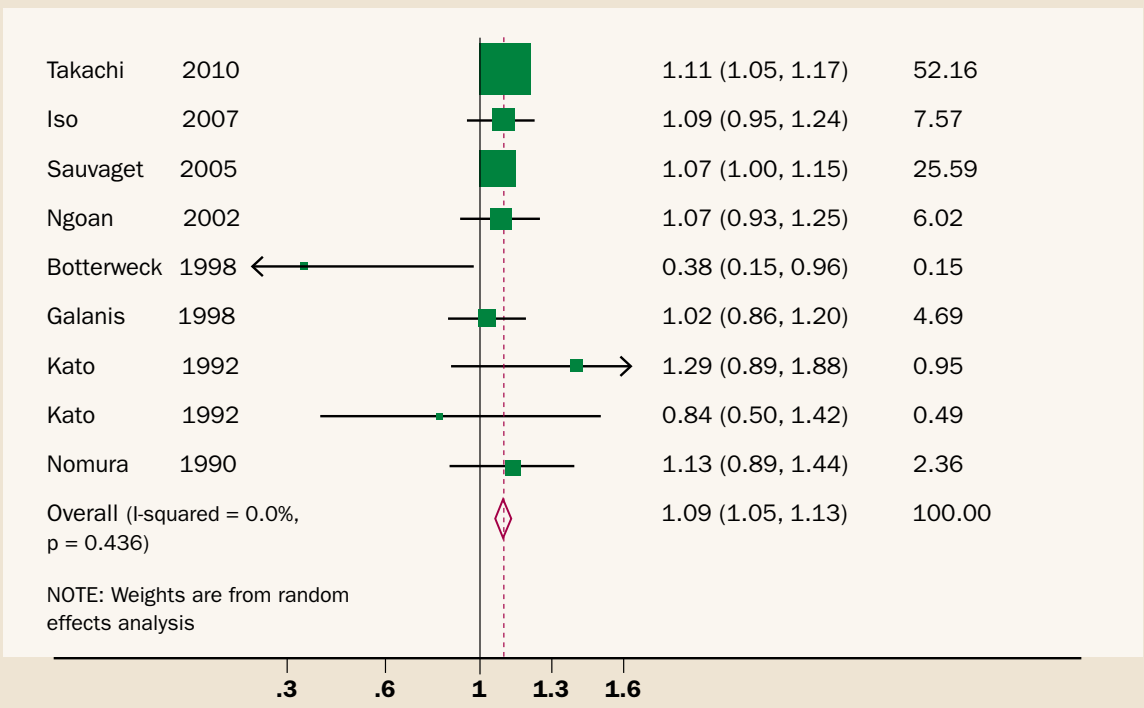
(Also see CUP Stomach SLR 2015: Section 2.2.1.5)

Evidence on salt-preserved vegetables came from studies in Asia, except for one study conducted in Europe. Except in the European study, salt-preserved vegetables consisted of 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. The European study examined pickles (vegetables pickled in vinegar).

The CUP identified two new or updated studies (three publications) [53, 59, 60] on salt-preserved vegetables and stomach cancer risk, giving a total of 14 studies (21 publications; see CUP Stomach SLR 2015 Tables 32 and 33 for a full list of references). Of eight studies (nine estimates) reporting on stomach cancer incidence, six reported positive associations when comparing the highest and the lowest categories of intake, of which one was significant; and two reported non-significant inverse associations. Of three studies (four estimates) reporting on stomach cancer mortality, three reported non-significant positive associations and one reported a non-significant inverse association when comparing the highest and the lowest categories of intake (see CUP Stomach SLR 2015 Figure 35).

Nine of the 14 studies were included in the dose-response meta-analysis (n = 3,932), which showed a statistically significant 9 per cent increased risk per 0.5 serving (20 grams) of salt-preserved vegetables consumed per day (RR = 1.09 (95% CI 1.05–1.13); see **Figure 2**; CUP Stomach SLR 2015 Figure 36). No heterogeneity was observed (I^2 = 0%).

Figure 2: Dose-response meta-analysis of intake of salt-preserved vegetables and stomach cancer, per 0.5 serving (20 grams) per day



When stratified by outcome, the dose-response meta-analysis showed an increased risk per 0.5 serving (20 grams) of salt-preserved vegetables consumed per day, which was significant for incidence but not mortality (see **Table 3** and CUP Stomach SLR 2015 Figure 38).

Table 3: Summary of CUP 2015 stratified dose-response meta-analysis – salt-preserved vegetables and stomach cancer

ANALYSIS	INCREMENT	RR (95% CI)	I^2	NO. STUDIES	NO. CASES
INCIDENCE	Per 20g/day	1.09 (1.02-1.16)	28%	6	2,701
MORTALITY	Per 20g/day	1.07 (0.97-1.18)	0%	3	820

All studies included in the dose-response meta-analysis were adjusted for, or stratified by, sex and age. None of the studies was adjusted for *H. pylori* status. The majority of the studies were conducted in Japan, or of Japanese residents of Hawaii [61, 62]. One study was conducted in the Netherlands [63]. Stratification by cancer sub-type was not possible.

One study [54] was not included in the CUP analysis as it did not report a risk estimate.

The CUP Stomach SLR 2015 findings were different from the dose-response meta-analysis in the 2005 SLR, which included six studies and reported no significant association per 20 grams of salt-preserved vegetables consumed per day (RR = 0.98 (95% CI 0.90–1.16)). The CUP Stomach SLR 2015 included more cohort studies and three times the number of cases of stomach cancer than the 2005 SLR.

Published pooled analyses and meta-analyses

No pooled analysis was identified. Two meta-analyses have been published on intake of salt-preserved and pickled vegetables and stomach cancer risk (see **Table 4**). Both reported a significant increased risk of stomach cancer at highest levels of intake compared with the lowest levels.

Table 4: Summary of published meta-analyses – salt-preserved vegetables

PUBLICATION	COMPARISON	RR (95% CI)	I^2	NO. STUDIES	NO. CASES
D'Elia (2012) [64]	Highest vs. lowest	1.27 (1.09-1.49)	25%	7	1,474
Ren (2012) [65]	Highest vs. lowest	1.32 (1.10-1.59)	70%	10	3,692

7.3.2 Salt-preserved fish

(Also see CUP Stomach SLR 2015: Section 2.5.2)

The exposure 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.

The CUP identified three new or updated studies (three publications) [47, 59, 60] on salt-preserved fish and stomach cancer risk, giving a total of 11 studies (13 publications; see CUP Stomach SLR 2015 Tables 84 and 85 for a full list of references). Of four studies (four estimates) reporting on stomach cancer incidence, two showed a non-significant positive association; one showed a non-significant inverse association; and one showed no effect when comparing the highest and lowest categories of intake (see CUP Stomach SLR 2015 Figure 106). Of four studies (six estimates) reporting on stomach cancer mortality, two showed a positive association, of which one was significant; one showed a positive association in men and an inverse association in women, both non-significant; and one showed a positive association in women and an inverse association in men, also non-significant, when comparing the highest and lowest intake categories.

Four of the 11 studies were included in the dose-response meta-analysis (*n* = 2,110), which showed no significant association between salt-preserved fish intake and stomach cancer per 20 grams consumed per day (RR = 1.06 (95% CI 0.98–1.15); see CUP Stomach SLR 2015 Figure 107). No heterogeneity was observed (I^2 = 0). As many studies could not be included in the dose-response meta-analysis, an analysis comparing the highest and the lowest levels of consumption was conducted on eight studies, which showed a statistically significant 15 per cent increased risk of stomach cancer (RR = 1.15 (95% CI 1.01–1.31)), with no heterogeneity (I^2 = 0%). When one study [60] was removed from the analysis, the risk estimate was no longer significant.

All studies included in the dose-response meta-analysis and highest versus lowest analysis were in Japanese or Korean populations, except for one conducted in Finland [66]. Studies were adjusted for age, sex and other potential confounders including smoking and alcohol, except for one study that was only adjusted for age and residence area [59].

