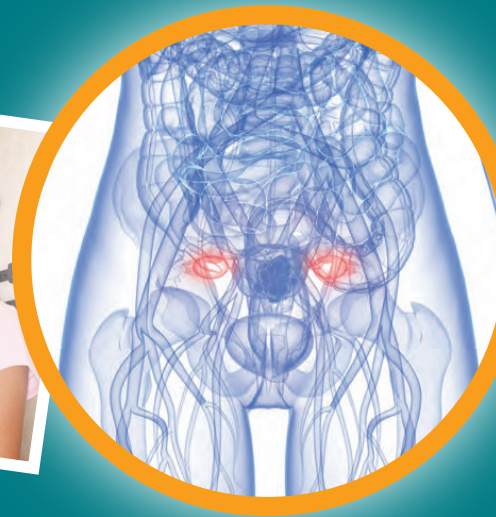


World  
Cancer  
Research Fund



American  
Institute for  
Cancer Research

Continuous Update Project  
**Keeping the science current**



# Ovarian Cancer 2014 Report

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

Continuous  
Update Project



## WORLD CANCER RESEARCH FUND GLOBAL NETWORK

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### OUR VISION

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

### OUR HERITAGE

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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

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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

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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:

World Cancer Research Fund / American Institute for Cancer Research. Continuous Update Project Report. Food, Nutrition, Physical Activity, and the Prevention of Ovarian Cancer 2014. Available at [http://www.dietandcancerreport.org/cup/cup\\_resources.php](http://www.dietandcancerreport.org/cup/cup_resources.php).

This report provides an updated version of section 7.11 Ovary 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 Ovarian Cancer Systematic Literature Review (SLR), prepared by the research team at Imperial College London, UK in 2013 (see acknowledgements). The SLR included research papers published until 31<sup>st</sup> December 2012. For further details please see the full Continuous Update Project Ovarian Cancer SLR 2013 ([http://www.dietandcancerreport.org/cup/cup\\_resources.php](http://www.dietandcancerreport.org/cup/cup_resources.php)).

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 on-going 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 CUP 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 the Recommendations for Cancer Prevention based on the SER [1].

In the same way that the SER 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 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 on-going 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 fatness and cancer.

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## Abbreviations

BMI	Body mass index
CUP	Continuous Update Project
HRT	Hormone replacement therapy
SER	Second Expert Report ' <i>Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective</i> '
SLR	Systematic literature review

FOOD, NUTRITION, PHYSICAL ACTIVITY AND OVARIAN CANCER 2014		
	DECREASES RISK	INCREASES RISK
Convincing		Adult attained height <sup>1</sup>
Probable		Body fatness <sup>2</sup>
Limited - suggestive	Lactation	
Limited - no conclusion	Vegetables; fruits; pulses (legumes); red meat; processed meat; poultry; fish; eggs; milk and dairy products; vegetarian and individual level dietary pattern; coffee; tea; dietary fibre; carbohydrates; protein; total fat; saturated fatty acids; monounsaturated fatty acids; polyunsaturated fatty acids; vegetable fat; animal fat; trans fatty acids; dietary cholesterol; alcohol; folate; vitamin A; lycopene; vitamin C; vitamin E; serum vitamin D; lactose; calcium; acrylamide; physical activity; abdominal fatness; energy intake	
Substantial effect unlikely		

**1** Adult attained height is unlikely to directly influence 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

**2** Body fatness marked by body mass index (BMI). The effect may vary in different subgroups such as tumour type

Overall, the Panel notes the strength of the evidence that developmental factors leading to greater linear growth (marked by adult attained height) and greater body fatness are causes of ovarian cancer.

The CUP Panel judges as follows:

The evidence that developmental factors leading to greater linear growth (marked by adult attained height) are a cause of ovarian cancer is convincing.

Greater body fatness (which the Panel interprets to be marked by body mass index (BMI)) is probably a cause of ovarian cancer.

The evidence suggesting that lactation protects against ovarian cancer is limited.

# 1. Trends, incidence, and survival

The ovaries are the sites of ovum (egg) production in women. They are also the main source of the hormones oestrogen and progesterone in premenopausal women. There are three types of ovarian tissue that can produce cancers: epithelial cells, which cover the ovary; stromal cells, which produce hormones; and germ cells, which become ova. About 85 to 90 per cent of ovarian cancers are epithelial carcinomas [2].

