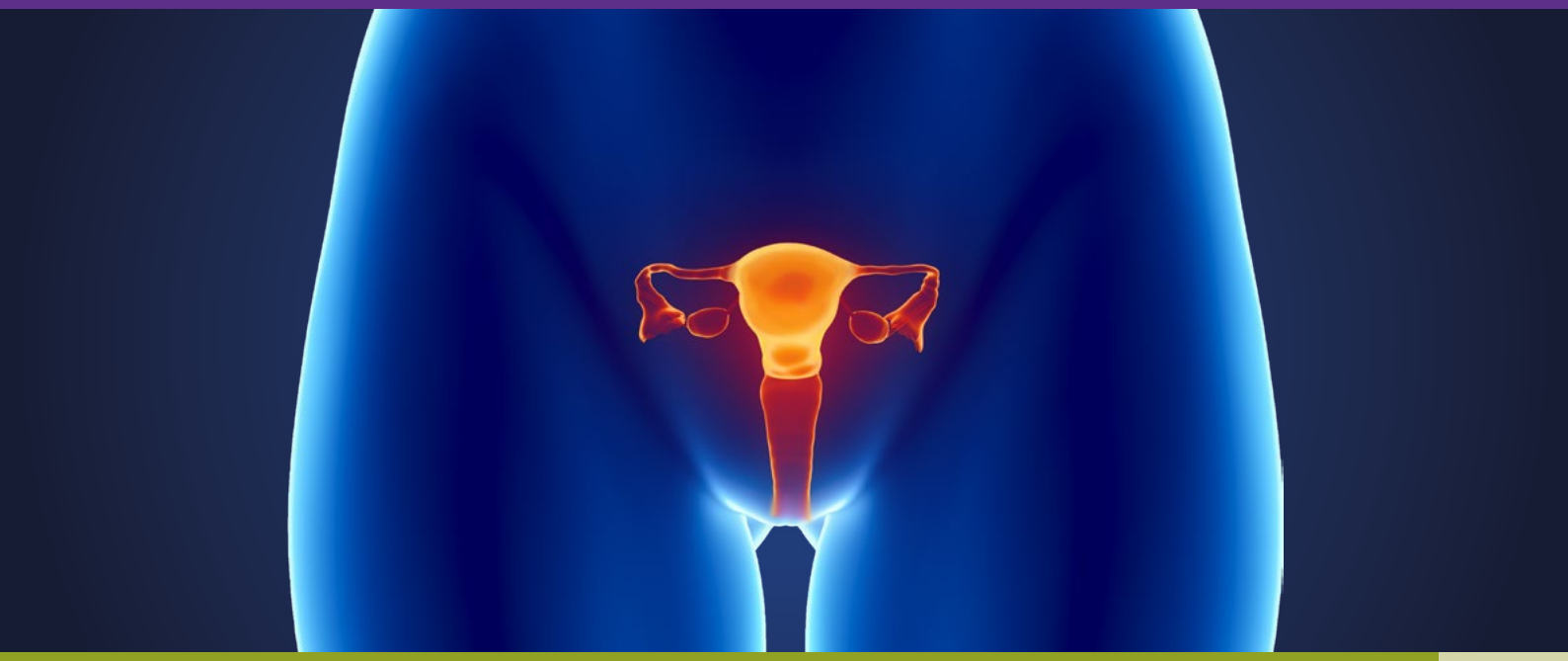
World Cancer Research Fund

American Institute for Cancer Research

CUP Continuous Update Project

Analysing research on cancer prevention and survival



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

2013

Revised 2018

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 endometrial 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 endometrial 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.

2013 DIET, NUTRITION, PHYSICAL ACTIVITY AND ENDOMETRIAL CANCER

		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	Convincing		**Body fatness**[1]
	Probable	**Physical activity**[2] **Coffee**[3]	**Glycaemic load** **Adult attained height**[4]
LIMITED EVIDENCE	Limited – suggestive		Sedentary habits[5]
	Limited – no conclusion	Cereals (grains) and their products; fruits; vegetables; pulses (legumes); soya and soya products; red meat; processed meat; poultry; fsh; eggs; milk and dairy products; dietary fbre; total fat; animal fat; saturated fatty acids; cholesterol; tea; glycaemic index; protein; retinol; beta-carotene; folate; vitamin C; vitamin E; multivitamins; alcohol; acrylamide; dietary pattern; and lactation	
STRONG EVIDENCE	Substantial effect on risk unlikely		

1 The Panel interpreted BMI (including BMI at age 18-25 years), measures of abdominal girth, and adult weight gain as interrelated aspects of body fatness as well as fat distribution.

