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 **breast cancer**

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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.

OUR CONTINUOUS UPDATE PROJECT (CUP)

The Continuous Update Project (CUP) analyses global cancer prevention and survival research linked to diet, nutrition, physical activity and weight. Among experts worldwide it is a trusted, authoritative scientific resource which underpins current guidelines and policy for cancer prevention.

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

The findings from the CUP are used to update our Cancer Prevention Recommendations, which were originally published in *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective* (our Second Expert Report) [1]. These ensure that everyone – from policymakers and health professionals to members of the public – has access to the most up-to-date information on how to reduce the risk of developing the disease.

As part of the CUP, scientific research from around the world is collated and added to a database of epidemiological studies on an ongoing basis and systematically reviewed by a team at Imperial College London. An independent panel of world-renowned experts then evaluates and interprets the evidence to make conclusions based on the body of scientific evidence. Their conclusions form the basis for reviewing and, where necessary, revising our Cancer Prevention Recommendations (see inside back cover).

A review of the Cancer Prevention Recommendations is expected to be published later this year, once an analysis of all of the cancers being assessed has been conducted. So far, new CUP reports have been published with updated evidence on colorectal, pancreatic, endometrial, ovarian, prostate, liver, gallbladder, kidney, bladder, stomach and oesophageal cancers. In addition, our first ever CUP report on breast cancer survivors was published in 2014. This report is the second CUP update on breast cancer; the first was published in 2010.

This CUP report on breast cancer updates the breast cancer section of the Second Expert Report (Section 7.10) and the 2010 CUP Breast Cancer Report. It is based on the findings of the 2017 CUP Breast Cancer Systematic Literature Review (SLR) and the CUP Expert Panel discussion in June 2016. For further details, please see the full CUP Breast SLR 2017 (**wcrf.org/breast-cancer–slr-2017**).

HOW TO CITE THIS REPORT

World Cancer Research Fund International/American Institute for Cancer Research. Continuous Update Project Report: Diet, Nutrition, Physical Activity and Breast Cancer. 2017. Available at: **wcrf.org/breast-cancer–2017.** All CUP reports are available at **wcrf.org/cupreports.**

EXECUTIVE SUMMARY

Background and context

Breast cancer is the most common cancer in women worldwide. Approximately 1.7 million new cases were recorded globally in 2012, accounting for 25 per cent of all new cases of cancer in women. It is the fifth most common cause of death from cancer in women [2].

Breast cancer risk doubles each decade until the menopause, after which the increase slows [3]. However, breast cancer is more common after the menopause. The highest incidence is in Northern America and the lowest incidence is in Middle Africa and Eastern Asia. In 2012, the rate of new cases of breast cancer in Northern America was more than double that in Africa [2].

Survival rates for breast cancer vary worldwide, but in general rates have improved. This is because breast cancer is diagnosed at an earlier and localised stage in nations where populations have access to medical care and because of progressive improvement in treatment strategies. In many countries with advanced medical care, the five-year survival rate of early stage breast cancers is 80-90 per cent, falling to 24 per cent for breast cancers diagnosed at a more advanced stage, indicating a critical need for improved treatment of metastatic disease.

Breast cancer is a heterogeneous disease, but most breast cancer subtypes are hormone-related. The natural history of the disease differs between those diagnosed before and after the menopause, which may be due to different kinds of tumour and possibly different effects of nutritional factors on hormones depending on menopausal status. Breast cancers have long been classified by their hormone receptor type; for example, to what extent the cancer cells have receptors for the hormones oestrogen and progesterone, which can predict the behaviour of the cancer and response to therapy. Breast cancer cells that have oestrogen receptors are referred to as oestrogen-positive (ER+), while those containing progesterone receptors are called progesterone-positive (PR+) cancers. Hormone receptor positive cancers are the most common subtypes of breast cancer at the time of diagnosis and have a relatively better prognosis than hormone receptor negative cancers, which are likely to be of higher pathological grade and can be more difficult to treat [4]. Many epidemiologic studies have classified breast cancer cases by menopausal status at time of diagnosis, and therefore in this report we chose to highlight associations between diet, weight and physical activity separately in premenopausal and postmenopausal breast cancer, where possible.

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

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

1. **Life events:**

- Early menarche (before the age of 12), late natural menopause (after the age of 55), not bearing children and first pregnancy over the age of 30 all increase lifetime exposure to oestrogen and progesterone and the risk of breast cancer. The reverse also applies: late menarche, early menopause, bearing children and pregnancy before the age of 30 all reduce the risk of breast cancer.

