World Cancer Research Fund

American Institute for Cancer Research

CUP Continuous Update Project

Analysing research on cancer prevention and survival
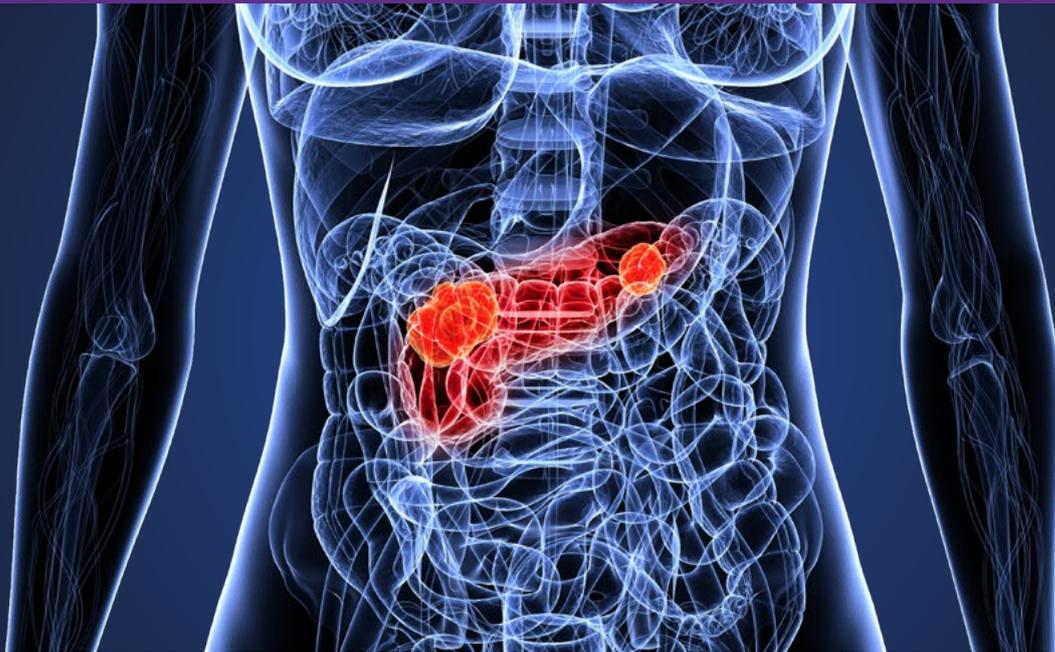
Diet, nutrition, physical activity and pancreatic cancer

2012

Revised 2018

Contents

WORLD CANCER RESEARCH FUND NETWORK

OUR VISION

We want to live in a world where no one develops a preventable cancer.

OUR MISSION

We champion the latest and most authoritative scientific research from around the world on cancer prevention and survival through diet, weight and physical activity, so that we can help people make informed choices to reduce their cancer risk.

As a network, we influence policy at the highest level and are trusted advisors to governments and to other official bodies from around the world.

OUR NETWORK

World Cancer Research Fund International is a not-for-profit organisation that leads and unifies a network of cancer charities with a global reach, dedicated to the prevention of cancer through diet, weight and physical activity.

The World Cancer Research Fund network of charities is based in Europe, the Americas and Asia, giving us a global voice to inform people about cancer prevention.

OUR CONTINUOUS UPDATE PROJECT (CUP)

The Continuous Update Project (CUP) is the World Cancer Research Fund (WCRF) Network's ongoing programme to analyse cancer prevention and survival research related to diet, nutrition and physical activity from all over the world. Among experts worldwide it is a trusted, authoritative scientific resource which informs current guidelines and policy on cancer prevention and survival.

Scientific research from around the world is continually added to the CUP's unique database, which is held and systematically reviewed by a team at Imperial College London. An independent panel of experts carries out ongoing evaluations of this evidence, and their findings form the basis of the WCRF Network's Cancer Prevention Recommendations (**see inside back cover**).

Through this process, the CUP ensures that everyone, including policymakers, health professionals and members of the public, has access to the most up-to-date information on how to reduce the risk of developing cancer.

The launch of the WCRF Network's Third Expert Report, *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*, in 2018 brings together the very latest research from the CUP's review of the accumulated evidence on cancer prevention and survival related to diet, nutrition and physical activity. Diet, nutrition, physical activity and pancreatic cancer is one of many parts that make up the CUP Third Expert Report: for a full list of contents, see **dietandcancerreport.org**.

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

HOW TO CITE THIS REPORT

This part: World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and pancreatic cancer. Available at **dietandcancerreport.org**

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

KEY

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

2012

DIET, NUTRITION, PHYSICAL ACTIVITY AND PANCREATIC CANCER

		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	**Convincing**		**Body fatness[1]**
	Probable		**Adult attained height[2]**
LIMITED EVIDENCE	**Limited – suggestive**		Red meat[3] Processed meat[4] Alcoholic drinks (heavier drinking)[5] Foods and beverages containing fructose[6] Foods containing saturated fatty acids
	Limited – no conclusion	Physical activity; fruits; vegetables; folate; fish; eggs; tea; soft drinks; coffee; carbohydrates; sucrose; glycaemic index; glycaemic load; total fat; monounsaturated fat; polyunsaturated fats; dietary cholesterol; vitamin C; and multivitamin/mineral supplements	
STRONG EVIDENCE	**Substantial effect on risk unlikely**		

1 The Panel interpreted BMI, measured of abdominal girth, and adult weight gain as indicating interrelated aspects of body fatness as well as fat distribution.

2 Adult attained height is unlikely to directly influence the risk of cancer. It is a marker for genetic, environmental, hormonal and nutritional growth factors affecting growth during the period from preconception to completion of linear growth.

3 The term 'red meat' refers to beef, pork, lamb and goat from domesticated animals.

4 The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.

5 Includes total alcoholic drinks and alcohol as ethanol. Limited to those drinking more than about three drinks/day (one drink contains about 10-15 grams ethanol).

6 Includes both foods natually containing the constituent and foods which have the constituent added.

1. Summary of Panel judgements

Overall, the Panel notes the strength of evidence that greater body fatness and adult attained height are causes of pancreatic cancer.

Convincing evidence

Body fatness: Greater body fatness is a convincing cause of pancreatic cancer.

Probable evidence

Adult attained height: Developmental factors leading to greater linear growth, marked by adult attained height, are probably a cause of pancreatic cancer.

Limited - suggestive evidence

Red meat: The evidence suggesting consumption of red meat increases the risk of pancreatic cancer is limited.

Processed meat: The evidence suggesting consumption of processed meat increases the risk of pancreatic cancer is limited.

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

Alcoholic drinks: The evidence suggesting consumption of alcoholic drinks increases the risk of pancreatic cancer is limited.

Foods and beverages containing fructose: The evidence suggesting consumption of foods and beverages containing fructose increase the risk of pancreatic cancer is limited.

Note: In 2012, the Panel made a judgement on coffee consumption and the risk of pancreatic cancer. The Panel has since reviewed the evidence further and updated their conclusion to ensure consistency across the Third Expert Report. For consumption of coffee and risk of pancreatic cancer, the evidence for an association was considered to be limited and no conclusion was possible.

2. Trends, incidence and survival

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

Cancer of the pancreas is the thirteenth most common type of cancer worldwide. About 280 000 cases were recorded in 2008, accounting for around 2 per cent of cancers overall. The incidence is somewhat higher in men than in women (144,859 and 133,825 cases in 2008 respectively). This cancer is almost always fatal and is the eighth most common cause of cancer death, accounting for somewhat over 3 per cent of all cancer deaths [2]. See **Box 1**.

Age-adjusted rates of pancreatic cancer have been generally stable since the 1970s, following an approximate threefold rise over the preceding 50 years in the countries for which data are available [3, 4].

Pancreatic cancer is mainly a disease of high-income countries, where overall rates are nearly three times higher than in middle-and low-income countries [2]. Around the world, age-adjusted incidence rates range from 10–15 per 100 000 people in parts of northern, central, and eastern Europe to less than 1 per 100 000 in areas of Africa and Asia, although rates are high in some of these areas, for example, Japan and Korea. In the USA, rates are higher among African-American people than in white people [5]. The risk of pancreatic cancer increases with age, with most diagnoses made in people between the ages of 60 and 80 [2].

The early stages of this cancer do not usually produce symptoms, so the disease is generally advanced when it is diagnosed. The 5-year prevalence of women globally living with pancreatic cancer is 3.5 per 100,000[1] [2].

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

3. Pathogenesis

The ductal cells in the head of the pancreas are exposed to pancreatic secretions, as well as bile, and environmental carcinogens can reach these cells through these fluids or the blood, through which endogenous factors may also act.

The pancreas is relatively inaccessible to routine medical examination, so the progression of this cancer through precursor lesions is not well understood. However, inflammation is implicated in this process through chronic pancreatitis, which is a risk factor for pancreatic cancer. The role of infection with *Helicobacter pylori* (see box 2 in CUP Stomach cancer report 2016) is the subject of ongoing research [6]. Conditions characterised by high insulin secretion, such as insulin resistance and type 2 diabetes, are associated with the risk of this cancer [7].

More than 90 per cent of pancreatic cancer cases are sporadic (due to spontaneous rather than inherited mutations), although a family history increases risk, particularly where more than one family member is involved [6]. Around 75–90 per cent of pancreatic cancer cases involve a point mutation in the K-ras oncogene [8] (see section 1.2.2 in The cancer process).

4. Other established causes

Tobacco use

Tobacco use is an established cause of pancreatic cancer [9] and approximately 25 per cent of cases of pancreatic cancer are attributable to tobacco smoking [10].

