

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

2015

In partnership with

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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 Recommendations for Cancer Prevention, 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 evaluate and interpret the evidence to make conclusions based on the body of scientific evidence. Their conclusions form the basis for reviewing and, where necessary, revising our Recommendations for Cancer Prevention (see inside back cover).

A review of the Recommendations for Cancer Prevention 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 and liver cancers. In addition, our first CUP report on breast cancer survivors was published in October 2014.

This CUP report on gallbladder cancer updates the gallbladder cancer section of the Second Expert Report (section 7.7) and is based on the findings of the CUP Gallbladder Cancer Systematic Literature Review (SLR) and the CUP Expert Panel discussion in June 2014. For further details, please see the full CUP Gallbladder Cancer SLR 2014 (wcrf.org/Gallbladder-Cancer-SLR-2014).

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

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EXECUTIVE SUMMARY

Background and context

Gallbladder cancer is the twentieth most common cancer worldwide and the seventeenth most common cause of death from cancer. Although rates of gallbladder cancer are generally declining, survival rates are low; about 178,100 new cases were diagnosed around the world in 2012, but the number of deaths from the disease was relatively high by comparison at 142,800 [2].

One of the reasons for the low survival rates is that gallbladder cancer symptoms do not generally manifest in the early stages of the disease, which means that the cancer is often advanced by the time it is diagnosed.

Gallbladder cancer is more common in women than men – about 57 per cent of cases occur in women – and the highest rates are seen in eastern Asia, which accounts for 45 per cent of all cases worldwide [2].

In this latest report from our Continuous Update Project – the world's largest source of scientific research on cancer prevention and survivorship through diet, weight and physical activity – we analyse worldwide research on how certain lifestyle factors affect the risk of developing gallbladder cancer. This includes new studies as well as studies published 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, it is known that having gallstones increases the risk of gallbladder cancer.

How the research was conducted

The global scientific research on diet, weight, physical activity and the risk of gallbladder cancer was systematically gathered and analysed, and then the results were independently assessed by a panel of leading international scientists in order to draw conclusions about whether 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 14 studies from around the world, comprising nearly 13 million (12,800,000) men and women and about 8,300 cases of gallbladder cancer.

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

Findings

Strong evidence

- ◆ There is strong evidence that being overweight or obese increases the risk of gallbladder cancer.

The degree of body fatness was assessed by body mass index (BMI). The research found a 25 per cent increased risk of gallbladder cancer for every five BMI units. The increased risk of gallbladder cancer was mainly observed in overweight and obese people, rather than those whose weight fell within the healthy range of BMI.

Thus the conclusion of our 2007 Second Expert Report [2] – that there is a link between being overweight obese and the risk of developing gallbladder cancer – remains unchanged.

Link between body fat and cancer

The precise way in which body fatness, obesity, or energy balance specifically influence the risk of gallbladder cancer needs more research.

Obesity is a known cause of gallstone formation and having gallstones increases the risk of gallbladder cancer.

Other more general factors may be involved. Body fatness increases the levels of hormones circulating in the body – such as insulin and insulin-like growth factors – creating an environment that may encourage the development or progression of cancer in a variety of organs.

Body fat also stimulates a general inflammatory response, which may contribute to the development of several cancers.

Recommendations

To reduce the risk of developing gallbladder cancer our advice is that people should:

1. Maintain a healthy weight.

This advice forms part of our existing Cancer Prevention Recommendations (available at www.wcrf.org). Our Cancer Prevention Recommendations are for preventing cancer in general and include eating a healthy diet, being physically active and maintaining a healthy weight.

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 (Second Expert Report). Available from www.wcrf.org
- 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>



1. Summary of Panel judgements

Overall the Panel notes the strength of the evidence that people with gallstones are more likely to develop gallbladder cancer.

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

- ◆ Greater body fatness (marked by BMI) probably causes gallbladder cancer.

