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 **kidney cancer**

2015

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World Cancer Research Fund International

World Cancer Research Fund UK

Wereld Kanker Onderzoek Fonds

World Cancer Research Fund 世界癌症研究基金會

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WORLD CANCER RESEARCH FUND 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.

CUP Continuous Update Project

Analysing research on cancer prevention and survival

THIRD EXPERT REPORT

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 kidney 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

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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

Globally, the incidence rates of kidney cancer are predicted to increase. Currently, kidney cancer – also known as renal cancer – is the 12th most common cancer worldwide, with 337,860 cases recorded in 2012. However, the International Agency for Research on Cancer predicts a 22 per cent increase in the number of people developing the disease by 2020, amounting to about 412,929 cases (an increase of 75,069) [2].

Statistics also show that incidence rates of the disease are twice as high among men than women and that 59 per cent of kidney cancer cases occur in more developed countries, with the highest rates seen in North America and Europe and the lowest in Africa and Asia [2].

Although kidney cancer is the 16th most common cause of death from cancer, survival rates are relatively high in developed countries. In the USA, overall survival rates are 72 per cent after five years; the survival rate beyond five years is even higher at 92 per cent for the two thirds (64%) of cases that are diagnosed in the early stages. However, these high survival rates are not seen in lower income countries where cancers are often detected at later, more advanced stages.

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

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

1. Smoking:

- Smoking is a cause of kidney cancer. Current smokers have a 52 per cent increased risk of kidney cancer, and ex-smokers a 25 per cent increased risk, compared with those who have never smoked.

2. Medication:

- Painkillers containing phenacetin are known to cause cancer of the renal pelvis. Phenacetin is no longer used as an ingredient in painkillers.

3. Kidney disease:

- Polycystic kidney disease predisposes people to developing kidney cancer.

4. Hypertension:

- High blood pressure is associated with a higher risk of kidney cancer.

How the research was conducted

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

More research has been conducted in this area since our 2007 Second Expert Report [1]. In total, this new report analyses 29 studies from around the world, comprising nearly 9.7 million adults and 15,039 cases of kidney cancer.

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

A summary of the mechanisms underpinning the following findings can be found under the relevant sections of this report.

Findings

There is strong evidence that:

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

Being overweight or obese was assessed by body mass index (BMI), waist circumference and waist-to-hip ratio. The analysis of the worldwide research found a 30 per cent increased risk of kidney cancer for every 5 kg/m^2 increase; an 11 per cent increased risk for every 10 cm increase in waist circumference; and a 26 per cent increase in risk for every 0.1 unit increase in waist-to-hip ratio.

The findings on being overweight or obese remain unchanged from our 2007 Second Expert Report [1].

- **There is strong evidence that being tall increases the risk of kidney cancer (the taller a person is, the greater his or her risk of kidney cancer).**

The analysis of research showed a 10 per cent increase in risk for every 5 cm of increased height, and the findings were the same for men and women.

It is unlikely that it is height itself that is the issue but rather, the developmental factors in the womb, and during childhood and adolescence, that influence growth that are linked to an increased risk of kidney cancer.

- **There is strong evidence that consuming alcoholic drinks *decreases* the risk of kidney cancer, when consuming up to 30 grams (about 2 drinks) a day. There is insufficient, specific evidence for higher levels of drinking – for example, 50 grams (about 3 drinks) or 70 grams (about 5 drinks) a day. It is also important to remember that there is strong evidence that alcohol is linked to an increased risk of five other cancers.**

There is some evidence that:

- **There is some – but only limited – evidence suggesting that consuming drinking water that contains arsenic increases the risk of kidney cancer.**

Water can become contaminated by arsenic as a result of natural deposits present in the earth or from agricultural and industrial practices.

The findings on consuming drinking water containing arsenic remain unchanged from our 2007 Second Expert Report [1].

Recommendations

Our Cancer Prevention Recommendations – for preventing cancer in general – include maintaining a healthy weight, being physically active and eating a healthy diet. The Cancer Prevention Recommendations are listed on the inside back cover of this report, with full details available in Recommendations and public health and policy implications.

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 KIDNEY CANCER		
		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	Convincing		**Body fatness**[1]
	Probable	**Alcoholic drinks**[2]	**Adult attained height**[3]
LIMITED EVIDENCE	**Limited – suggestive**		Arsenic in drinking water[4]
	Limited – no conclusion	Cereals (grains) and their products, dietary fibre, vegetables, fruits, meat, poultry, fish, eggs, milk and dairy products, total fat, soft drinks, tea, coffee, carbohydrate, protein, calcium, vitamin A, retinol, vitamin C, vitamin E, beta-carotene, alpha-carotene, lycopene, beta-cryptoxanthin, lutein and zeaxanthin, flavonol, folate, vitamin B6, Seventh-day Adventist diets, physical activity, birth weight, age at menarche and energy intake	
STRONG EVIDENCE	Substantial effect on risk unlikely		

1 Body fatness marked by body mass index (BMI), waist circumference and waist-hip ratio.

2 Based on evidence for alcohol intake up to 30 grams per day (about 2 drinks a day). There is insufficient evidence for intake greater than 30 grams per day.

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

4 The International Agency for Research on Cancer (IARC) has graded arsenic and arsenic compounds as Class 1 carcinogens. The grading for this entry applies specifically to inorganic arsenic in drinking water [3].

1. Summary of Panel judgements

Overall the Panel notes the strength of the evidence that body fatness and adult attained height are causes of kidney cancer and that alcoholic drinks protect against kidney cancer.

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

- **Body fatness: Greater body fatness (marked by BMI, waist circumference and waist-hip ratio) is a convincing cause of kidney cancer.**
- **Adult attained height: Developmental factors leading to greater linear growth (marked by adult attained height) are probably a cause of kidney cancer.**
- **Alcoholic drinks: Consumption of alcoholic drinks probably protects against kidney cancer. This is based on evidence for alcohol intakes up to 30 grams per day (about two drinks a day).**
- **Arsenic in drinking water: The evidence suggesting that consumption of arsenic in drinking water increases the risk of kidney cancer is limited.**

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

The Panel judgements for kidney cancer are shown in the matrix on **page 8**.

2. Trends, incidence and survival

The kidneys are a pair of organs located at the back of the abdomen outside the peritoneal cavity. They filter waste products and water from the blood, producing urine, which empties into the bladder through the ureters. They are also important endocrine organs concerned with salt and water metabolism and maintaining blood pH, and they play a key role in vitamin D metabolism.