2 Physical activity of all types: occupational, household, transport and recreational.

3 The effect is found in both caffeinated and decaffeinated coffee and cannot be attributed to caffeine.

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

5 Sedentary habits as marked by sitting time.

1. Summary of Panel judgements

Overall, the Panel notes the strength of evidence that physical activity and consumption of coffee protects against endometrial cancer and greater body fatness and glycaemic load cause endometrial cancer.

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

Convincing evidence

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

Probable evidence

Physical activity: Physical activity probably protects against endometrial cancer.

Coffee: Consumption of coffee probably protects against endometrial cancer.

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

Glyceamic load: Glycaemic load is probably a cause of endometrial cancer.

Limited - suggestive evidence

Sedentary habits: The evidence suggesting that sedentary habits might increase the risk of endometrial cancer is limited.

For a full description of the definitions of, and criteria for, the terminology of 'convincing', 'probable', 'limited - suggestive', 'limited - no conclusion' and 'substantial effect on risk unlikely', see the **Appendix** on page 31. The Panel judgements for cancer of the endometrium are shown in the matrix on **page 5**.

2. Trends, incidence and survival

The endometrium is the lining of the uterus. It is subject to a process of cyclical change during the fertile years of a woman's life. The majority of cancers that occur in the body of the uterus (womb) are endometrial cancers, mostly adenocarcinomas [2].

Endometrial cancer is the sixth most common cancer in women worldwide (and the twelfth most common cancer overall) [3]. Around 290,000 new cases were recorded in 2008, accounting for nearly 5 per cent of all new cases of cancer in women (2 per cent overall).

It is mainly a disease of high-income countries, where the highest incidence of endometrial cancer is in North America, and Central and Eastern Europe; and the lowest incidence in Middle and Western Africa [3]. Age-adjusted rates of endometrial cancer are increasing in countries undergoing transition from low- to high-income economies; although there is no clear, overall trend in high-income countries. Around the world, age-adjusted incidence rates range from around 15 per 100 000 women in North America and parts of Europe, to less than 5 per 100 000 in most of Africa and Asia [3]. In the USA, rates are higher in white women than among those from other ethnic groups, although mortality rates are higher in black women [4, 5]. Risk increases with age, with most cases diagnosed after menopause.

Endometrial cancer often produces symptoms at relatively early stages, so the disease is generally diagnosed early. The overall 5-year survival rate is relatively high, although it is lower in middle- than in high-income countries [6, 7]. For example in the US, the 5-year relative survival rate (which compares the 5-year survival of people with the cancer to the survival of others the same age who don't have cancer) for all endometrial cancer cases is about 69% [8].

Endometrial cancer accounts just under 1 per cent of all cancer deaths (2 per cent of cancer deaths in women) [3]. Also see box 7.1.1.

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 higher than the figures given here. The cancer survival rates given here and elsewhere are usually overall global averages. 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 and well established treatment facilities. Survival also is often a function of the stage at which a cancer is detected and diagnosed. The symptoms of some internal cancers are often evident only at a late stage, which accounts for relatively low survival rates. In this context, 'survival' means that the person with diagnosed cancer has not died 5 years after diagnosis.

3. Pathogenesis

Type 1 endometrial tumours are oestrogen driven, account for around 80 per cent of endometrial cancers, and have a favourable prognosis [9]. They follow a clear development pathway, starting with endometrial hyperplasia (an increase in the number of cells), and are relatively well differentiated. Type 2 tumours are less common, accounting for around 10 per cent of endometrial cancers. Most are associated with endometrial atrophy (wasting), tend to metastasise, and have a less favourable prognosis.

Many cases of endometrial cancers are reported in women who have no recognised risk factors – such as those that might disrupt endocrine (hormone) processes [2]. Some studies have shown that polycystic ovary syndrome and insulin insensitivity (or resistance), which are both components of metabolic syndrome, may play a role in the pathogenesis of endometrial cancer, perhaps through hormonal disruption [10]. The tumour-suppressor gene PTEN is also involved in the development of endometrial cancers [9]. See also section 1.2.2 of The cancer process.

4. Other established causes

Life events. Not bearing children increases the risk of endometrial cancer [11]. The reverse also applies: bearing children reduces the risk of, and may be seen as protective against, endometrial cancer [9, 10, 12, 13]. There is also substantial evidence that, as with breast and ovarian cancer, late natural menopause increases the risk of endometrial cancer [13]. The reverse also applies: early menopause reduces the risk of, and may be seen as protective against, this cancer [14].

Medication. Oral contraceptives, which contain either a combination of oestrogen and progesterone, or progesterone only, protect against this cancer [13, 14]. Oestrogen-only hormone replacement therapy is a cause of this cancer and is normally only prescribed to women who have had a hysterectomy [13, 15]. Tamoxifen, a hormonal therapy used for breast cancer, can also cause endometrial cancer [16].