2. **Radiation:**

- Ionising radiation exposure from medical treatment such as X-rays, particularly during puberty, increases the risk of breast cancer, even at low doses.

3. **Medication:**

- Hormone therapy (containing oestrogen with or without progesterone) increases the risk of breast cancer, and the risk is greater with combined oestrogen plus progesterone preparations. Oral contraceptives containing both oestrogen and progesterone also cause a small increased risk of breast cancer in young women, among current and recent users only [5].

How the research was conducted

The global scientific research on diet, weight, physical activity and the risk of breast cancer was systematically gathered and analysed, and then independently assessed by a panel of leading international scientists in order to draw conclusions about which of these factors increase or decrease the risk of developing the disease. Although breast cancer can occur in men, it is rare and the evidence was not reviewed for this report.

This new report includes all new relevant studies as well as studies included in our 2007 Second Expert Report [1]. In total, this new report analysed 119 studies from around the world, comprising more than 12 million women and over 260,000 cases of breast cancer.

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

A summary of the mechanisms underpinning the findings can be found in **Section 7**, Evidence and Judgements of this report.

Findings

Premenopausal breast cancer

There is strong evidence that:

- undertaking vigorous physical activity decreases the risk of premenopausal breast cancer.
- being overweight or obese between the ages of about 18 and 30 years decreases the risk of premenopausal breast cancer.
- being overweight or obese in adulthood before the menopause decreases the risk of premenopausal cancer.
- breastfeeding decreases the risk of breast cancer (unspecified)[1] in the mother.
- consuming alcoholic drinks increases the risk of premenopausal breast cancer.
- developmental factors leading to greater linear growth (marked by adult attained height) increase the risk of premenopausal breast cancer.
- factors that lead to greater birthweight, or its consequences, increase the risk of premenopausal breast cancer.

There is limited evidence that:

- consuming non-starchy vegetables might decrease the risk of oestrogen-receptor-negative (ER–) breast cancer (unspecified)[1].
- consuming foods containing carotenoids might decrease the risk of breast cancer (unspecified).
- consuming dairy products might decrease the risk of premenopausal breast cancer.
- consuming diets high in calcium might decrease the risk of premenopausal breast cancer.
- being physically active might decrease the risk of premenopausal breast cancer.

1 Evidence presented did not specify pre- or postmenopausal breast cancer

Postmenopausal breast cancer

There is strong evidence that:

- **being physically active (including vigorous physical activity) decreases the risk of postmenopausal breast cancer.**
- **breastfeeding decreases the risk of breast cancer (unspecified)[1] in the mother.**
- **being overweight or obese between the ages of about 18 and 30 years decreases the risk of postmenopausal breast cancer.**
- **being overweight or obese throughout adulthood increases the risk of postmenopausal breast cancer.**
- **greater weight gain in adulthood increases the risk of postmenopausal breast cancer.**
- **developmental factors leading to greater linear growth (marked by adult attained height) increase the risk of postmenopausal breast cancer.**
- **consuming alcoholic drinks increases the risk of postmenopausal breast cancer.**

There is limited evidence that:

- **consuming non-starchy vegetables might decrease the risk of oestrogen-receptor-negative (ER–) breast cancer (unspecified)[1].**
- **consuming foods containing carotenoids might decrease the risk of breast cancer (unspecified)[1].**
- **consuming diets high in calcium might decrease the risk of postmenopausal breast cancer.**

1 Evidence presented did not specify pre- or postmenopausal breast cancer

Recommendations

Our Cancer Prevention Recommendations – for preventing cancer in general – include maintaining a healthy weight, being physically active, eating a healthy diet and limiting alcohol consumption (if consumed at all). The Cancer Prevention Recommendations are listed on the inside back cover of this report, with full details available at **wcrf.org/recommendations**.

References

[1] World Cancer Research Fund/American Institute for Cancer Research, *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective.* **wcrf.org/int/research-we-fund/continuous-update-project-cup/second-expert-report**. 2007.

[2] Ferlay J, Soerjomataram I, Ervik M et al. GLOBOCAN 2012 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. 2015; available from **http://globocan.iarc.fr.**

[3] McPherson K, Steel CM and Dixon JM. ABC of breast diseases. Breast cancer epidemiology, risk factors, and genetics. *BMJ* 2000; 321: 624–8.

[4] Putti TC, El-Rehim DM, Rakha EA *et al*. Estrogen-receptor-negative breast carcinomas: a review of morphology and immunophenotypical analysis. *Mod Pathol* 2005; 18: 26–35.