Three studies were excluded from the CUP analysis, two because they did not report sufficient data [54, 56] and one because it reported extremely low intakes that were not comparable with other studies [67].

The CUP findings are similar to the 2005 SLR, which also reported a positive association between salt-preserved fish intake and stomach cancer risk, although unlike in the CUP, the 2005 SLR dose-response meta-analysis was statistically significant (RR = 1.43 (1.09–1.89) per 20 grams per day, from four studies). The CUP Stomach SLR 2015 included more recent studies than the 2005 SLR analysis, and more than double the number of cases of stomach cancer.

Published pooled analyses and meta-analyses

No pooled analysis was identified on salt-preserved fish intake and stomach cancer risk. One meta-analysis of eight studies was published on intake of salted fish and stomach cancer risk [64] and reported a significant 24 per cent increased risk of stomach cancer for the highest levels of salted fish intake compared with the lowest (RR = 1.24 (95% CI 1.03–1.50)), with no heterogeneity (I^2 = 0%).

7.3.3 Salt-preserved foods

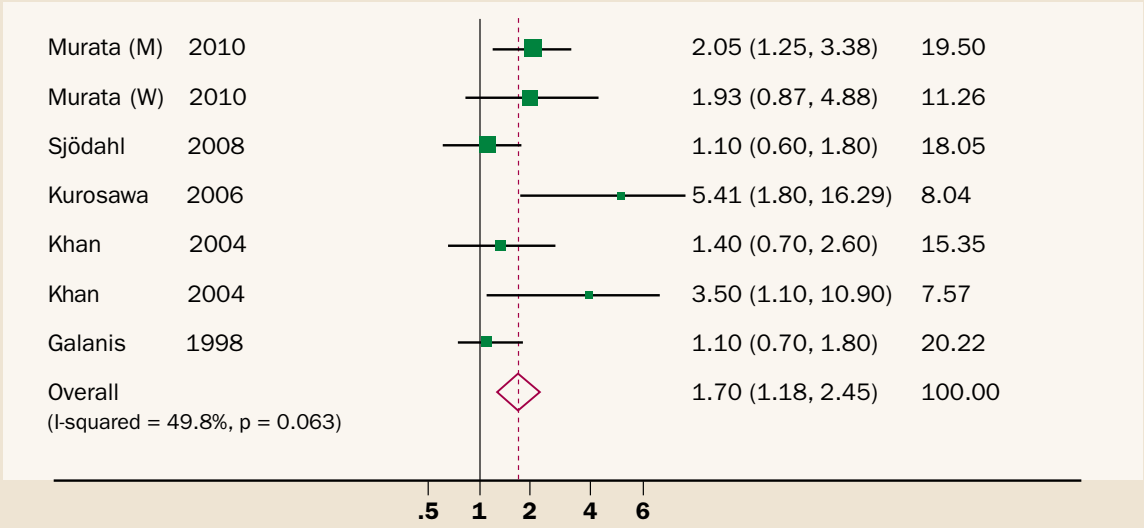
(Also see CUP Stomach SLR 2015: Section 4.2.5.3)

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 with other exposures within the category of foods preserved by salting. Studies were conducted in Asia, except for one study conducted in Norway. 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.

The CUP identified three new or updated studies (three publications) [53, 68, 69] on intake of salted foods and stomach cancer risk, giving a total of six studies (seven publications; see CUP Stomach SLR 2015 Table 135 for a full list of references). Both studies reporting on stomach cancer incidence reported a non-significant positive association. All three studies reporting on stomach cancer mortality also reported a positive association, of which one was significant, one significant in men only and one significant in women only.

There were not enough studies to conduct a dose-response meta-analysis. However, there was a statistically significant 70 per cent increased risk of stomach cancer for the highest compared with the lowest level of intake of salted foods (RR = 1.70 (95% CI 1.18–2.45), I^2 = 50%, *n* = 635; see **Figure 3**, CUP Stomach SLR 2015 Figure 160).

Figure 3: Highest versus lowest analysis of intake of salt-preserved foods and stomach cancer



All except one of the studies identified were based in Japan, or of Japanese residents of Hawaii. One study was based in Norway [69]. All studies except one [61] adjusted for smoking.

One study was excluded from the CUP analysis [70] because it did not report sufficient data.

The CUP findings are stronger than the dose-response meta-analysis in the 2005 SLR, which reported no significant association per 1 serving per day from three studies (RR = 1.32 (95% CI 0.90–1.95), I^2 = 0%). The CUP Stomach SLR 2015 included more studies than the 2005 SLR and more than double the number of cases of stomach cancer.

Published pooled analyses and meta-analyses

No pooled analysis or published meta-analysis was identified on intake of salt-preserved foods and stomach cancer risk.

Evidence from regional dietary patterns

Three studies on regional diet in Japan, or Japanese residents of Hawaii, were identified in the CUP. The first study [59] investigated breakfast type (Japanese or western) and reported a significant decreased risk of stomach cancer mortality with usual consumption of a western-style breakfast compared with not usually consumed, in men only (RR = 0.66 (95% CI 0.50–0.89); women RR = 0.88 (95% CI 0.63–1.24)). The second study [71] reported a significant increased risk of stomach cancer in the fourth compared with the first quartile of consumption of a traditional dietary pattern including salted foods (with beer for men only; men: RR = 2.88 (95% CI 1.76–4.72), women: RR = 2.40 (95% CI 1.32–4.35)). The third study [72] reported a significant increased risk of stomach cancer and consumption of a mixed southeast Asian and western diet, compared with only western diet (RR = 2.10 (95% CI 1.10–4.10)).

Evidence from preference for salty food

The CUP identified two new or updated studies [59, 73] on preference for salty food, giving a total of four studies (seven publications; see CUP Stomach SLR 2015 Table 132 for a full list of references). Three of the studies were conducted in Asia, and one in the Netherlands. Although dose-response meta-analysis could not be conducted, all four studies were included in the highest versus lowest analysis, and reported a 9 per cent increased risk of stomach cancer for a strong preference for salty food compared with the lowest level of preference (RR = 1.09 (95% CI 1.04–1.15), I^2 = 0%; see CUP Stomach SLR 2015 Figure 159).

Given that the measurement of total salt intake in the diet is subject to methodological difficulties, preference for salty food may be considered to be an accurate indicator of total salt intake [74].

7.3.4 Foods preserved by salting: Summary

(Also see CUP Stomach SLR 2015: Section 4.2.5.3)

Mechanisms

Note: A full review of mechanisms for this exposure will form part of a larger review of mechanisms (see Section 6.1 in this report).

It has been thought that any effect of salt on stomach cancer is principally the result of regular consumption of salted and salt-preserved foods, rather than salt as such. This is partly because such foods are a substantial part of traditional Japanese and other Asian diets, where incidence of stomach cancer has been and still is high. Salt-preserved vegetables in particular are characterised by lower micronutrient content than fresh vegetables, as well as higher salt content, and some may undergo fermentation

during preservation. Preserved foods in general may be eaten more by those to whom refrigeration is not available. The use of pickled vegetables may therefore be associated with poor socio-economic status, and thus with a high prevalence of *H. pylori* infection, leading to the possibility of association by confounding factors.

However, the incidence of this cancer is also high in countries where traditional diets contain substantial amounts of salty as distinct from salt-preserved foods; and the concentration of salt in many processed foods consumed in Europe and North America approaches that of salt-preserved foods.

There is evidence from laboratory experiments that high salt intake can damage the lining of the stomach, leading to inflammation and atrophy. Such damage to the lining of the stomach may increase *H. pylori* colonisation [75], which poses a risk factor for stomach cancer. However, salt intake may contribute to gastric cancer only in individuals who have *H. pylori* infection and are also exposed to a chemical carcinogen. In addition, traditional processing for pickling vegetables in some regions of China, Japan and Korea involves fermentation of local vegetables, with or without salting. Both this processing and high salt intake are associated with the endogenous formation of N-nitrosamines, which may be carcinogenic [76].

