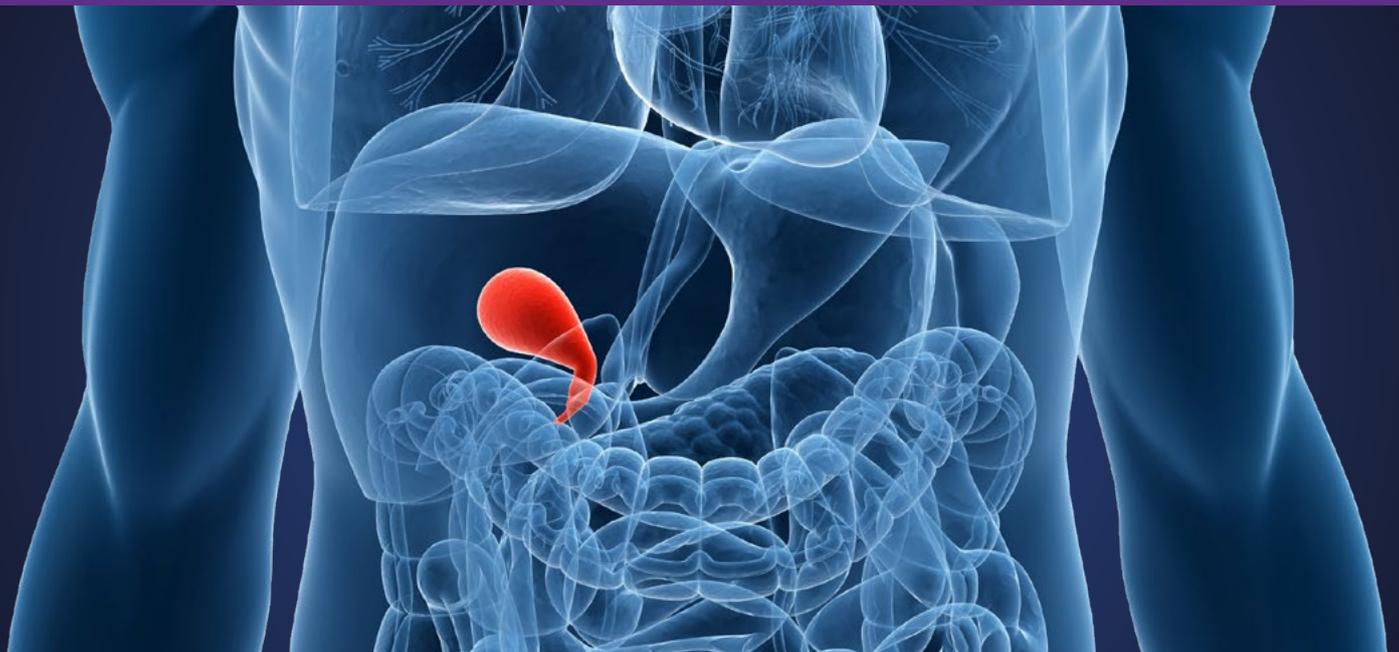World Cancer Research Fund

American Institute for Cancer Research

CUP Continuous Update Project

Analysing research on cancer prevention and survival

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

2015

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 gallbladder 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 gallbladder 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.

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

There is strong evidence that:

- **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 , please see Recommendations and public health and policy implications for more information. 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. Available at **wcrf.org/about-the-report**

[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**

2015

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).

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.**

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

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 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 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**.

6.1 Mechanistic evidence

The evidence for mechanisms is summarised under each exposure. These summaries were developed from mechanistic reviews conducted for the 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