[5] International Agency for Research on Cancer. Combined Estrogen-Progestogen Contraceptives. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* 2012; 100A: 283–317.

2017 DIET, NUTRITION, PHYSICAL ACTIVITY AND PREMENOPAUSAL BREAST CANCER

		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	Convincing		**Adult attained height[1]**
	Probable	**Vigorous physical activity** **Body fatness[2]** **Lactation[3]**	**Alcoholic drinks[4]** **Greater birthweight[5]**
LIMITED EVIDENCE	**Limited – suggestive**	Non-starchy vegetables (ER– breast cancers only)[6] Dairy products Foods containing carotenoids[7] Diets high in calcium Physical activity[8]	
	Limited – no conclusion	Cereals (grains) and their products; dietary fibre; potatoes; non-starchy vegetables (ER+ breast cancers); fruits; pulses (legumes); soya and soya products; red and processed meat; poultry; fish; eggs; fats and oils; total fat; vegetable fat; fatty acid composition; saturated fatty acids; mono-unsaturated fatty acids; polyunsaturated fatty acids; trans-fatty acids; cholesterol; sugar (sucrose); other sugars; sugary foods and drinks; coffee; tea; carbohydrate; starch; glycaemic index; glycaemic load; protein; vitamin A; riboflavin; vitamin B6; folate; vitamin B12; vitamin C; vitamin D; vitamin E; calcium supplements; iron; selenium; phytoestrogens; isoflavones; dichlorodiphenyldichloroethylene; dichlorodiphenyltrichloroethane; dieldrin; hexachlorobenzene; hexachlorocyclohexane; trans-nonachlor; polychlorinated biphenyls; acrylamide; dietary patterns; culturally defined diets; sedentary behaviour; adult weight gain; 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 linear growth.

2 Body fatness marked by body mass index (BMI), waist circumference and waist-hip ratio. Also includes evidence on young women aged about 18 to 30 years. Body fatness in young adulthood is marked by BMI.

3 The Panel's conclusion relates to the evidence for overall breast cancer (unspecified). The evidence for premenopausal and postmenopausal breast cancers separately was less conclusive, but consistent with the overall finding.

4 No threshold was identified.

5 Birthweight is a marker both for prenatal growth, reflecting fetal nutrition, and is a predictor of later growth and maturation – e.g., age at menarche – which are also determinants of breast cancer risk.

6 The Panel's conclusion relates to the evidence for overall breast cancer (unspecified). The observed association was in oestrogen-receptor-negative (ER–) breast cancer only.

7 The Panel's conclusion relates to the evidence for overall breast cancer (unspecified). The observed association was stronger for oestrogen-receptor-negative (ER–) breast cancer. Includes both foods that naturally contain carotenoids and foods that have carotenoids added.

8 Physical activity, including occupational, recreational, walking and household activity. There was sufficient evidence for the Panel to make a separate judgement for vigorous physical activity.

2017 DIET, NUTRITION, PHYSICAL ACTIVITY AND POSTMENOPAUSAL BREAST CANCER

		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	**Convincing**		**Alcoholic drinks**[1] **Body fatness**[2] **Adult weight gain** **Adult attained height**[3]
	Probable	**Physical activity**[4] **Body fatness in young adulthood**[5] **Lactation**[6]	
LIMITED EVIDENCE	**Limited – suggestive**	Non-starchy vegetables (ER– breast cancers only)[7] Foods containing carotenoids[8] Diets high in calcium	
	Limited – no conclusion	Cereals (grains) and their products; dietary fibre; potatoes; non-starchy vegetables (ER+ breast cancers); fruits; pulses (legumes); soya and soya products; red and processed meat; poultry; fish; eggs; dairy products; fats and oils; total fat; vegetable fat; fatty acid composition; saturated fatty acids; mono-unsaturated fatty acids; polyunsaturated fatty acids; trans-fatty acids; cholesterol; sugar (sucrose); other sugars; sugary foods and drinks; coffee; tea; carbohydrate; starch; glycaemic index; glycaemic load; protein; vitamin A; riboflavin; vitamin B6; folate; vitamin B12; vitamin C; vitamin D; vitamin E; calcium supplements; iron; selenium; phytoestrogens; isoflavones; dichlorodiphenyldichloroethylene; dichlorodiphenyltrichloroethane; dieldrin; hexachlorobenzene; hexachlorocyclohexane; trans-nonachlor; polychlorinated biphenyls; acrylamide; dietary patterns; culturally defined diets; sedentary behaviour; energy intake	
STRONG EVIDENCE	**Substantial effect on risk unlikely**		

