World Cancer Research Fund

American Institute for Cancer Research

CUP Continuous Update Project

Analysing research on cancer prevention and survival

Diet, nutrition, physical activity and ovarian cancer

2014

Revised 2018

World Cancer Research Fund International

World Cancer Research Fund UK

Wereld Kanker Onderzoek Fonds

World Cancer Research Fund 世界癌症研究基金會

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WORLD CANCER RESEARCH FUND NETWORK

OUR VISION

We want to live in a world where no one develops a preventable cancer.

OUR MISSION

We champion the latest and most authoritative scientific research from around the world on cancer prevention and survival through diet, weight and physical activity, so that we can help people make informed choices to reduce their cancer risk.

As a network, we influence policy at the highest level and are trusted advisors to governments and to other official bodies from around the world.

OUR NETWORK

World Cancer Research Fund International is a not-for-profit organisation that leads and unifies a network of cancer charities with a global reach, dedicated to the prevention of cancer through diet, weight and physical activity.

The World Cancer Research Fund network of charities is based in Europe, the Americas and Asia, giving us a global voice to inform people about cancer prevention.

CUP Continuous Update Project

Analysing research on cancer prevention and survival

THIRD EXPERT REPORT

OUR CONTINUOUS UPDATE PROJECT (CUP)

The Continuous Update Project (CUP) is the World Cancer Research Fund (WCRF) Network's ongoing programme to analyse cancer prevention and survival research related to diet, nutrition and physical activity from all over the world. Among experts worldwide it is a trusted, authoritative scientific resource which informs current guidelines and policy on cancer prevention and survival.

Scientific research from around the world is continually added to the CUP's unique database, which is held and systematically reviewed by a team at Imperial College London. An independent panel of experts carries out ongoing evaluations of this evidence, and their findings form the basis of the WCRF Network's Cancer Prevention Recommendations (**see inside back cover**).

Through this process, the CUP ensures that everyone, including policymakers, health professionals and members of the public, has access to the most up-to-date information on how to reduce the risk of developing cancer.

The launch of the WCRF Network's Third Expert Report, *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*, in 2018 brings together the very latest research from the CUP's review of the accumulated evidence on cancer prevention and survival related to diet, nutrition and physical activity. Diet, nutrition, physical activity and ovarian cancer is one of many parts that make up the CUP Third Expert Report: for a full list of contents, see **dietandcancerreport.org**.

The CUP is led and managed by World Cancer Research Fund International in partnership with the American Institute for Cancer Research, on behalf of World Cancer Research Fund UK, Wereld Kanker Onderzoek Fonds and World Cancer Research Fund HK.

HOW TO CITE THIS REPORT

This part: World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and ovarian cancer. Available at **dietandcancerreport.org**

The whole report: World Cancer Research Fund/American Institute for Cancer Research. *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*. Continuous Update Project Expert Report 2018. Available at **dietandcancerreport.org**

KEY

References to other parts of the Third Expert Report are highlighted in purple.

2014	DIET, NUTRITION, PHYSICAL ACTIVITY AND OVARIAN CANCER		
		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	Convincing		Adult attained height[1]
	Probable		Body fatness[2]
LIMITED EVIDENCE	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	
STRONG EVIDENCE	Substantial effect on risk 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 linea growth.

2 Body fatness marked by body mass index (BMI). The effect may vary in different subgroups such as by tumour type, hormone replacement therapy use, and menopausal status.

1. Summary of Panel judgements

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

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

Convincing evidence

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

Probable evidence

Body fatness: Greater body fatness is probably a cause of ovarian cancer.

Limited - suggestive evidence

Lactation: The evidence suggesting lactation decreases the risk of ovarian cancer is limited.

For a full description of the definitions of, and the criteria for, the terminology of 'convincing', 'probable', 'limited – suggestive', 'limited – no conclusion' and 'substantial effect on risk unlikely', see the **Appendix** on page 27.

2. 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.

3. 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, produces high-grade carcinomas, with a poorer prognosis [7].

4. Other established causes

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].

5. Interpretation of the evidence

5.1 General

For general considerations that may affect interpretation of the evidence, see Judging the evidence.