Ovarian cancer is the seventh most common cancer in women (and the 18th most common cancer overall) worldwide. Approximately 239 000 cases were recorded in 2012, accounting for nearly 4 per cent of all new cases of cancer in women (2 per cent overall). This cancer is usually fatal, and is the eighth most common cause of cancer death in women worldwide (14th overall) [3].

Ovarian cancer incidence rates are greater in high than in middle- to low-income countries. Around the world, age-standardised incidence rates range from more than 11 per 100 000 women in Central and Eastern Europe to less than 5 per 100 000 in parts of Africa. Incidence rates are 11.7 per 100 000 in the UK, 8.0 per 100 000 in the US, 5.2 per 100 000 in Brazil and 4.1 per 100 000 in China [3].

Risk increases with age, although the rate of increase slows after the menopause. Only 10–15 per cent of cases occur before the menopause, although germ cell cancers, which are uncommon, peak in women aged between 15 and 35 [2]

Ovarian cancer often has no symptoms at the early stages, so the disease is generally advanced when it is diagnosed. The 5-year survival rate ranges from approximately 30 to 50 per cent [4, 5]. Also see Box 1.

## Box 1 Cancer incidence and survival

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

## 2. Pathogenesis

The pathogenesis of ovarian cancer is not well characterised, although various mechanisms have been suggested. Over many cycles of ovulation, the ovarian surface epithelium undergoes repeated disruption and repair. The epithelial cells are stimulated to proliferate, which increases the probability of spontaneous mutations. Alternatively, following ovulation, these cells may become trapped within the connective tissue surrounding the ovary, which can lead to the formation of inclusion cysts. If this happens, the epithelial cells are subjected to a unique pro-inflammatory microenvironment, which may increase the rate of DNA damage, thus affecting cancer risk.

Most ovarian cancers occur spontaneously, although 5–10 per cent of cases develop due to a genetic predisposition [6]. The latter, involving dysfunctional BRCA1 or BRCA2 genes (see SER chapter 2.4.1.1), produces high-grade carcinomas, with a poorer prognosis [7].

## 3. Other established causes

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

### *Life events*

The risk of ovarian cancer is affected by the number of menstrual cycles during a woman's lifetime. Not bearing children increases the risk of, and may be seen as a cause of, ovarian cancer. The reverse also applies: bearing children reduces the risk of, and may be seen as protective against, ovarian cancer [8-10]. There is substantial evidence that, as with breast cancer, early menarche and late natural menopause increase the risk of, and may be seen as causes of, ovarian cancer. The reverse also applies: late menarche, lactation (breast feeding) and early menopause reduce the risk of, and may be seen as protective against, ovarian cancer [8-10]. Recent evidence from epigenetic profiles suggests that in fact timing of sexual maturation and related life course events are mediated by DNA methylation affecting transcription of key genes. For each yearly increase in age at menarche, the likelihood of having genome wide methylation below the median level was increased by 32 per cent [11].

### *Medication*

Oral contraceptives protect against this cancer [12]. Use of hormone replacement therapy has been shown to increase risk [13, 14].

## 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 ovary include:

### *Patterns*

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

### *Confounding*

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

### *Tumour heterogeneity*

There is growing evidence that different histologic subtypes of ovarian cancer have different aetiologies and clinical cause. However, most studies lack the statistical power to evaluate associations by histologic subtype [\[15\]](#).

## 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 case-control studies. Due to their methodological limitations, case-control studies were not analysed in the Ovarian Cancer SLR 2013.

The previous review of ovarian cancer combined mortality and incidence outcomes for the meta-analyses. Where possible, meta-analyses for incidence and mortality in this update were conducted separately. However, because survival from ovarian cancer is low, analyses combining studies on ovarian cancer incidence and mortality were also conducted to explore if this outcome can explain any heterogeneity.

Studies reporting mean difference as a measure of association are not included in the Ovarian Cancer SLR 2013, as relative risks estimated from the mean differences are not adjusted for possible confounders, and thus not comparable to adjusted relative risks from other studies.