		DIET, NUTRITION, PHYSICAL ACTIVITY AND GALLBLADDER CANCER	
		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	Convincing		
	Probable		Body fatness ¹
LIMITED EVIDENCE	Limited – suggestive		
	Limited – no conclusion	Peppers (capsicums), fish, coffee, tea, alcohol, sugar, vitamin C, calcium and vitamin D supplements, low fat diets, height	
STRONG EVIDENCE	Substantial effect on risk unlikely		

1. Directly and indirectly through the formation of gallstones. Body fatness is marked by body mass index (BMI).

2. Trends, incidence and survival

The gallbladder is a small sac-like organ that forms part of the biliary tract. Bile, produced in the liver, flows into the gallbladder, where it is stored and concentrated until released into the small intestine. Approximately 90–95 per cent of gallbladder cancers are adenocarcinomas, while only a small proportion are squamous cell carcinomas [3].

Gallbladder cancer is the 20th most common cancer worldwide, with 178,000 new cases diagnosed in 2012, and is more common in women than in men [2]. It accounts for about 1 per cent of incidence of all cancers, and rates are generally declining. The highest rates occur in eastern Asia, and it is rare in Africa. This cancer is the 17th most common cause of cancer death. Gallbladder cancer is usually advanced at diagnosis, and survival rates are low.

3. Pathogenesis

The pathogenesis of gallbladder cancer is not well understood, partly because it is often diagnosed at a late stage. Having gallstones increases the risk of this cancer [4]. Inflammation associated with gallstones decreases the speed at which bile empties from the gallbladder; gallstones may also have a direct effect by blocking the transit of bile [5] or by causing direct mechanical irritation to the surrounding mucosal surface [6]. Other factors may also be involved, and many toxins, whether they come from diet, smoke inhalation or other environmental sources (and their metabolic products), are excreted and concentrated in the bile. For more information on the pathogenesis of gallbladder cancer, see section 7.7.2 in the Second Expert Report [1].

4. Other established causes

(Also see Second Expert Report sections 2.4 and 7.1.3.1)

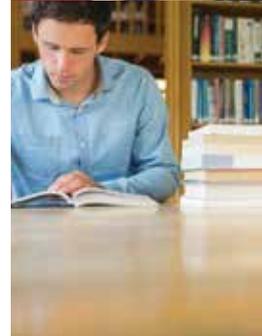
Other causes, with the exception of gallstones, have not been established.

5. Interpretation of the evidence

5.1 General

For general considerations that may affect interpretation of the evidence, see Second Expert Report sections 3.3 and 3.5, and boxes 3.1, 3.2, 3.6 and 3.7.

‘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 gallbladder include:

Confounding

Having gallstones increases the risk of gallbladder cancer. Exposures with an apparent link to gallbladder cancer may act indirectly, through gallstones, or directly, either after gallstone formation or in their absence. It is not yet possible to separate these effects.

6. Methodology

To ensure consistency, the methodology for reviewing the epidemiological evidence in the CUP remains largely unchanged from that used previously for the Second Expert Report [1]. However, based upon the experience of conducting the systematic literature reviews (SLRs) 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. Due to their methodological limitations, case-control studies, although identified, were not included in the CUP Gallbladder SLR 2014, unlike in the 2005 SLR for the Second Expert Report.

Where possible, meta-analyses for incidence and mortality in this update were conducted separately. However, analyses combining studies on gallbladder cancer incidence and mortality were also conducted to explore if this outcome could explain any heterogeneity. 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 Gallbladder SLR 2014, 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.

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 about the non-linear meta-analyses can be found in the CUP Gallbladder SLR 2014.

The Gallbladder SLR 2014 included studies published up to 31 March 2013.

For more information on methodology, see the full CUP Gallbladder SLR 2014 at wcrf.org/Gallbladder-Cancer-SLR-2014.

6.1 Mechanistic evidence

A brief summary of possible mechanisms for body fatness is included in this report, adapted from that previously included in the Second Expert Report (see chapters 2 and 6 for more information).

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

7. Evidence and judgements

7.1 Body fatness

(Also see CUP Gallbladder SLR 2014: Section 8.1.1)

The 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 mass and fat mass.