5. Interpretation of the evidence

5.1 General

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

'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 cancer of the pancreas include:

Measurement

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

Confounding

High-quality studies adjust for smoking.

6. Methodology

To ensure consistency with evidence collected and analysed for the Second Expert Report, much of the methodology for the Continuous Update Project remains unchanged from that used previously. However, based upon the experience of conducting the systematic literature reviews for the Second Expert Report, some modifications to the methodology were made. The literature search was restricted to Medline and included only randomised controlled trials, cohort and case- control studies. The reference lists of all review articles identified in the search were also checked, as a result of the relatively high number of articles (30) identified in this way during the SLR of pancreatic cancer. The search was not limited to "human studies" as it was not guaranteed that all studies on PubMed would be coded as human. The CUP Pancreatic Cancer SLR included studies published up to September 2011. Publications in foreign languages were not included.

Due to the large number of cohort studies, analysis and interpretation of case-control studies was not included in the Continuous Update Project SLR. Given that pancreatic cancer is most often diagnosed at a very advanced stage, survival rates beyond a few months are extremely low. There is, therefore, very little difference between cancer incidence and mortality rates, and study results on incidence and mortality have been presented and analysed together in the CUP SLR. If there were sufficient studies,

meta-analyses and forest plots of highest versus lowest categories were prepared for pancreatic cancer incidence and mortality separately. Studies reporting mean difference as a measure of association are not included in the 2011 Continuous Update Project SLR, as relative risks estimated from the mean differences are not adjusted for possible confounders, and thus not comparable to adjusted relative risks from other studies. For more information on methodology see the full CUP Pancreatic Cancer SLR.

6.1 Mechanistic evidence

The evidence for mechanisms is summarised under each exposure. These summaries were developed from mechanistic reviews conducted for the 2007 Second Expert Report [1], updates from CUP Panel members and published reviews.

*Update: The evidence for site specific mechanisms of carcinogenesis has been updated for the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report 2018 (our Third Expert Report, available at **dietandcancerreport.org**). The evidence is based on both human and animal studies. It covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature. A signpost to the relevant section in the Third Expert Report which summarises the updated mechanisms evidence can be found under each exposure within this report.*

7. Evidence and judgements

The updated search identified 79 new articles from cohort studies and randomised controlled trials, added to the 129 pancreatic cancer articles included in the SER.

The CUP Panel's conclusions will be reviewed again after 2015, when the CUP database is up to date, in preparation for the review of the 10 Recommendations for Cancer Prevention in 2017. This report includes the conclusions of the SER, with an updated description of the epidemiological evidence and revised conclusions. It also includes a brief description of potential mechanisms for each exposure.

For information on the criteria for grading the epidemiological evidence see **Appendix** in this report. References to studies added as part of the CUP have been included in the following sections; for details of references to other studies see the SER. Summary estimates from dose- response meta-analyses were regarded as non-significant if the 95% confidence interval included 1.0. A study reporting a summary estimate of 1.0 was considered to observe no effect.

7.1 Red meat

(Also see CUP Pancreatic Cancer SLR 2011: Section 2.5.1.3)

The CUP identified four new papers (from three cohort studies) [11-14] giving a total of 10 studies (including studies from the SER). Overall, the CUP found three of seven studies on pancreatic cancer incidence reported an increased risk for the highest intake group compared to the lowest, two of which were statistically significant. For pancreatic cancer mortality, two of three studies showed an increased risk, one of which was statistically significant.

Eight studies (three new) were included in the dose-response meta-analyses for red meat and pancreatic cancer (incidence and mortality combined). The CUP analyses were conducted per 100g/day compared to 20g/day in the SER. Overall, the analyses showed a non-significant positive association between red meat intake and pancreatic cancer risk (RR 1.19 (95% CI 0.98- 1.45) with moderate heterogeneity (I²= 52%) (see CUP 2011 Figure 25). In the SER, there was no clear association from the meta-analysis (RR 1.00 (95% CI 0.95-1.05)) and based on this meta- analysis of two cohort studies (incidence only) and review of five additional studies not included in the meta-analysis, it was concluded that the evidence suggesting an increased risk was limited.

The CUP dose-response meta-analysis showed an overall statistically significant increased risk of pancreatic cancer (incidence and mortality combined) in men, but not women (RRs 1.43 (95% CI 1.10-1.86) and 1.06 (95% CI 0.86-1.30) respectively (see CUP 2011 Figure 28). In women, most studies showed an increased risk, but these were not statistically significant.

Results from two other published meta-analysis were similar to the CUP analysis, both finding a non-significant positive association between red meat intake and pancreatic cancer risk [15, 16].

Mechanisms

High intake of red meat may result in more absorption of haem iron, greater oxidative stress, and potential for DNA damage [17, 18]. In addition, iron overload can also activate oxidative responsive transcription factors and inflammation in the colon [19]. Iron metabolism and transport are strictly regulated to reduce the likelihood of cells being exposed to free iron and so to oxidative damage; most iron in living tissues is bound to proteins, such as transferrin and ferritin, which prevent its involvement in free radical generation.

Red meat consumption is also associated with the formation of *N*-nitroso compounds. Some *N*-nitroso compounds are carcinogens, and are formed in foods containing added nitrates or nitrites; examples include fish and meat preserved with salting or preservatives, and smoking or drying. These carcinogens can also be generated from ingested foods containing nitrate or nitrite. *N*-nitroso compounds are also produced endogenously in the stomach and colon of people who eat large amounts of red meat [20].

When cooked at high temperatures, red meat can also contain heterocyclic amines and polycyclic aromatic hydrocarbons. Heterocyclic amines are formed when muscle meats such as beef, pork, fowl, and fish are cooked. High cooking temperatures cause amino acids and creatine (a chemical found in muscles) to react together to form these chemicals. So far, different heterocyclic amines have been identified as being formed by cooking muscle meats and which may pose a cancer risk [21, 22].

Update: As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see Exposures: Meat, fish and dairy products (Appendix – Mechanisms) for the updated mechanisms summary.

CUP Panel's conclusion:

More studies were available for the CUP analysis. Overall the evidence is not considered to have changed since the SER.

The CUP Panel concluded the following:

> **The evidence is inconsistent. The evidence suggesting that red meat is a cause of pancreatic cancer is limited.**

7.2 Processed meat

(Also see CUP Pancreatic Cancer SLR 2011: Section 2.5.1.2)

The CUP identified three new papers (from two cohort studies) [12-14], giving a total of eight studies (including studies from the SER). Overall, the CUP found four of six studies on pancreatic cancer incidence reported an increased risk for the highest intake group compared to the lowest, one of which was statistically significant. For pancreatic cancer mortality, one of two studies reported a non-significant increased risk. The other reported a non-significant decreased risk.

Seven studies (two new) were included in the dose-response meta-analyses for processed meat and pancreatic cancer (incidence and mortality combined). The CUP analyses were conducted per 50g/day compared to 20g/day in the SER. Overall, the analyses showed a 17% increased risk per 50g processed meat per day, and this was statistically significant (RR 1.17 (95% CI 1.01- 1.34)) (see CUP 2011 Figure 21). No heterogeneity was observed compared to high heterogeneity in the SER (I^2= 0 vs. 63%). In the SER, there was limited and inconclusive evidence for an association based on three cohort studies (incidence only) (RR 0.93 (95% CI 0.82-1.05)).

In the CUP, when stratified by sex, the effect was significant in men but not in women (RRs 1.21 (95% CI 1.01-1.45) and 1.09 (95% CI 0.69-1.73) respectively)) (see CUP 2011 Figure 23). There was no indication of publication bias and no evidence of significant heterogeneity in the analyses overall, although study results in women were inconsistent with moderate heterogeneity (I^2= 43%).

Results from the CUP analysis are consistent with that from another published meta-analysis, which also found a statistically significant increased risk per 50g/day increase in processed meat consumption [16].

Epidemiological evidence evaluating the relation of nitrate and nitrite to pancreatic cancer risk is limited and inconsistent [23-26].

Mechanisms

Human exposure to *N*-nitroso compounds through tobacco smoking is an established risk factor for pancreatic cancer [27]. Aside from tobacco smoking, humans are exposed to *N*-nitroso compounds mainly through intestinal absorption of dietary sources, which can be ingested preformed or endogenously produced. *N*-nitrosoamines form in foods containing protein that are preserved with nitrite (cured, smoked or pickled) or dried at high temperatures [27]. *N*-nitroso compounds can be further formed in the stomach from nitrite and ingested amides in foods of animal origin [28], and importantly, are α-hydroxylated to their proximate reactive forms in hepatocytes and pancreatic ductal epithelium and acini. These reach the pancreas via the bloodstream and are potent carcinogens that can induce pancreatic cancer in animal models [27].

Update: As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see Exposures: Meat, fish and dairy products *(Appendix – Mechanisms) for the updated mechanisms summary.*

CUP Panel's conclusion:

The evidence for processed meat and pancreatic cancer risk remains limited but is now stronger with more studies included in the CUP analysis, and no heterogeneity compared to the SER. In the SER, the Panel judged the evidence as too limited to draw a conclusion. In the CUP, a statistically significant positive association was observed and is supported by results from another published meta-analysis, which also found a significant positive association. Overall the evidence is limited, but suggests that processed meat increases risk of pancreatic cancer.