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 endometrium include:

Patterns. Because endometrial cancer is hormone related, factors that modify risk might have different effects at different times of life.

Confounding. High-quality cohort studies exclude women who have had hysterectomies from 'at-risk' populations.

6. Methodology

To ensure consistency with evidence collected and analysed for the Second Expert Report, much of the methodology for the Continuous Update Project remains unchanged from that used previously. However, based upon the experience of conducting the systematic literature reviews for the Second Expert Report, some modifications to the methodology were made. The literature search was restricted to Medline and included only randomised controlled trials, cohort and case- control studies. Due to the large number of cohort studies, analysis and interpretation of case- control studies was not included in the Continuous Update Project SLR.

The number of studies showing separate results for pre- and post-menopausal women was low and analyses stratified by menopausal status could not be conducted other than for BMI.

Studies reporting mean difference as a measure of association are not included in the 2012 Continuous Update Project SLR, as relative risks estimated from the mean differences are not adjusted for possible confounders, and thus not comparable to adjusted relative risks from other studies.

The CUP Endometrial Cancer SLR included studies published up to 31st December 2012. For more information on methodology see the full CUP Endometrial Cancer SLR 2012.

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

There were 159 endometrial cancer articles included in the CUP analyses, including 91 new articles identified in the CUP updated search.

This report includes an updated description of the epidemiological evidence, the Panel's conclusions, and a comparison with the conclusions from the SER. It also includes a brief description of potential mechanisms for each exposure.

For information on the criteria for grading the epidemiological evidence see **Appendix** in this report. References to studies added as part of the CUP have been included; for details of references to other studies see the SER. Summary estimates from dose-response meta-analyses were regarded as non-significant if the 95% confidence interval included 1.0.

7.1 Glycaemic load

(Also see CUP Endometrial Cancer SLR 2012: Sections 5.1 and 5.1.6)

The evidence for glycaemic load[1] and total carbohydrate is presented in the following section, and is followed by an overall conclusion that incorporates both these exposures.

Glycaemic load

The CUP identified four new papers (from four cohort studies) [17-20] giving a total of six studies (including studies from the SER). All studies reported an increased risk for the highest comparison group compared to the lowest, one of which was statistically significant.

All six studies (four new) were included in the dose-response meta-analysis for glycaemic load and endometrial cancer (*n*=3869). No meta-analysis was conducted in the SER. The CUP analysis showed a 15% increased risk per 50 units per day, and this was statistically significant (RR 1.15 (95% CI 1.06-1.25)) (see CUP 2012 Figure 35). No heterogeneity was observed.

Results from three other published meta-analyses of cohort studies were similar to the results of the CUP analysis, all finding a significant positive association when comparing the highest comparison group to the lowest [21-23]. One of the published meta-analyses also reported a significant positive association per 50 units [23].

Carbohydrate

The CUP identified three new papers (from three cohort studies) [17, 18, 20] giving a total of five studies (including studies from the SER). Overall, the CUP found four of five studies reported an increased risk for the highest intake group compared to the lowest, one of which was borderline statistically significant. The other study reported a non-significant inverse association.

All five studies (three new) were included in the dose-response meta-analysis for carbohydrate and endometrial cancer (*n*=2629). The CUP analysis was conducted per 100 grams carbohydrate intake per day (corrected for energy intake). Overall, the CUP analysis showed an 18% increased risk per 100g per day, and this was statistically significant (RR 1.18 (95% CI 1.02-1.37)), with no heterogeneity observed (see CUP 2012 Figure 27). All studies included in the meta-analysis adjusted for both energy intake and body mass index (BMI) as potential confounding factors, except one study that only adjusted for energy intake and not BMI. In the SER, there was no clear association from the meta-analysis (RR 1.03 (95% CI 097-1.10)) per 15% energy intake for carbohydrate. The SER Panel judged the evidence to be limited, and no conclusion was possible.

1 'Glycaemic load' is the glycaemic index of a food multiplied by the number of grams of carbohydrate in the serving of food

Mechanisms

There are several potential underlying mechanisms for a positive association of glycaemic load (and carbohydrate) with endometrial cancer. Long-term consumption of a high glycaemic load diet results in hyperinsulinemia, which in turn increases the bioavailability of insulin-like growth factor 1 (IGF-1) and directly promotes cell growth, reduces cell death and stimulates cell division in endometrial cancer cell lines [23, 24]. Insulin and IGF-1 are also powerful negative regulators of sex hormone-binding globulin synthesis in vitro and may therefore stimulate endometrial cancer [23]. High glycemic load diets may also influence the risk of endometrial cancer by increasing oxidative stress [23].

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

CUP Panel's conclusion:

More studies were available for the CUP analyses and the evidence was generally consistent. A significant positive association was observed for glycaemic load and for total carbohydrate independently. Results from several published meta-analyses on glycaemic load were also consistent with the CUP result.