Non-linear meta-analysis was applied when the data suggested that the dose-response curve is non-linear, and when detecting a threshold of exposure might be of interest. Details about the non-linear meta-analyses can be found in the Ovarian Cancer SLR 2013.

The Ovarian Cancer SLR 2013 included studies published up to 31<sup>st</sup> December 2012. For more information on methodology see the full Ovarian Cancer SLR 2013.

## 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 (see below). Where an exposure presented in this report was previously judged as 'limited-no conclusion' or was not discussed for the SER there was no review of the mechanisms. A brief summary of possible mechanisms for body fatness is given.

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 [www.dietandcancerreport.org](http://www.dietandcancerreport.org) for further information). A full review of the mechanistic evidence for ovarian cancer will form part of this larger review.

## 6. Evidence and judgements

There were 128 ovarian cancer articles included in the Continuous Update Project (CUP) analyses, including 80 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 Second Expert Report. It also includes a brief description of potential mechanisms for each exposure.

For information on the criteria for grading the epidemiological evidence see the Appendix in this report. References to studies added as part of the CUP have been included; for details of references to other studies see the SER [\[1\]](#).

### 6.1 Breastfeeding

(Also see Ovarian Cancer SLR 2013: Section 1.6)

The Ovarian Cancer SLR 2013 identified two new papers (from two cohort studies) [\[16, 17\]](#) giving a total of three studies (including one study from the SER). One study showed a non-significant decreased risk, one showed a non-significant increased risk, and one showed no significant association when comparing the highest versus the lowest categories (ever versus never).

All three studies (two new) were included in a meta-analysis ( $n = 817$ ), and a non-significant decreased risk was observed for comparisons among parous women having ever or never breastfed (RR 0.90 (95% CI 0.75-1.08)), with no observed heterogeneity (see Ovarian Cancer SLR 2013 figure 2). It was not possible to conduct a dose-response meta-analysis.

No meta-analysis of cohort studies was conducted for the SER. A dose-response meta-analysis of case-control studies showed a significant decreased risk with accumulated lifetime duration of breastfeeding (RR 0.96 (95% CI 0.93-0.99)) per 6 months breastfeeding, with high heterogeneity.

## **Mechanisms**

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

Lactation delays the return of menstruation and ovulation after childbirth. There is evidence that the reduced number of menstrual cycles associated with breastfeeding protects against some cancers. Decreased lifetime exposure to menstrual cycles causes alteration of hormone levels, particularly androgens, which can influence cancer risk [18].

### **CUP Panel's conclusion:**

Only three studies were available for the Ovarian Cancer SLR 2013 analyses and were included in an ever versus never meta-analysis. A non-significant decreased risk was observed for comparisons between having ever breastfed versus never breastfed among parous women. A dose-response meta-analysis of case-control studies in the SER showed a significant decreased risk with accumulated lifetime duration of breastfeeding.

There are sparse prospective epidemiological data, with some evidence for a dose-response relationship from case-control studies. The mechanistic evidence is speculative. The evidence suggesting that breastfeeding protects against ovarian cancer is limited.

## **6.2 Body fatness**

(Also see Ovarian Cancer SLR 2013: Sections 8.1.1, 8.1.3, 8.2.1, 8.2.2 and 8.2.3)

The Panel interpreted body mass index (BMI) as a measure of body fatness. The Panel is aware that BMI is an imperfect measure and cannot distinguish between lean mass and body fat.

The evidence for BMI, waist circumference and waist-to-hip ratio is presented below.

### **Body mass index (BMI)**

The Ovarian Cancer SLR 2013 identified 18 new papers [17, 19-35] giving a total of 26 studies (including studies from the SER). Overall, of 23 studies (22 estimates) reporting on ovarian cancer incidence comparing highest versus lowest BMI groups, three reported a significant positive association, nine showed a non-significant positive association, and 11 (10 estimates) showed a non-significant inverse association. Two studies reporting mortality estimates both showed a positive association, though only one was significant. One study did not report a risk estimate.