The CUP Panel concluded the following:

> **The evidence is inconsistent. The evidence suggesting that processed meat is a cause of pancreatic cancer is limited.**

7.3 Foods containing total fat and saturated fatty acids

(Also see CUP Pancreatic Cancer SLR 2011: Sections 5.2.1 and 5.2.2)

The CUP identified four new papers (from four cohort studies) [12, 29-31], giving a total of six studies. Overall, the CUP found four of six studies on pancreatic cancer incidence showed an increased risk of pancreatic cancer when comparing the highest versus lowest intakes of saturated fatty acids, one of which was significant. Two studies reported a non-significant decreased risk.

Five studies (four new) were included in the dose-response meta-analyses for saturated fatty acids and pancreatic cancer incidence. Overall, the CUP analysis found an 11% statistically significant increased risk of pancreatic cancer per 10g saturated fatty acids per day (RR 1.11 (95% CI 1.01-1.21)) with moderate heterogeneity observed (see CUP 2011 Figure 130). A non- significant increased risk was previously reported in the SER (RR 1.08 (95% CI 0.89-1.31) and the SER Panel judged the evidence too limited to draw a conclusion.

The CUP meta-analysis for total fat intake (including 8 studies) (see CUP 2011 Section 5.2.1) showed a marginally significant positive association (RR 1.05 (95% CI 1.00-1.12), with no evidence of heterogeneity. However, the evidence for total fat intake is limited and inconsistent, with four of seven studies reporting a non-significant decreased risk when comparing the highest intakes versus the lowest, and three reporting an increased risk (two of which were significant).

Mechanisms

The involvement of total dietary fat in pancreatic carcinogenesis through promotion of tumour formation in animal models is well established [32] and several mechanisms have been suggested to play a role. In animal models, pancreatic hypertrophy or hyperplasia can result from long-term exposure to large amounts of free fatty acids, which in turn causes the pancreas to become more vulnerable to carcinogens and lead to uncontrolled growth of abnormal cells [33].

In addition, it is suggested that increased bile acids may promote pancreatic cancer [34]. Higher intake of fat may stimulate bile acid secretion into the pancreatic duct and in turn stimulate the tumour promoter cyclooxygenase-2 (COX-2). Expression of COX-2 is greater in pancreatic cancer patients, and both conjugated and unconjugated bile acids induce COX-2 in pancreatic cancer cell lines [34].

Saturated fatty acids have been linked with insulin resistance in several randomised controlled trials, and diabetes or insulin resistance may be associated with pancreatic cancer via metabolic, immunological and hormonal alterations in the body [33].

Update: As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see Exposures: Other dietary exposures (Appendix – Mechanisms) for the updated mechanisms summary.

CUP Panel's conclusion:

Overall the evidence on saturated fatty acids and pancreatic cancer risk is limited and inconsistent. However, a significant positive association was observed compared to the non- significant positive association observed in the SER. A marginally significant positive association was observed for total fat intake, although generally the evidence is limited and inconsistent. It is not clear whether total fat intake has any effect independent of the association with saturated fatty acids.

The CUP Panel therefore concludes for foods containing saturated fatty acids:

> **The evidence is limited and inconsistent. The evidence suggesting that intake of saturated fatty acids is a cause of pancreatic cancer is limited. It is uncertain whether total fat intake has any independent effect.**

7.4 Coffee

(Also see CUP Pancreatic Cancer SLR 2011: Section 3.6.1)

Note: In 2012, the Panel made a judgement on coffee consumption and the risk of pancreatic cancer. The Panel has since reviewed the evidence further and updated their conclusion to ensure consistency across the Third Expert Report.

The CUP identified two new papers (from two cohort studies) [35, 36], giving a total of 20 studies. Overall, the CUP found eight of 12 studies on pancreatic cancer incidence showed a decreased risk when comparing the highest versus lowest intakes of coffee (one of which was significant) and four reported an increased risk (two of which were significant). For pancreatic cancer mortality, three of five studies showed a decreased risk (one of which was significant) when comparing highest versus lowest intakes and two showed a non-significant increased risk.

A total of 13 studies (two new) were included in the dose-response meta-analyses. The CUP analysis found an overall small positive association between coffee and pancreatic cancer (incidence and mortality combined) but this was not significant (RR 1.02 (95% CI 0.95-1.09) and (see CUP 2011 Figure 53). This finding is similar to that reported in the SER (RR 1.00 (95% CI 0.94-1.07). When stratified by outcome, meta-analysis on three studies reporting on mortality showed a slight non-significant decreased risk (RR 0.99 (95% CI 0.76-1.28), but the summary estimate for studies on incidence only was similar to the overall estimate (RR 1.03 (95% CI 0.95- 1.11).

Published pooled analyses

Results from one pooled analysis have been published [37], reporting no significant association between coffee and pancreatic cancer risk. The results are presented in **Table 1**.

Table 1: Summary of pooled analyses and CUP meta-analyses – Coffee

		RR (95% CI)	I^2	No. Studies	No. Cases	Factors adjusted for
CUP 2011	Per 240ml/d	1.02 (0.95-1.09)	29	13	1460	
Harvard Pooling Project [37]	Per 237g/d	1.01 (0.97-1.04)	38	11	1595	Smoking status, alcohol intake, diabetes, BMI and energy intake

Overall, the evidence for coffee and risk of pancreatic cancer was inconsistent with studies identified by the CUP showing both positive and inverse associations. The dose-response meta-analysis found no significant association. Results from the Harvard Pooling Project also showed no significant association.

> For coffee and risk of pancreatic cancer, the evidence for an association was considered to be limited and no conclusion was possible.

7.5 Alcoholic drinks

(Also see CUP Pancreatic Cancer SLR 2011: Sections 3.7.1 and 5.4)

The evidence for total alcoholic drinks and alcohol (as ethanol) is presented in the following section, and is followed by an overall conclusion that incorporates both these exposures.

Total alcohol drinks

The CUP identified four new papers (from three cohort studies) [38-41], giving a total of nine studies (including studies from the SER). Overall, the CUP found five of six studies on pancreatic cancer incidence showed an increased risk of pancreatic cancer when comparing the highest versus lowest consumers, one of which was significant. For studies of pancreatic cancer mortality, all three studies showed an increased risk, two of which were significant.

Six studies (three new) were included in the dose-response meta-analyses for total alcoholic drinks and pancreatic cancer (incidence and mortality combined). The CUP analyses were conducted per drink/week. Overall, the CUP analyses found no clear association between total alcoholic drinks and pancreatic cancer risk (RR 1.00 (95% CI 0.99-1.01)) (see CUP 2011 Figure 64). In the SER, a marginally significant decreased risk was observed (RR 0.98 (95% CI 0.97- 0.99)). In the CUP analyses, high heterogeneity was observed overall (I^2= 93 vs. 0% in the SER), most likely explained by one small study in men [42] that reported a strong positive association. There was evidence of a nonlinear association between total alcoholic drinks and pancreatic cancer risk, but this was only significant for those consuming 17.6 or more drinks per week (see CUP 2011 Figure 69 and Table 62).

In a stratified analysis by sex (for incidence and mortality combined), there was no clear association in women (RR 1.00 (95% CI 0.98-1.01)), but in men there was a marginally significant increased risk (RR 1.01 (95% CI 1.00-1.02)) (see CUP 2011 Figure 67).

A published meta-analysis [43] reported an overall significant inverse association of low to moderate alcohol intake (<3 drinks/day) and pancreatic cancer risk (RR 0.92 (95% CI: 0.86– 0.97) and a significant increased association for higher levels of alcohol intake (RR 1.22 (95% CI: 1.12–1.34) compared with non-drinking. This meta-analysis included studies that reported on alcoholic drinks and on ethanol from alcoholic drinks. A pooled analysis of the PanScan project investigated ethanol from alcoholic drinks (see below).

Alcohol (as ethanol)

The CUP identified four new papers (from four cohort studies) [31, 40, 44, 45], giving a total of 10 studies (including studies from the SER). All studies reported pancreatic cancer incidence. Overall, the CUP found five of nine studies showed an increased risk of pancreatic cancer when comparing the highest versus lowest consumers, two of which were significant. Three studies reported a non-significant decreased risk. One study reported no effect.

Nine studies (four new) were included in the dose-response meta-analyses for alcohol (as ethanol) and pancreatic cancer. Overall, the CUP analyses found no clear linear association between alcohol (as ethanol) (per 10g a day) and pancreatic cancer risk (RR 1.00 (95% CI 0.99- 1.01)) with no heterogeneity observed (see CUP 2011 Figure 149). This is similar to that reported in the SER (RR 1.00 (95% CI 0.98-1.02)). A summary estimate from a highest versus lowest comparison did result in a statistically significant increased risk (RR 1.30 (95% CI 1.09-1.54)). There was also evidence of a nonlinear association between alcohol (as ethanol) and pancreatic cancer risk. The risk was significant for those consuming 53.4g ethanol or more a day (see CUP 2011 Figure 153 and Table 132).

In a stratified analysis by sex, a non-significant increased risk in men and a non-significant decreased risk in women were observed (RRs 1.02 (95% CI 0.99-1.04) and 0.99 (95% CI 0.95- 1.02) respectively) (see CUP 2011 Figure 152), and in a separate analysis stratified by smoking, the summary estimates were similar to the overall finding (see CUP 2011 Table 130).

Published pooled analyses

Results from two separate pooled analyses on alcohol (as ethanol) and pancreatic cancer risk have been published [46, 47]. In the PanScan [46], no overall significant association was observed between total alcohol (ethanol) intake and pancreatic cancer risk for 60g/d vs 0- 5g/day, although a statistically significant increase in risk was observed among men consuming 45 or more grams of alcohol from liquor per day. Similar to the CUP finding for the highest versus lowest categories, the Harvard Pooling Project [47] found a statistically significant increased risk for 30g or more per day vs no alcohol. Only three single studies were included in all three analyses. In a CUP sensitivity analysis, adding in studies from PanScan and Harvard pooling projects, a statistically significant increased risk was observed (see CUP 2011 Figure 155). The results are presented in **Table 2**.