Body mass index

The CUP identified five new or updated studies (six publications) [7-12], giving a total of 11 studies (14 publications) on gallbladder cancer in the CUP (see CUP Gallbladder SLR 2014 table 13 for a full list of references). Eight studies (14 estimates) reported on gallbladder cancer incidence (see CUP Gallbladder SLR 2014 figure 7). Most studies reported on men and women separately, and so the results comparing highest versus lowest BMI categories are presented by sex where possible. One study reporting a combined estimate for both men and women showed a non-significant positive association. Seven of the incidence studies reported on men: four showing a positive association (of which two were significant), two showing a non-significant inverse association, and the other showing a significant positive association in white men and a non-significant inverse association in black men. Five of the incidence studies reported on women: four showing a positive association (of which three were significant) and one showing a non-significant inverse association. Of two studies reporting on gallbladder cancer mortality, one reported a significant positive association for both men and women, and the other reported a positive association in men and an inverse association in women, neither of which were statistically significant.

Eight of 11 studies on gallbladder cancer were included in the dose-response meta-analysis ($n = 6,004$), which showed a statistically significant 25 per cent increased risk of cancer per 5 kg/m² (RR 1.25 (95% CI 1.15–1.37)) (see **figure 1** (CUP Gallbladder SLR 2014 figure 8)). High heterogeneity was observed ($I^2 = 52\%$), which appeared to be mainly due to the size of the effect. There was evidence of non-linearity ($p < 0.01$), with an increased risk at BMI of approximately 24 kg/m² or greater (see **figure 2** (CUP Gallbladder SLR 2014 figures 14 and 15, and table 14)).



Figure 1: Dose-response meta-analysis of BMI and gallbladder cancer, per 5 kg/m²

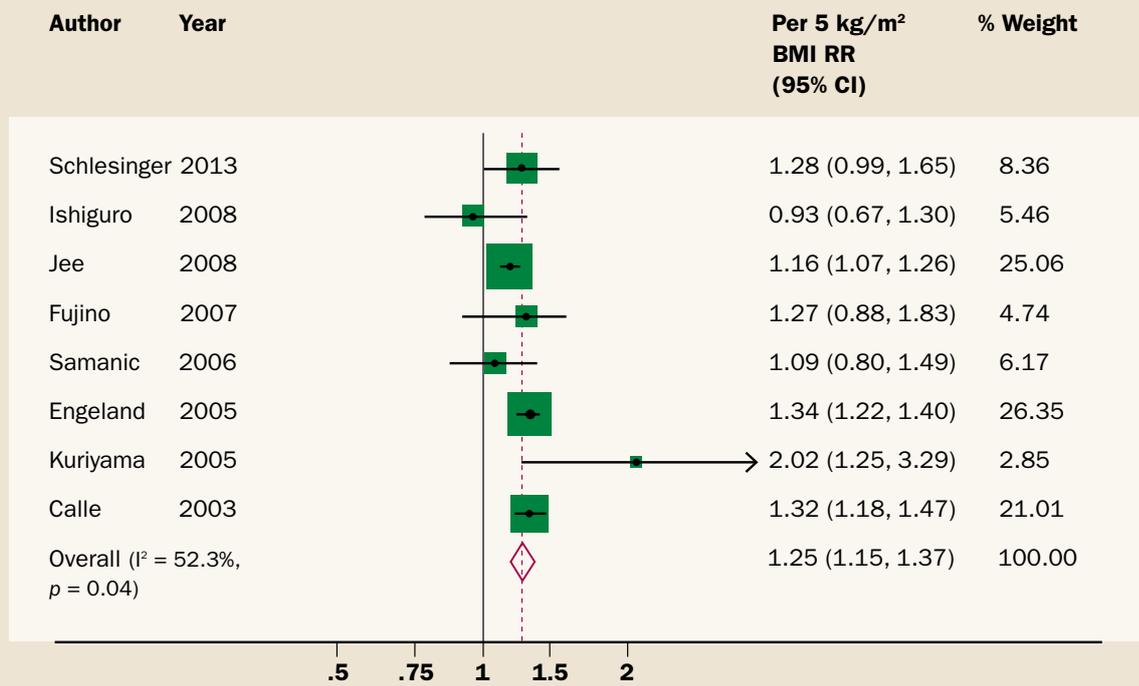
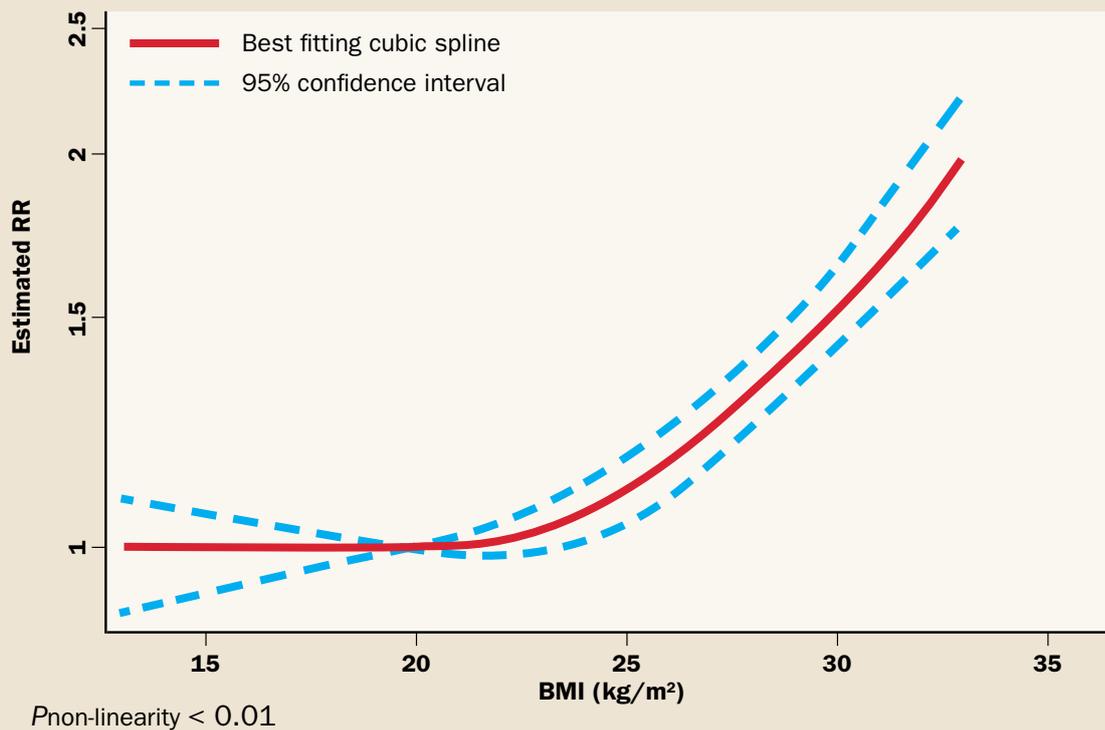