Renal parenchymal cancer is the most common kidney cancer, accounting for approximately 80–90 per cent of all primary kidney cancer; renal pelvis cancer accounts for most of the remainder [4]. About three-quarters of kidney cancers show clear cell histology [5]. Adults may also show papillary or sarcomatoid histology, and Wilms tumour (nephroblastoma) is a childhood cancer [4]. Renal pelvis cancer is typically transitional cell carcinoma and behaves similarly to ureteral and bladder cancer. Epidemiologic studies of kidney cancer do not always differentiate between renal parenchymal cancers and those of the renal pelvis, which likely have different risk factors.

Signs and symptoms of kidney cancer may include blood in the urine, a pain or lump in the lower back or abdomen, fatigue, weight loss, fever or swelling in the legs and ankles.

Cancers of the kidney are the 12th most common type worldwide with 338,000 cases recorded in 2012, accounting for about 2.4 per cent of all cancers. It is the 16th most common cause of death from cancer [2]. About 59 per cent of kidney cancer cases occur in more developed countries, with the highest incidence of kidney cancer in North

America and Europe and the lowest in Africa and Asia [2]. The age-standardised rate of this cancer is almost ten times higher in North America than in Africa, and globally rates are twice as high in men than women [2].

Increasingly, kidney cancers are diagnosed in developed nations by radiographic imaging, such as CT scans, often performed for unrelated reasons. Kidney cancers diagnosed in this way tend to be detected at earlier stages, when they are small and asymptomatic. Survival rates depend on stage at diagnosis. In the United States of America almost two-thirds of cases (64 per cent) are diagnosed at a local stage, when the five-year survival is 92 per cent; overall survival at five years is about 70–80 per cent [6]. These high survival rates are not seen in lower-income countries, where opportunistic diagnosis following imaging for unrelated conditions is rare and cancers are detected at later, more advanced stages. For further information, see **box 1**.

Box 1. Cancer incidence and survival

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

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

3. Pathogenesis

The kidneys filter blood and excrete metabolic waste products. These waste products include potential carcinogens, consumed as or derived from pharmaceuticals or foods and drinks, or through exposure from other environmental sources such as cigarette smoke. Some of these may play a role in kidney carcinogenesis.

Inherited genetic predisposition accounts for only a minority of kidney cancers [7]. Von Hippel-Lindau (VHL) syndrome is the most common, with up to 40 per cent of those inheriting the mutated VHL tumour suppressor gene developing kidney cancer [8]. Tuberous sclerosis is less common and predisposes to multiple cancer types, kidney cysts and kidney cancer [9]. About three-quarters of kidney cancers without a familial component are a clear cell type, of which about 60 per cent have a mutation in the VHL gene [10]. A further 12 per cent of non-familial kidney cancers are papillary, which are less likely to metastasise [11].

4. Other established causes

Tobacco use

Smoking is a cause of kidney cancer [12]. Both current and former smokers have an increased risk of renal cell cancer compared to people who have never smoked (52 per cent and 25 per cent respectively) [13]. Male smokers have a 54 per cent increased risk and female smokers have a 22 per cent increased risk compared with those who have never smoked, and there is a strong dose-dependent increase in risk for both men and women [14].

Medications

Analgesics containing phenacetin are a cause of cancer of the renal pelvis [15].

Kidney disease

Polycystic kidney disease predisposes people to kidney cancer [16].

Hypertension

Hypertension is associated with higher risk of kidney cancer [4].

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 kidney include:

Classification

Different subtypes of kidney cancer likely have different aetiologies, yet some epidemiologic studies do not distinguish clear cell, the predominant parenchymal renal cancer, from papillary or other subtypes. Cancers of the renal pelvis are typically transitional cell carcinoma, which probably shares aetiologic risk factors with other transitional cell carcinomas of the ureter and bladder, in particular smoking.

Confounding

Smoking is a possible confounder or effect modifier. Most studies in the analyses adjusted for smoking, although only two of the four studies on arsenic and kidney cancer controlled for smoking.

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 nested case-control studies. Due to their methodological limitations, case-control studies, although identified, were not included in the CUP Kidney SLR 2015, unlike in the 2005 SLR for the Second Expert Report.

Where possible for this update, meta-analyses for incidence and mortality were conducted separately. However, analyses combining studies on kidney cancer incidence and mortality were also conducted to explore whether the outcome can 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 Kidney SLR 2015, as relative risks estimated from the mean differences are not adjusted for possible confounders and thus not comparable with adjusted relative risks from other studies.

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

The CUP Kidney SLR 2015 included studies published up to 31 March 2014. For more information on methodology, see the full CUP Kidney SLR 2015 at **wcrf.org/kidney-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

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

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

7.1 Arsenic in drinking water

(Also see CUP Kidney SLR 2015: Section 4.1.2.7.2)

The CUP identified one new cohort study [17], giving a total of four studies (four publications). This study showed no significant association for either a 1 microgram per litre increase in time-weighted average exposure (drinking water) or for a 5 microgram increase in cumulative exposure (drinking water) over the 33-year period of observation (see **table 1**, CUP Kidney SLR 2015, table 51).

Three other cohort studies [18-20] were identified in the 2005 SLR. The studies were relatively small. Exposure to arsenic was measured in drinking water or well water in the areas where the study participants lived, and exposure values were individually estimated according to the time they lived in the area. A small study from Taiwan [18] showed a significant positive association (standard incidence ratio compared with general population). Neither of the two other studies reported significant associations of kidney cancer incidence with arsenic in well water [19] or with kidney cancer mortality [20] (see **table 1** (CUP Kidney SLR 2015, table 51)). A variety of measures were used to collect the data, so meta-analyses were not possible.

Table 1: Summary of cohort studies – arsenic

Study description	No. Cases / Year of follow-up	Sex	RR (95% CI)	Exposure / Contrast
Diet, Cancer and Health, 2008 [17]	53 incident cases ~10 years follow-up	Men and women	0.88 (0.58–1.35)	For 1 µg/L increase in time-weighted average exposure (drinking water)
			0.94 (0.81–1.09)	For 5 mg increase in cumulative exposure (drinking water)
Residents in arseniasisendemic area in Taiwan, 2001 [18]	9 incident cases ~5 years follow-up	Men and women	2.82 (1.29–5.36)	Standardised incidence ratio compared with general population in Taiwan
Finns living outside municipal drinking-water system area during 1967-1980, 1999 [19]	49 incident cases ~14 years follow-up	Men and women	Daily dose of arsenic in well water 10 years before cancer diagnosis	
			0.94 (0.39–2.27)	≥1 vs. <0.2 µg/d
			Cumulative dose of arsenic in well water 10 years before cancer diagnosis	
			0.47 (0.21–1.04)	≥2 vs. <0.5 g/d
Historical records of Mormons in Utah, 1999 [20]	~9 years follow-up	Men	1.75 (0.80–3.32)	Standardised mortality ratio compared with white male population in Utah
	~4 years follow-up	Women	1.60 (0.44–4.11)	Standardised mortality ratio compared with white female population in Utah

Ecological studies were not reviewed for the CUP Kidney SLR 2015, although nine were reviewed in the 2005 SLR. All studies showed an increased risk for the highest exposure levels compared with the lowest. Effect sizes, particularly from ecological studies in areas of high exposure levels, tend to be relatively large.