Twenty-five studies (22 risk estimates) were included in the dose-response meta-analysis for BMI and ovarian cancer ( $n = 15\,899$ ) and a 6 per cent increased risk per 5 BMI units was observed, and this was statistically significant (RR 1.06 (95% CI 1.02-1.11)) (see Ovarian Cancer SLR 2013 figure 182). There was evidence of substantial heterogeneity ( $I^2 = 55\%$ ) largely due to the size of effect. The non-linear analysis showed a statistically significant increase in risk of ovarian cancer for BMI greater than 28.4 kg/m<sup>2</sup> (see Ovarian Cancer SLR 2013 figures 185 and 186).

The Ovarian Cancer SLR 2013 findings were in contrast to a dose-response meta-analysis from the SER SLR (RR 1.00 (95% CI 0.99-1.01) per 2 unit increase in BMI), but the Ovarian Cancer SLR 2013 included more studies and cases of ovarian cancer.

### ***Published pooled analyses***

Results from two pooled analyses on BMI and ovarian cancer risk were published and identified in the Ovarian Cancer SLR 2013 [36, 37]. One pooled study reported non-significant associations between BMI and increased risk in both highest versus lowest and continuous analyses of cohort studies. The second pooled study conducted a continuous analysis and reported a borderline significant positive association [37]. This was consistent with an additional Ovarian Cancer SLR 2013 analysis that included the Collaborative Group on Epidemiological Studies of Ovarian Cancer [37] combined with non-overlapping studies from the Ovarian Cancer SLR 2013 [17, 21-24, 28, 31, 33-35, 38-42]. Results are presented in table 1.

**Table 1: Summary of CUP meta-analysis and pooled analyses - BMI**

		<b>RR (95% CI)</b>	<b>I<sup>2</sup></b>	<b>No. cohort studies</b>	<b>No. cases</b>	<b>Factors adjusted for</b>
CUP Ovarian Cancer SLR 2013	Per 5 units	1.06 (1.02-1.11)	55	25*	15 899	
Pooling Project of Prospective Studies of Diet and Cancer [36]	BMI ≥ 30 vs. 18.5-23	1.03 (0.86-1.22)		12	2036	Adjusted for age at menarche, oral contraceptive use, parity, smoking status, physical activity, energy intake, menopausal status at baseline and hormone replacement therapy use among postmenopausal women.
	Per 4 units	1.01 (0.95-1.07)			2036	No statistically significant heterogeneity between studies.  BMI in early adulthood was not associated with ovarian cancer risk.
Collaborative Group on Epidemiological Studies of Ovarian Cancer [37]	Per 5 units	1.03 (1.00-1.06)		17	10 643	Results shown for prospective studies only. Stratified by study, age at diagnosis, parity, menopausal status/hysterectomy, height, duration of oral contraceptive use, and ever use of hormone therapy
Ovarian Cancer SLR 2013 additional analysis: Collaborative Group on Epidemiological Studies of Ovarian Cancer [37] combined with non-overlapping studies from the CUP [17, 21-24, 28, 31, 33-35, 38-42]	Per 5 units	1.06 (1.00-1.12)	38	34	12 787	

\* Number of risk estimates = 22

\*\* New York University Women's Health Study was not included in the category ≥ 30 because there were no cases in that category.

## ***Sources of heterogeneity***

A pooled analysis of case-control studies from the Ovarian Cancer Association Consortium (15 case-control studies,  $n = 13\,548$ ) published in 2013 (not included in the Ovarian Cancer SLR 2013) has helped to shed light on the sources of heterogeneity and specifically the interaction between hormone use, menopausal status, tumour type, BMI and ovarian cancer risk [15]. Stratified results from this study and from the other pooled analyses [36] [37] are summarised below. In summary, the new data indicate there is a general increase in the risk of ovarian cancer with increasing BMI, irrespective of menopausal status and hormone therapy, with the exception of serous invasive cancers in postmenopausal women. It appears that the slightly stronger effect of BMI observed in premenopausal women at least partly accounts for the higher relative risk attributed to those who have never used hormone replacement therapy (HRT).