The Panel noted issues with regard to characterising carbohydrate-related exposures and given their complex nature, the difficulty in interpreting these. The Panel considered the primary exposure with an observed effect to be 'glycaemic load', with the evidence for 'total carbohydrate' as supporting evidence for this effect. The Panel also noted that the evidence for carbohydrate is derived largely from developed countries where a large proportion of carbohydrate is in the form of sugars and highly processed foods.

The CUP Panel concluded:

There is a substantial amount of generally consistent evidence from cohort studies, and there is evidence of biological plausibility. Glycaemic load is probably a cause of endometrial cancer.

7.2 Coffee

(Also see CUP Endometrial Cancer SLR 2012: Sections 3.6.1 and 3.6.1.1)

The evidence for coffee and decaffeinated coffee is presented in the following section, and is followed by an overall conclusion that incorporates both these exposures.

Coffee

The CUP identified six new papers (from six cohort studies) [25-30], giving a total of eight studies (including studies from the SER). All eight studies reported a decreased risk for the highest intake group compared to the lowest, four of which were statistically significant.

Seven studies (six new) were included in the dose-response meta-analysis for coffee and endometrial cancer (*n*=3571), and the CUP analysis was conducted per one cup per day. No meta-analysis was conducted in the SER. Overall, the CUP analysis showed a 7% decreased risk per one cup per day, and this was statistically significant (RR 0.93 (95% CI 0.91-0.96)) (see CUP 2012 Figure 14). There was little evidence of heterogeneity (I^2= 10%), which was due to differences in the size of the effect. There was no evidence of publication bias with Egger's test (p=0.39), but visual inspection of the funnel plot suggested that a small study [26] reported an inverse association much stronger than the association reported by other studies (see CUP 2012 Figure 15).

Two other published meta-analyses of cohort studies found a statistically significant decreased risk of endometrial cancer when comparing the highest coffee drinkers to the lowest [31, 32], and one of these studies also reported a significant decreased risk per one cup per day [32]. Another published meta-analysis of cohort studies reported non-significant inverse associations for the highest versus lowest categories and per one cup per day [33].

Decaffeinated coffee

The CUP identified three new papers (from three cohort studies) [28-30]. No studies were identified in the SER. All three studies reported a non-significant decreased risk for the highest intake group compared to the lowest.

All three studies were included in the dose-response meta-analysis for decaffeinated coffee and endometrial cancer (*n*=2585), and the CUP analysis was conducted per one cup per day. Overall, the analysis showed an 8% decreased risk per one cup per day, and this was statistically significant (RR 0.92 (95% CI 0.87-0.97)) (see CUP 2012 Figure 18). There was no evidence of heterogeneity.

No other published meta-analyses of cohort studies reporting on decaffeinated coffee and endometrial cancer risk were identified.

Mechanisms

Several biological mechanisms have been suggested to explain the inverse relationship of coffee drinking with endometrial cancer development. Several bioactive components, including chlorogenic acid, have strong antioxidant properties that can prevent oxidative DNA damage, improve insulin sensitivity and inhibit glucose absorption in the intestine [32].

Hyperinsulinemia has been positively associated with endometrial cancer development and endometrial cancer cell lines express high affinity insulin receptors, consistent with there being a direct biologic effect of insulin on the growth of endometrial cancer cells [29]. Coffee consumption has been demonstrated to improve insulin sensitivity and both caffeinated and decaffeinated coffee are associated with reduced insulin levels, particularly among overweight women [29].

Hyperinsulinemia may also impact on endometrial cancer development through indirect mechanisms, for example, through up-regulation of free, or bioavailable, insulin-like growth factor[1] (IGF-I), or through suppression of sex hormone binding globulin (SHBG), which elevates oestradiol bioactivity. Coffee drinking has been associated with higher SHBG levels, which reduce endometrial cancer risk through decreased oestradiol exposure [29, 32]. In addition, caffeine and some bioactive compounds in coffee seem to up-regulate hepatic expression of CYP1A2 and CYP3A4 which leads to increase in clearance of oestradiol overall, or even stimulate synthesis of oestrogen metabolites that may inhibit oestradiol-mediated carcinogenesis on endometrial cells [29].

Finally, high coffee consumption (including decaffeinated coffee) has been associated with lower circulating levels of C-peptide and higher levels of adiponectin [32].

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:

More studies were available for the CUP to allow meta-analyses. A significant inverse association was observed for both coffee and decaffeinated coffee intake. Little heterogeneity was observed for coffee and this was due to differences in the size of the effect (no heterogeneity was observed for decaffeinated coffee). The findings for coffee were also consistent with results from other published meta-analyses. In the SER, the Panel judged the evidence as too limited to draw a conclusion. The CUP Panel concluded:

There is a substantial amount of epidemiological evidence, which is consistent, and there is a dose-response relationship. There is evidence for biological plausibility. Coffee probably protects against endometrial cancer.

