



American Institute for Cancer Research

Continuous Update Project Keeping the science current



Endometrial Cancer 2013 Report

Food, Nutrition, Physical Activity, and the Prevention of Endometrial Cancer



WORLD CANCER RESEARCH FUND GLOBAL NETWORK

OUR VISION

The World Cancer Research Fund global network helps people make choices that reduce their chances of developing cancer.

OUR HERITAGE

We were the first cancer charity:

- To create awareness of the relationship between diet and cancer risk
- To focus funding on research into diet and cancer prevention
- To consolidate and interpret global research to create a practical message on cancer prevention

OUR MISSION

Today the World Cancer Research Fund global network continues:

- Funding research on the relationship of nutrition, physical activity and weight management to cancer risk
- Interpreting the accumulated scientific literature in the field
- Educating people about choices they can make to reduce their chances of developing cancer

THE WCRF GLOBAL NETWORK

The World Cancer Research Fund (WCRF) global network comprises WCRF International, which operates as the umbrella association for the global network's four charitable organisations: The American Institute for Cancer Research (AICR); World Cancer Research Fund (WCRF UK); World Cancer Research Fund Netherlands (WCRF NL); World Cancer Research Fund Hong Kong (WCRF HK). Please cite the Report as follows:

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This report provides an updated version of section 7.12 Endometrium from the Second Expert Report: *Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective*. This section has been updated based on Panel discussions in June 2013 on the Continuous Update Project Endometrial Cancer Systematic Literature review (SLR), prepared by the research team at Imperial College London, UK in 2012 (see acknowledgements). The SLR included research papers published until 31st December 2012. For further details please see the full 2012 Continuous Update Project Endometrial Cancer SLR (www.dietandcancerreport.org).

To keep the evidence current and updated into the future, WCRF/AICR is undertaking the Continuous Update Project (CUP), in collaboration with Imperial College London. The project is an ongoing review of food, nutrition, physical activity, body fatness, and cancer research. The CUP builds upon the foundations of the WCRF/AICR Second Expert Report (SER) [1].

The Continuous Update Project provides a comprehensive and up to date depiction of scientific developments on the relationship between food, nutrition, physical activity, body fatness and cancer. It also provides an impartial analysis and interpretation of the data as a basis for reviewing and where necessary revising WCRF/AICR's Recommendations for Cancer Prevention based on the Second Expert Report [1].

In the same way that the Second Expert Report was informed by a process of SLRs, the Continuous Update Project systematically reviews the science. The updates to the SLRs are being conducted by a team of scientists at Imperial College London in liaison with the original SLR centres. WCRF/AICR has convened a panel of experts (the Continuous Update Project Panel (see acknowledgements)) consisting of leading scientists in the field, who consider the updated evidence from systematic literature reviews and draw conclusions.

Once all the cancers have been updated in the CUP database in 2015, the Panel will formally review the WCRF/AICR Recommendations for Cancer Prevention, and any changes will be communicated through the WCRF global network science, health information and communications programmes in 2017. From 2015 the CUP database will be continuously updated with new evidence for each cancer. Prior to 2017 the Panel will revise one or more Recommendations only if they agree there is strong evidence for a change.

Instead of periodically repeating the extensive task of conducting multiple systematic literature reviews that cover a long period of time, the continuous review process is based on a live system of scientific data. The database is updated on an ongoing basis from which, at any point in time, the most current review of scientific data (including meta-analyses where appropriate) can be performed.

Periodically WCRF/AICR will produce updated SLRs, peer reviewed by scientists, which will outline the scientific developments in the field of food, nutrition, physical activity, body weight and cancer.

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Abbreviations

- CUP Continuous Update Project
- SER Second Expert Report 'Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective'
- SLR Systematic literature review

FOOD, NUTRITION, PHYSICAL ACTIVITY AND ENDOMETRIAL CANCER 2013

	DECREASES RISK	INCREASES RISK		
Convincing		Body fatness ¹		
Probable	Physical activity ² Coffee ³	Glycaemic load		
Limited - suggestive		Sedentary habits ⁴ Adult attained height ⁵		
Limited - no conclusion	Cereals (grains) and their products; fruits; vegetables; pulses (legumes); soya and soya products; red meat; processed meat; poultry; fish; eggs; milk and dairy products; dietary fibre; 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			
Substantial effect unlikely				
1 The Panel interpreted BMI (including BMI at age 18-25 years), measures of abdominal girth, and adult				

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 Sedentary habits as marked by sitting time

5 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

Overall, the Panel notes the strength of the evidence that body fatness and glycaemic load are a cause of endometrial cancer, and that physical activity and coffee protect against endometrial cancer.