1 No threshold was identified.
2 Body fatness, throughout adulthood, marked by body mass index (BMI), waist circumference and waist-hip ratio.
3 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.
4 Physical activity including vigorous, occupational, recreational, walking and household activity.
5 Young women aged about 18 to 30 years. Body fatness in young adulthood is marked by BMI.
6 The Panel's conclusion relates to the evidence for overall breast cancer (unspecified). The evidence for premenopausal and postmenopausal breast cancers separately was less conclusive, but consistent with the overall finding.
7 The Panel's conclusion relates to the evidence for overall breast cancer (unspecified). The observed association was in oestrogen-receptor-negative (ER–) breast cancer only.
8 The Panel's conclusion relates to the evidence for overall breast cancer (unspecified). The observed association was stronger for oestrogen-receptor-negative (ER–) breast cancer. Includes both foods that naturally contain carotenoids and foods that have carotenoids added.

1. Summary of Panel judgements

Breast cancer is hormone related, and the factors that modify the risk of this cancer when diagnosed premenopausally and when diagnosed (much more commonly) postmenopausally are not the same. For evidence presented that did not specify pre- or postmenopausal breast cancer, we refer to 'breast cancer (unspecified)'.

The Panel notes the strength of the evidence that lactation protects against breast cancer (unspecified), but evidence was insufficient to specify association separately in premenopausal compared with postmenopausal breast cancer.

For premenopausal breast cancer, the Panel notes the strength of the evidence that consumption of alcoholic drinks, developmental factors leading to greater linear growth (marked by adult attained height) and greater birthweight (or its consequences) are causes of this cancer, and that vigorous physical activity, greater body fatness in adulthood (before the menopause) (marked by BMI, waist circumference and waist-hip ratio) and greater body fatness in young women (aged about 18 to 30 years, marked by BMI) protect against premenopausal breast cancer.

For postmenopausal breast cancer, the Panel notes the strength of the evidence that greater body fatness throughout adulthood (marked by BMI, waist circumference and waist-hip ratio), adult weight gain, developmental factors leading to greater linear growth (marked by adult attained height) and consumption of alcoholic drinks are causes of this cancer, and that total (including vigorous) physical activity and greater body fatness in young women (aged about 18 to 30 years, marked by BMI) protect against postmenopausal breast cancer.

Box 1. Cancer subtypes

Historically cancers were classified simply according to the tissue from which they arise. Later they were also characterised according to pathological features (such as degree of differentiation) that carried prognostic significance.

As knowledge has accrued, it is apparent that such simple categorisations are inadequate to describe the structural and functional diversity of cancer subtypes. For many years it has been clear that the natural history and pattern of risk factors for breast cancer diagnosed before the menopause differs from that diagnosed after. Equally, there are different risk factors for colon cancers arising from different sites in the colon, and between colon and rectal cancers. The prognosis from screen-detected cancers of prostate or breast is better than for those diagnosed following the development of symptoms. These variations imply phenotypic variability that has not been characterised at a more biological level.

More recently, the characterisation of tumours according to molecular characteristics has highlighted an ever increasing diversity among tumours, which is likely to increase further as biological and technological developments arise. For instance, breast cancers have for many years been characterised according to the preponderance of tumour cells carrying receptors for oestrogen or progesterone, and more recently carrying the human epidermal growth factor, HER2. The presence or absence of these markers, or combinations of them, carry therapeutic and prognostic implications of clinical importance indicating wide biological diversity in the behaviour of cancer cells and of tumours. Increasingly, cancers arising from several different sites can now be characterised according to several molecular markers with different clinical implications.

However, there is as yet insufficient epidemiological information on many of these cancer subtypes classified according to molecular or other markers. Where such information is available, different cancer subtypes show different patterns of risk according to different patterns of exposure. It is likely that this also applies to those subtypes where epidemiological information is lacking. The resulting lack of specificity in characterising cancers likely leads to failure to identify associations between exposures and cancers that are limited to particular subtypes. In future, greater capability to identify more specific patterns of association will likely lead to better appreciation of the patterns of causality between exposures and cancers. Currently, conclusions can be drawn with confidence only for cancer subtypes where sufficient epidemiological data have accrued. Firm conclusions on likely causal associations for cancer subtypes with more detailed molecular characterisation will have to await better epidemiological data.

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

Premenopausal breast cancer

Convincing evidence

Adult attained height: Developmental factors leading to greater linear growth (marked by adult attained height) are a convincing cause of premenopausal breast cancer.

Probable evidence

Vigorous physical activity: Vigorous physical activity probably protects against premenopausal breast cancer.