Table 2: Summary of pooled analyses and CUP meta-analyses– Alcohol (as ethanol)

Analysis	Contrast	RR (95% CI)	I²	No. Studies	No. Cases	Factors adjusted for
CUP 2011	Per 10g/d	1.00 (0.99-1.01)	0	9	3096	
CUP 2011	Highest vs. lowest	1.30 (1.09-1.54)		9	3096	
CUP Sensitivity analysis	Highest vs. lowest	1.29 (1.13-1.48)		25	4795	
PanScan [46]	>60g/d vs. 0-5g/d	1.38 (0.86-2.23)		12	1530	Smoking status, diabetes, BMI, and energy intake
Harvard Pooling Project [47]	>30g/d vs.0g/d	1.22 (1.03-1.45)		14	2187	Smoking status, diabetes,BMI and energy intake

Mechanisms

Alcohol (ethanol) is classified as a Group 1 carcinogen [48]. It is thought that ethanol metabolites, such as acetaldehyde, might be more important carcinogens [49]. The risk of pancreatic cancer may be increased with heavy alcohol consumption via mechanisms that promote the effects of other risk factors such as tobacco smoking. Heavy alcohol consumption may also alter metabolic pathways involved in the inflammatory response and carcinogenesis, for example increased production of reactive oxygen species resulting in oxidative DNA damage, and dysregulation of proliferation and apoptosis, and there may also be other independent genetic and epigenetic effects [49, 50].

Update: As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see Exposures: Alcoholic drinks (Appendix – Mechanisms) for the updated mechanisms summary.

CUP Panel's conclusion:

Overall, findings are similar to that reported in the SER, with no clear linear association between alcohol and risk of pancreatic cancer. However, dose-response analyses revealed a suggestion of an increased risk in heavier drinkers (more than about 3 drinks/day).

The CUP Panel concluded the following:

> **There is ample evidence, but this is inconsistent across the range of intakes. At higher levels of consumption, there is evidence of an increased risk of pancreatic cancer. There is limited evidence of a nonlinear association between alcohol and pancreatic cancer, suggesting an increased risk limited to those consuming more than about 3 drinks a day.**

7.6 Foods and beverages containing fructose

(Also see CUP Pancreatic Cancer SLR 2011: Sections 5.1.4)

The CUP identified five new papers (from five cohort studies) [51-55], giving a total of seven studies (including studies from the SER). Overall, the CUP found five of seven studies on pancreatic cancer incidence showed an increased risk of pancreatic cancer when comparing the highest versus lowest intakes of fructose, two of which were significant. One study reported a non-significant decreased risk and one reported no effect.

Six studies (four new) were included in the dose-response meta-analyses for foods and beverages containing fructose and pancreatic cancer incidence. Overall, the CUP analysis found a 22% statistically significant increased risk of pancreatic cancer per 25g fructose per day (RR 1.22 (95% CI 1.08-1.37)) with no heterogeneity observed (see CUP 2011 Figure 97). No differences were observed between men and women. No meta-analysis was conducted in the SER. Of the two studies identified in the SER, one reported a non-significant positive association and one reported no effect. The SER Panel judged the evidence too limited to draw a conclusion.

For other related exposures (total carbohydrate, sucrose and soft drinks) there were no clear associations with pancreatic cancer risk and the CUP Panel judged the evidence too limited to draw any conclusions (see CUP 2011 SLR Sections 5.1, 5.1.4 and 3.4).

Mechanisms

Fructose is known to increase postprandial plasma glucose levels, which may have a direct effect on pancreatic cancer risk, given that glucose intolerance and insulin resistance are related to pancreatic cancer [56]. Fructose has also been shown to contribute directly to oxidative stress in hamster islet tumour cells, by inhibiting glutathione peroxidase activity [57]. Metabolism of glucose and fructose are different, and cancer cells readily metabolise fructose to increase cell proliferation. Fructose induces thiamine-dependent transketolase flux and is preferentially used in the non-oxidative pentose phosphate pathway to produce nucleotides essential for DNA synthesis and cell proliferation [58].

Update: As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see Exposures: Other dietary exposures (Appendix – Mechanisms) for the updated mechanisms summary.

More evidence was available for the CUP analysis and the evidence is generally consistent. Overall a significant positive association was observed between fructose intake and pancreatic cancer risk, and there was no heterogeneity. However, fructose comes from many sources (e.g. soft drinks, fruit juices and sucrose), which may differ between population groups, and makes it difficult to interpret. It is also unclear whether fructose may be acting as a marker for other linked exposures.

The CUP Panel concluded the following:

> **Although there is ample evidence, which is generally consistent and there is some evidence for a dose-response relationship, fructose comes from many sources making the evidence difficult to interpret. The evidence suggesting that foods and beverages containing fructose are a cause of pancreatic cancer is limited.**

7.7 Body fatness

(Also see CUP Pancreatic Cancer SLR 2011: Sections 8.1.1, 8.1.6, 8.2.1 and 8.2.3)

The Panel interpreted body mass index (BMI), measures of abdominal girth, and adult weight gain as indicating interrelated aspects of body fatness and fat distribution. Anthropometric measures are imperfect and cannot distinguish reliably between lean and fat, between total and abdominal fat, or between visceral and subcutaneous fat. Increases in body weight during adulthood depend on accumulation of fat more than lean tissue, and therefore any change may better reflect fatness than adult weight itself, which is more dependent on lean mass.

The evidence for BMI, weight gain (including increase in BMI), waist circumference and waist-to- hip ratio is presented in the following section, and is followed by an overall conclusion that incorporates all these exposures.

Body mass index (BMI)

The CUP identified 23 new papers (from 17 cohort studies) [31, 39, 41, 59-79] giving a total of 30 studies (including studies from the SER). Overall, the CUP found 19 of 23 studies on pancreatic cancer incidence, and four of seven studies on pancreatic cancer mortality, showed an increased risk for the highest BMI groups compared to the lowest.

Dose-response meta-analyses for pancreatic cancer incidence and mortality were conducted separately. A total of 23 studies (12 of which were new) were included in the dose-response meta-analysis for BMI and pancreatic cancer incidence, and seven studies (five of which were new) were included in the dose-response meta-analysis of BMI and pancreatic cancer mortality.

The analyses showed, for both incidence and mortality separately, a 10% statistically significant increased risk per 5 BMI units (RRs 1.10 (95% CI 1.07-1.14) and 1.10 (95% CI 1.02-1.19) respectively)) (see CUP 2011 Figures 181 and 188). With more studies

and lower heterogeneity (I²= 23 vs. 51%), this is consistent with the finding from the SER, which gave an estimate for incidence and mortality combined (RR 1.14 (95% CI 1.07-1.22)). No differences were observed between men and women. There was evidence of a nonlinear dose-response with an increased risk apparent for BMI of 25 kg/m2 or more (see CUP 2011 Figures 185 and 191).

Published pooled analyses

Results from four separate pooled analyses on BMI and pancreatic cancer risk have been published [80-83], three of which are consistent with the CUP findings [80-82] (results from the PanScan only gave an estimate for the highest versus lowest categories). The fourth pooled analysis of studies in the Asia-Pacific Cohort Studies Collaboration was not consistent with the CUP result, but had fewer cases than the other pooled analyses and CUP meta-analysis. These results are presented in **Table 3** with the CUP result for pancreatic cancer incidence.

Table 3: Summary of pooled analyses and CUP meta- analyses - BMI

Analysis	Contrast	RR (95% CI)	I²	No. Studies	No. Cases	Factors adjusted for
CUP 2011	Per 5 units	1.10 (1.07-1.14)	19	23	9504	
Harvard Pooling Project [80]	Per 5 units	1.14 (1.07-1.21)		14	2135	Smoking status, diabetes, alcohol, energy intake
NCI pooled analysis [82]	Per 5 units	1.08 (1.03-1.14)	0	7	2454	Age, sex, cohort, smoking status
Asia-Pacific cohort studies collaboration [83]	Per 5 units	1.08 (1.03-1.14)		39	301	Age, smoking status
PanScan [81]*	BMI>35 vs. 18.5-24.9kg/m²	1.55 (1.16-2.07)**		13	2095	Cohort, age, sex, anthropometric factor source (self-reported or measured), smoking status

* Includes 12 cohort studies and 1 case-control study.
** This was attenuated when adjusting for history of diabetes mellitus (RR 1.26 (95% CI 0.93-1.71)).

Weight change (including an increase in BMI)

The CUP identified three new papers on weight change [64, 70, 72], and one on change in BMI [84], giving a total of nine studies (including studies from the SER). None of these studies reported a statistically significant association. Meta-analysis was not possible because weight change was reported inconsistently.

Published pooled analyses

The result from one pooled analysis on increase in BMI and pancreatic cancer risk has been published [80], reporting a statistically significant increased risk with increasing BMI from <25 in early adulthood to >30 at recruitment (RR 1.38 (95% CI 1.14-1.66)). This adjusted for smoking status, diabetes, alcohol intake and energy intake.

Waist circumference

The CUP identified three new papers (from 3 cohort studies) [68, 70, 76], giving a total of five studies (including studies from the SER). All five studies reported on pancreatic cancer incidence and showed a non-significant increased risk when comparing the highest versus lowest groups for waist circumference.