CUP Panel's conclusion:

The evidence was 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 analysis comparing highest and lowest levels of intake. Evidence on salt-preserved fish was less strong than for the other exposures; significance did not persist after one study was removed from analysis. There is evidence of plausible mechanisms in humans. The CUP Panel concluded:

Greater consumption of foods preserved by salting is probably a cause of stomach cancer.

7.4 Processed meat

(Also see CUP Stomach SLR 2015: Section 2.5.1.2)

Evidence on processed meat came from diverse geographical locations, including the United States, Asia and Europe. Processed meat was defined variously as meat items having undergone salt-preservation, smoking or fermentation, including sausages, bacon, ham, meatballs, burgers and cold meats.

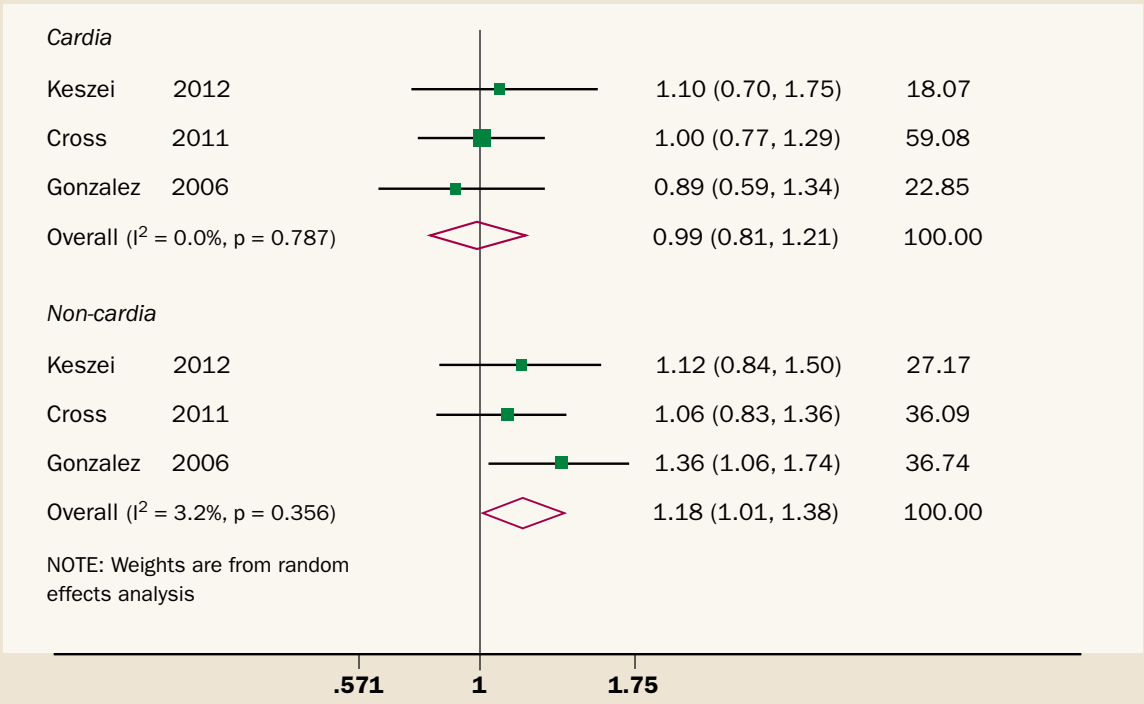
Analyses were performed for processed meat and overall stomach cancer, cardia and non-cardia cancers, but conclusions could only be drawn for non-cardia cancer. The CUP identified five new or updated studies (seven publications) [44, 59, 77-81] on processed meat and overall stomach cancer risk, giving a total of 12 studies (16 publications; see CUP Stomach SLR 2015 Tables 64 and 65 for a full list of references).

For non-cardia cancer, three new studies (three publications) were identified on processed meat intake and non-cardia cancer incidence [44, 78, 79]. All reported a positive association when comparing the highest and lowest categories of intake, of which one was significant (see CUP Stomach SLR 2015 Figure 74).

All three studies were included in the dose-response meta-analysis (n = 1,149), which showed a statistically significant 18 per cent increased risk of non-cardia cancer per 50 grams of processed meat consumed per day, with low heterogeneity (RR = 1.18 (95% CI 1.01–1.38), I^2 = 3%; see **Figure 4**; CUP Stomach SLR Figure 79). However, the association was strongly influenced by one study that contributed 37 per cent of the weight of the analysis.

No significant association was observed with cardia cancer risk (presented for comparison in **Figure 4**).

Figure 4: Dose-response meta-analysis of processed meat intake and stomach cancer, per 50 grams per day



All studies included in the meta-analysis were adjusted for age, smoking and other potential confounders. No study was adjusted for *H. pylori* status; however, one study [44] using a nested case-control design reported a significant positive association between processed meat intake and non-cardia cancer risk in individuals testing positive for *H. pylori* (n = 113), but not those testing negative, although patient numbers were low (n = 12).

There was no analysis by cancer site in the 2005 SLR.

Published pooled analyses and meta-analyses

No pooled analysis was identified. One meta-analysis (including cohort and case-control studies) has been published on processed meat intake and non-cardia cancer risk [82]. It reported a significant increased risk when comparing the highest and lowest levels of processed meat intake (RR = 1.27 (95% CI 1.07–1.52), I^2 = 42%).

Mechanisms

Note: A full review of mechanisms for this exposure will form part of a larger review of mechanisms (see Section 6.1 in this report).

Many processed meats contain high levels of salt, nitrite and nitrate. Nitrite is used to preserve processed meat (it is extremely toxic to bacteria) and gives cured meat its recognisable colour and flavour. The addition of nitrite and nitrate to food is regulated and monitored in most countries. However, there is concern that nitrite and nitrate from processed meat may be involved in carcinogenesis, due to reactions during the curing process or in the body. In the stomach in particular, nitrite and nitrate can react with the degradation products of amino acids (from meat) to form N-nitroso compounds [83]. Several N-nitroso compounds are known human or animal carcinogens.

Smoked meat is also often salted or cured, meaning that it is likely to raise endogenous production of N-nitroso compounds in the stomach. Smoked meat may also contain carcinogenic and mutagenic polycyclic aromatic hydrocarbons, depending on the fuel burned to produce the smoke.

A further potential mechanism linking processed meat intake to stomach cancer includes haem iron, which is found in red meat that is processed [84]. Haem iron contributes to endogenous formation of N-nitroso compounds; it also causes oxidative stress and DNA damage, both of which are thought to be essential growth factors for *H. pylori* [85].

Finally, the salt included in cooking, processing and preserving meat can damage the gastric mucosa and lead to inflammation [86].

CUP Panel's conclusion:

The evidence for non-cardia cancer was consistent, with a clear dose-response relationship showing a significant increased risk of non-cardia cancer with increasing processed meat intake, with low heterogeneity. Although only three cohort studies were identified, these were large cohorts with more than 1,000 cases [44, 78, 79]. One published meta-analysis also reported significant increased risk. There is evidence of plausible mechanisms in humans.

For cardia cancer, evidence was limited and conclusions could not be drawn.

The CUP Panel concluded:

Greater consumption of processed meat is probably a cause of non-cardia cancer.

7.5 Alcoholic drinks

(Also see CUP Stomach SLR 2015: Section 5.4.1)

The CUP identified 15 new or updated studies (16 publications) [36, 46, 87-100] on alcohol intake (as ethanol) and stomach cancer risk, giving a total of 30 studies (39 publications; see CUP Stomach SLR 2015 Tables 106 and 107 for a full list of references).

Of 18 studies (20 estimates) reporting on stomach cancer incidence, 12 reported a positive association, of which three were significant; three reported an inverse association, of which one was significant; and one reported no effect, when comparing the highest and lowest categories of intake (see CUP Stomach SLR 2015 Figure 128). One study reported a positive association for cardia cancer and an inverse association for non-cardia cancer (both non-significant), and one study reported a non-significant inverse association for cardia cancer and no effect for non-cardia cancer. Of eight studies (10 estimates) reporting on stomach cancer mortality, seven reported a positive association, two of which were significant and one of which was significant in females only; and one reported a non-significant inverse association, when comparing the highest and lowest intake categories.