Body fatness: Greater body fatness in women before the menopause (marked by BMI, waist circumference and waist-hip-ratio) probably protects against premenopausal breast cancer.

Body fatness in young adulthood: Greater body fatness in young women (aged about 18 to 30 years) (marked by BMI) probably protects against premenopausal breast cancer.

Lactation: Lactation probably protects against breast cancer (unspecified).

Alcoholic drinks: Consumption of alcoholic drinks is probably a cause of premenopausal breast cancer.

Birthweight: The factors that lead to greater birthweight, or its consequences, are probably a cause of premenopausal breast cancer.

Limited – suggestive evidence

Non-starchy vegetables: The evidence suggesting that consumption of non-starchy vegetables decreases the risk of oestrogen-receptor-negative (ER–) breast cancer (unspecified) is limited.

Dairy products: The evidence suggesting that consumption of dairy products decreases the risk of premenopausal breast cancer is limited.

Foods containing carotenoids: The evidence suggesting that consumption of foods containing carotenoids decreases the risk of breast cancer (unspecified) is limited.

Diets high in calcium: The evidence suggesting that diets high in calcium decrease the risk of premenopausal breast cancer is limited.

Total physical activity: The evidence suggesting that being physically active decreases the risk of premenopausal breast cancer is limited.

Postmenopausal breast cancer

Convincing evidence

Alcoholic drinks: Consumption of alcoholic drinks is a convincing cause of postmenopausal breast cancer.

Body fatness: Greater body fatness throughout adulthood (marked by BMI, waist circumference and waist-hip ratio) is a convincing cause of postmenopausal breast cancer.

Adult weight gain: Greater weight gain in adulthood is a convincing cause of postmenopausal breast cancer.

Adult attained height: Developmental factors leading to greater linear growth (marked by adult attained height) are a convincing cause of postmenopausal breast cancer.

Probable evidence

Total (including vigorous) physical activity: Being physically active (including vigorous physical activity) probably protects against postmenopausal breast cancer.

Body fatness in young adulthood: Greater body fatness in young women (aged about 18 to 30 years) (marked by BMI) probably protects against postmenopausal breast cancer.

Lactation: Lactation probably protects against breast cancer (unspecified).

Limited – suggestive evidence

Non-starchy vegetables: The evidence suggesting that consumption of non-starchy vegetables decreases the risk of oestrogen-receptor-negative (ER–) breast cancer (unspecified) is limited.

Foods containing carotenoids: The evidence suggesting that consumption of foods containing carotenoids decreases the risk of breast cancer (unspecified) is limited.

Diets high in calcium: The evidence suggesting that diets high in calcium decrease the risk of postmenopausal breast cancer is limited.

For a full description of the definitions of, and criteria for, the terminology of ‘convincing’ and ‘probable’, (and also ‘limited – suggestive’, ‘limited – no conclusion’ and ‘substantial effect on risk unlikely’), see the Appendix on page 114. The Panel judgements for premenopausal breast cancer and postmenopausal breast cancer are shown in the matrices on page 8–9.

2. Trends, incidence and survival

Breast tissue comprises mainly fat, glandular tissue (arranged in lobes), ducts and connective tissue. Breast tissue develops in response to hormones such as oestrogens, progesterone, insulin and growth factors. The main periods of development are during puberty, pregnancy and lactation. The glandular tissue atrophies after menopause. Breast cancers are almost all carcinomas of the epithelial cells lining the breast ducts (the channels in the breast that carry milk to the nipple) [6]. Although breast cancer can occur in men, it is rare (less than 1 per cent of cases) and is not included in this review.

Breast cancer is the most common cancer in women worldwide, with nearly 1.7 million new cases diagnosed in 2012, representing about 25 per cent of all cancers in women. Incidence rates vary widely across the world, from 27 per 100,000 in Middle Africa and Eastern Asia to 92 per 100,000 in Northern America. It is the fifth most common cause of death from cancer in women, with an estimated 522,000 deaths (6.4 per cent of the total). It is also the most frequent cause of cancer death in women from regions characterised by lower indices of development and/or income (14.3 per cent of deaths), and the second most frequent from regions characterised by higher indices of development and/or income (15.4 per cent of deaths), after lung cancer [2].

Breast cancer risk doubles each decade until the menopause, after which the increase slows. However, breast cancer is more common after the menopause. Studies of women who migrate from areas of low risk to areas of high risk show that they assume the rate in the host country within one or two generations. This shows that environmental factors are important in the development of the disease [3].