Figure 2: Non-linear dose-response association of BMI (kg/m²) and gallbladder cancer



When stratified by outcome, the dose-response meta-analysis showed significant increased risk per 5 kg/m² for both gallbladder cancer incidence and mortality, and when stratified by sex, significant increased risk for both men and women. Finally, when stratified by geographic location, dose-response meta-analyses showed an increased risk per 5 kg/m² in both European and Asian studies, but this was significant only in European studies (see **table 1** and CUP Gallbladder SLR 2014 figures 9, 10 and 11).

Table 1: Summary of CUP 2014 stratified dose-response meta-analyses – BMI

ANALYSIS	INCREMENT	RR (95% CI)	I ²	NO. STUDIES	NO. CASES
Incidence	Per 5 kg/m ²	1.23 (1.10–1.39)	64%	6	5,364
Mortality	Per 5 kg/m ²	1.31 (1.18–1.46)	0%	2	640
Men	Per 5 kg/m ²	1.23 (1.13–1.33)	0%	6	3,298
Women	Per 5 kg/m ²	1.25 (1.07–1.46)	69%	6	2,630
Europe	Per 5 kg/m ²	1.32 (1.24–1.41)	0%	3	1,900
Asia	Per 5 kg/m ²	1.22 (0.98–1.52)	56%	4	3,620



The CUP findings were consistent with the dose-response meta-analysis from the 2005 SLR, which included four studies and showed a significant positive association per 5 kg/m² (RR 1.23 (95% CI 1.15–1.32); *n* = 2,561). The CUP Gallbladder SLR 2014 included more than twice as many cases of gallbladder cancer.