All five studies were included in the CUP meta-analysis. The CUP analysis was conducted per 10cm compared to per 1cm in the SER. The meta-analysis showed an 11% statistically significant increased risk per 10cm (RR 1.11 (95% CI 1.05-1.18)) with no heterogeneity (see CUP 2011 Figure 201). In a stratified analysis, the effect was statistically significant in women, but not in men (RRs 1.14 (95% CI 1.02-1.28) and 1.13 (95% CI 0.89-1.44) respectively) (see CUP 2011 Figure 204). The risk estimate for the SER was a 2% increased risk per 1cm (RR 1.02 (95% CI 1.00-1.04)) (this approximately equates to a 20% increased risk per 10cm).

Published pooled analyses

Results from two separate pooled analyses on waist circumference and pancreatic cancer risk have been published [80, 81]. Both analyses reported positive associations when comparing the highest versus lowest categories, but these were not statistically significant. However, the PanScan [81] reported a statistically significant positive trend with greater waist circumference (p_{trend}= 0.04). No single study was included in all three analyses. These results are presented in **Table 4**

Table 4: Summary of pooled analyses and CUP meta- analyses – Waist circumference

Analysis	Contrast	RR (95% CI)	I²	No. Studies	No. Cases	Factors adjusted for
CUP 2011	Per 10cm	1.11 (1.05-1.18)	0	5	949	
Harvard Pooling Project [80]	Highest vs. lowest	1.16 (0.92-1.46)	10	7	743	Smoking status, diabetes, alcohol intake, energy intake
	Highest vs. lowest (additionally adjusted for BMI)	1.04 (0.73-1.47)	26			
PanScan [81]*	Highest vs. lowest	1.23 (0.94-1.62) **p$_{trend}$ = 0.04		6	812	Cohort, age, sex, anthropometric factor source (self-reported or measured), smoking status and height

* Includes 12 cohort studies and 1 case-control study.
** There was no difference when adjusting for diabetes mellitus history (RR 1.21 (95% CI 0.91-1.60)).

Waist-hip ratio

The CUP identified three new papers (from three cohort studies) [68, 70, 76], giving a total of four studies (including studies from the SER). All four studies reported on pancreatic cancer incidence and showed a non-significant increased risk when comparing the highest versus lowest groups for waist-hip ratio.

All four studies were included in the CUP meta-analysis. The meta-analysis showed a 19% statistically significant increased risk per 0.1 units (RR 1.19 ((95% CI 1.09-1.31)) with little heterogeneity (I² = 11%) (see CUP 2011 Figure 211). No meta-analysis was conducted in the SER.

Published pooled analyses

Results from two separate pooled analyses on waist-hip ratio and pancreatic cancer risk have been published [80, 81]. Both reported statistically significant positive associations for the highest versus lowest categories, and results are presented in **Table 5** with the CUP result. No single study was included in all three analyses.

Table 5: Summary of pooled analyses and CUP meta-analyses – Waist-hip ratio

Analysis	Contrast	RR (95% CI)	I²	No. Studies	No. Cases	Factors adjusted for
CUP 2011	Per 0.1 units	1.19 (1.09-1.31)	11	4	1047	
Harvard Pooling Project [80]	Highest vs. lowest	1.35 (1.03-1.78)	0	6	552	Smoking status, diabetes, alcohol intake, energy intake
	Highest vs. lowest (additionally adjusted for BMI)	1.34 (1.00-1.79)	0			
PanScan [81]*	Highest vs. lowest	1.71 (1.27-2.30)**		6	750	Cohort, age, sex, anthropometric factor source (self-reported or measured), smoking status and height

* Includes 12 cohort studies and 1 case-control study.
** There was no difference when adjusting for diabetes mellitus history (RR 1.69 (95% CI 1.24-2.30)).

Mechanisms

It is biologically plausible that body fatness is a cause of pancreatic cancer. There is an established connection between increasing BMI or body fatness and insulin resistance and diabetes. The risk of this cancer is increased in people with insulin resistance or diabetes. It also directly affects levels of many circulating hormones, such as insulin, insulin-like growth factors, and oestrogens, creating an environment that encourages carcinogenesis and discourages apoptosis. Body fatness stimulates the inflammatory response, which may contribute to the initiation and progression of several cancers.

Obesity influences the levels of a number of hormones and growth factors [85]. Insulin-like growth factor 1 (IGF-1), insulin, and leptin are all elevated in obese people, and can promote the growth of cancer cells. In addition, insulin resistance is increased, in particular by abdominal fatness, and the pancreas compensates by increasing insulin production. This hyperinsulinaemia increases the risk of cancers of the colon and endometrium, and possibly of the pancreas and kidney [86].

Obesity is characterised by a low-grade chronic inflammatory state, with up to 40 per cent of fat tissue comprising macrophages. The adipocyte (fat cell) produces pro-inflammatory factors, and obese individuals have elevated concentrations of circulating tumour necrosis factor (TNF)-alpha [86] interleukin (IL)-6, and C-reactive protein, compared with lean people [87], as well as of leptin, which also functions as an inflammatory cytokine [88]. Such chronic inflammation can promote cancer development.

Update: As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see Exposures: Body fatness and weight gain (Appendix – Mechanisms) for the updated mechanisms summary.

CUP Panel's conclusion:

The SER Panel judged the evidence that greater body fatness (as BMI) is a cause of pancreatic cancer as convincing, and that abdominal fatness (incorporating waist circumference and waist-to-hip ratio) is a probable cause of pancreatic cancer.

Overall the evidence from the CUP for an association between body fatness (which the CUP Panel interprets to be reflected by BMI, measures of abdominal girth and weight gain) is stronger, with more studies available than the SER, and results from several pooled analyses generally consistent with the CUP findings. The evidence for abdominal fatness and weight gain is less robust than that where BMI is used as the measure of body fatness, but supports the evidence for an association between overall body fatness and pancreatic cancer risk.

The CUP Panel concluded the following:

> **Body fatness is reflected by BMI, measures of abdominal girth, and adult weight gain. There is ample evidence for an association between various measures of body fatness and pancreatic cancer incidence and mortality. The evidence is generally consistent, and there is a dose- response relationship. There is evidence for plausible mechanisms that operate in humans. The evidence that greater body fatness, including abdominal fatness and adult weight gain, is a cause of pancreatic cancer is convincing.**

7.8 Adult attained height

(Also see CUP Pancreatic Cancer SLR 2011: Section 8.3.1)

Note: In 2012, the Panel made a judgement on 'greater childhood growth' and the risk of pancreatic cancer, drawing on evidence on both 'adult attained height' and 'BMI at aged ~20 years'. The Panel has since reviewed the evidence further and made a conclusion on 'adult attained height' to ensure consistency across the Third Expert Report. See also Exposures: Height and birthweight.

The CUP identified 12 new papers (from 8 cohort studies) [31, 39, 66, 70, 76, 84, 89-94], giving a total of 14 studies (including studies from the SER). Overall, the evidence was generally consistent with eight of 10 studies on pancreatic cancer incidence showing an increased risk (three of which were statistically significant) and one study on pancreatic cancer mortality showing a non-significant increased risk when comparing the highest versus lowest groups.

Ten studies (seven of which were new) were included in the dose-response meta-analysis for height and pancreatic cancer (incidence and mortality combined). The meta-analysis showed a 7% statistically significant increased risk per 5cm (RR 1.07 (95% CI 1.03-

1.12)) with considerably greater heterogeneity observed compared with the SER (I^2= 57 vs. 8%), which could be due to one study [70] reporting a risk in the opposite direction (see CUP 2011 Figure 216). The CUP analysis included more studies. The summary estimate is consistent with the SER, which reported an 11% statistically significant increased risk per 5cm (RR 1.11 (95% CI 1.05-1.17)).

Stratified analyses for the risk of pancreatic cancer per 5 centimetres increase in height were conducted for sex; a statistically significant increased risk was observed in men (RR 1.07 95% CI 1.01–1.14), but not women (RR 1.07 95% CI 0.99-1.15; see CUP pancreatic cancer SLR 2011, Figure 219).

There was no evidence of a non-linear dose-response relationship (p = 0.14).

Published pooled analyses

Results from three separate pooled analyses on height and pancreatic cancer risk have been published [80, 81, 83], none of which found a statistically significant association, in contrast to the CUP. However, the CUP included several large cohort studies that were not included in the pooled analyses, and had 2-3 times as many cases. This may have provided more statistical power to detect a modest association. Only three of the same studies were included in all three pooled analyses. The results are presented in **Table 6**.

Table 6: Summary of pooled analyses and CUP meta- analyses - Height

Analysis	Contrast	RR (95% CI)	I²	No. Studies	No. Cases	Factors adjusted for
CUP 2011	Per 5cm	1.07 (1.03-1.12)	57	10	6147	
Harvard Pooling Project [80]	>180 vs. <170cm Men	1.18 (0.93-1.49)	11	14	1019 (M) 1115 (F)	Smoking status, diabetes, alcohol intake, energy intake
	>180 vs. <170cm Men (adjusted for BMI)	1.20 (0.96-1.51)	9			
	>170 vs. <160cm Women	1.03 (0.84-1.25)	0			
	>170 vs. <160cm Women (adjusted for BMI)	1.06 (0.87-1.29)	1			
PanScan [81]*	Highest vs. lowest	0.99 (0.83-1.18)		13	2095	Cohort, age, sex, anthropometric factor source and smoking status
Asia-Pacific cohort studies collaboration [83]	Per 6cm Men	1.08 (0.94-1.24)		38	294	Age, study and year of birth
	Per 6cm Women	0.99 (0.82-1.21)				

* Includes 12 cohort studies and 1 case-control study.