Overall survival rates for breast cancer vary worldwide, but in general they have improved. This is because access to medical care is improving in many nations and the majority of breast cancer cases are diagnosed at an earlier and localised stage. In addition, improved surgery and tailored adjuvant treatment regimens are available. In many countries the five-year survival rate for women diagnosed with Stage I/II (small tumours or limited local spread to nodes under the arm) breast cancer is 80–90 per cent. For stages III/IV (larger tumours or more distant spread beyond the breast or to distant organs), the survival rate falls to 24 per cent [7]. The prevalence of breast cancer[1] in women per 100,000 is 665 in Western Europe, 745 in North America and 170 in Eastern Asia [2].

[1] The prevalence of breast cancer is defined as the number of persons in a defined population who were diagnosed five years before and who are still alive at the end of a given year. Prevalence reported here is for the adult population only (ages 15 and over) and presented as numbers per 100,000.

Box 2. 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 probably higher than the figures given here.

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

3. Pathogenesis

Breast tissue varies at different stages of life in response to host hormonal status and other environmental influences. It is therefore possible that some risk factors will have different effects at different life stages (see **Section 4** on page 16 in this report).

Hormones play an important role in breast cancer progression because they modulate the structure and growth of epithelial tumour cells [8]. Different cancers vary in hormone sensitivity. Breast cancers can be classified by their hormone receptor type; for example, to what extent the cancer cells have receptors for the hormones oestrogen and progesterone, which can affect the growth of the breast cancer cells. Breast cancer cells that have oestrogen receptors are referred to as oestrogen-positive (ER+), while those containing progesterone receptors are called progesterone-positive (PR+) cancers. Hormone-receptor-positive cancers are the most common subtypes of breast cancer, but vary by population (60–90 per cent) [9]. They have a relatively better prognosis than hormone-receptor-negative cancers, which are likely to be of higher pathological grade and can be more difficult to treat [4]. Many breast cancers also produce hormones, such as growth factors,that act locally, and these can both stimulate and inhibit the tumour's growth [10, 11].

Family history of breast cancer is associated with a higher risk of the disease: women with one first-degree relative with breast cancer have almost twice the risk of women without a family history; and women with more than one first-degree relative have about a three- to four-fold higher risk [12–14]. Some inherited mutations, particularly in BRCA1, BRAC2 and p53, result in a very high risk of breast cancer. Germline mutations in these genes are infrequent and account for only 2 to 5 per cent of cases [15]. During the carcinogenic process, mutations and epigenetic modifications in oncogenes and tumour suppressor genes may be acquired by cancer cells [8].

4. Other established causes

Life events

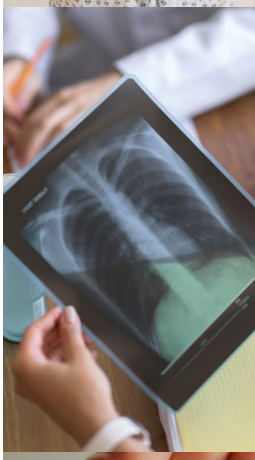
Early menarche (before the age of 12), late natural menopause (after the age of 55), not bearing children and first pregnancy over the age of 30 all increase lifetime exposure to oestrogen and progesterone and the risk of breast cancer [3, 16]. The reverse also applies: late menarche, early menopause, bearing children and pregnancy before the age of 30 all reduce the risk of breast cancer. Age of menarche, of breast development and of menopause, are influenced by nutrition, with high protein and energy diets promoting earlier puberty and late menopause [17].

Radiation

Ionising radiation exposure from medical treatment such as X-rays, particularly during puberty, increases the risk of breast cancer, even at low doses [18, 19].

Medication

Hormone therapy (also known as hormone replacement therapy) (containing oestrogen with or without progesterone) increases the risk of breast cancer, and the risk is greater with combined oestrogen plus progesterone preparations [20]. Oral contraceptives containing both oestrogen and progesterone also cause a small increased risk of breast cancer in young women, among current and recent users only [5].



5. Interpretation of the evidence

5.1 General

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

5.2 Specific

Considerations specific to breast cancer include the following:

Patterns

The preponderance of data from high-income countries is an issue. Breast cancer is hormone related, and factors that modify risk have different effects on cancers diagnosed pre- and postmenopause.

Classification

Because of the importance of menopausal status as an effect modifier, studies should stratify for menopause status, but many do not. A few studies also reported results separately for different hormone receptor profiles within cancers.

Confounding

Use of hormone therapy is an important possible confounder in postmenopausal breast cancer. High-quality studies adjust for age, number of reproductive cycles, age at which children were born and the use of hormone-based medications.