The new study identified in the CUP Kidney SLR 2015 [17] was inconsistent with the overall finding from the 2005 SLR as it showed a non-significant inverse association. The CUP Panel also considered the ecological data and the International Agency for Research on Cancer (IARC) grading of arsenic and arsenic compounds as Class 1 carcinogens.

Mechanisms

IARC has judged arsenic and arsenic compounds to be carcinogenic to humans [3]. They may cause chromosomal abnormalities, inhibition of DNA repair and an increase in cell proliferation [21]. In addition, arsenic in drinking water is well absorbed in the gastrointestinal tract, and both inorganic arsenic and its methylated metabolites are excreted in urine. Arsenic can modify the urinary excretion of porphyrins in animals and humans. Inorganic arsenic has several genotoxic effects, including the induction of changes in chromosome structure and number, increases in sister chromatid exchanges and micronuclei, gene amplification, cell transformation and aneuploidy [22-24]. A role for inorganic arsenic as a carcinogen, such as a tumour promoter rather than a tumour initiator, has also been hypothesised [25].

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: Non-alcoholic drinks (Appendix – Mechanisms) for the updated mechanisms summary.

CUP Panel's conclusion:

The overall evidence for a relationship between arsenic and kidney cancer was inconsistent. One study reported a significant positive association and there was strong ecological evidence, but no meta-analysis was conducted. Although arsenic is a known carcinogen and is convincingly linked to cancer risk at some sites, evidence linking it specifically to kidney cancer remains inconclusive. The CUP Panel concluded:

The evidence suggesting that consumption of arsenic in drinking water increases the risk of kidney cancer is limited.

7.2 Alcoholic drinks

(Also see CUP Kidney SLR 2015: Sections 5.4.1, 5.4.1.1, 5.4.1.2 and 5.4.1.3)

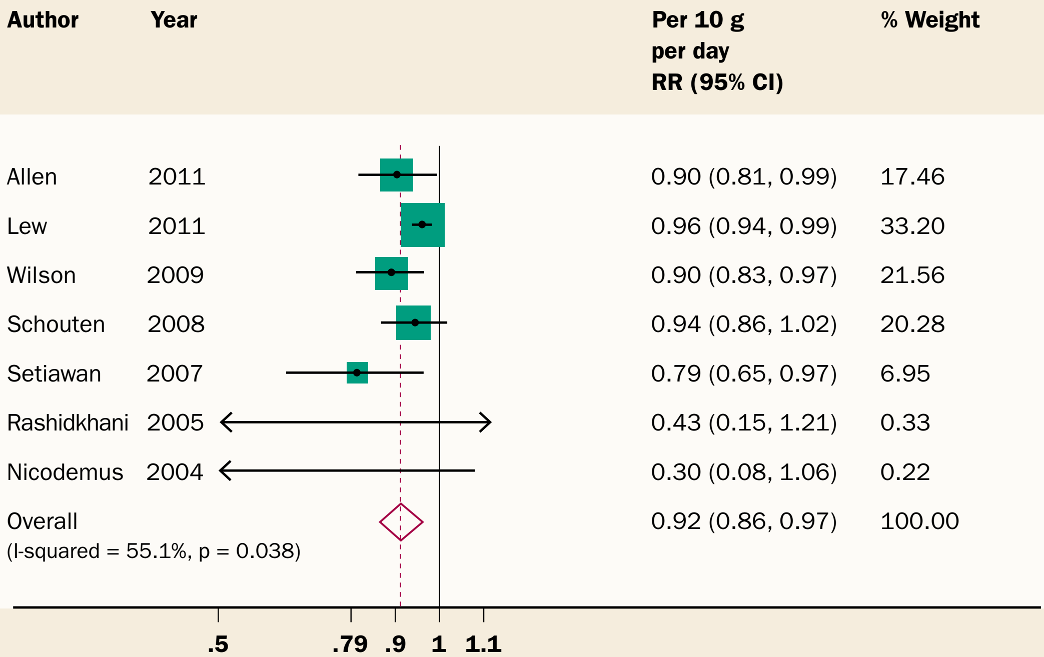
Alcohol as ethanol

The CUP identified five new or updated studies [26-30], giving a total of eight studies (12 publications) (see CUP Kidney SLR 2015, table 63, for a full list of references). All seven studies (seven estimates) reporting on kidney cancer incidence reported an inverse association when comparing the highest and the lowest categories, of which six were statistically significant (see CUP Kidney SLR 2015, figure 53).

Seven of the eight studies were included in the dose-response meta-analysis (n = 3,525), which showed a statistically significant 8 per cent decreased risk per 10 grams of alcohol per day (RR 0.92 (95% CI 0.86–0.97)) (see **figure 1** (CUP Kidney SLR 2015, figure 54)). High heterogeneity was observed (I^2 = 55%). The overall heterogeneity appeared to be explained by the weaker inverse association (compared with other studies) reported by one study, mainly for men [26]. The heterogeneity decreased after exclusion of this study (I^2 = 25%). There was evidence of small study bias with Egger's test (p = 0.001).

Two smaller studies found stronger inverse associations than the other studies (see CUP Kidney SLR 2015, figure 55). The highest category reported in studies is 30 grams or more per day (see Kidney CUP SLR 2015, figure 53). There is insufficient specific evidence on higher levels of drinking – for example, 50 grams or 70 grams per day – to assess the effect of drinking alcohol at these levels on kidney cancer (see CUP Kidney SLR 2015, figure 56).

Figure 1: Dose-response meta-analysis of alcohol (as ethanol) intake and kidney cancer, per 10g per day



When stratified by sex, the dose-response meta-analysis showed a decreased risk per 10 grams per day, which was statistically significant in women but not men (see **table 2** and CUP Kidney SLR 2015, figure 57).

Table 2: Summary of CUP 2015 stratified dose-response meta-analysis – alcohol

Analysis	Increment	RR (95% CI)	I^2	No. Studies	No. Cases
MEN	Per 10 g/day	0.92 (0.84-1.00)	71%	3	1,796
WOMEN	Per 10 g/day	0.81 (0.68-0.96)	44%	5	1,318

The results were consistent in analyses conducted by type of alcoholic drink consumed (as ethanol) for beer, wine and spirits but reached statistical significance only for beer (RR = 0.77 (95% CI 0.65–0.92) per 10 grams of alcohol per day).

One study [31] was not included in any of the CUP analyses because it did not report sufficient data.