7.1 Body fatness

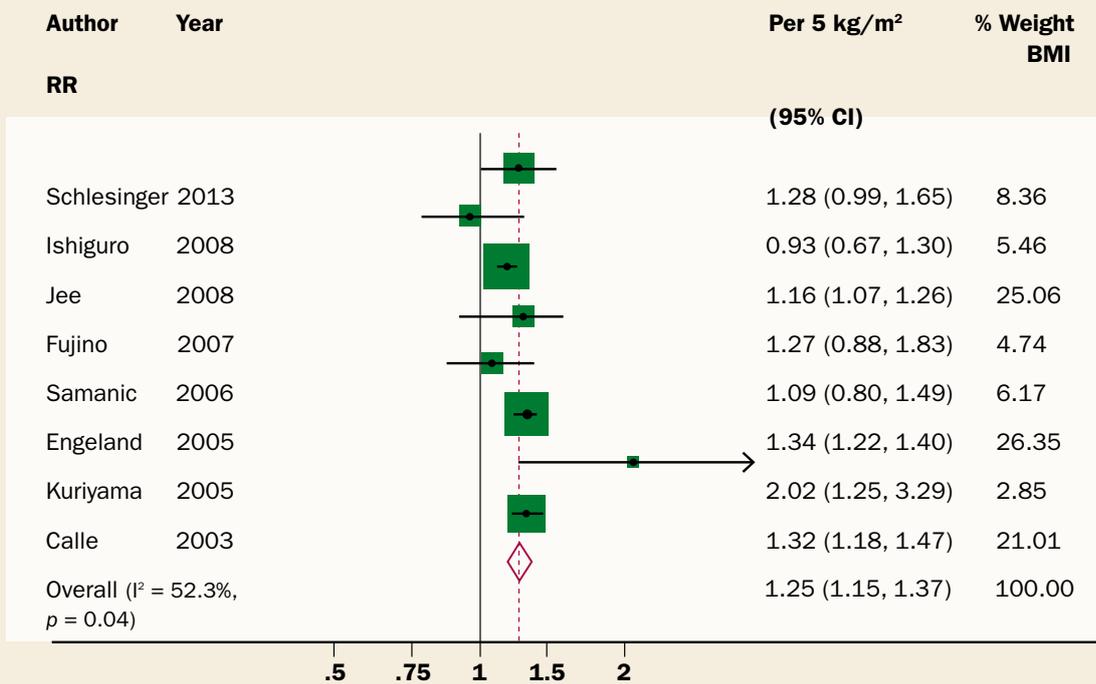*(Also see CUP Gallbladder SLR 2014: Section 8.1.1)*

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/m^2 (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/m^2 or greater (see **figure 2** (CUP Gallbladder SLR 2014 figures 14 and 15, and table 14)). When stratified by outcome, the dose-response meta-analysis showed significant increased risk per 5 kg/m^2 for both gallbladder cancer incidence and mortality, and when stratified by sex, significant increased risk for both men and women.

Figure 1: Dose-response meta-analysis of BMI and gallbladder cancer, per 5 kg/m^2

Author	Year		Per 5 kg/m² RR (95% CI)	% Weight BMI
Schlesinger	2013		1.28 (0.99, 1.65)	8.36
Ishiguro	2008		0.93 (0.67, 1.30)	5.46
Jee	2008		1.16 (1.07, 1.26)	25.06
Fujino	2007		1.27 (0.88, 1.83)	4.74
Samanic	2006		1.09 (0.80, 1.49)	6.17
Engeland	2005		1.34 (1.22, 1.40)	26.35
Kuriyama	2005		2.02 (1.25, 3.29)	2.85
Calle	2003		1.32 (1.18, 1.47)	21.01
Overall (I² = 52.3%, p = 0.04)			1.25 (1.15, 1.37)	100.00