Tumour subtypes

There is growing evidence that the impact of obesity and dietary exposures on risk of breast cancer may differ according to the particular molecular subtypes of cancer. For instance, there was limited evidence suggesting a possible protective effect of vegetables in oestrogen-negative-receptor cancers only, and in future, as tumours are better characterised by molecular subtype, better discrimination of effects on cancer risk that are specific to one or other type might be possible.

6. Methodology

To ensure consistency with evidence collected and analysed for the Second Expert Report [1], the methodology for reviewing the epidemiological evidence in the CUP remains largely unchanged. However, on the basis of the experience of conducting the systematic literature reviews for the Second Expert Report, some modifications were made to the methodology. The updated literature search was restricted to Medline and included only randomised controlled trials, cohort and nested case-control studies. Owing to their methodological limitations, case-control studies were not analysed in the CUP Breast SLR 2017, except where they were included as part of a pooled analysis that did not report results individually by study type.

Breast cancer in women of unspecified menopausal status, in premenopausal women (premenopausal breast cancer) and in postmenopausal women (postmenopausal breast cancer) were reviewed separately. Conclusions are presented for premenopausal and postmenopausal breast cancer where data allow. For lactation, non-starchy vegetables and carotenoids (dietary and circulating), most of the evidence available did not specify menopausal status, and the results that did showed no clear difference between pre- and postmenopausal breast cancer. Therefore conclusions were made for breast cancer (unspecified) and apply to both pre- and postmenopausal breast cancer.

Where possible for this update, meta-analyses for incidence and mortality were also conducted separately. However, analyses combining studies on breast cancer incidence and mortality were conducted to explore heterogeneity in the results. Linear dose-response meta-analyses were updated when at least three new publications with enough data for dose-response meta-analysis were identified during the CUP and if there were in total five cohort studies or five randomised controlled trials. Pooled analyses were included with other individual studies in the meta-analysis when possible. Separate meta-analyses were also conducted by geographical location, anthropometric assessment method, adjustment for confounders, use of hormone therapy and hormone receptor type where possible.

Studies reporting mean difference as a measure of association were not included in the CUP Breast SLR 2017, as relative risks estimated from mean differences are not adjusted for confounders and thus are not comparable with adjusted relative risks from other studies.

Non-linear meta-analysis was applied when the data suggested that the dose-response curve was non-linear and when detecting a threshold or plateau of effect might be of interest. Details on the non-linear meta-analyses can be found in the CUP Breast SLR 2017.

The CUP Breast SLR 2017 included studies published up to 30 April 2015. For more information on methodology, see the full CUP Breast SLR 2017 at **wcrf.org/breast-cancer–slr-2017**.

6.1 Mechanistic evidence

Where relevant, mechanistic reviews previously conducted for the Second Expert Report [1] are included in this report (more details can be found in chapters 2 and 4 of the Second Expert Report). The CUP Panel has updated these reviews. A brief summary is given of plausible mechanisms linking premenopausal and/or postmenopausal breast cancer with body fatness, height, adult weight gain, alcoholic drinks, lactation, birthweight and physical activity. Where an exposure presented in this report was previously judged as 'limited – no conclusion' or was not discussed for the Second Expert Report, there was no formal review of the mechanisms, although plausible mechanisms identified by CUP Panel members or observers and published reviews are included in this report for body fatness in young adulthood, non-starchy vegetables, foods containing carotenoids and diets high in calcium.

Work is under way to develop a method for systematically reviewing animal, human and other experimental studies (see **wcrf.org** for further information).

7. Evidence and judgements

The following sections summarise the evidence identified in the CUP Breast SLR 2017 and provide a comparison with the findings from the Second Expert Report [1] where possible (where there was no analysis for the Second Expert Report, a comparison with the CUP Breast SLR 2008 is given where possible). They also include a brief description of plausible mechanisms for each exposure and the Panel's conclusions.

For information on the criteria for grading the epidemiological evidence, see the **Appendix** on page 114 in this report. References to studies added as part of the CUP have been included; for details of references to other studies from the Second Expert Report, see the CUP Breast SLR 2017.

7.1 Non-starchy vegetables

(Also see CUP Breast SLR 2017: Section 2.2.1)

Breast cancer (unspecified)

The CUP identified 11 new or updated studies (18 publications) [21–38], giving a total of 15 studies (26 publications) reviewing the evidence for non-starchy vegetables and breast cancer (unspecified) (for a full list of references, see CUP Breast SLR 2017 Tables 34 and 35).