The CUP 2015 findings were consistent with the dose-response meta-analysis from the 2005 SLR, which included three studies (one did not adjust for smoking) and showed a significant inverse association per serving per day (RR = 0.48 (95% CI 0.25–0.90)). The effect observed in the CUP Kidney SLR 2015 was smaller but included more than double the number of studies and many more cases of kidney cancer. The results strengthen the evidence showing a decreased risk, and both the 2005 SLR and the CUP Kidney SLR 2015 consistently show no adverse effect of consuming alcohol.

Published pooled analyses and meta-analyses

One published pooled analysis of cohort studies [32] and two meta-analyses [33, 34] on alcohol and kidney cancer were identified in the CUP Kidney SLR 2015. The pooled analysis reported a significant decreased risk when comparing the highest and lowest drinkers and the dose-response meta-analysis showed a statistically significant 19 per cent decreased risk per 10 grams per day. When the studies identified by the CUP 2015 (but not in the pooled analysis) were combined with the results of the pooled analysis, a significant 12 per cent decreased risk was observed per 10 grams per day. Both meta-analyses reported significant decreased risks when comparing the highest and the lowest drinkers (26 per cent decreased risk (12.5–49.9 grams per day compared with non-drinking) [33] and 29 per cent decreased risk (for the highest compared to the lowest alcohol intake) [34]). Results from the CUP and the pooled analyses are presented in **table 3**.

Table 3: Summary of CUP 2015 meta-analysis and published pooled analyses – alcohol

Analysis	Increment	RR (95% CI)	I^2	No. Studies	No. Cases	Factors adjusted for
CUP Kidney Cancer SLR 2015	Per 10 g/day	0.92 (0.86-0.97)	55%	7	3,525	
Pooling Project of Cohort Studies [32]	≥ 15 g/day vs. non-drinker	0.72 (0.60-0.86)	-	12	1,430	Adjusted for age, history of hypertension (Y/N), BMI, pack years of smoking (continuous), combination of parity and age at first birth (age at first birth < 25 years and parity of 1 or 2, age at first birth ≥ 25 years and parity of 1 or 2 or nulliparous, age at first birth < 25 years and parity of ≥ 3, and age at first birth ≥ 25 years and parity of ≥ 3), and total energy intake (kcal/day, continuous).
	Per 10 g/day ethanol intake*	0.81 (0.74-0.90)				
CUP Kidney Cancer SLR 2015 additional analysis: Pooling Project of Cohort Studies [32] combined with studies from the CUP**	Per 10 g/day	0.88 (0.79-0.97)	80%	15	≈4,179***	

*   Participants in the Pooling Project with intake >30 g/day were excluded
**   Pooling Project meta-analysed with three studies from the CUP [26, 27, 29]
*** For the category ≥ 15 g/day

Mechanisms

The mechanisms whereby alcohol might reduce kidney cancer risk are unclear, although there are several hypotheses. Moderate alcohol intake is related to reduced risks of hyperinsulinemia and type 2 diabetes, which may be determinants of kidney cancer [32, 35].

In addition, alcoholic beverages may contain antioxidant phenolic compounds, which might lower kidney cancer risk through various mechanisms [36].

A further potential mechanism may be related to the diuretic effect of alcohol, which may reduce exposure of kidney epithelial cells to carcinogenic solutes because of dilution and shorter duration of exposure [32, 37].

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:

The evidence was consistent with a clear inverse dose-response relationship for alcohol and kidney cancer. There was evidence of heterogeneity, which appeared to be due to differences in the size of the effect. When stratified by sex, the association was significant for women but not for men. The results were consistent with the findings from the 2005 SLR, but with more studies and cases. The results were also consistent with findings from a published pooled analysis. The protective effect is apparent up to 30 grams per day (about 2 drinks a day). There is insufficient evidence beyond 30 grams per day. There is evidence of plausible mechanisms in humans. The CUP Panel concluded:

Consumption of alcoholic drinks probably protects against kidney cancer. This is based on evidence for alcohol intakes up to 30 grams per day (about two drinks a day).

7.3 Body fatness

(Also see CUP Kidney SLR 2015: Sections 8.1, 8.2.1 and 8.2.3)

The Panel interpreted body mass index (BMI), waist circumference and waist-hip ratio as measures of body fatness. These anthropometrical measures are imperfect and cannot distinguish between lean mass and body fat.

The CUP identified 28 studies (36 publications) on body fatness, all of which reported on BMI, three of which also reported on waist circumference and four of which also reported on waist-hip ratio.