7.3 Physical activity

(Also see CUP Endometrial Cancer SLR 2012: Section 6)

The evidence for recreational physical activity, occupational physical activity, and walking/biking (mainly for transportation) is presented below, and is followed by an overall conclusion that incorporates all these exposures. Dose-response meta-analyses were not possible for these exposures due to differences in assessing physical activity across studies.

Recreational physical activity

The CUP identified six new papers (from six cohort studies) [34-39], giving a total of nine studies (including studies from the SER). The CUP found eight of the nine studies showed a decreased risk of endometrial cancer when comparing the highest versus the lowest levels of activity, three of which were significant, and the other study showed a non-significant increased risk (see CUP 2012 Figure 70). In general, adjustment for BMI in all studies made no difference to the direction of the effect or the statistical significance.

Occupational physical activity

The CUP identified two new papers (from two cohort studies) [35, 38], giving a total of five studies (including studies from the SER). All five studies reported a decreased risk of endometrial cancer when comparing the highest versus lowest levels of activity, three of which were statistically significant (see CUP 2012 Figure 68).

Walking/ biking (mainly for transportation)

The CUP identified four new papers (from four cohort studies) [35, 37-39], giving a total of five studies (including studies from the SER). The CUP found three of the five studies showed a decreased risk of endometrial cancer when comparing the highest versus the lowest levels of activity, one of which was significant, and two studies reported a non-significant increased risk (see CUP 2012 Figure 73).

Mechanisms

Sustained moderate physical activity raises the metabolic rate and increases maximal oxygen uptake [40]. In the long term, regular periods of such activity increase the body's metabolic efficiency and capacity (the amount of work that it can perform), as well as reducing circulating insulin levels and insulin resistance [41].

Physical activity is hypothesised to decrease endometrial cancer risk because it reduces serum levels of oestradiol and increases levels of sex hormone binding globulin (SHBG), the binding protein for oestradiol. These effects of physical activity may be mediated through prevention of weight gain [42]. More generally, effects on oestrogen metabolism may at least in part operate directly, or through decreasing body fat stores [43].

Hyperinsulinaemia also promotes endometrial carcinogenesis by stimulating endometrial cell growth directly, or indirectly by increasing insulin-like growth factor (IGF)-1 levels within the endometrium and decreasing levels of its binding proteins [44].

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: Physical activity (Appendix – Mechanisms) for the updated mechanisms summary.

CUP Panel's conclusion:

More studies were available for the CUP and nearly all of the cohort studies reported a decreased risk of endometrial cancer with increased physical activity. Although dose-response meta- analyses were not possible due to the wide variety in measures used, comparisons of high with low activity levels showed a consistent association with decreased risk. The CUP Panel concluded:

There is generally consistent evidence showing lower risk of cancer of the endometrium with higher levels of physical activity and there is strong evidence of mechanisms operating in humans. Physical activity probably protects against endometrial cancer.

7.4 Sedentary habits

(Also see CUP Endometrial Cancer SLR 2012: Section 6.2)

The CUP identified three new papers (from three cohort studies) on sitting time [36, 42, 45]. No studies were identified in the SER. The CUP found all three studies showed a statistically significant increased risk of endometrial cancer when comparing the highest versus the lowest levels of sitting time (see CUP 2012 Figure 77). After adjustment for BMI, all studies still reported an increased risk of endometrial cancer although only one was significant.

Mechanisms

Spending excessive amounts of time sitting is associated with increased risk of insulin resistance [46, 47], which increases the risk of endometrial cancer. Sitting time may also be linked to endometrial cancer risk through insulin-related mechanisms via low levels of energy expenditure [48], as well as via weight gain [49], which are both associated with sitting time.

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: Physical activity (Appendix – Mechanisms) for the updated mechanisms summary.

CUP Panel's conclusion:

The CUP Panel considered sitting time to be a marker of sedentary habits. Although dose- response meta-analysis was not possible, comparisons of high with low sitting time showed a consistent association with increased risk. However, the effect was attenuated in two of the studies after adjustment for BMI, and the possibility of confounding cannot be excluded. The CUP Panel therefore concluded:

The evidence is limited and the possibility of confounding cannot be excluded. The evidence suggesting that sedentary habits (marked by sitting time) are a cause of endometrial cancer is limited.