Published pooled analyses and meta-analyses

The results from one published pooled analysis [13] and two meta-analyses [14, 15] on BMI and gallbladder cancer were identified in the CUP Gallbladder SLR 2014. The published pooled analysis reported a non-significant positive association per 5 kg/m², but included only deaths from gallbladder cancer. One of the meta-analyses of cohort studies reported a significant positive association per 5 kg/m² for women only (RRs 1.59 (95% CI 1.02–2.47); *n* = 1,111; *I*² = 67% and 1.09 (95% CI 0.99–1.21); *n* = 928; *I*² = 0% for women and men respectively) [14]. The other meta-analysis of eight cohort studies reported a significant positive association when comparing obese (BMI > 30 kg/m²) and normal weight (BMI < 25 kg/m²) categories (RR 1.69 (95% CI 1.48–1.92); *n* = 2,920; *I*² = 14%) [15]. The details from the published pooled analysis are presented in **table 2**.

Table 2: Summary of CUP 2014 meta-analysis and published pooled analyses – BMI

ANALYSIS	INCREMENT	RR (95% CI)	I ²	NO. STUDIES	NO. CASES	FACTORS ADJUSTED FOR
CUP Gallbladder SLR 2014	Per 5 kg/m ²	1.25 (1.15–1.37)	52%	8	6,004	-
Prospective Studies Collaboration [13]	Per 5 kg/m ²	1.12 (0.90–1.38)	-	57	222 deaths	Age, smoking

Mechanisms

*Note: This section is adapted from the Second Expert Report sections 6.1.3.1 and 7.7.5.1. In the future, an updated review of mechanisms for this exposure will form part of a larger review of mechanisms (see **section 6.1** in this report).*

Body fatness directly affects levels of many circulating hormones, such as insulin, insulin-like growth factors and oestrogens [16], creating an environment that encourages carcinogenesis and discourages apoptosis. It also stimulates the body's inflammatory response, which may contribute to the initiation and progression of several cancers.

In addition, obesity is a known cause of gallstone formation. Having gallstones increases the risk of gallbladder cancer, possibly through bile cholesterol supersaturation, leading to cholesterol-based gallstones. High cholesterol in the bile is not necessarily related to dietary cholesterol; it can also be caused by insulin resistance, which can result from obesity. Insulin resistance can independently increase cholesterol synthesis in the liver and decrease cholesterol absorption [17]. Bile cholesterol levels are also gender-linked; women secrete more cholesterol in bile than men.

Owing to the link between gallstones and gallbladder cancer, the 2007 Second Expert Report Panel also reviewed dietary causes of gallstones, especially in relation to body fatness. Having a relatively high BMI increases the risk of gallstones in a linear fashion [18]. Waist circumference is associated with gallstone risk in men, independently of BMI [19]. Gallstone formation is associated with repeated dieting, especially where it involves rapid weight loss, such as that from very low-energy diets and bariatric surgery [20, 21]. Rapid weight loss is also a common feature of weight cycling. Weight cycling is associated with obesity and independently associated with gallstones; people who are more severe weight cyclers have a higher risk of gallstones [22].

CUP Panel's conclusion:

The evidence for BMI and gallbladder cancer was generally consistent, and the dose-response relationship showed a statistically significant positive association. This significant association was still apparent when stratified by outcome and sex, but when stratified by geographical location was significant only in European studies. Results from one published pooled analysis and two meta-analyses were also consistent with the CUP Gallbladder SLR 2014 in the direction of the effect, although not all showed findings that were statistically significant. Non-linear analysis showed an increased risk with higher BMI. There is also evidence of plausible mechanisms operating in humans. The CUP Panel concluded:

Greater body fatness (marked by BMI) probably causes gallbladder cancer.

7.2 Other

Other exposures were evaluated. However, data were either of too low quality or 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 5.

Evidence for the following exposures previously judged as 'limited – no conclusion' in the Second Expert Report remain unchanged after updating the analyses with new data identified in the CUP Gallbladder SLR 2014: peppers (capsicums), fish, coffee, tea, alcohol and vitamin C.

In addition, evidence for the following new exposures, for which no judgement was made in the Second Expert Report, is too limited to draw any conclusions: sugar (as a nutrient), calcium and vitamin D supplements, low-fat diets and height.



8. Comparison with the Second Expert Report

Overall the evidence from the additional cohort studies identified in the CUP was consistent with that reviewed as part of the Second Expert Report. Much of the new evidence was related to body fatness, for which the conclusion from the Second Expert Report was confirmed.