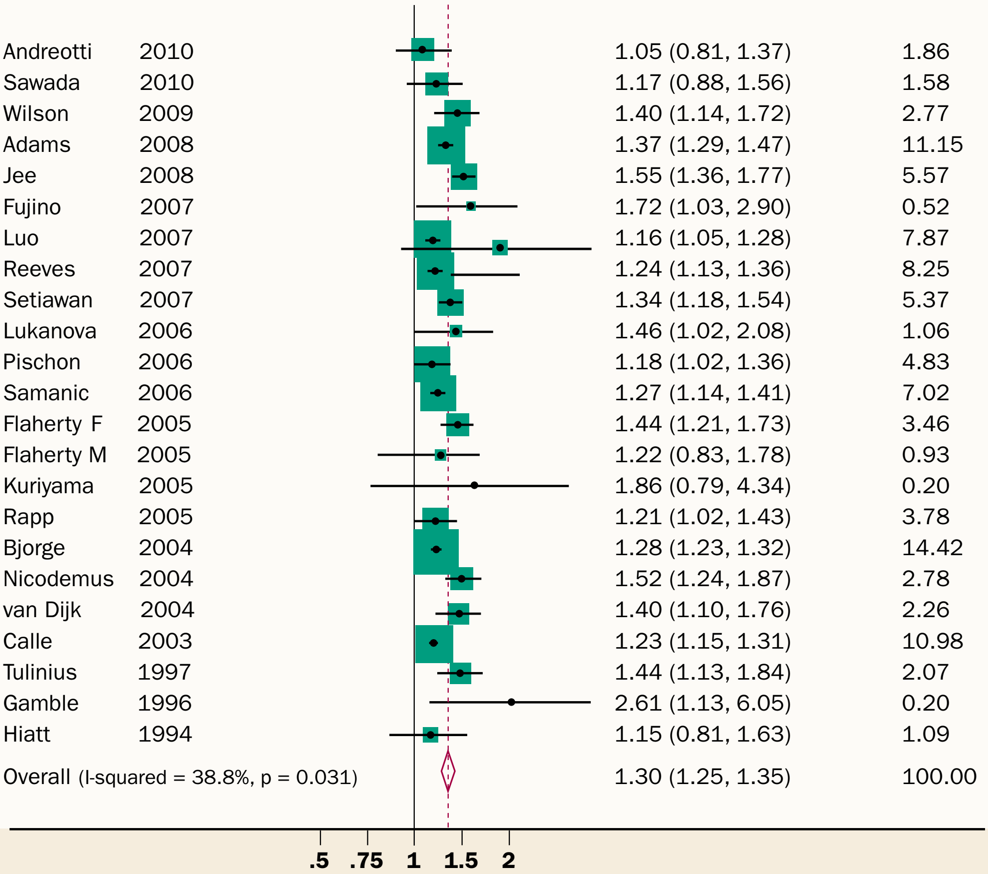
Body mass index

The CUP identified 14 new or updated studies (17 publications) [29, 38-53], giving a total of 28 studies (37 articles) (see CUP Kidney SLR 2015, table 140, for a full list of references). Of 30 estimates (21 studies) reporting on kidney cancer incidence, 28 showed a positive association when comparing the highest and the lowest categories, 14 of which were significant. One other study reported a positive association for women and an inverse association for men, both of which were not significant. Both studies reporting on kidney cancer mortality reported positive associations for both men and women, one of which was significant in women (see CUP Kidney Cancer SLR 2015, figure 115).

Twenty-three of the 28 studies were included in the dose-response meta-analysis (n = 15,575), which showed a statistically significant 30 per cent increased risk per 5 kg/m^2 (RR 1.30 (95% CI 1.25–1.35)) (see **figure 2** (CUP Kidney SLR 2015, figure 116)). Moderate heterogeneity was observed (I^2 = 39%).

Figure 2: Dose-response meta-analysis of BMI and kidney cancer, per 5 kg/m²

Author	Year	Per 5 kg/m² RR (95% CI)	% Weight
Andreotti	2010	1.05 (0.81, 1.37)	1.86
Sawada	2010	1.17 (0.88, 1.56)	1.58
Wilson	2009	1.40 (1.14, 1.72)	2.77
Adams	2008	1.37 (1.29, 1.47)	11.15
Jee	2008	1.55 (1.36, 1.77)	5.57
Fujino	2007	1.72 (1.03, 2.90)	0.52
Luo	2007	1.16 (1.05, 1.28)	7.87
Reeves	2007	1.24 (1.13, 1.36)	8.25
Setiawan	2007	1.34 (1.18, 1.54)	5.37
Lukanova	2006	1.46 (1.02, 2.08)	1.06
Pischon	2006	1.18 (1.02, 1.36)	4.83
Samanic	2006	1.27 (1.14, 1.41)	7.02
Flaherty F	2005	1.44 (1.21, 1.73)	3.46
Flaherty M	2005	1.22 (0.83, 1.78)	0.93
Kuriyama	2005	1.86 (0.79, 4.34)	0.20
Rapp	2005	1.21 (1.02, 1.43)	3.78
Bjorge	2004	1.28 (1.23, 1.32)	14.42
Nicodemus	2004	1.52 (1.24, 1.87)	2.78
van Dijk	2004	1.40 (1.10, 1.76)	2.26
Calle	2003	1.23 (1.15, 1.31)	10.98
Tulinius	1997	1.44 (1.13, 1.84)	2.07
Gamble	1996	2.61 (1.13, 6.05)	0.20
Hiatt	1994	1.15 (0.81, 1.63)	1.09
Overall (I-squared = 38.8%, p = 0.031)		1.30 (1.25, 1.35)	100.00



When stratified by outcome, a dose-response meta-analysis showed a significant increase risk per 5 kg/m² for kidney cancer incidence and for mortality. When stratified by sex, there was significant increased risk per 5 kg/m² for both men and women. Finally, when stratified by geographical location, there was a significant increased risk per 5 kg/m² in North American, European and Asian studies (see **table 4** and CUP Kidney SLR 2015, figures 119 and 120).

Table 4: Summary of CUP 2015 stratified dose-response meta-analyses – BMI

Analysis	Increment	RR (95% CI)	I^2	No. Studies	No. Cases
Incidence	Per 5 kg/m^2	1.30 (1.25-1.36)	39%	21	14,148
Mortality	Per 5 kg/m^2	1.32 (1.01-1.71)	37%	2	1,427
Men	Per 5 kg/m^2	1.29 (1.23-1.36)	30%	17	8,741
Women	Per 5 kg/m^2	1.28 (1.24-1.32)	0%	17	5,708
North America	Per 5 kg/m^2	1.29 (1.20-1.39)	56%	10	4,117
Europe	Per 5 kg/m^2	1.27 (1.24-1.31)	0%	9	8,739
Asia	Per 5 kg/m^2	1.47 (1.26-1.72)	16%	4	2,719

Four studies [54-57] were not included in any of the CUP analyses because they did not report sufficient data.

The CUP 2015 findings were similar to the dose-response meta-analysis from the 2005 SLR, which included seven studies and showed a significant positive association per 5 kg/m^2 (RR 1.31 (95% CI 1.24–1.39), n = 8,602) for incidence and mortality combined, the CUP 2015 included more than three times as many studies and many more cases of kidney cancer.

Published pooled analyses and meta-analyses

Results from three pooled analyses [58-60] and three meta-analyses [61-63] on BMI and kidney cancer were identified by the CUP Kidney SLR 2015. All published pooled and meta-analyses reported positive associations for continuous and highest estimates compared with lowest estimates, consistent with the CUP Kidney SLR 2015, but not all were statistically significant. The CUP included more kidney cancer cases than any of the published pooled analyses. All three meta-analyses reported significant positive associations for continuous estimates. Results from the published pooled analyses are presented in **table 5**.

Table 5: Summary of CUP 2015 meta-analyses and published pooled analysis – BMI

Analysis	Increment	RR (95% CI)	I^2	No. Studies	No. Cases	Factors adjusted for
CUP Kidney SLR 2015	Per 5 kg/m^2	1.30 (1.25-1.35)	39%	23	15,575	
Asia-Pacific Cohort Studies Collaboration [60]	BMI ≥30 vs. 18.5–24.9 kg/m^2	1.59 (0.78-3.24)	-	39	93	Adjusted for age and smoking
	Per 5 kg/m^2	1.20 (0.86-1.66)				
Metabolic Syndrome and Cancer Project – Me-Can project [58]	BMI 31.7 vs. 21.5 kg/m^2 (men)	1.51 (1.13-2.03)	-	7	592	Adjusted for categories of birth year and age at measurement, and stratified at cohort
	BMI 31.7 vs. 20.0 kg/m^2 (women)	2.21 (1.32-3.70)		7	263	
Prospective Studies Collaboration [59]	Per 5 kg/m^2	1.23 (1.06-1.43)	-	57	422	Adjusted for study, sex, age at risk (in 5-year groups) and baseline smoking status