7.5 Body fatness

(Also see CUP Endometrial Cancer SLR 2011: Sections 8.1.1, 8.2.2 and 8.2.3)

The Panel interpreted body mass index (BMI) (including BMI at age 18-25 years), measures of abdominal girth, and adult weight gain as indicating interrelated aspects of body fatness and fat distribution. Anthropometric measures are imperfect and cannot distinguish reliably between lean and fat, between total and abdominal fat, or between visceral and subcutaneous fat. Increases in body weight during adulthood depend on accumulation of fat more than lean tissue, and therefore any change may better reflect fatness than adult weight itself.

The evidence for BMI, BMI at age 18-25 years, weight gain (including increase in BMI), waist circumference and waist-to-hip ratio is presented below, and is followed by an overall conclusion that incorporates all these exposures.

Body mass index (BMI)

The CUP identified 24 new papers (from 18 cohort studies) [37, 50-72] giving a total of 34 studies (including studies from the SER). Overall, the CUP found 28 studies (27 risk estimates) (including one study on mortality) reported an increased risk for the highest BMI groups compared to the lowest. Only two of these were not statistically significant. Reasons for excluding the other studies can be found in section 8.1.1 (Table 112) of the CUP 2012 SLR.

Twenty six studies (25 risk estimates) were included in the dose-response meta-analysis for BMI and endometrial cancer (*n*=18717). Overall, the CUP analysis found a 50% increased risk of endometrial cancer per 5 BMI units (RR 1.50 (95% CI: 1.42-1.59)) (see CUP 2012 Figure 79). There was evidence of high heterogeneity (I^2 = 86%) but this was due to differences in the size of the effect and not the direction. All studies reported in the direction of an increased risk. The result is consistent with the SER finding, which also reported a significant positive association (RR 1.52 (95% CI: 1.48-1.57)) per 5 BMI units (15 studies, *n*=3484).

In subgroup analysis for the CUP by menopausal status, a significant increased risk was observed for both pre and postmenopausal women (RRs 1.41 (95% CI: 1.37-1.45) and 1.54 (1.39-1.71) respectively) (see CUP 2012 Figure 80). Additional subgroup analysis

by hormone replacement therapy (HRT) use, showed a significant increased risk for both those who used HRT and those who had never used HRT, although the effect was stronger in those who had never used HRT (see CUP 2012 Figure 81).

There was evidence of a non-linear dose-response relationship with a steeper increase in risk at higher BMI levels (see CUP 2012 Figure 84). For further details of the non-linear dose response analysis, see section 8.1.1 in the CUP 2012 SLR.

Results from two other published meta-analyses of cohort studies are consistent with the CUP finding, both reporting a significant increased risk of endometrial cancer per 5 BMI units [73, 74].

Body mass index (BMI) at age 18 - 25 years

The CUP identified five new papers (from five cohort studies) [53, 59, 67, 68, 72], giving a total of eight studies (including studies from the SER). All eight studies reported an increased risk of endometrial cancer when comparing the highest BMI groups to the lowest, four of which were statistically significant and one of which was borderline significant.

Seven studies were included in the CUP dose-response meta-analysis for BMI at age 18-25 years and endometrial cancer (*n*=3476). Overall, the CUP analysis found a 42% increased risk of endometrial cancer per 5 BMI units (RR 1.42 (95% CI: 1.22-1.66)) (see CUP 2012 Figure 87). There was evidence of high heterogeneity (I^2 = 79%) but this was due to differences in the size of the effect and not the direction. All studies reported in the direction of an increased risk. The result is consistent with the SER finding, which also reported a significant positive association (RR 1.31 (95% CI: 1.12-1.54)) (3 studies, *n*=466). Four of the studies reported attenuation of the association when further adjusted for current BMI, but only two of these could be included in a dose-response analysis, yielding a summary RR of 1.02 (95% CI: 0.94-1.11, I^2=0%) per 5 BMI units.

Weight change

The CUP identified four new papers on weight change [53, 54, 67, 68], giving a total of five studies (including studies from the SER). All five studies reported an increased risk of endometrial cancer for the highest versus the lowest categories, four of which were significant.

All five studies were included in the CUP dose-response meta-analysis for weight change and endometrial cancer (*n*=1971). Overall, the CUP analysis found a 16% increased risk of endometrial cancer per 5kg gain in weight between early adulthood and baseline (RR 1.16 (95% CI: 1.10-1.22)) (see CUP 2012 Figure 93). There was evidence of high heterogeneity (I^2 = 66%) but this appeared to be due to differences in the size of the effect and not the direction. All studies reported in the direction of an increased risk. No meta-analysis was conducted in the SER.

Waist circumference

The CUP identified three new papers (from 3 cohort studies) [37, 54, 67], giving a total of four studies (including studies from the SER). All four studies reported an increased

risk of endometrial cancer when comparing the highest versus lowest groups for waist circumference, three of which were statistically significant. No meta-analysis was conducted in the SER as only one cohort study was identified.