The Panel judges as follows:

The evidence that body fatness (which the Panel interprets to be reflected by body mass index (BMI), measures of abdominal girth and adult weight gain) is a cause of endometrial cancer is convincing. Glycaemic load is probably a cause of endometrial cancer, and physical activity and coffee both probably protect against this cancer.

The evidence suggesting that sedentary habits (marked by sitting time) and adult attained height are causes of endometrial cancer is limited. Evidence for red meat and non-starchy vegetables is less consistent and is no longer suggestive of an association for either exposure, so no conclusions could be drawn.

1. 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 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.

2. 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]. Also see also box 2.2 on page 35 of the Second Expert Report.

3. Other established causes

(Also see chapters 2.4 and 7.1.3.1, Second Expert Report)

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].

4. Interpretation of the evidence

4.1 General

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

'Relative risk' (RR) is used in this report to denote ratio measures of effect, including 'risk ratios', 'rate ratios', 'hazard ratios', and 'odds ratios'.

4.2 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.

5. 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 casecontrol studies. Due to the large number of cohort studies, analysis and interpretation of casecontrol 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.

5.1 Mechanistic evidence

Where relevant, mechanistic reviews previously conducted for the SER are included in this report (more details can be found in chapters 2, 4 and 6 of the SER). These reviews have not been updated, but will be updated as part of a systematic review for the CUP of the mechanistic evidence for the CUP (see below). Where an exposure presented in this report was previously judged as 'limited-no conclusion' or was not discussed for the SER (and therefore was no review of the mechanisms), a brief summary of possible mechanisms for that particular exposure is given. This comprises the following exposures:

- Glycaemic load
- Coffee
- Sedentary habits (sitting time)

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

6. 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 1 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.

6.1 Glycaemic load

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

The evidence for glycaemic load¹ 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% Cl 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.

Mechanisms

Note: A full review of mechanisms for this exposure will form part of a larger review of mechanisms (see 5.1 in this report).

 $^{^{\}rm 1}$ 'Glycaemic load' is the glycaemic index of a food multiplied by the number of grams of carbohydrate in the serving of food

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].

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 a probable cause of endometrial cancer.

6.2 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

Note: A full review of mechanisms for this exposure will form part of a larger review of mechanisms (see 5.1 in this report).

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].

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.

6.3 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

Note: This is taken from Chapters 2 and 6 of the SER. An updated review of mechanisms for this exposure will form part of a larger review of mechanisms (see 5.1 in this report)

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].

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 metaanalyses 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.

6.4 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

Note: A full review of mechanisms for this exposure will form part of a larger review of mechanisms (see 5.1 in this report).

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.

CUP Panel's conclusion:

The CUP Panel considered sitting time to be a marker of sedentary habits. Although doseresponse 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.

6.5 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% Cl: 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 (I² = 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, I²=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 (I² = 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 (I² = 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-to-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-to-hip ratio, four of which were statistically significant.

All five studies were included in the CUP dose-response meta-analysis for waist-to-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

Note: This is taken from Chapters 2 and 6 of the SER. An updated review of mechanisms for this exposure will form part of a larger review of mechanisms (see 5.1 in this report).

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.

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.

6.6 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% Cl 1.03-1.11)) with evidence of high heterogeneity (I²=69) (see CUP 2012 Figure 106). 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% Cl: 0.96-.42)), and additional meta-analysis of eleven case-control studies showed a borderline significant increased risk per 10cm (RR 1.10 (95% Cl: 1.00-1.21)).

Mechanisms

Note: This is taken from Chapters 2 and 6 of the SER. An updated review of mechanisms for this exposure will form part of a larger review of mechanisms (see 5.1 in this report).