Twenty-three of the 30 studies were included in the dose-response meta-analysis (n = 11,926), which reported no significant association with stomach cancer risk per 10 grams of alcohol as ethanol consumed per day (RR = 1.02 (95% CI 1.00–1.04); see **Figure 5**; CUP Stomach SLR 2015 Figure 129). Moderate heterogeneity was observed (I^2 = 39%). The meta-analysis became statistically significant when one study that reported exceptionally high intakes of alcohol was removed [101] (RR = 1.03 (95% CI 1.01–1.04) per 10 grams per day).

Non-linear analysis showed that, while the test for non-linearity was not significant (p = 0.32), the linear dose-response association was statistically significant at quantities of alcohol (expressed as grams of ethanol) of 45 grams consumed per day and above (see **Figure 6** and **Table 5**; CUP Stomach SLR 2015 Figure 138 and Table 108).

Figure 5: Dose-response meta-analysis of alcohol (as ethanol) and stomach cancer, per 10 grams per day

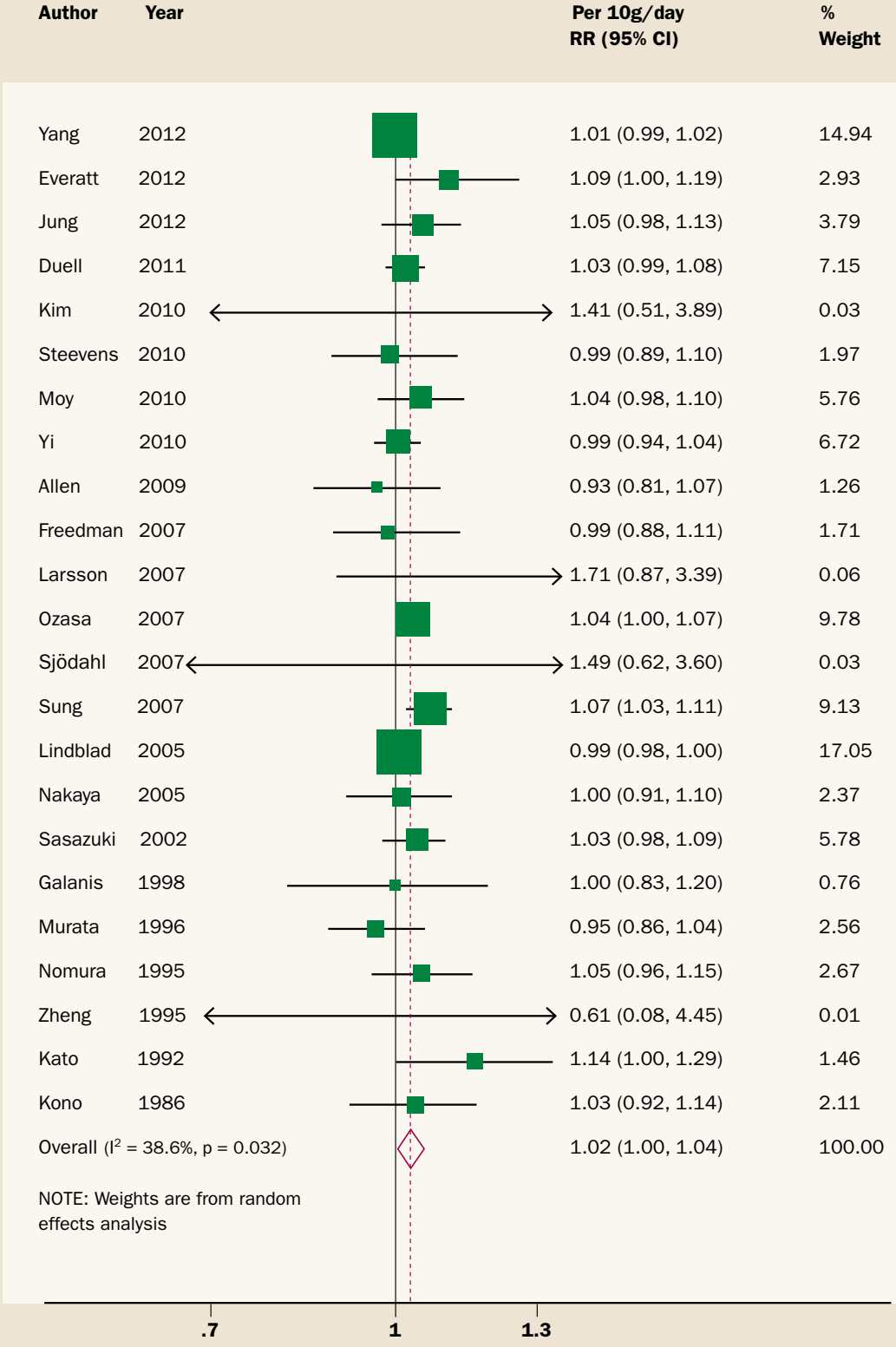


Figure 6: Non-linear dose-response association of alcohol (as ethanol) intake and stomach cancer

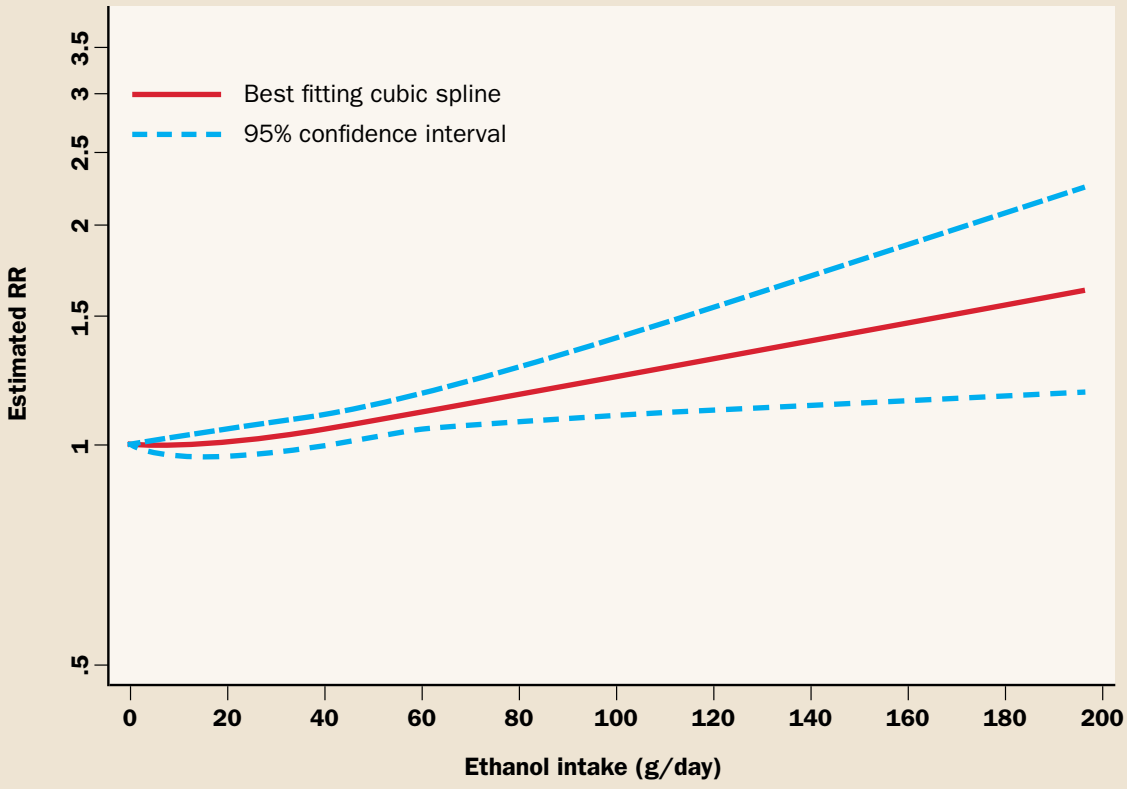


Table 5: Non-linear dose-response estimates of alcohol (as ethanol) intake and stomach cancer