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

5.1 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].

6. Methodology

To ensure consistency with evidence collected and analysed for the Second Expert Report, much of the methodology for the Continuous Update Project remains unchanged from that used previously. However, based upon the experience of conducting the systematic literature reviews for the Second Expert Report, some modifications to the methodology were made. The literature search was restricted to Medline and included only randomised controlled trials, cohort and case-control studies. Due to 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 31st December 2012. For more information on methodology see the full Ovarian Cancer SLR 2013.

6.1 Mechanistic evidence

The evidence for mechanisms is summarised under each exposure. These summaries were developed from mechanistic reviews conducted for the Second Expert Report [1], updates from CUP Panel members and published reviews.

Update: The evidence for site specific mechanisms of carcinogenesis has been updated for the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report 2018 (our Third Expert Report, available at ***dietandcancerreport.org****). The evidence is based on both human and animal studies. It covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature. A signpost to the relevant section in the Third Expert Report which summarises the updated mechanisms evidence can be found under each exposure within this report.*

7. Evidence and judgements

There were 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].

7.1 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

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].

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

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.

7.2 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/m2 (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

Analysis	Increment	RR (95% CI)	I^2	No. Studies	No. Cases	Factors adjusted for
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. No statistically significant heterongeneity between studies. BMI in early adulthood was not associated with ovarian cancer risk.
	Per 4 units	1.01 (0.95-1.07)			2036	
Collaborative Group on Epidemiological Studies of Ovarian Cancer [37]	Per 5 units	1.03 (1.00-1.06)		17	10643	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	12787	

* 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 ≥ 30 kg/m2 with BMI 18.5 to 23 kg/m2 (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-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-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-hip ratio and ovarian cancer (*n* = 1166). No 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

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.

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

CUP Panel's conclusion:

Overall the evidence from the 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-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 probably a cause of ovarian cancer in women.

7.3 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 (I2 = 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

Analysis	Increment	RR (95% CI)	I^2	No. Studies	No. Cases	Factors adjusted for
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 5 cm	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)			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] combine 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 [28]. Thirteen risk estimates are included in the analysis

Mechanisms

Factors that lead to greater adult attained height, or their consequences, are a cause of a number of cancers. Adult height is related to the rate of growth during fetal life and childhood. 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].

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

CUP Panel's conclusion:

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.

7.4 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.

8. 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.

9. Conclusions

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

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

Convincing evidence

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

Probable evidence

Body fatness: Greater body fatness is probably a cause of ovarian cancer.

Limited - suggestive evidence

Lactation: The evidence suggesting lactation decreases the risk of ovarian cancer is limited.

For a full description of the definitions of, and the criteria for, the terminology of 'convincing', 'probable', 'limited – suggestive', 'limited – no conclusion' and 'substantial effect on risk unlikely', see the **Appendix** on page 27.

The Cancer Prevention Recommendations were reviewed by the CUP Panel and published in 2018. Please see Recommendations and public health and policy implications for further details.

Each conclusion on the likely causal relationship between an exposure and the risk of cancer forms a part of the overall body of evidence that is considered during the process of making Cancer Prevention Recommendations. Any single conclusion does not represent a Recommendation in its own right. The 2018 Cancer Prevention Recommendations are based on a synthesis of all these separate conclusions, as well as other relevant evidence.

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Abbreviations

AICR	American Institute for Cancer Research
BMI	body mass index
CI	confidence interval
CUP	Continuous Update Project
DNA	deoxyribonucleic acid
ER(+/-)	oestrogen-receptor (positive/negative)
IARC	International Agency for Research on Cancer
n	number of cases
PR(+/-)	progesterone-receptor (positive/negative)
RR	relative risk
SD	standard deviation
SER	Second Expert Report 'Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective'
SLR	systematic literature review
WCRF	World Cancer Research Fund

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Appendix: Criteria for grading evidence for cancer prevention

See also Judging the evidence, section 8.

Adapted from Chapter 3 of the 2007 Second Expert Report. Listed here are the criteria agreed by the Panel that were necessary to support the judgements shown in the matrices. The grades shown here are 'convincing', 'probable', 'limited – suggestive', 'limited – no conclusion', and 'substantial effect on risk unlikely'. In effect, the criteria define these terms.