All four studies were included in the CUP dose-response meta-analysis for waist circumference and endometrial cancer (*n*=1641). The meta-analysis showed a 13% statistically significant increased risk per 5cm (RR 1.13 (95% CI 1.08-1.18)) with evidence of high heterogeneity (I^2 = 71%) due to differences in the size of the effect but not the direction (see CUP 2012 Figure 96).

There was evidence of a non-linear dose-response relationship with a steeper increase in risk at higher waist circumference, but this was driven by a limited number of observations (see CUP 2012 Figure 98). For further details of the non-linear dose response analysis, see section 8.2.1 in the CUP 2012 SLR.

Waist-hip ratio

The CUP identified four new papers (from four cohort studies) [37, 54, 67, 69], giving a total of five studies (including studies from the SER). All five studies reported an increased risk of endometrial cancer when comparing the highest versus lowest groups for waist-hip ratio, four of which were statistically significant.

All five studies were included in the CUP dose-response meta-analysis for waist-hip ratio and endometrial cancer (*n*=2330). The meta-analysis showed a 21% statistically significant increased risk of endometrial cancer per 0.1 units (RR 1.21 (95% CI 1.13-1.29)) with no evidence of heterogeneity (see CUP 2012 Figure 101). No meta-analysis was conducted in the SER as only one cohort study was identified.

Mechanisms

Obesity influences the levels of a number of hormones and growth factors [75]. Insulin and leptin are all elevated in obese people, and can promote the growth of cancer cells. In addition, insulin resistance is increased, in particular by abdominal fatness, and the pancreas compensates by increasing insulin production. This hyperinsulinaemia increases the risk of cancers of the colon and endometrium, and possibly of the pancreas and kidney [76].

Sex steroid hormones, including oestrogens, androgens, and progesterone, are likely to play a role in obesity and cancer. Adipose tissue is the main site of oestrogen synthesis in postmenopausal women [76] due to aromatase activity in subcutaneous fat, which increases the conversion of androgen to oestrogen [77]. Increased levels of oestrogens are strongly associated with risk of endometrial and postmenopausal breast cancers [44, 78], and may impact on other cancers.

Obesity is associated with a low-grade chronic inflammatory state. Obese adipose tissue is characterised with macrophage infiltration and these macrophages are an important source of inflammation in this tissue [79]. The adipocyte (fat cell) produces pro-inflammatory factors, and obese individuals have elevated concentrations of circulating tumour necrosis factor (TNF)-alpha interleukin (IL)-6, and C-reactive protein, compared

with lean people [80], as well as of leptin, which also functions as an inflammatory cytokine [81]. Such chronic inflammation can promote cancer development.

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

CUP Panel's conclusion:

Overall the evidence from the CUP for an association between body fatness (which the CUP Panel interprets to be reflected by BMI (including at age 18-25 years), measures of abdominal girth and weight gain) was stronger, with more studies available than the SER, and all studies reporting an increased risk. The evidence for abdominal fatness and weight gain was less robust than that where BMI was used as the measure of body fatness, but supported the evidence for an association between overall body fatness and endometrial cancer risk. The CUP Panel concluded:

Body fatness is reflected by BMI (including at age 18-25 years), measures of abdominal girth, and adult weight gain. There is ample evidence for an association between various measures of body fatness and endometrial cancer. The evidence is generally consistent, and there is a dose-response relationship. There is evidence for plausible mechanisms that operate in humans. The evidence that greater body fatness, including abdominal fatness and adult weight gain, is a cause of endometrial cancer is convincing.

7.6 Adult attained height

(Also see CUP Endometrial Cancer SLR 2012: Sections 8.3.1)

The CUP identified seven new papers (from eight cohort studies) [52, 54, 56, 68, 82-84], giving a total of thirteen cohort studies (including studies from the SER). Overall, the CUP found six of nine studies (eight estimates) on endometrial cancer incidence showed an increased risk when comparing the highest versus lowest categories, three of which were significant. The other three studies (2 estimates) reported a non-significant decreased risk. Two other studies were excluded because they did not report highest versus lowest analyses, one did not report a risk estimate, and another included participants were patients with breast cancer.

Ten studies were included in the dose-response meta-analyses for adult attained height and endometrial cancer (*n*=17732). Overall, the CUP analysis found a 7% statistically significant increased risk of endometrial cancer per 5cm (RR 1.07 (95% CI 1.03-1.11)) with evidence of high heterogeneity (I^2=69%) (see CUP Endometrial Cancer SLR 2012 Figure 106). There was no evidence of a non-linear dose–response relationship (p = 0.39).

All studies included in the dose–response meta-analysis adjusted for age, most studies adjusted for tobacco smoking and some for reproductive factors and/or physical activity.