ALCOHOL INTAKE (GRAMS OF ETHANOL/DAY)	RR (95% CI)
0	1.00
10	1.00 (0.98–1.03)
22	1.01 (0.97–1.06)
32	1.03 (0.98–1.08)
45	1.06 (1.01–1.11)
53	1.08 (1.03–1.13)
58	1.09 (1.04–1.14)
71	1.13 (1.05–1.21)
80	1.15 (1.06–1.26)
90	1.19 (1.07–1.32)
106	1.24 (1.08–1.42)
120	1.28 (1.08–1.52)

When stratified by sex, outcome and geographical region, the dose-response meta-analysis showed a significant increased risk of stomach cancer in men and in Asian cohorts. Significant increased risk was also seen in comparisons of the highest and lowest levels of intake in both never-smokers and current/former smokers (see **Table 6** and CUP Stomach SLR 2015 Figures 131, 135 and 139). Analysis by cancer subtype revealed no significant association for both cardia and non-cardia cancers (see CUP Stomach SLR 2015 Figure 134).

Table 6: Summary of CUP 2015 stratified dose-response meta-analyses – alcohol

ANALYSIS	INCREMENT/ COMPARISON	RR (95% CI)	I^2	NO. STUDIES	NO. CASES
MEN	Per 10g/day	1.03 (1.01-1.05)	37%	13	6,956
WOMEN	Per 10g/day	1.02 (0.90-1.15)	19%	5	1,308
ASIA	Per 10g/day	1.03 (1.01-1.04)	21%	14	7,282
EUROPE	Per 10g/day	1.02 (0.98-1.06)	46%	7	2,667
NORTH AMERICA	Per 10g/day	0.98 (0.87-1.11)	0%	2	401
NEVER-SMOKERS	Highest vs. lowest	1.23 (1.03-1.46)	0%	6	>807
CURRENT & FORMER SMOKERS	Highest vs. lowest	1.84 (1.43-2.36)	51%	6	>621

All studies included in the dose-response analysis were adjusted for age, sex and smoking. None was adjusted for *H. pylori* status. One study [101] reported an exceptional highest level of alcohol intake (≥34 units of alcohol per day), and the estimate for this category was excluded from the CUP non-linear meta-analysis.

Four studies were excluded from CUP analysis because they did not report sufficient data [67, 102-104].

The CUP findings are different from the dose-response meta-analysis in the 2005 SLR, which reported no significant association from five studies per 10 grams of alcohol as ethanol consumed per day (RR = 0.99 (95% CI 0.97–1.02), I^2 = 27%). The CUP Stomach SLR 2015 included many more studies and cases of stomach cancer than the 2005 SLR, and additional non-linear and stratified analyses.

Published pooled analyses and meta-analyses

No pooled analysis was identified. One meta-analysis [105] of 15 cohort studies has been published on alcohol and stomach cancer risk, which reported no significant association with stomach cancer in alcohol drinkers compared with non-drinkers (RR = 1.04 (95% CI 0.97–1.11), I^2 = 31%, *n* = 13,343).

Mechanisms

Note: A full review of mechanisms for this exposure will form part of a larger review of mechanisms (see Section 6.1 in this report).

Acetaldehyde, the reactive metabolite of alcohol, is carcinogenic to humans [106]. In addition, the effects of alcohol on stomach cancer risk may be mediated by the production of prostaglandins, lipid peroxidation and the generation of oxygen radical species. Alcohol also acts as a solvent, enhancing penetration of carcinogens into cells. Alcohol has been demonstrated to interfere with retinoid metabolism, which may adversely affect cellular growth, cellular differentiation and apoptosis.

For all these pathways, genetic polymorphisms might also influence risk. Notably, the observation of a strong positive association between alcohol intake and stomach cancer risk among Asians suggests that genetic differences in ethanol metabolism may play a role [105]. For example, alcohol dehydrogenase-2 *(ALDH2)* polymorphisms have been related to increased gastric cancer risk in Japanese populations [107].

Lastly, heavy consumers of alcohol may have diets deficient in essential nutrients, rendering tissues more susceptible to carcinogenesis [108].

CUP Panel's conclusion:

Overall, the evidence tended to show increased risk of stomach cancer with greater alcohol intake. The dose-response meta-analysis was statistically significant when one study with exceptionally high reported intakes of alcohol was excluded. Non-linear analysis showed that the dose-response association was significant at higher levels of alcohol intake (from 45 grams per day). Stratified analysis revealed significant increased risk in men, for incidence in men and in Asian studies. Highest versus lowest analysis stratified by smoking status showed significant increased risk in both smokers and non-smokers. Results were consistent for cardia and non-cardia cancers. There is evidence of plausible mechanisms in humans. The CUP Panel concluded:

Greater consumption of alcoholic drinks probably increases the risk of stomach cancer. This is based on evidence for intakes greater than 45 grams per day (about 3 drinks a day).

7.6 Grilled (broiled) and barbecued (charbroiled) animal foods

(Also see CUP Stomach SLR 2015: Section 4.4.2.6)

No new studies were identified in the CUP. Three studies were identified in the 2005 SLR: two on consumption of grilled fish, and one on consumption of grilled meat (three publications; see CUP Stomach SLR 2015 Section 4.4.2.6). Dose-response meta-analysis could not be conducted.

The first study on grilled fish [54] reported a significant positive association between the highest compared with the lowest level of grilled fish consumption and stomach cancer mortality (RR = 1.7, $p < 0.05$). However, the second study [109] did not report a significant association between the highest compared with the lowest level of consumption and stomach cancer incidence (RR = 0.84 (95% CI 0.55–1.29); n = 1,270). The study on grilled meat [70] reported a significant positive association between the highest compared with the lowest level of grilled meat consumption and stomach cancer mortality (RR = 2.27 (95% CI 1.06–4.85); 57 deaths).

All studies were conducted in Japan, and were adjusted for age and sex. Two studies were also adjusted for smoking and other variables.

Published pooled analyses and meta-analyses

No published pooled analysis or meta-analysis was identified on consumption of grilled and barbecued meat or fish and stomach cancer risk.

Evidence from polycyclic aromatic hydrocarbons

One study identified in the CUP [79] estimated intake of benzo[a]pyrene (B[a]P), a marker of polycyclic aromatic hydrocarbons, using information collected on meat cooking methods (grilled/barbecued, pan-fried and microwaved) and doneness levels (well-done and medium/rare). Dose-response meta-analysis and highest versus lowest quintile analysis indicated that B[a]P was not significantly associated with stomach cancer risk (cardia cancer: RR = 1.00 (95% CI 0.97–1.04); non-cardia cancer: RR = 0.99 (95% CI 0.94–1.03) per 10ng/day).

Evidence from heterocyclic amines

One study identified in the CUP [79] estimated heterocyclic amine intake. A significant positive association was observed between cardia cancer risk and the highest compared with the lowest quintile of DiMeIQx (RR = 1.44 (95% CI 1.01–2.07)), but not non-cardia cancer risk (RR = 0.97 (95% CI 0.68–1.39)). No significant associations were observed in dose-response analyses or for other heterocyclic amines (MeIQx and PhIP).

Mechanisms

Note: A full review of mechanisms for this exposure will form part of a larger review of mechanisms (see Section 6.1 in this report).

Meat cooked at high temperatures, such as by grilling and barbecuing, can contain mutagenic and carcinogenic heterocyclic amines and polycyclic aromatic hydrocarbons [110, 111]. Haem, present in meat and fish products, promotes the formation of N-nitroso compounds and also contains iron. Free iron can lead to the production of free radicals, which can damage cells and lead to cancer development.