These criteria were used in a modified form for breast cancer survivors (see CUP Breast cancer survivors report 2014).

CONVINCING (STRONG EVIDENCE)

Evidence strong enough to support a judgement of a convincing causal (or protective) relationship, which justifies making recommendations designed to reduce the risk of cancer. The evidence is robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates.

All of the following are generally required:

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

PROBABLE (STRONG EVIDENCE)

Evidence strong enough to support a judgement of a probable causal (or protective) relationship, which generally justifies recommendations designed to reduce the risk of cancer.

All of the following are generally required:

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

LIMITED – SUGGESTIVE

Evidence that is too limited to permit a probable or convincing causal judgement but is suggestive of a direction of effect. The evidence may be limited in amount or by methodological flaws but shows a generally consistent direction of effect. This judgement is broad and includes associations where the evidence falls only slightly below that required to infer a probably causal association through to those where the evidence is only marginally strong enough to identify a direction of effect. This judgement is very rarely sufficient to justify recommendations designed to reduce the risk of cancer; any exceptions to this require special, explicit justification.

All of the following are generally required:

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

LIMITED – NO CONCLUSION

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

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

There are also many exposures for which there is such limited evidence that no judgement is possible. In these cases, evidence is recorded in the full CUP SLRs on the World Cancer Research Fund International website (**dietandcancerreport.org**). However, such evidence is usually not included in the summaries.

SUBSTANTIAL EFFECT ON RISK UNLIKELY (STRONG EVIDENCE)

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

All of the following are generally required:

- Evidence from more than one study type.
- Evidence from at least two independent cohort studies.
- Summary estimate of effect close to 1.0 for comparison of high- versus low-exposure categories.
- No substantial unexplained heterogeneity within or between study types or in different populations.
- Good-quality studies to exclude, with confidence, the possibility that the absence of an observed association results from random or systematic error, including inadequate power, imprecision or error in exposure measurement, inadequate range of exposure, confounding and selection bias.
- Absence of a demonstrable biological gradient ('dose-response').
- Absence of strong and plausible experimental evidence, from either human studies or relevant animal models, that typical human exposure levels lead to relevant cancer outcomes.

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

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

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

SPECIAL UPGRADING FACTORS

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

Factors may include the following:

- Presence of a plausible biological gradient ('dose-response') in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.
- A particularly large summary effect size (an odds ratio or relative risk of 2.0 or more, depending on the unit of exposure) after appropriate control for confounders.
- Evidence from randomised trials in humans.
- Evidence from appropriately controlled experiments demonstrating one or more plausible and specific mechanisms actually operating in humans.
- Robust and reproducible evidence from experimental studies in appropriate animal models showing that typical human exposures can lead to relevant cancer outcomes.

Our Cancer Prevention Recommendations

Be a healthy weight
Keep your weight within the healthy range and avoid weight gain in adult life

Be physically active
Be physically active as part of everyday life – walk more and sit less

Eat a diet rich in wholegrains, vegetables, fruit and beans
Make wholegrains, vegetables, fruit, and pulses (legumes) such as beans and lentils a major part of your usual daily diet

Limit consumption of 'fast foods' and other processed foods high in fat, starches or sugars
Limiting these foods helps control calorie intake and maintain a healthy weight

Limit consumption of red and processed meat
Eat no more than moderate amounts of red meat, such as beef, pork and lamb. Eat little, if any, processed meat

Limit consumption of sugar sweetened drinks
Drink mostly water and unsweetened drinks

Limit alcohol consumption
For cancer prevention, it's best not to drink alcohol

Do not use supplements for cancer prevention
Aim to meet nutritional needs through diet alone

For mothers: breastfeed your baby, if you can
Breastfeeding is good for both mother and baby

After a cancer diagnosis: follow our Recommendations, if you can
Check with your health professional what is right for you

Not smoking and avoiding other exposure to tobacco and excess sun are also important in reducing cancer risk.

Following these Recommendations is likely to reduce intakes of salt, saturated and trans fats, which together will help prevent other non-communicable diseases.

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