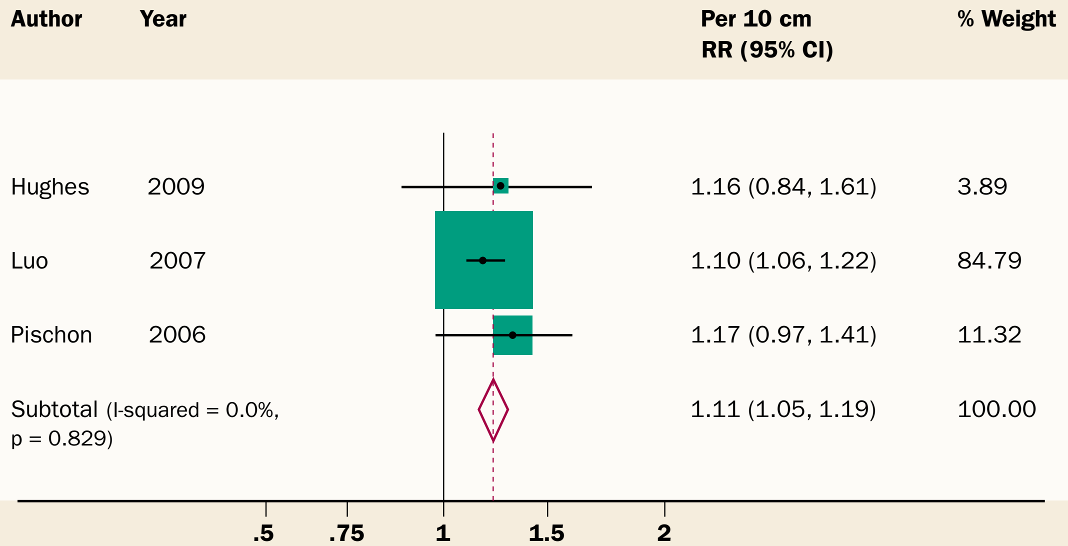
Waist circumference

The CUP identified three studies (three publications) [48, 51, 64]. No studies were identified in the 2005 SLR (see CUP Kidney SLR 2015, table 150, for a full list of references). All three studies reporting on waist circumference and the incidence of kidney cancer showed a non-significant positive association when comparing the highest and the lowest categories (see CUP Kidney SLR 2015, figure 128).

All three studies were included in the dose-response meta-analysis (n = 751), which showed a statistically significant 11 per cent increased risk per 10 centimetres (RR 1.11 (95% CI 1.05–1.19)) (**see figure 3** (CUP Kidney SLR 2015, figure 129)). No heterogeneity was observed (I^2 = 0%).

No cohort studies were identified in the 2005 SLR.

Figure 3: Dose-response meta-analysis of waist circumference and kidney cancer, per 10 cm



Waist-hip ratio

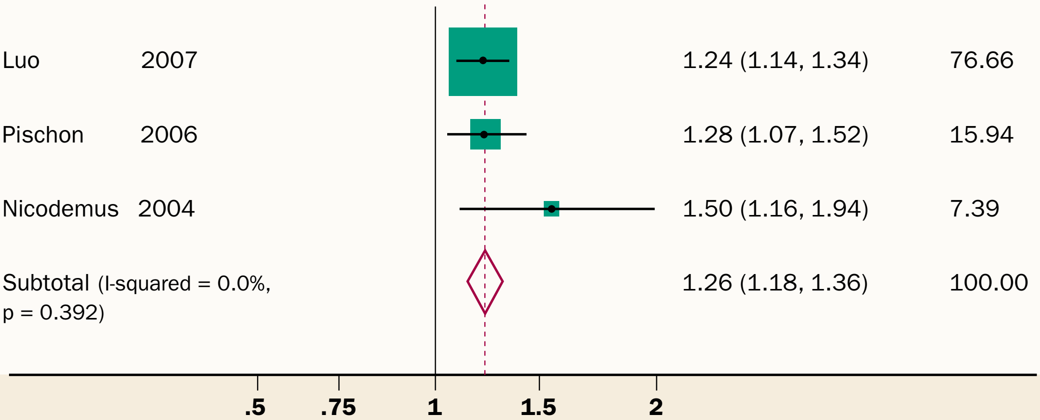
The CUP identified three new studies (three publications) [46, 48, 51], giving a total of four studies (five publications) in the CUP (see CUP Kidney SLR 2015, table 154, for a full list of references). All four studies reporting on waist-hip ratio and the incidence of kidney cancer showed a positive association when comparing the highest and the lowest categories, of which two were statistically significant (see Kidney Cancer SLR 2015, figure 128).

Three studies were included in the dose-response meta-analysis (n = 751), which showed a statistically significant 26 per cent increased risk per 0.1 unit (RR 1.26 (95% CI 1.18–1.36)) (see **figure 4** (CUP Kidney SLR 2015, figure 132). No heterogeneity was observed (I^2 = 0%).

Only one cohort study was identified in the 2005 SLR, and no meta-analysis could be conducted.

Figure 4: Dose-response meta-analysis of waist-hip ratio and kidney cancer, per 0.1 unit

Author	Year	Per 0.1 unit RR (95% CI)	% Weight
Luo	2007	1.24 (1.14, 1.34)	76.66
Pischon	2006	1.28 (1.07, 1.52)	15.94
Nicodemus	2004	1.50 (1.16, 1.94)	7.39
Subtotal (I-squared = 0.0%, p = 0.392)		1.26 (1.18, 1.36)	100.00



Mechanisms

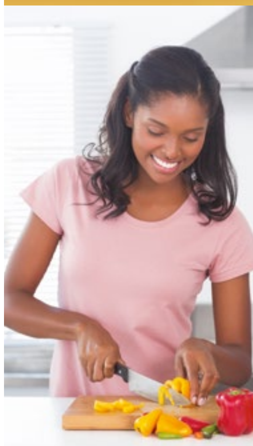
The specific mechanisms whereby obesity increases risk of kidney cancer are speculative, but excess body fat directly affects circulating insulin levels [65] and it increases the risk of high blood pressure [66] – factors positively related to the development of kidney cancer [67]. In addition, obesity is associated with a low-grade chronic inflammatory state. Such chronic inflammation is accompanied by metabolic and physiological alterations that could increase cancer risk. In obesity, adipose tissue is characterised by macrophage infiltration, and these macrophages are an important source of inflammatory signals. The adipocyte (fat cell) produces pro-inflammatory factors, and obese individuals have elevated concentrations of circulating tumour necrosis factor-alpha, interleukin-6 and C-reactive protein compared with lean people, as well as of leptin, which also functions as an inflammatory cytokine [68].

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:

Body fatness is reflected by BMI and measures of abdominal girth. There was consistent epidemiological evidence for an association between various measures of body fatness and kidney cancer, with a clear dose-response relationship. The association was still apparent when stratified by outcome, sex and geographical location. Results from several published pooled analyses and meta-analyses were also consistent with the CUP results in the direction of the effect, although not all showed findings that were statistically significant. Multiple mechanisms have been demonstrated in humans through which obesity and energy balance might increase kidney cancer risk. The CUP Panel concluded:

Greater body fatness (marked by BMI, waist circumference and waist-hip ratio) is a convincing cause of kidney cancer.