### ***Tumour type***

Results from the 2013 Ovarian Cancer Association Consortium pooled analysis of case-control studies [15] found that the association between greater BMI and increased risk of ovarian cancer was most pronounced for borderline serous, invasive endometrioid and invasive mucinous tumours (recent BMI pooled ORs per 5 BMI units 1.24 (95% CI 1.18-1.30), 1.17 (95% CI 1.11-1.23) and 1.19 (95% CI 1.06-1.32) respectively). There was no association with serous invasive cancer overall (pooled OR 0.98 (95% CI 0.94-1.02)). Results from the Collaborative Group on Epidemiological Studies of Ovarian Cancer [37] were consistent with the above pooled analysis, finding the trend with increasing BMI considerably greater for borderline serous tumours than for fully malignant serous tumours when data were subdivided by level of malignancy (RRs 1.29 and 1.00 respectively).

### ***Hormone Replacement Therapy (HRT) use***

In a pooled analysis of the association of BMI and ovarian cancer among ever-users and never-users of HRT, the Collaborative Group on Epidemiological Studies of Ovarian Cancer found a significant increased risk only in women who had never used HRT (RR 1.10 (95% CI 1.07-1.13) per 5 units BMI for never users compared to 0.95 (95% CI 0.92-0.99) for ever users [37]). Similarly, the 2013 Ovarian Cancer Association Consortium [15] pooled analysis of case-control studies observed a significant association between BMI and ovarian cancer risk only among women who had never used HRT compared to those who had used HRT (ORs per 5 units 1.10 (95% CI 1.07-1.14) and 1.02 (95% CI 0.97-1.07) respectively). However, markedly different patterns of association were observed when considering pre- and postmenopausal women and the different histological subtypes separately. For example, for invasive serous cancers, a significant trend of increasing risk with increasing BMI was observed in premenopausal women, with no association in postmenopausal women who had never used HRT, and a significant inverse association among those who had used HRT (RRs per 5 BMI units 1.11 (95% CI 1.04-1.18), 0.97 (95% CI 0.92-1.03) and 0.92 (95% CI 0.87-0.98) respectively).

### ***Menopausal status***

Results from the 2013 Ovarian Cancer Association Consortium pooled analysis of case-control studies [15] found that the positive association with BMI was overall stronger among premenopausal women (see above section on HRT). One of the pooled analyses [36] also found the association between BMI at baseline and ovarian cancer risk was stronger for premenopausal women than

postmenopausal women when comparing women with a BMI  $\geq 30$  kg/m<sup>2</sup> with BMI 18.5 to 23 kg/m<sup>2</sup> (cohort studies only) (RRs 1.72 (95% CI 1.02-2.89) and 1.07 (95% CI 0.87-1.33) respectively), but there was no difference in the continuous analysis per 4 units BMI. The other pooled analysis found no difference when stratifying by menopausal status [37].

### **Waist circumference**

The Ovarian Cancer SLR 2013 identified five new papers [19, 22-25], giving a total of six studies (including one from the SER that did not report a risk estimate). Of the five studies reporting estimates on ovarian cancer incidence, three reported a non-significant positive association and two reported a non-significant inverse association, comparing highest versus lowest categories of waist circumference.

Four studies were included in the dose-response meta-analysis ( $n = 1049$ ); two studies were excluded as one reported only two categories of exposure and the other did not report a risk estimate. The meta-analysis showed a non-significant positive association (RR 1.03 (95% CI 0.97-1.10 per 10 cm)) with no evidence of heterogeneity (see Ovarian Cancer SLR 2013 figure 191). No meta-analysis was conducted for the SER.

### **Waist-to-hip ratio**

The Ovarian Cancer SLR 2013 identified four new papers [19, 22, 24, 25], giving a total of seven studies (including studies from the SER). Of six studies reporting on ovarian cancer incidence, one study showed a significant positive association, two showed a non-significant positive association, three showed a non-significant inverse association when comparing the highest versus the lowest categories of waist-to-hip ratio. One study did not report a risk estimate.

Four studies were included in the Ovarian Cancer SLR 2013 dose-response meta-analysis for waist-to-hip ratio and ovarian cancer ( $n = 1166$ ). A non-significant association was observed (RR 0.99 (95% CI 0.92-1.06)) per 10cm, with no evidence of heterogeneity (see Ovarian Cancer SLR 2013 figure 197). No meta-analysis was conducted for the SER.

### **Mechanisms**

*Note: This is adapted 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 [43]. Circulating concentrations of insulin and leptin are elevated in obese people, and both can promote the growth of cancer cells. In addition, insulin resistance is increased, 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 [44].