In the SER, a dose-response meta-analysis of fewer studies (4 studies) showed a non-significant increased risk of endometrial cancer per 10cm (RR 1.17 (95% CI: 0.96-.42)), and additional meta-analysis of eleven case-control studies showed a borderline significant increased risk per 10cm (RR 1.10 (95% CI: 1.00-1.21)).

Mechanisms

Factors that lead to greater adult attained height, or their consequences, are a cause of a number of cancers. Adult height is related to the rate of growth during fetal life and childhood. The number of cell divisions in fetal life and childhood, health and nutrition status in childhood, and age of sexual maturity can alter the hormonal microenvironment, and affect circulating levels of growth factors, insulin, and oestrogens. Taller people have undergone more cell divisions stimulated by IGF-1 and pituitary-derived growth hormone [85], and there is therefore more potential for error during DNA replication, which increases the likelihood of cancer development.

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

CUP Panel's conclusion:

The evidence was generally consistent and the CUP dose-response meta-analysis showed a statistically significant increased risk of endometrial cancer with increasing height. There was evidence of high heterogeneity, which appeared to be due to one study reporting a larger increase in risk. There was no evidence of a non-linear dose-response relationship. There is also evidence of plausible mechanisms operating in humans.

The CUP Panel concluded:

Developmental factors leading to greater growth in length in childhood (marked by adult attained height) are probably a cause of endometrial cancer.

7.7 Other

Other exposures were evaluated. However, data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. This list of exposures judged as 'Limited-no conclusion' is summarised in the matrix on **page 5**. The evidence for two exposures previously judged as 'limited-suggestive' in the SER, non-starchy vegetables and red meat, was less consistent and the Panel could not draw any conclusions on the updated evidence.

Evidence for the following exposures previously judged as 'limited-no conclusion' in the SER, remain unchanged after updating the analyses with new data identified in the CUP: fruits; dietary fibre; total fat; alcohol and dietary pattern.

The following exposures, also previously too limited to draw conclusions in the SER and not updated as part of the CUP, remain 'limited-no conclusion': Cereals (grains) and their products; pulses (legumes); soya and soya products; poultry; fish; eggs; milk and dairy products; protein; animal fat; saturated fatty acids; cholesterol; retinol; beta-carotene; vitamin C; vitamin E; and lactation.

In addition, evidence for the following new exposures, for which no judgement was made in the SER, is too limited to draw any conclusions: Processed meat; tea; glycaemic index; folate; multivitamins; and acrylamide.

8. Comparison with the Second Expert Report

Overall, the evidence from the additional cohort studies identified in the CUP was consistent with those reviewed as part of the SER for exposures graded convincing or probable. The CUP Panel grouped several individual anthropometric exposures to reflect 'body fatness' (BMI, measures of abdominal girth and adult weight gain), where previously these exposures were judged individually in the SER.

The evidence that non-starchy vegetables protect against endometrial cancer was weak, and the evidence that red meat is a cause of endometrial cancer was also weak. More cohort studies were available for these exposures for the CUP analyses, but the evidence failed to demonstrate significant associations and was no longer suggestive of an association with endometrial cancer. Previous conclusions for these exposures were based on meta-analyses of case-control data. Overall, the Panel concluded the evidence for non-starchy vegetables and red meat was too limited and inconsistent to allow a conclusion to be reached (see CUP Endometrial Cancer SLR 2012: Sections 2.2.2 and 2.5.1.3).

More data for additional exposures were available for inclusion in the CUP analyses. New exposures for which the Panel could make a judgement with regard to risk of endometrial cancer, included processed meat, coffee, tea, glycaemic load, glycaemic index, folate, multivitamins, acrylamide, and sitting time. The Panel considered the evidence for glycaemic load was strong enough to conclude that it probably causes endometrial cancer, and for coffee that it probably protects against this cancer. For sitting time (which the Panel considered to be a marker of sedentary habits) there was limited evidence suggesting that it is a cause of endometrial cancer. For all the other new exposures, the evidence was limited and no conclusion was possible.

9. Conclusions

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

Convincing evidence

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

Probable evidence

Physical activity: Physical activity probably protects against endometrial cancer.

Coffee: Consumption of coffee probably protects against endometrial cancer.

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

Glyceamic load: Glycaemic load is probably a cause of endometrial cancer.

Limited - suggestive evidence

Sedentary habits: The evidence suggesting that sedentary habits might increase the risk of endometrial cancer is limited.

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
CUP	Continuous Update Project
DNA	deoxyribonucleic acid
ER(+/-)	oestrogen-receptor (positive/negative)
IARC	International Agency for Research on Cancer
n	number of cases
PR(+/-)	progesterone-receptor (positive/negative)
RR	relative risk
SD	standard deviation
SLR	systematic literature review
WCRF	World Cancer Research Fund

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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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