.5   .75   1   1.5   2

Figure 2: Non-linear dose-response association of BMI (kg/m^2) and gallbladder cancer
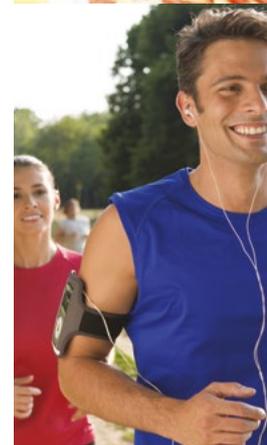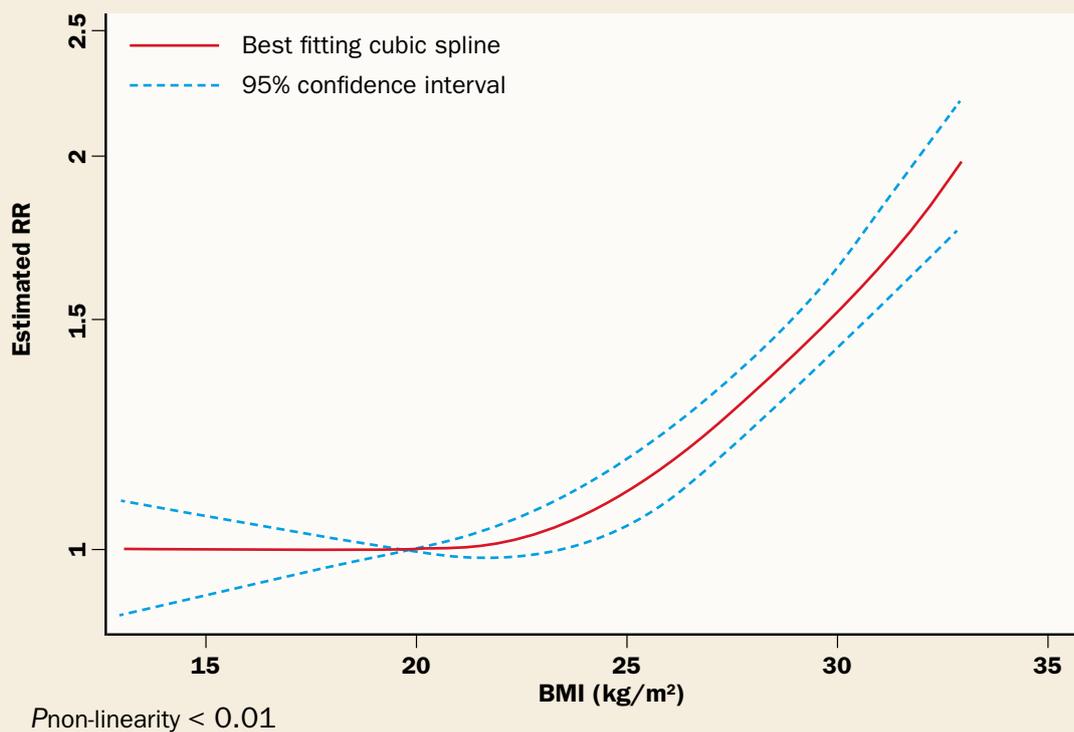
Best fitting cubic spline
95% confidence interval

Estimated RR

BMI (kg/m²)

Pnon-linearity < 0.01

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)	I²	No. Studies	No. Cases
Incidence	Per 5 kg/m²	1.23 (1.10-1.39)	64%	6	5,364
Mortality	Per 5 kg/m²	1.31 (1.18-1.46)	0%	2	640
Men	Per 5 kg/m²	1.23 (1.13-1.33)	0%	6	3.298
Women	Per 5 kg/m²	1.25 (1.07-1.46)	69%	6	2,630
Europe	Per 5 kg/m²	1.32 (1.24-1.14)	0%	3	1,900
Asia	Per 5 kg/m²	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; I²= 67% and 1.09 (95% CI 0.99–1.21); *n* = 928; I²= 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; I²= 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)	I²	No. Studies	No. Cases	Factors adjusted for
CUP Gallbladder SLR 2014	Per 5 kg/m²	1.25 (1.15-1.37)	52%	8	6,004	-
Prospective Studies Collaboration [13]	Per 5 kg/m²	1.12 (0.90-1.38)	-	57	222 deaths	Age, smoking

Mechanisms

Body fatness directly affects levels of many circulating hormones, such as insulin, insulin-like growth factors and oestrogens [16], creating an environment that encourages carcinogeneis 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].

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 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 7**.

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 the following:

Probable evidence

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

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.
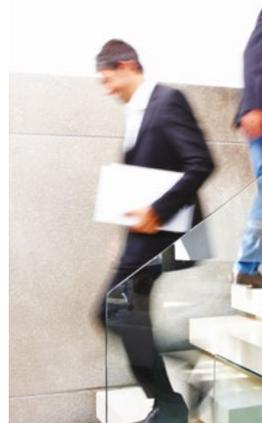
Acknowledgements

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Abbreviations

AICR   American Institute for Cancer Research

BMI   Body mass index

CI   Confidence interval

CUP   Continuous Update Project

n   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 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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