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 [44] due to aromatase activity in subcutaneous fat, which increases the conversion of

androgen to oestrogen [45]. Increased levels of oestrogens are strongly associated with risk of endometrial and postmenopausal breast cancers [46, 47], and may impact on other cancers.

Recent studies suggest a link between age at menarche and DNA patterns. Early life events have detectable effects both on age at menarche and methylation patterns [48].

Obesity is associated with a low-grade chronic inflammatory state. In obesity, adipose tissue is characterised by macrophage infiltration and these macrophages are an important source of inflammation [49]. 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 [50], as well as of leptin, which also functions as an inflammatory cytokine [51]. Such chronic inflammation can promote cancer development

### **CUP Panel's conclusion:**

Overall the evidence from the Ovarian Cancer SLR 2013 was supportive of an association between body fatness (which the CUP Panel interprets to be marked by BMI) and ovarian cancer. Results from pooled analyses identified several possible sources of heterogeneity – tumour type, HRT use and menopausal status. Considering results from both the Ovarian Cancer SLR 2013 analysis and pooled analyses, the Panel concluded there was evidence of an association between overall body fatness and ovarian cancer risk. The evidence for abdominal fatness, as marked by waist circumference and waist-to-hip ratio, was limited and inconsistent.

There is evidence for an association between overall body fatness (marked by BMI) and ovarian cancer. There is evidence for plausible mechanisms that operate in humans. Greater body fatness is a probably cause of ovarian cancer in women.

## **6.3 Adult attained height**

(Also see Ovarian Cancer SLR 2013: Section 8.3.1)

The Ovarian Cancer SLR 2013 identified 10 new papers [17, 23, 25, 27, 28, 33, 52-54] giving a total of 18 cohort studies (including studies from the SER). Of 11 studies (10 estimates) reporting on ovarian cancer incidence, nine reported an increased risk, five of which were significant, and two studies reported a non-significant decreased risk when comparing the highest versus the lowest categories of height. One study reporting on ovarian cancer mortality reported a non-significant increased risk for the highest versus the lowest categories. Six studies were excluded for reasons given in table 213 of the Ovarian Cancer SLR 2013.

Fourteen studies (13 risk estimates) were included in a dose-response meta-analysis ( $n = 17\ 312$ ) and an 8 per cent increased risk per 5 cm was observed. A significant positive association was observed for all studies combined (RR 1.08 (95% CI 1.05-1.10) per 5 cm increase in height) with moderate heterogeneity ( $I^2 = 35\%$ ) (see Ovarian Cancer SLR 2013 figure 202). Although a non-linear model was used, the dose-response appeared to be linear over most of the exposure range (see Ovarian Cancer SLR 2013 figure 205).



## Published pooled analyses

Results from three pooled analyses have been published on height and ovarian cancer risk [36, 37, 55] and, consistent with the Ovarian Cancer SLR 2013 analyses, all observed significant positive associations in both highest versus lowest and continuous analyses. There was no difference observed between pre and postmenopausal women. The results are presented in table 2.

**Table 2: Summary of CUP meta-analysis and pooled analyses - Height**

		<b>RR (95% CI)</b>	<b>I<sup>2</sup></b>	<b>No. studies</b>	<b>No. cases</b>	<b>Factors adjusted for</b>
CUP Ovarian Cancer SLR 2013	Per 5 cm	1.08 (1.05-1.10)	34.8	14*	17 312	
Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012 [37]	Per 5cm	1.08 (1.06-1.10)		17	10 858	Stratified by study, age at diagnosis, parity, menopausal status/hysterectomy, BMI, duration of oral contraceptive use, and ever use of hormone therapy
The Emerging Risk Factors Collaboration, 2012 [55]	Per 6.5 cm	1.07 (1.01-1.14)	0		1428	Cancer deaths Adjusted for age, sex, year of birth and smoking status
Pooling Project of Prospective Studies of Diet and Cancer [36]	≥ 170 vs. < 160 cm, all	1.38 (1.16-1.65)		12	2036	Adjusted for age at menarche, oral contraceptive use, parity, BMI, smoking status, physical activity, energy intake, menopausal status at baseline (all) and hormone replacement therapy use among postmenopausal women
	Per 5 cm, all	1.10 (1.05-1.15)			2036	
Ovarian Cancer SLR 2013 additional analysis: Pooling Project of Prospective Studies of Diet and Cancer [36] combined with non-overlapping studies from the CUP [17, 25, 28, 52, 53, 56]	Per 5 cm	1.08 (1.06-1.11)		24	16 062	