7.4 Adult attained height

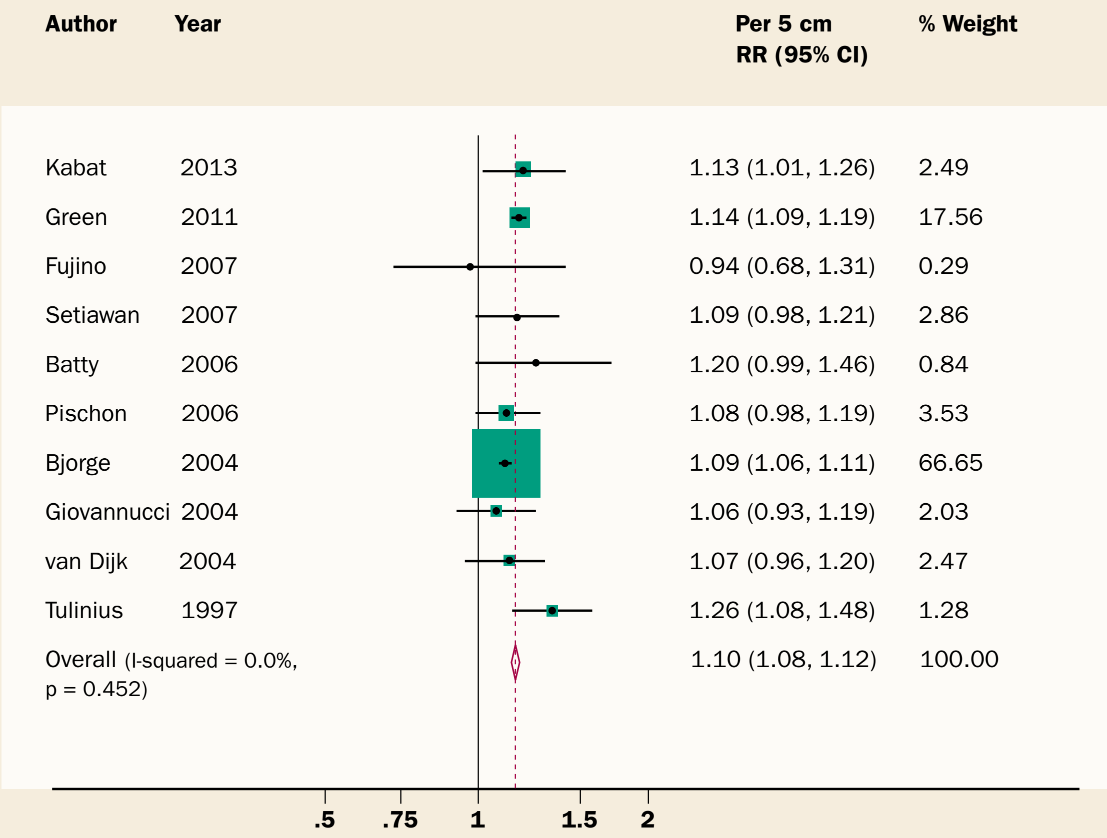
(Also see CUP Kidney SLR 2015: Section 8.3.1)

The CUP Kidney SLR 2015 identified six new studies (six publications) [29, 47, 51, 69-71], giving a total of 11 studies (11 publications) (see CUP Kidney SLR 2015, table 158, for a full list of references).

Of the four studies (eight estimates) reporting on kidney cancer incidence, three showed a positive association when comparing the highest and the lowest categories, which was statistically significant in one study, and the fourth study showed an inverse association for men and a positive association for women, both of which were not significant. Of the two studies reporting on kidney cancer mortality, one showed a non-significant inverse association and one showed a non-significant positive association (see Kidney Cancer SLR 2015, figure 134).

Ten studies were included in the dose-response meta-analysis (*n* = 9,874), which showed a statistically significant 10 per cent increased risk per 5 centimetres (RR 1.10 (95% CI 1.08–1.12)) (see **figure 5** (CUP Kidney SLR 2015, figure 135)). No heterogeneity was observed ($I^2 = 0\%$).

Figure 5: Dose-response meta-analysis of height and kidney cancer, per 5 cm



When stratified by sex, the dose-response meta-analysis showed a significant increased risk per 5 centimetres in men and women (see **table 6** and CUP Kidney SLR 2015, figure 139).

Table 6: Summary of CUP 2015 stratified dose-response meta-analysis – height

Analysis	Increment	RR (95% CI)	I^2	No. Studies	No. Cases
MEN	Per 5 cm	1.10 (1.06-1.13)	5%	9	1,272
WOMEN	Per 5 cm	1.10 (1.07-1.14)	11%	6	409

One study [72] was not included in any of the CUP analyses because it did not report sufficient data.

The CUP Kidney SLR 2015 findings showed a significant positive dose-response relationship between adult attained height and kidney cancer, which strengthened the findings from the 2005 SLR, in which the meta-analysis showed no significant association (RR = 1.13 (0.96–1.33)). The CUP Kidney SLR 2015 included five times as many studies and many more cases of kidney cancer and reported results per 10 centimetres compared with 5 centimetres in the 2005 SLR.

Published pooled analyses and meta-analysis

Results from one published pooled analysis of cohort studies on height and kidney cancer were identified in the CUP Kidney SLR 2015 [73]. The study, which contained very few cases of kidney cancer, reported no significant associations between height and kidney cancer risk in men or women. Results from the CUP Kidney SLR 2015 and the pooled analysis are presented in **table 7**.

Table 7: Summary of CUP 2015 meta-analysis and pooled analyses – height

Analysis	Increment	RR (95% CI)	I^2	No. Studies	No. Cases	Factors adjusted for
CUP Kidney SLR 2015	Per 5 cm	1.10 (1.08-1.12)	0	10	9,874	
Asia-Pacific Cohort Studies Collaboration [73]	Per 6 cm (men)	1.04 (0.83-1.31)		38	67	Age, study and year of birth adjusted
	Per 6 cm (women)	1.21 (0.81-1.83)			23	

Mechanisms

Adult height is related to the rate of growth during fetal life and childhood [74, 75]. The number of cell divisions in fetal life and childhood, health and nutrition status in childhood, and age of sexual maturity are all determined by the hormonal microenvironment (plasma levels of growth factors and oestrogens and their respective binding protein). Conversely, total body adiposity and visceral adiposity can alter the circulating concentration of some plasma hormones and their respective binding protein (insulin, sex steroids, insulin-like growth factors (IGFs)) [76]. Many of these mechanisms, such as early-life nutrition affecting body composition, altered circulating and free hormone profiles, can modulate the rate of tissue growth and sexual maturation. It is therefore plausible that nutritional factors that affect height could also influence cancer risk. Specific tissues in taller people are exposed to higher levels of insulin, pituitary-derived growth hormone and IGFs, and thus may have undergone more cell divisions. This increased number of cell divisions may contribute to greater potential for error during DNA replication, resulting in an increased risk of developing cancer [77, 78].