CUP Panel's conclusion:

Evidence was limited, as few studies were identified and meta-analysis could not be conducted. However, evidence was generally consistent with an increased risk of stomach cancer with greater consumption of grilled fish and meat. Evidence on polycyclic aromatic hydrocarbons and heterocyclic amines did not provide strong mechanistic support. The CUP Panel concluded:

The evidence suggesting that greater consumption of grilled (broiled) or barbecued (charbroiled) animal foods increases the risk of stomach cancer is limited.

7.7 Body fatness

(Also see CUP Stomach SLR 2015: Section 8.1.1)

Analyses were performed for body fatness and overall stomach cancer, cardia and non-cardia cancers, but conclusions could be drawn only for cardia cancer.

The CUP Panel interpreted body mass index (BMI) as a measure of body fatness. The Panel is aware that this anthropometric measure is imperfect and does not distinguish between lean and fat mass.

Body mass index

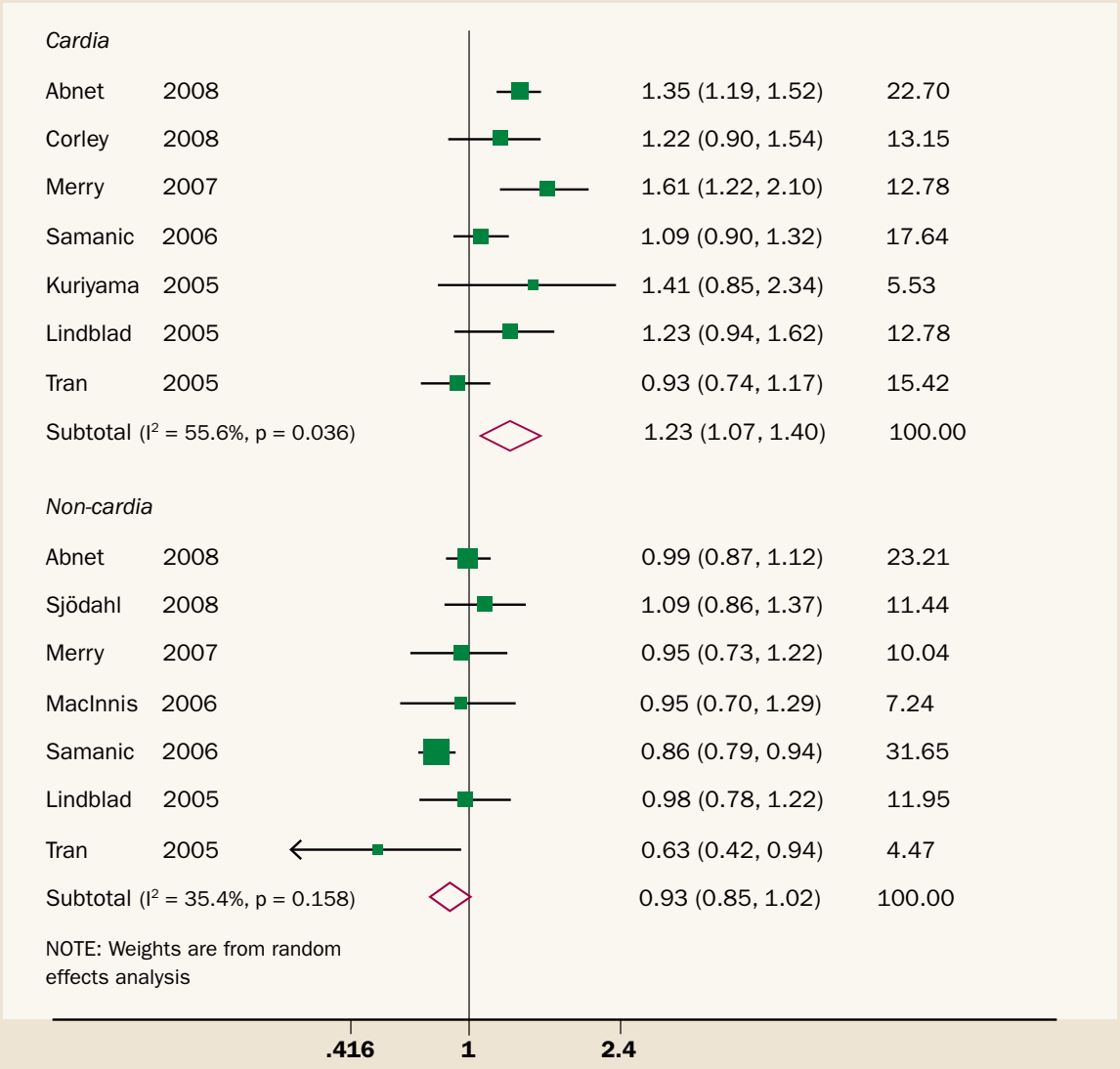
The CUP identified 15 new or updated studies (18 publications) on BMI and overall stomach cancer risk, giving a total of 30 studies (38 publications; see CUP Stomach SLR 2015 Tables 172 and 173 for a full list of references).

For cardia cancer, five new or updated studies (seven publications) were identified on BMI [112-117], giving a total of 10 studies (twelve publications). Seven studies (seven estimates) reported on cardia cancer incidence. Six reported a positive association when comparing the highest and lowest categories of intake, of which two were significant; and one reported a non-significant inverse association (see CUP Stomach SLR 2015 Figure 188).

All seven studies were included in the dose-response meta-analysis (n = 2,050), which showed a significant 23 per cent increased risk of cardia cancer per 5kg/m², with moderate heterogeneity (RR = 1.23 (95% CI 1.07–1.40), I^2 = 56%; see **Figure 7**, CUP Stomach SLR 2015 Figure 194).

No significant association was observed with non-cardia cancer risk (presented for comparison in **Figure 7**).

Figure 7: Dose-response meta-analysis of BMI and stomach cancer, per 5kg/m² per day



When stratified by geographical location and measurement of weight and height, the dose-response meta-analysis showed a significant positive association with cardia cancer risk in European and North American studies, and where height and weight were self-reported. One study [113] reported a significant positive association with cardia cancer risk in both smokers and non-smokers (see **Table 7** and CUP Stomach SLR 2015 Figures 196 and 198).

Table 7: Summary of CUP 2015 stratified meta-analyses – BMI

ANALYSIS	INCREMENT/ COMPARISON	RR (95% CI)	I^2	NO. STUDIES	NO. CASES
EUROPE	Per 5 kg/m^2	1.27 (1.01-1.60)	62%	3	505
NORTH AMERICA	Per 5 kg/m^2	1.32 (1.18-1.48)	0%	2	406
ASIA	Per 5 kg/m^2	1.08 (0.73-1.59)	54%	2	1,139
BMI SELF-REPORTED	Per 5 kg/m^2	1.39 (1.25-1.55)	0%	3	520
BMI MEASURED	Per 5 kg/m^2	1.06 (0.92-1.23)	17%	3	1,417
BMI MEDICAL RECORDS	Per 5 kg/m^2	1.23 (0.94-1.62)	-	1	113
SMOKERS*	Highest vs. lowest	3.39 (1.21-9.50)	-	1	58
NON-SMOKERS*	Highest vs. lowest	2.54 (1.58-4.10)	-	1	245

*Smokers: current smokers and those who quit less than 1 year before baseline. Non-smokers: never-smokers and those who quit 1 year or more before baseline.

Non-linear analysis revealed a significant non-linear relationship ($p < 0.001$). There was a significant increased risk of cardia cancer at higher BMI levels (26kg/m^2 and above; see **Figure 8**, CUP Stomach SLR 2015 Figure 201 and **Table 8**, CUP Stomach SLR 2015 Table 175).