Mechanisms

Factors that lead to greater adult attained height, or its consequences, are a cause of a number of cancers. Adult height is related to the rate of growth during fetal life and childhood. The number of cell divisions in fetal life and childhood, health and nutrition status in childhood, and age of sexual maturity can alter the hormonal microenvironment, and affect circulating levels of growth factors, insulin, and oestrogens. Taller people have undergone more cell divisions stimulated by IGF-1 and pituitary derived growth hormone [95], and there is therefore more potential for error during DNA replication, which may result in cancer development.

Update: As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see Exposures: Height and birthweight (Appendix – Mechanisms) for the updated mechanisms summary.

CUP Panel's conclusion:

The SER Panel judged the evidence that factors leading to greater adult attained height, or its consequences, are probably a cause of pancreatic cancer.

The evidence was generally consistent and the CUP dose-response meta-analysis showed a statistically significant increased risk of pancreatic cancer with increasing height. High heterogeneity was observed, which seemed to be due to one study reporting a decreased rather than an increased risk. When stratified by sex, the statistically significant increase in risk remained for men, but not women. There was no evidence of a non-linear dose-response relationship. Three published pooled analyses reported no significant increase or decrease in risk. There is also evidence of plausible mechanisms operating in humans.

The CUP Panel concluded:

> **Developmental factors that lead to greater growth in length in childhood (marked by adult attained height) are a probable cause of pancreatic cancer.**

7.9 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.

The evidence that foods containing folate protect against pancreatic cancer risk is weak. More studies were available for the CUP analysis, but summary estimates were not significant in contrast to the SER, which found a marginally significant association for dietary folate. Higher heterogeneity was observed overall in the CUP. Results from the Harvard Pooling Project strengthen the null association. Overall, the Panel concluded the evidence is too inconsistent to allow a conclusion to be drawn (see CUP Pancreatic Cancer SLR 2011: Section 5.5.3).

The evidence for a protective effect of fruits and physical activity is also weak and the evidence failed to demonstrate a significant association for either exposure. Overall, the Panel concluded the evidence for fruits and for physical activity is too limited and inconsistent to allow a conclusion to be reached (see CUP Pancreatic Cancer SLR 2011: Sections 2.2.2 and 6).

Evidence for the following exposures previously judged as 'limited-no conclusion' in the SER, remain unchanged: Fish, eggs, vegetables, tea, total dietary fat, dietary cholesterol, carbohydrates, sucrose, and vitamin C.

In addition, evidence for the following exposures, for which no judgement was made in the SER, is too limited to draw any conclusions: Soft drinks (including diet soft drinks and fruit juice), monounsaturated fat, polyunsaturated fats (including linolenic and linoleic acid), glycaemic index, glycaemic load, and multivitamin/mineral supplements.

8. Comparison with the Second Expert Report

Overall, the evidence from the additional cohort studies identified in the CUP was consistent with those reviewed as part of the SER for exposures graded convincing or probable. The CUP Panel grouped several individual anthropometric exposures to reflect 'body fatness' (BMI, measures of abdominal girth and adult weight gain), where previously these exposures were judged individually in the SER. The Panel also combined two exposures under 'greater childhood growth' to reflect factors relating to development and maturation that influence later risk of cancer. These include BMI in early adulthood (at aged ~20 years), and factors leading to adult attained height. In the SER, an individual judgement was made for adult attained height, and no judgement was made for BMI at aged ~20 years.

The evidence for a protective effect of fruits, foods containing folate, and physical activity, has weakened, and the Panel could not draw any conclusions on the updated evidence. The evidence for higher consumers of alcoholic drinks has strengthened, and is suggestive of a causal effect in this group (for those consuming more than approximately 3 drinks per day).

More data for additional exposures was available for inclusion in the CUP analyses. New exposures for which the Panel could make a judgement with regard to risk of pancreatic cancer, included processed meat, foods containing saturated fatty acids, and foods and beverages containing fructose, all of which there was limited evidence suggesting a causal effect.

9. Conclusions

The CUP Panel concluded the following:

Convincing evidence

Body fatness: Greater body fatness is a convincing cause of pancreatic cancer.

Probable evidence

Adult attained height: Developmental factors leading to greater linear growth, marked by adult attained height, are probably a cause of pancreatic cancer.

Limited - suggestive evidence

Red meat: The evidence suggesting consumption of red meat increases the risk of pancreatic cancer is limited.

Processed meat: The evidence suggesting consumption of processed meat increases the risk of pancreatic cancer is limited.

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

Alcoholic drinks: The evidence suggesting consumption of alcoholic drinks increases the risk of pancreatic cancer is limited.

Foods and beverages containing fructose: The evidence suggesting consumption of foods and beverages containing fructose increase the risk of pancreatic cancer is limited.

Note: In 2012, the Panel made a judgement on coffee consumption and the risk of pancreatic cancer. The Panel has since reviewed the evidence further and updated their conclusion to ensure consistency across the Third Expert Report. For consumption of coffee and risk of pancreatic cancer, the evidence for an association was considered to be limited and no conclusion was possible.

The Cancer Prevention Recommendations were reviewed by the CUP Panel and published in 2018. Please see Recommendations and public health and policy implications for further details.

Each conclusion on the likely causal relationship between an exposure and the risk of cancer forms a part of the overall body of evidence that is considered during the process of making Cancer Prevention Recommendations. Any single conclusion does not represent a Recommendation in its own right. The 2018 Cancer Prevention Recommendations are based on a synthesis of all these separate conclusions, as well as other relevant evidence.

Abbreviations

AICR   American Institute for Cancer Research

BMI   body mass index

CI   confidence interval

CUP   Continuous Update Project

DNA   deoxyribonucleic acid

ER(+/-)   oestrogen-receptor (positive/negative)

IARC   International Agency for Research on Cancer

n   number of cases

PR(+/-)   progesterone-receptor (positive/negative)

RR   relative risk

SER   Second Expert Report 'Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective'

SD   standard deviation

SLR   systematic literature review

WCRF   World Cancer Research Fund

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References

1. World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective.* Washington DC: AICR, 2007. Available at **wcrf.org/about-the-report**

2. Ferlay J, Shin HR, Bray F *et al*. 'GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: **http://globocan.iarc.fr 2010**

3. Parkin DM, Whelan SL, Ferlay J *et al*. 'Cancer Incidence in Five Continents, Vol. I to VIII. Lyon: IARC 2005. International Agency for Research on Cancer. *Globocan* 2002. **http://wwwdep.iarc.fr/**. 2006.

4. Stewart BW and Kleihues P. 'World Cancer Report. Lyon: International Agency for Research on Cancer. 2003.

5. Howlader N, Noone AM, Krapcho M *et al*. 'SEER Cancer Statistics Review, 1975-2008, National Cancer Institute, Bethesda, MD, **http://seer.cancer.gov/csr/1975_2008/**. 2010.

6. Zalatnai A. 'Pancreatic cancer - a continuing challenge on oncology. Pathology Oncology Research, 2003; 9: 252-63.

7. Stolzenberg-Solomon RZ, Graubard BI, and Chari S. 'Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. *JAMA*, 2005; 294: 2872-8.

8. Li D, Xie K, Wolff R *et al*. 'Pancreatic cancer. *Lancet*, 2004; 363: 1049-57.

9. Secretan B, Straif K, Baan R *et al*. 'A review of human carcinogens–Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncol*, 2009; 10: 1033-4.

10. Lowenfels AB and Maisonneuve P. 'Epidemiology and risk factors for pancreatic cancer. *Best Pract Res Clin Gastroenterol*, 2006; 20: 197-209.

11. Inoue-Choi M, Flood A, Robien K *et al*. 'Nutrients, food groups, dietary patterns, and risk of pancreatic cancer in postmenopausal women. *Cancer Epidemiol Biomarkers Prev*, 2011; 20: 711-4.

12. Heinen MM, Verhage BA, Goldbohm RA *et al*. 'Meat and fat intake and pancreatic cancer risk in the Netherlands Cohort Study. *Int J Cancer*, 2009; 125: 1118-26.

13. Stolzenberg-Solomon RZ, Cross AJ, Silverman DT *et al*. 'Meat and meat-mutagen intake and pancreatic cancer risk in the NIH-AARP cohort. *Cancer Epidemiol Biomarkers Prev*, 2007; 16: 2664-75.

14. Cross AJ, Leitzmann MF, Gail MH *et al*. 'A prospective study of red and processed meat intake in relation to cancer risk. *PLoS Med*, 2007; 4: e325.

15. Paluszkiewicz P, Smolinska K, Debinska I *et al*. 'Main dietary compounds and pancreatic cancer risk. The quantitative analysis of case-control and cohort studies. *Cancer Epidemiol*, 2011.

16. Larsson SE and Wolk A. 'Red and processed meat consumption and risk of pancreatic cancer: meta-analysis of prospective studies. *Br J Cancer*, 2012; 106: 603-7.

17. Weinberg ED. 'The role of iron in cancer. *Eur J Cancer Prev*, 1996; 5: 19-36.

18. McCord JM. 'Iron, free radicals, and oxidative injury. *Semin Hematol*, 1998; 35: 5-12.

19. Huang X. 'Iron overload and its association with cancer risk in humans: evidence for iron as a carcinogenic metal. *Mutat Res*, 2003; 533: 153-71.

20. Lewin MH, Bailey N, Bandaletova T *et al*. 'Red meat enhances the colonic formation of the DNA adduct O6-carboxymethyl guanine: implications for colorectal cancer risk. *Cancer Res*, 2006; 66: 1859-65.