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.

CUP Panel's conclusion:

More evidence was available for the CUP analysis and the evidence was generally consistent. Overall a significant positive association was observed between height and endometrial cancer risk, and the direction of the effect was consistent with the result from the SER. However, there was evidence of high heterogeneity and the mechanistic data is speculative. The Panel noted the need for better characterisation and interpretation of measures, of growth, development and maturation. The CUP Panel concluded:

Although there is generally consistent evidence from prospective epidemiological data, the mechanistic evidence is speculative. The evidence suggesting that greater adult attained height, or the factors that lead to it, are a cause of endometrial cancer is limited. The causal factor is unlikely to be tallness itself, but factors that promote linear growth in childhood.

6.7 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.

7. 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.

8. Conclusions

The CUP Panel will review the evidence relating to endometrial cancer again after 2015 once the CUP database is being continuously updated for all cancers. The Recommendations for Cancer Prevention will be reviewed in 2017 when the Panel has reviewed the conclusions for the other cancers.

The Continuous Update Project Panel concluded:

The evidence that greater body fatness (reflected by BMI, measures of abdominal girth and adult weight gain) is a cause of endometrial cancer is convincing. Glycaemic load is probably a cause of endometrial cancer, and physical activity and coffee both probably protect against this cancer.

The evidence suggesting that sedentary habits (marked by sitting time) and adult attained height are causes of endometrial cancer is limited. For height, the causal factor is unlikely to be tallness itself, but factors that promote linear growth in childhood.

Evidence for non-starchy vegetables and red meat was no longer suggestive of an association and was too limited to draw a conclusion.

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Appendix 1 Criteria for grading evidence

(Taken from Chapter 3 of the Second Expert Report)

This box lists the criteria finally agreed by the Panel that were necessary to support the judgements shown in the matrices. The grades shown here are 'convincing', 'probable', 'limited — suggestive', 'limited — no conclusion', and 'substantial effect on risk unlikely'. In effect, the criteria define these terms.

Convincing

These criteria are for evidence strong enough to support a judgement of a convincing causal relationship, which justifies goals and recommendations designed to reduce the incidence of cancer. A convincing relationship should be robust enough to be highly unlikely to be modified in the foreseeable future as new evidence accumulates.

All of the following were generally required:

- Evidence from more than one study type.
- Evidence from at least two independent cohort studies.
- No substantial unexplained heterogeneity within or between study types or in different populations relating to the presence or absence of an association, or direction of effect.
- Good quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error, and selection bias.
- Presence of a plausible biological gradient ('dose response') in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.
- Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes.

Probable

These criteria are for evidence strong enough to support a judgement of a probable causal relationship, which would generally justify goals and recommendations designed to reduce the incidence of cancer.

All the following were generally required:

- Evidence from at least two independent cohort studies, or at least five case control studies.
- No substantial unexplained heterogeneity between or within study types in the presence or absence of an association, or direction of effect.
- Good quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error, and selection bias.
- Evidence for biological plausibility.

Limited – suggestive

These criteria are for evidence that is too limited to permit a probable or convincing causal judgement, but where there is evidence suggestive of a direction of effect. The evidence may have methodological flaws, or be limited in amount, but shows a generally consistent direction of effect. This almost always does not justify recommendations designed to reduce the incidence of cancer. Any exceptions to this require special explicit justification.

All the following were generally required:

- Evidence from at least two independent cohort studies or at least five case control studies.
- The direction of effect is generally consistent though some unexplained heterogeneity may be present.
- Evidence for biological plausibility.

Limited – no conclusion

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

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

There are also many exposures for which there is such limited evidence that no judgement is possible. In these cases, evidence is recorded in the full CUP SLRs on the Diet and Cancer Report website (<u>www.dietandcancerreport.org</u>). However, such evidence is usually not included in the summaries.

Substantial effect on risk unlikely

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

All of the following were generally required:

- Evidence from more than one study type.
- Evidence from at least two independent cohort studies.
- Summary estimate of effect close to 1.0 for comparison of high 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, either from human studies or relevant animal models, that typical human exposures lead to relevant cancer outcomes.

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

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

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

Special upgrading factors

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

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



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