Figure 8: Non-linear dose-response association of BMI and cardia cancer

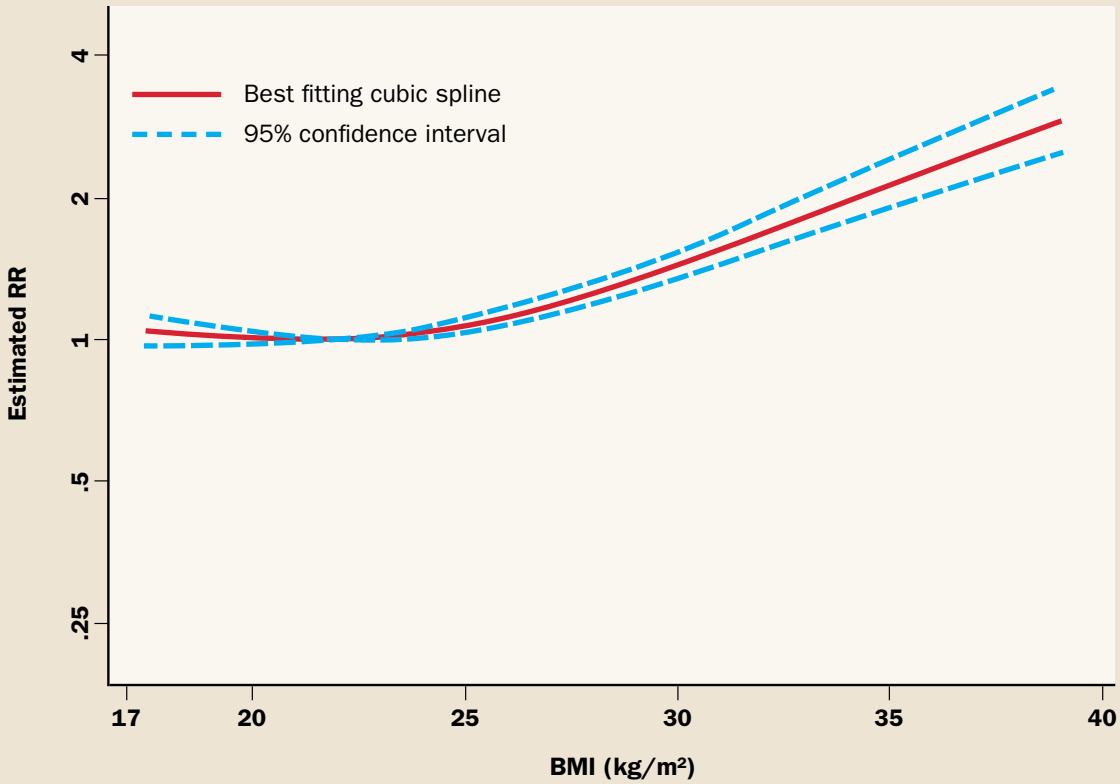


Table 8: Non-linear dose-response estimates of BMI and cardia cancer

BMI (kg/m²)	RR (95% CI)
17.40	1.04 (0.96–1.13)
18.95	1.02 (0.97–1.07)
21.70	1.00
23.45	1.02 (1.00–1.04)
26.20	1.13 (1.08–1.18)
28.70	1.32 (1.24–1.40)
32.00	1.68 (1.54–1.84)

All studies included in the dose-response meta-analysis were adjusted for age, sex and smoking. None of the studies was adjusted for *H. pylori* status.

Three studies were excluded from all CUP analyses because they did not report sufficient data [118, 119] or combined cardia cancer with oesophageal cancer [117].

There was no analysis by cancer site in the 2005 SLR.

Published pooled analyses and meta-analyses

No pooled analysis was identified. One meta-analysis of cohort studies has been published on BMI and cardia cancer risk [120]. It reported a significant increased risk per 5kg/m^2 (RR = 1.32 (95% CI 1.07–1.64), I^2 = 51%).

Other measures

One study reported a non-significant positive association between BMI at age 20 and cardia cancer risk [115].

One study reported a significant positive association between waist circumference and cardia cancer risk [112]. The same study reported a non-significant positive association with waist-to-hip ratio.

Mechanisms

Note: A full review of mechanisms for this exposure will form part of a larger review of mechanisms (see Section 6.1 in this report).

Obesity is characterised by a low-grade chronic inflammatory state, with increased production of pro-inflammatory factors, such as tumour necrosis factor (TNF)-alpha, interleukin (IL)-6 and C-reactive protein. Such chronic inflammation can promote cancer development. Obesity also leads to elevated levels of insulin and leptin, and upregulated production of endogenous hormones including sex steroids and insulin, which may increase cell proliferation and impair apoptosis and consequently promote cancer cell growth [121].

Obesity also promotes gastroesophageal reflux, possibly caused by elevated intra-abdominal pressure, and transition to potentially precancerous Barrett's oesophagus [122]. This increases the risk of cardia cancer together with oesophageal adenocarcinoma [123, 124].

Interestingly, an inverse association has been observed between BMI and prevalence of *H. pylori* infection, which has been identified as an important risk factor for non-cardia cancer [125].

CUP Panel's conclusion:

The evidence for cardia cancer was consistent. The dose-response meta-analysis showed a significant increased risk, although with high heterogeneity, which may partially be explained by the size of the effect. Significant increased risk was also seen in analyses stratified by geographical area and by smoking status. A significant non-linear meta-analysis indicated that the association was significant at a BMI of approximately 26kg/m^2 and above. Results were supported by one published meta-analysis. There is evidence of plausible mechanisms in humans.

For non-cardia cancer, evidence was limited and conclusions could not be drawn.

The CUP Panel concluded:

Greater body fatness, as marked by BMI, is probably a cause of cardia cancer.

7.8 Other

Other exposures were evaluated. However, data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. This list of exposures judged as 'limited – no conclusion' is summarised in the matrix on page 6.

The evidence for vegetables, pulses (legumes), foods containing selenium and chilli, which was previously judged as 'probable' or 'limited – suggestive' in the Second Expert Report [1], was less consistent and the Panel could not draw any conclusions on the updated evidence.

Evidence for the following exposures previously judged as 'limited – no conclusion' in the Second Expert Report remained unchanged after updating the analyses with new data identified in the CUP Stomach SLR 2015: meat (unprocessed), poultry, eggs, coffee and tea.

The following exposures, which were also previously too limited to draw conclusions in the Second Expert Report and not updated as part of the CUP Stomach SLR 2015 due to a lack of new evidence, remained 'limited – no conclusion': cereals (grains) and their products, dietary fibre, potatoes, starchy roots, tubers and plantains, nuts and seeds, herbs, spices and condiments, milk and dairy products, fats and oils, total fat, fatty acid composition, cholesterol, sugars, sugar (sucrose), fruit juices, dietary nitrate and nitrite, N-nitrosodimethylamine, drying or dried food, protein, thiamin, riboflavin, vitamin C, vitamin D, multivitamin/mineral supplements, calcium, iron, selenium supplements, carotenoids, culturally defined diets, meal frequency, eating speed and energy intake.

In addition, evidence for the following new exposures, for which no judgement was made in the Second Expert Report, was too limited to draw any conclusions: soy products, fish (unprocessed), frying, retinol, physical activity and height. New evidence for processed meat and cardia cancer, and body fatness and citrus fruit and non-cardia cancer, was also too limited to draw any conclusions.

8. Comparison with the Second Expert Report

New site-specific evidence was included in the CUP that was not available in the Second Expert Report [1], notably on body fatness and citrus fruit and cardia cancer, and processed meat and non-cardia cancer. Much of the new evidence was on alcoholic drinks, which was upgraded from 'limited – no conclusion' to 'probable' increased risk, and salt-preserved vegetables, evidence for which was not previously examined as a separate category. The updated evidence on vegetables and fruit was less strong than in the Second Expert Report.