Therefore, adult attained height is a marker of an aggregated fetal and childhood experience and is clearly also a surrogate for important nutritional exposures, which affect several hormonal and metabolic axes and which may influence cancer risk.

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 overall evidence was generally consistent with a clear dose-response relationship. When stratified by sex, the association remained significant in both men and women. The results strengthened the findings from the 2005 SLR. The results of the published pooled analysis, with few cases, showed an increased risk but were not statistically significant. There is evidence of plausible mechanisms operating in humans. The CUP Panel concluded:

Developmental factors leading to greater linear growth (marked by adult attained height) are probably a cause of kidney cancer.

7.5 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. The list of exposures judged as 'Limited – no conclusion' is summarised in the matrix on **page 8**.

Evidence for the following exposures, previously judged as 'Limited – no conclusion' in the Second Expert Report [1], remains unchanged after updating the analyses with new data identified in the CUP Kidney SLR 2015: Cereals (grains) and their products, vegetables, fruits, meat, poultry, fish, eggs, milk and dairy products, total fat, soft drinks, tea, carbohydrate, protein, vitamin A, retinol, vitamin C, vitamin E, beta-carotene, flavonol, Seventh-day Adventist diets, physical activity, birth weight, and energy intake.

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: dietary fibre, vitamin B6, folate, calcium, alpha-carotene, beta-cryptoxanthin, lycopene, lutein and zeaxanthin.

8. Comparison with the Second Expert Report

Overall the evidence from the additional cohort studies identified by the CUP was consistent with that reviewed as part of the Second Expert Report [1]. Much of the new evidence was related to height, which has been upgraded from 'limited – no conclusion' to 'probably a cause', and also to alcoholic drinks, for which the conclusion from the Second Expert Report was upgraded from 'Limited – no conclusion' alcoholic drinks (for a protective effect) and 'Substantial effect on risk unlikely' alcoholic drinks (for an adverse effect) to 'probably protects' against kidney cancer (up to 30 grams a day).

9. Conclusions

The CUP Panel concluded the following:

- **Body fatness: Greater body fatness (marked by BMI, waist circumference and waist-hip ratio) is a convincing cause of kidney cancer.**
- **Adult attained height: Developmental factors leading to greater linear growth (marked by adult attained height) are probably a cause of kidney cancer.**
- **Alcoholic drinks: Consumption of alcoholic drinks probably protects against kidney cancer. This is based on evidence for alcohol intakes up to 30 grams per day (about two drinks a day).**
- **Arsenic in drinking water: The evidence suggesting that consumption of arsenic in drinking water increases the risk of kidney cancer is limited.**

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

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.

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Abbreviations

AICR	American Institute for Cancer Research
BMI	Body mass index
CI	Confidence interval
CT	Computerised tomography
CUP	Continuous Update Project
DNA	Deoxyribonucleic acid
IARC	International Agency for Research on Cancer
IGF	Insulin-like growth factor
No.	Number
RR	Relative risk
SLR	Systematic literature review
VHL	von Hippel-Lindau
WCRF	World Cancer Research Fund
n	Number of cases

Glossary

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

Aneuploidy
The presence of an abnormal number of chromosomes in a cell, such as having 45 or 47 chromosomes when 46 are expected.

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.

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 distant or recent history of an exposure such as smoking, genetic profile, alcohol consumption or dietary intake is associated with the risk of disease.

Cell transformation
Transformation is the genetic alteration of a cell resulting from the direct uptake and incorporation of genetic material from outside the cell (exogenous DNA) from its surroundings, taken up through the cell membrane(s).

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 true exposure–disease relationship. An example is that smoking is related both to coffee drinking and to risk of lung cancer and thus, unless adjusted for (controlled) in studies, might make coffee drinking appear falsely as a possible cause of lung cancer.

CT scans
A computerized tomography (CT) scan combines a series of X-ray images taken from different angles and uses computer processing to create cross-sectional images, or slices, of the bones, blood vessels and soft tissues inside the body.

Deoxyribonucleic acid (DNA)
The double-stranded, helical molecular chain found in the chromosomes within the nucleus of cells, which carries the genetic information.

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 [1]).

Ecological studies
Ecological studies are observational studies of the effect of risk-modifying factors on health or other outcomes defined by the level at which data are analysed, namely at the population or group level rather than the individual level. Both risk-modifying factors and outcomes are averaged for the populations in each geographical or temporal unit, and then compared using standard statistical methods. Ecological studies are often used to measure the prevalence and incidence of disease, particularly when disease is rare.

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

Exposure
A factor to which an individual may be exposed to varying degrees, such as intake of a food, level or type of physical activity, or aspect of body composition.

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

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

Heterogeneity
A measure of difference between the results of different studies addressing a similar question in meta-analysis. The degree of heterogeneity may be calculated statistically, 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 (cytokines), causing redness, heat, pain and swelling.

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

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

Malignant
The capacity of a tumour to spread to surrounding tissue (invasion) or to other sites in the body (metastasis).

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

Metastasis
The spread of malignant cancer cells to distant locations around the body from the original site.

Micronuclei
Small nucleus that forms whenever a chromosome or a fragment of a chromosome is not incorporated into one of the daughter nuclei during cell division.

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

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.

Pharmaceuticals
More commonly known as medicines or drugs, used to diagnose, cure, treat, or prevent disease.

Physical activity
Any movement using skeletal muscles.

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.

Publication bias
A bias in the overall balance of evidence in the published literature due to selective publication. Not all studies carried out are published, and those that are may differ from those that are not. The likelihood of publication bias can be tested, for example, with either Begg's or Egger's tests.

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 with 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.

Sister chromatid exchanges
The exchange of genetic material between two identical sister chromatids.

Standardised mortality ratio
A quantity, expressed as either a ratio or percentage, quantifying the increase or decrease in death of a study cohort with respect to the general population.

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.

Tumour initiator
An agent that damages cellular DNA, a necessary condition for the production of a new tumour.

Tumour promoter
A chemical, complex of chemicals or biological agent that promotes a later stage of carcinogenesis, called tumor promotion, by altering expression of the genetic information, rather than altering the structure of DNA.

Tumour suppressor gene
A gene that protects a cell from one step on the path to cancer. When this gene mutates to cause a loss or reduction in its function, the cell can progress to cancer, usually in combination with other genetic changes.

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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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