21. Sugimura T, Nagao M, and Wakabayashi K. 'Heterocyclic amines in cooked foods: candidates for causation of common cancers. *J Natl Cancer Inst*, 1994; 86: 2-4.

22. Anderson KE, Kadlubar FF, Kulldorff M *et al*. 'Dietary intake of heterocyclic amines and benzo(a) pyrene: associations with pancreatic cancer. *Cancer Epidemiol Biomarkers Prev*, 2005; 14: 2261-5.

23. Aschebrook-Kilfoy B, Cross AJ, Stolzenberg-Solomon RZ *et al*. 'Pancreatic cancer and exposure to dietary nitrate and nitrite in the NIH-AARP Diet and Health Study. *Am J Epidemiol*, 2011; 174: 305-15.

24. Stolzenberg-Solomon RZ, Pietinen P, Taylor PR *et al*. 'Prospective study of diet and pancreatic male smokers. *Am J Epidemiol*, 2002; 155: 783-92.

25. Weyer PJ, Cerhan JR, Kross BC *et al*. 'Municipal drinking water nitrate level and cancer risk in older women: the Iowa Women's Health Study. *Epidemiology*, 2001; 12: 327-38.

26. Lin Y, Kikuchi S, Tamakoshi A *et al*. 'Dietary habits and pancreatic cancer risk in a cohort of middle-aged and elderly Japanese. *Nutrition and Cancer*, 2006; 56: 40-9.

27. Risch HA. 'Etiology of pancreatic cancer, with a hypothesis concerning the role of *N*-nitroso compounds and excess gastric acidity. *J Natl Cancer Inst* 2003; 95: 948-60.

28. Sen NP, Seaman SW, Burgess C *et al*. 'Investigation on the possible formation of *N- nitroso-N*-methylurea by nitrosation of creatine in model systems and in cured meats at gastric pH. *J Agric Food Chem*, 2000; 48: 5088-96.

29. Meinhold CL, Dodd KW, Jiao L *et al*. 'Available carbohydrates, glycemic load, and pancreatic cancer: is there a link? *Am. J. Epidemiol*., 2010; 171: 1174-82.

30. Thiebaut AC, Jiao L, Silverman DT *et al*. 'Dietary fatty acids and pancreatic cancer in the NIH-AARP diet and health study. *J Natl Cancer Inst*, 2009; 101: 1001-11.

31. Meinhold CL, Berrington de GA, Albanes D *et al*. 'Predictors of fasting serum insulin and glucose and the risk of pancreatic cancer in smokers. *Cancer Causes Control*, 2009; 20: 681-90.

32. Woutersen RA, Appel MJ, van Garderen-Hoetmer A *et al*. 'Dietary fat and carcinogenesis. *Mutat Res*, 1999; 443: 111-27.

33. Sanchez GV, Weinstein SJ, and Stolzenberg-Solomon RZ. 'Is dietary fat, vitamin D, or folate associated with pancreatic cancer? *Molecular Carcinogenesis*, 2012; 51: 119-27.

34. Tucker ON, Dannenberg AJ, Yang EK *et al*. 'Bile acids induce cyclooxygenase-2 expression in human pancreatic cancer cell lines. *Carcinogenesis*, 2004; 25: 419-23.

35. Nilsson LM, Johansson I, Lenner P *et al*. 'Consumption of filtered and boiled coffee and the risk of incident cancer: a prospective cohort study. *Cancer Causes Control*, 2010; 21: 1533-44.

36. Luo J, Inoue M, Iwasaki M *et al*. 'Green tea and coffee intake and risk of pancreatic cancer in a large-scale, population-based cohort study in Japan (JPHC study). *Eur J Cancer Prev*, 2007; 16: 542-8.

37. Genkinger J, Li R, Spiegelman D *et al*. 'Coffee, tea and sugar-sweetened carbonated soft drink intake and pancreatic cancer risk: a pooled analysis of 14 cohort studies. *Cancer Epidemiol Biomarkers Prev*, 2011.

38. Gapstur SM, Jacobs EJ, Deka A *et al*. 'Association of alcohol intake with pancreatic cancer mortality in never smokers. *Arch Intern Med*, 2011; 171: 444-51.

39. Stevens RJ, Roddam AW, Spencer EA *et al*. 'Factors associated with incident and fatal pancreatic cancer in a cohort of middle-aged women. *Int J Cancer*, 2009; 124: 2400-5.

40. Jiao L, Silverman DT, Schairer C *et al*. 'Alcohol use and risk of pancreatic cancer: the NIH- AARP Diet and Health Study. *Am J Epidemiol*, 2009; 169: 1043-51.

41. Jiao L, Mitrou PN, Reedy J *et al*. 'A combined healthy lifestyle score and risk of pancreatic cancer in a large cohort study. *Arch Intern Med*, 2009; 169: 764-70.

42. Zheng W, McLaughlin JK, Gridley G *et al*. 'A cohort study of smoking, alcohol consumption, and dietary factors for pancreatic cancer (United States). *Cancer Causes Control*, 1993; 4: 477-82.

43. Tramacere I, Scotti L, Jenab M *et al*. 'Alcohol drinking and pancreatic cancer risk: a meta- analysis of the dose-risk relation. *Int J Cancer*, 2010; 126: 1474-86.

44. Rohrmann S, Linseisen J, Vrieling A *et al*. 'Ethanol intake and the risk of pancreatic cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Cancer Causes Control*, 2009; 20: 785-94.

45. Heinen MM, Verhage BA, Ambergen TA *et al*. 'Alcohol consumption and risk of pancreatic cancer in the Netherlands cohort study. *Am. J. Epidemiol*., 2009; 169: 1233-42.

46. Michaud DS, Vrieling A, Jiao L *et al*. 'Alcohol intake and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium (PanScan). *Cancer Causes Control*, 2010; 21: 1213-25.

47. Genkinger JM, Spiegelman D, Anderson KE *et al*. 'Alcohol intake and pancreatic cancer risk: a pooled analysis of fourteen cohort studies. *Cancer Epidemiol Biomarkers Prev*, 2009; 18: 765-76.

48. Baan R, Grosse Y, Straif K *et al*. 'A review of human carcinogens-Part F: Chemical agents and related occupations. *Lancet Oncol*, 2009; 10: 1143-4.

49. Duell EJ. 'Epidemiology and potential mechanisms of tobacco smoking and heavy alcohol consumption in pancreatic cancer. *Molecular Carcinogenesis*, 2012; 51: 40-52.

50. Go VLW, Gukovskaya A, and Pandol SJ. 'Alcohol and pancreatic cancer. *Alcohol*, 2005; 35: 205-11.

51. Simon MS, Shikany JM, Neuhouser ML *et al*. 'Glycemic index, glycemic load, and the risk of pancreatic cancer among postmenopausal women in the women's health initiative observational study and clinical trial. *Cancer Causes Control*, 2010; 21: 2129-36.

52. Meinhold CL, Dodd KW, Jiao L *et al*. 'Available carbohydrates, glycemic load, and pancreatic cancer: is there a link? *Am J Epidemiol*, 2010; 171: 1174-82.

53. Jiao L, Flood A, Subar AF *et al*. 'Glycemic index, carbohydrates, glycemic load, and the risk of pancreatic cancer in a prospective cohort study. *Cancer Epidemiol Biomarkers Prev*, 2009; 18: 1144-51.

54. Patel AV, McCullough ML, Pavluck AL *et al*. 'Glycemic load, glycemic index, and carbohydrate intake in relation to pancreatic cancer risk in a large US cohort. *Cancer Causes Control*, 2007; 18: 287-94.

55. Nothlings U, Murphy S P, Wilkens LR *et al*. 'Dietary glycemic load, added sugars, and carbohydrates as risk factors for pancreatic cancer: the Multiethnic Cohort Study. *Am J Clin Nutr,* 2007; 86: 1495-501.

56. Michaud D, Liu S, Giovannucci E *et al*. 'Dietary sugar, glycaemic load and pancreatic cancer risk in a prospective study. *J Natl Cancer Inst*, 2002; 94: 1293-300.

57. Suzuki K, Islam KN, and Kaneto H. 'The contribution of fructose and nitric oxide to oxidatove stress in hamster islet tumor (HIT) cells through the inactivation of glutathione peroxidase. *Electrophoresis*, 2000; 21: 285-8.

58. Liu H, Huang D, and McArthur D. 'Fructose induces transketolase flux to promote pancreatic cancer growth. *Cancer Res*, 2010; 70: 6368.

59. Nakamura K, Nagata C, Wada K *et al*. 'Cigarette smoking and other lifestyle factors in relation to the risk of pancreatic cancer death: a prospective cohort study in Japan. *Jpn J Clin Oncol*, 2011; 41: 225-31.

60. Andreotti G, Freeman LE, Hou L *et al*. 'Agricultural pesticide use and pancreatic cancer risk in the Agricultural Health Study Cohort. *Int J Cancer*, 2009; 124: 2495-500.

61. Andreotti G, Hou L, Beane Freeman LE *et al*. 'Body mass index, agricultural pesticide ue, and cancer incidence in the Agricultural Health Study Cohort. *Cancer Causes Control*, 2010; 21: 1759-75.

62. Arnold LD, Patel AV, Yan Y *et al*. 'Are racial disparities in pancreatic cancer explained by smoking and overweight/obesity? *Cancer Epidemiol Biomarkers Prev*, 2009; 18: 2397- 405.

63. Batty GD, Kivimaki M, Morrison D *et al*. 'Risk factors for pancreatic cancer mortality: extended follow-up of the original Whitehall Study. *Cancer Epidemiol Biomarkers Prev*, 2009; 18: 673-5.