\* One study reported a risk estimate for two studies combined (Lundqvist et al, 2007). Thirteen risk estimates are included in the analysis

## Mechanisms

*Note: This is adapted 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. Health and nutrition status in the neonatal period and childhood may impact the age of sexual maturity. These processes are mediated by changes in the hormonal microenvironment that may have both short- and long-term effects on circulating levels of growth factors, insulin, oestrogens, and other endocrine or tissue specific mediators that may influence cancer risk [57].

### CUP Panel's conclusion:

More evidence was available for the Ovarian Cancer SLR 2013 analysis and the evidence was consistent. Overall a significant positive association was observed between height and ovarian cancer risk, and this was consistent with the result from the SER. The Panel noted the need for better characterisation and interpretation of measures, of growth, development and maturation.

The evidence is consistent with a clear dose-response relationship. There is strong evidence for plausible mechanisms operating in humans. The evidence that developmental factors leading to greater linear growth (marked by adult attained height) are causal for ovarian cancer is convincing. 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 non-starchy vegetables, previously judged as 'limited - suggestive' in the SER, 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 Ovarian Cancer SLR 2013: fruits, poultry; fish; eggs; milk and dairy products; coffee; tea; dietary fibre; lactose; total fat; alcohol; folate; vitamin A; vitamin C; vitamin E; abdominal fatness and physical activity.

The following exposures, also previously too limited to draw conclusions in the SER and not updated as part of the Ovarian Cancer SLR 2013 due to a lack of new evidence, remain 'limited - no conclusion': pulses (legumes); carbohydrate; protein; dietary cholesterol and energy intake.

In addition, evidence for the following new exposures, for which no judgement was made in the SER, is too limited to draw any conclusions: dietary patterns; processed meat; red meat; lycopene;

calcium; acrylamide; saturated fatty acids; monounsaturated fatty acids; polyunsaturated fatty acids; animal fat; vegetable fat; trans fatty acids; and serum vitamin D.

## 7. Comparison with the Second Expert Report

More studies were available for adult attained height and the Panel upgraded its judgement from probable to convincing - increases risk.

More evidence was available for body fatness and the CUP Panel concluded that overall greater body fatness (marked by BMI) is probably a cause of ovarian cancer.

The evidence that non-starchy vegetables protect against ovarian cancer was weak. More cohort studies were available for the Ovarian Cancer SLR 2013 analyses, and the evidence failed to demonstrate significant associations and was no longer suggestive of a protective association with ovarian cancer. The Panel therefore concluded the evidence for non-starchy vegetables was too limited and inconsistent to allow a conclusion to be reached (see Ovarian Cancer SLR 2013: Section 2.2.1).

More data for additional exposures were available for inclusion in the Ovarian Cancer SLR 2013 analyses. New exposures for which the Panel could make a judgement with regard to risk of ovarian cancer, included dietary patterns; processed meat; red meat; lycopene; calcium; acrylamide; saturated fatty acids; monounsaturated fatty acids; polyunsaturated fatty acids; animal fat; vegetable fat; trans fatty acids; and serum vitamin D. The evidence for all these new exposures was limited and no conclusion was possible.

## 8. Conclusions

The CUP Panel will review the evidence relating to ovarian cancer again after 2015. 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 CUP Panel concluded:**

The evidence that developmental factors leading to greater linear growth (marked by adult attained height) are a cause of ovarian cancer is convincing.

Greater body fatness (which the Panel interprets to be marked by body mass index (BMI)) is probably a cause of ovarian cancer.

The evidence suggesting that lactation protects against ovarian cancer is limited.

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## Appendix - Criteria for grading evidence

(Taken from Chapter 3 of the Second Expert Report)

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

### **Convincing**

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 ([www.dietandcancerreport.org](http://www.dietandcancerreport.org)). 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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