9. Conclusions

The CUP Panel concluded:

- **Alcoholic drinks: Consumption of alcoholic drinks is probably a cause of stomach cancer. This is based on evidence for intakes greater than 45 grams per day (about 3 drinks a day).**
- **Foods preserved by salting: Consumption of foods preserved by salting is probably a cause of stomach cancer.**
- **Processed meat: Consumption of processed meat is probably a cause of non-cardia cancer.**
- **Body fatness: Greater body fatness (as marked by BMI) is probably a cause of cardia cancer.**
- **Grilled (broiled) or barbecued (charbroiled) meat and fish: The evidence suggesting that consumption of grilled (broiled) or barbecued (charbroiled) meat and fish increases the risk of stomach cancer is limited.**
- **Low fruit intake: The evidence suggesting that low intake of fruit increases the risk of stomach cancer is limited.**
- **Citrus fruit: The evidence suggesting that consumption of citrus fruit decreases the risk of cardia cancer is limited.**

For a full description of the definitions of, and criteria for, the terminology of 'convincing', 'probable', 'limited – suggestive', 'limited – no conclusion' and 'substantial effect on risk unlikely', see the **Appendix**.

The CUP database is continually being updated for all cancers. The Cancer Prevention Recommendations will be reviewed in 2017 when the Panel has reviewed the conclusions for the other cancers.

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Abbreviations

AICR	American Institute for Cancer Research
B[a]P	benzo[a]pyrene
BMI	body mass index
CI	confidence interval
CUP	Continuous Update Project
DiMeIQx	2-amino-3,4,8-dimethylimidazo[4,5-f]quinoxaline
IARC	International Agency for Research on Cancer
MeIQx	2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline
n	number of cases
RR	relative risk
PhIP	2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine
SLR	systematic literature review
WCRF	World Cancer Research Fund

Glossary

Adenocarcinoma
Cancer of glandular epithelial cells.

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

Anthropometric measures
Measures of body dimensions.

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

Body mass index (BMI)
Body weight expressed in kilograms divided by the square of height expressed in metres (BMI = kg/m^2). It provides an indirect measure of body fatness. Also known as Quetelet's Index.

C-reactive protein
A protein whose concentration in the blood rises in response to inflammation.

Carcinogen
Any substance or agent capable of causing cancer.

Carcinoma
Malignant tumour derived from epithelial cells, usually with the ability to spread into the surrounding tissue (invasion) and produce secondary tumours (metastases).

Cardia cancer
A subtype 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 based on their disease or condition (cases) or lack of it (controls), to test whether distant or recent history of an exposure such as smoking, genetic profile, alcohol consumption or dietary intake is associated with the risk of disease.

Cohort study
A study of a (usually large) group of people whose characteristics are recorded at recruitment (and sometimes later), 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, 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 to another.

Confidence interval (CI)
A measure of the uncertainty in an estimate, usually reported as 95% confidence interval (CI), which is the range of values within which there is a 95% chance that the true value lies. For example, the effect of smoking on the relative risk of lung cancer in one study may be expressed as 10 (95% CI 5–15). This means that in this particular analysis, 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
A variable that is associated both with 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 smoking is related both to coffee drinking and to risk of lung cancer, and thus unless accounted for (controlled) in studies, might make coffee drinking appear falsely as a cause of lung cancer.

Dose-response
A term derived from pharmacology that describes the degree to which an effect changes with the level of an exposure, for instance, intake of a drug or food (see Second Expert Report Box 3.2).

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.

Heterocyclic amines
Gene amplification is an increase in the number of copies of a gene sequence. Cancer cells sometimes produce multiple copies of genes in response to signals from other cells or their environment.

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 a gross average annual national product of more than an agreed figure per head (in 2006 this was more than US$10,726). This term is more precise than, and used in preference to, ‘economically developed countries’.

Immune response
The production of antibodies or specialised cells in response to foreign proteins or other substances.

Incidence rates
The number of new cases of a condition appearing during a specified period of time expressed relative to the size of the population; for example, 60 new cases of breast cancer per 100,000 women per year.

Inflammation
The immunologic response of tissues to injury or infection. Inflammation is characterised by accumulation of white blood cells that produce several bioactive chemicals (cytokines), causing redness, pain, heat and swelling.

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.

Interleukin-6
The insulin-like growth factors (IGFs) are proteins with high similarity to insulin. IGFs are part of a complex system that cells use to communicate with their environment.

Leptin
A hormone secreted by adipose cells that helps to regulate energy balance by inhibiting hunger.

Lesion
A general term for any abnormality of cells or tissues, including those due to cancer.

Low-income countries
As defined by the World Bank, countries with a gross average annual national product of less than an agreed figure per head (in 2006, this was US$875). This term is more precise than and used in preference to 'economically developing countries'.

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

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

Mutation
In biology, a mutation is a permanent change of the nucleotide sequence of the genome (an organism's complete set of DNA).

N-nitroso compound
A substance that is present in foods treated with sodium nitrate, particularly processed meat and fish. It may also be formed endogenously, e.g., 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 cancer
A subtype of stomach cancer that occurs in the lower portion of the stomach.

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 the relative risk.

Pathogenesis
The origin and development of disease. The mechanisms by which causal factors increase the risk of disease.

Polymorphisms
Common variations (more than 1 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.

Processed meat
Meat (usually red meat) that is preserved by smoking, curing or salting, or by the addition of preservatives. Definitions vary between countries and studies as to what precisely is included (see Second Expert Report Box 4.3.1).

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

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

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

Statistical significance
The probability that any observed result has or has not occurred by chance. Conventionally, a probability of less than 5% ($p < 0.05$) that a study result has occurred by chance is considered 'statistically significant' (see confidence interval).

Systematic literature review (SLR)
A means of compiling and assessing published evidence that addresses a scientific question with a predefined protocol and transparent methods (see Second Expert Report Box 3.4).

Tumour necrosis factor
A cell-signalling protein involved in inflammation that can cause cell death.

Waist-hip ratio (WHR)
A measure of body shape indicating fat distribution.

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Appendix – Criteria for grading evidence

(Taken from Chapter 3 of the Second Expert Report [1])

This appendix lists 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.

CONVINCING (STRONG EVIDENCE)

This judgement is for evidence strong enough to support a judgement of a convincing causal relationship, which justifies goals and recommendations designed to reduce the incidence of cancer. A convincing relationship should be robust enough to be highly 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)

This judgement is for evidence strong enough to support a judgement of a probable causal relationship, which would generally justify goals and recommendations designed to reduce the incidence of cancer.

All 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

This judgement is for evidence that is too limited to permit a probable or convincing causal judgement, but is suggestive of a direction of effect. The evidence may have methodological flaws, or be limited in amount, 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 incidence of cancer; any exceptions to this require special explicit justification.

All 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 might be limited by the amount of evidence in terms of the number of studies available, by inconsistency of direction of effect, by poor quality of studies (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 **(wcrf.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, an insufficient range of exposure in the study population and inadequate statistical power. Defects in these and 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 in 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 it 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.

Our Cancer Prevention Recommendations

Be a healthy weight
Keep your weight as low as you can within the healthy range.

Move more
Be physically active for at least 30 minutes every day, and sit less.

Avoid high-calorie foods and sugary drinks
Limit high-calorie foods (particularly processed foods high in fat or added sugar, or low in fibre) and avoid sugary drinks.

Enjoy more grains, veg, fruit and beans
Eat a wide variety of whole grains, vegetables, fruit and pulses such as beans.

Limit red meat and avoid processed meat
Eat no more than 500g (cooked weight) a week of red meat, such as beef, pork and lamb. Eat little, if any, processed meat such as ham and bacon.

For cancer prevention, don't drink alcohol
For cancer prevention, it's best not to drink alcohol. If you do, limit alcoholic drinks and follow national guidelines.

Eat less salt, and avoid mouldy grains and cereals
Limit your salt intake to less than 6g (2.4g sodium) a day by adding less salt and eating less food processed with salt. Avoid mouldy grains and cereals as they may be contaminated by aflatoxins.

For cancer prevention, don't rely on supplements
Eat a healthy diet rather than relying on supplements to protect against cancer.

If you can, breastfeed your baby
If you can, breastfeed your baby for six months before adding other liquids and foods.

Cancer survivors should follow our Recommendations (where possible)
After cancer treatment, the best advice is to follow the Cancer Prevention Recommendations. Check with your health professional.

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