9. Conclusions

The CUP Panel concluded:

- ◆ **Greater body fatness (marked by BMI) probably causes gallbladder cancer.**

The CUP database is being continually updated for all cancers. The Recommendations for Cancer Prevention 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
BMI	Body mass index
CI	Confidence interval
CUP	Continuous Update Project
<i>n</i>	Number of cases
No.	Number
RR	Relative risk
SLR	Systematic literature review
WCRF	World Cancer Research Fund



Glossary

Adjustment

A statistical tool for taking into account the effect of known confounders.

Anthropometric measures

Measures of body dimensions.

Bias

In epidemiology, 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.

Bile

A greenish-yellow fluid secreted by the liver and stored in the gallbladder. Bile plays an important role in the intestinal absorption of fats. Bile contains cholesterol, bile salts and waste products such as bilirubin.

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 called Quetelet's Index.

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).

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 past 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 per cent confidence interval (CI), which is the range of values within which there is a 95 per cent 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 point estimate of the relative risk was calculated as 10, and that there is a 95 per cent chance that the true value lies between 5 and 15.

Confounder

A variable, within a specific epidemiological study, that is associated with both an exposure and the disease but is not in the causal pathway from the exposure to the disease. If not adjusted for, 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 possible cause of lung cancer.

Confounding factor (see confounder)

Dose-response

A term derived from pharmacology that describes the degree to which an effect changes with the level of an exposure, for instance the 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.

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, for example using the I^2 test.

Hormone

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

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, causing redness, pain 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.

Malignant

The capacity of a tumour 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.

Odds ratio (OR)

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 (RR).

Pathogenesis

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



Pooled analysis (see pooling)

Pooling

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

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 or death among people exposed to a factor compared to the rate among the unexposed, usually used in cohort studies.

Selection bias

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

Statistical significance

The probability that any observed result might not have occurred by chance. In most epidemiologic work, a study result whose probability is less than 5 per cent ($p < 0.05$) is considered sufficiently unlikely to have occurred by chance to justify the designation 'statistically significant' (see confidence interval).

Systematic literature review (SLR)

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

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Appendix – Criteria for grading evidence

(Taken from Chapter 3 of the Second Expert Report)

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)

These criteria are 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 were 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, from either human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes.

PROBABLE (STRONG EVIDENCE)

These criteria are 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 were 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

These criteria are 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 almost always does not justify recommendations designed to reduce the incidence of cancer. Any exceptions require special, explicit justification.

All the following were 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 category 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’.

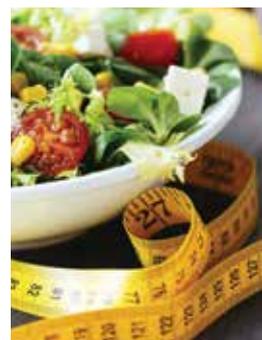
There are also many exposures for which there is such limited evidence that no judgement is possible. In these cases, evidence is recorded in the full CUP SLRs on the World Cancer Research Fund International website (www.wcrf.org). However, such evidence is usually not included in the summaries.

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 were 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 and 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, either from human studies or relevant animal models, that typical human exposures 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. So an exposure that might be deemed a 'limited – suggestive' causal factor in the absence, say, of a biological gradient, might be upgraded to 'probable' in its presence. 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.

- ◆ 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 it 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 Recommendations for Cancer Prevention

Body fatness

Be as lean as possible without becoming underweight

Physical activity

Be physically active for at least 30 minutes every day

Foods and drinks that promote weight gain

Limit consumption of energy-dense foods and avoid sugary drinks

Plant foods

Eat more of a variety of vegetables, fruits, wholegrains and pulses such as beans

Animal foods

Limit consumption of red meats (such as beef, pork and lamb), and avoid processed meats

Alcoholic drinks

If consumed at all, limit alcohol to a maximum of 2 drinks a day for men and 1 drink a day for women

Preservation, processing, preparation

Limit consumption of salt, and avoid mouldy cereals and pulses

Dietary supplements

Don't use supplements to protect against cancer

Breastfeeding

It is best for mothers to breastfeed exclusively for up to six months and then add other liquids and foods

Cancer survivors

After treatment, cancer survivors should follow the recommendations for cancer prevention



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