64. Johansen D, Borgstrom A, Lindkvist B *et al*. 'Different markers of alcohol consumption, smoking and body mass index in relation to risk of pancreatic cancer. A prospective cohort study within the Malmo Preventive Project. *Pancreatology*, 2009; 9: 677-86.

65. Inoue M, Noda M, Kurahashi N *et al*. 'Impact of metabolic factors on subsequent cancer risk: results from a large-scale population-based cohort study in Japan. *Eur J Cancer Prev*, 2009; 18: 240-7.

66. Berrington de GA, Yun JE, Lee SY *et al*. 'Pancreatic cancer and factors associated with the insulin resistance syndrome in the Korean cancer prevention study. *Cancer Epidemiol Biomarkers Prev*, 2008; 17: 359-64.

67. de Martel C, Llosa AE, Friedman GD *et al*. 'Helicobacter pylori infection and development of pancreatic cancer. *Cancer Epidemiol Biomarkers Prev*, 2008; 17: 1188-94.

68. Stolzenberg-Solomon RZ, Adams K, Leitzmann M *et al*. 'Adiposity, physical activity, and pancreatic cancer in the National Institutes of Health-AARP Diet and Health Cohort. *Am. J. Epidemiol.*, 2008; 167: 586-97.

69. Jee SH, Yun JE, Park EJ *et al*. 'Body mass index and cancer risk in Korean men and women. *Int J Cancer*, 2008; 123: 1892-6.

70. Luo J, Margolis KL, Adami HO *et al*. 'Obesity and risk of pancreatic cancer among postmenopausal women: the Women's Health Initiative (United States). Br J Cancer, 2008; 99: 527-31.

71. Verhage BA, Schouten LJ, Goldbohm RA *et al*. 'Anthropometry and pancreatic cancer risk: an illustration of the importance of microscopic verification. *Cancer Epidemiol Biomarkers Prev*, 2007; 16: 1449-54.

72. Lin Y, Kikuchi S, Tamakoshi A *et al*. 'Obesity, physical activity and the risk of pancreatic cancer in a large Japanese cohort. *Int J Cancer*, 2007; 120: 2665-71.

73. Luo J, Iwasaki M, Inoue M *et al*. 'Body mass index, physical activity and the risk of pancreatic cancer in relation to smoking status and history of diabetes: a large-scale population-based cohort study in Japan–the JPHC study. *Cancer Causes Control*, 2007; 18: 603-12.

74. Reeves GK, Pirie K, Beral V *et al*. 'Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ*, 2007; 335: 1134.

75. Nothlings U, Wilkens LR, Murphy SP *et al*. 'Body mass index and physical activity as risk factors for pancreatic cancer: the Multiethnic Cohort Study. *Cancer Causes Control*, 2007; 18: 165-75.

76. Berrington de GA, Spencer EA, Bueno-de-Mesquita HB *et al*. 'Anthropometry, physical activity, and the risk of pancreatic cancer in the European prospective investigation into cancer and nutrition. *Cancer Epidemiol Biomarkers Prev*, 2006; 15: 879-85.

77. Yun JE, Jo I, Park J *et al*. 'Cigarette smoking, elevated fasting serum glucose, and risk of pancreatic cancer in Korean men. *Int J Cancer*, 2006; 119: 208-12.

78. Lukanova A, Bjor O, Kaaks R *et al*. 'Body mass index and cancer: results from the Northern Sweden Health and Disease Cohort. *Int J Cancer*, 2006; 118: 458-66.

79. Samanic C, Chow WH, Gridley G *et al*. 'Relation of body mass index to cancer risk in 362,552 Swedish men. *Cancer Causes Control*, 2006; 17: 901-9.

80. Genkinger JM, Spiegelman D, Anderson KE *et al*. 'A pooled analysis of 14 cohort studies of anthropometric factors and pancreatic cancer risk. Int J Cancer, 2011; 129: 1708-17.

81. Arslan AA, Helzlsouer KJ, Kooperberg C *et al*. 'Anthropometric measures, body mass index, and pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). *Arch Intern Med*, 2010; 170: 791-802.

82. Jiao L, Berrington de GA, Hartge P *et al*. 'Body mass index, effect modifiers, and risk of pancreatic cancer: a pooled study of seven prospective cohorts. *Cancer Causes Control*, 2010; 21: 1305-14.

83. Parr L, Batty GD, Lam TH *et al*. 'Body mass index and cancer mortality in the Asia-Pacific Cohort Studies Collaboration: pooled analyses of 424,519 participants. *Lancet Oncol*, 2010; 11: 741-52.

84. Verhage BA, Schouten LJ, Goldbohm RA *et al*. 'Anthropometry and pancreatic cancer risk: an illustration of the importance of microscopic verification. *Cancer Epidemiol.Biomarkers Prev.*, 2007; 16: 1449-54.

85. Hursting SD, Lavigne JA, Berrigan D *et al*. 'Calorie restriction, aging, and cancer prevention: mechanisms of action and applicability to humans. *Annu Rev Med*, 2003; 54: 131-52.

86. Calle EE and Kaaks R. 'Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer,* 2004; 4: 579-91.

87. Rexrode KM, Pradhan A, Manson JE *et al*. 'Relationship of total and abdominal adiposity with CRP and IL-6 in women. *Ann Epidemiol*, 2003; 13: 674-82.

88. Loffreda S, Yang SQ, Lin HZ *et al*. 'Leptin regulates proinflammatory immune responses. *Faseb J*, 1998; 12: 57-65.

89. Green J, Cairns BJ, Casabonne D *et al*. 'Height and cancer incidence in the Million Women Study: prospective cohort and meta-analysis of height and total cancer risk. *Lancet Oncol*, 2011; 12: 785-94.

90. Sung J, Song YM, Lawlor DA *et al*. 'Height and site-specific cancer risk: A cohort study of a Korean adult population. *Am J Epidemiol*, 2009; 170: 53-64.

91. Stolzenberg-Solomon RZ, Adams K, Leitzmann M *et al*. 'Adiposity, physical activity, and pancreatic cancer in the National Institutes of Health-AARP Diet and Health Cohort. *Am J Epidemiol*, 2008; 167: 586-97.

92. Song YM and Sung J. 'Adult height and the risk of mortality in South Korean women. *Am J Epidemiol*, 2008; 168: 497-505.

93. Batty GD, Shipley MJ, Langenberg C *et al*. 'Adult height in relation to mortality from 14 cancer sites in men in London (UK): evidence from the original Whitehall Study. *Cancer Causes Control*, 2006; 15: 873-81.

94. Stolzenberg-Solomon RZ, Limburg P, Pollak M *et al*. 'Insulin-like growth factor (IGF)-1, IGF- binding protein-3 and pancreatic cancer in male smokers (Finland). *Cancer Epidemiol Biomarkers Prev*, 2004; 13: 438-44.

95. Le Roith D, Bondy C, Yakar S *et al*. 'The somatomedin hypothesis: 2001. *Endocr Rev*, 2001; 22: 53-74.

Appendix: Criteria for grading evidence for cancer prevention

See also Judging the evidence, section 8.

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

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

CONVINCING (STRONG EVIDENCE)

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

All of the following are generally required:

- Evidence from more than one study type.

- Evidence from at least two independent cohort studies.

- No substantial unexplained heterogeneity within or between study types or in different populations relating to the presence or absence of an association, or direction of effect.

- Good-quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error and selection bias.

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

- Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes.

PROBABLE (STRONG EVIDENCE)

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

All of the following are generally required:

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

- No substantial unexplained heterogeneity between or within study types in the presence or absence of an association, or direction of effect.

- Good-quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error and selection bias.

- Evidence for biological plausibility.

LIMITED – SUGGESTIVE

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

All of the following are generally required:

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

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

- Evidence for biological plausibility.

LIMITED – NO CONCLUSION

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

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

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

SUBSTANTIAL EFFECT ON RISK UNLIKELY (STRONG EVIDENCE)

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

All of the following are generally required:

- Evidence from more than one study type.

- Evidence from at least two independent cohort studies.

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

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

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

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

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

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

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

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

SPECIAL UPGRADING FACTORS

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

Factors may include the following:

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

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

- Evidence from randomised trials in humans.

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

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

Our Cancer Prevention Recommendations

Be a healthy weight
Keep your weight within the healthy range and avoid weight gain in adult life

Be physically active
Be physically active as part of everyday life – walk more and sit less

Eat a diet rich in wholegrains, vegetables, fruit and beans
Make wholegrains, vegetables, fruit, and pulses (legumes) such as beans and lentils a major part of your usual daily diet

Limit consumption of 'fast foods' and other processed foods high in fat, starches or sugars
Limiting these foods helps control calorie intake and maintain a healthy weight

Limit consumption of red and processed meat
Eat no more than moderate amounts of red meat, such as beef, pork and lamb. Eat little, if any, processed meat

Limit consumption of sugar sweetened drinks
Drink mostly water and unsweetened drinks

Limit alcohol consumption
For cancer prevention, it's best not to drink alcohol

Do not use supplements for cancer prevention
Aim to meet nutritional needs through diet alone

For mothers: breastfeed your baby, if you can
Breastfeeding is good for both mother and baby

After a cancer diagnosis: follow our Recommendations, if you can
Check with your health professional what is right for you

Not smoking and avoiding other exposure to tobacco and excess sun are also important in reducing cancer risk.

Following these Recommendations is likely to reduce intakes of salt, saturated and trans fats, which together will help prevent other non-communicable diseases.

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