The majority (eight) of the studies showed an inverse association when comparing the highest and lowest categories of non-starchy vegetable intake, one of which was significant. The remaining three studies reported a positive association, with one of borderline significance (see CUP Breast SLR 2017 Figure 37).

Twelve studies were included in the dose-response meta-analysis for breast cancer (unspecified) (*n* = 24,756 cases), which showed no significant association per 200 grams of non-starchy vegetables per day (RR 0.98 (95% CI 0.93–1.02)) (see CUP Breast SLR 2017 Figure 40). Low heterogeneity was observed (I^2 = 27%). The association remained non-significant when stratified by geographical location (see CUP Breast SLR 2017 Figure 42).

A separate dose-response meta-analysis of three studies reporting on premenopausal breast cancer (*n* = 1,635 cases) found no significant association per 200 grams of non-starchy vegetables per day (RR 0.96 (95% CI 0.83–1.11)) with no heterogeneity (I^2 = 0%). Another dose-response meta-analysis of eight studies reporting on postmenopausal breast cancer (*n* = 10,891 cases) also showed no significant association (RR 1.03 (95% CI 0.97–1.09)) with no heterogeneity (I^2 = 0%) (see CUP Breast SLR 2017 Figure 41).

One individual study was not included in any of the CUP analyses because it reported on adolescent diet [39]. The results from two pooled analyses [40, 41] are shown in **Table 1**.

All studies adjusted for at least age, and most of the studies adjusted for parity, age at menarche, age at menopause, physical activity, BMI and alcohol consumption.

The CUP finding was similar to the 2005 SLR which showed no significant association for breast cancer (unspecified) (RR 0.95 (95% CI 0.88–1.03) per 100g per day for two studies).

Published pooled analyses and meta-analyses

Results have been published from two published pooled analyses [40, 41] and one published meta-analysis (with results from the 2008 CUP SLR) [42] on non-starchy vegetable intake and breast cancer risk. The published pooled analyses were not included in the CUP dose-response meta-analysis. However, in an additional analysis for the CUP, results from the most recent pooled analysis [41] were combined with non-overlapping studies from the CUP and showed no significant association per 200 grams intake per day (see CUP Breast SLR 2017 Figure 39). Results from the CUP meta-analysis and published pooled analyses are shown in **Table 1**.

Table 1: Summary of CUP 2017 meta-analyses and published pooled analyses[1] of breast cancer (unspecified) – non–starchy vegetables

Analysis	Increment/ contrast	RR (95% CI)	I^2	No. Studies	No. Cases
CUP Breast Cancer SLR 2017	Per 200 g/day	0.98 (0.93–1.02)	27%	12	24,756
The Pooling Project 2013 [41][2]	Incidence Quintile 5 vs. Quintile 1	0.99 (0.95–1.04)	-	20	34,526
The Pooling Project 2001 [40][3]	Incidence Per 100 g/day	1.00 (0.97–1.02)	-	8	7,377
CUP additional analysis: Pooled analysis of The Pooling Project studies [41] combined with five non-overlapping studies from the CUP [25–27, 34, 43]	Highest vs. lowest	0.97 (0.91–1.02)	31%	25	46,743

[1] Pooled analysis not included in the CUP meta-analysis.

[2] Adjusted for ethnicity, family history of breast cancer, personal history of benign breast disease, alcohol consumption, smoking status, education, physical activity, age at menarche, body mass index, height, oral contraceptive use, menopausal status, energy intake, combination between parity and age of first birth.

[3] Adjusted for age at menarche, interaction between parity and age at birth of first child, oral contraceptive use, history of benign breast disease, menopausal status at follow-up, postmenopausal hormone use, smoking status, education, BMI, BMI–menopausal status interaction, height, alcohol intake and energy intake.

Hormone receptor status

In the CUP meta-analysis of three studies reporting results by hormone receptor status, a statistically significant inverse association was observed with ER–PR– breast cancer per 200 grams per day with moderate heterogeneity (see **Table 2** and CUP Breast SLR 2017 Figure 46). No significant associations were observed for ER+PR+ and ER+PR– breast cancers. Another study (The Nurses' Health Study) [32] reported no significant association with ER– breast cancer in postmenopausal women when comparing the highest versus the lowest levels of intake (RR 0.81 (95% CI 0.61–1.06)).

In addition to the CUP analysis, in The Pooling Project of Cohort Studies [41] a significant inverse association was observed for total vegetable consumption and risk of ER– breast cancer but not with the risk of ER+ breast cancer, PR– cancer and PR+ cancer (see **Table 2**). For a 300 grams per day increment (approximately three servings per day), a significant 12 per cent decreased risk of ER– breast cancer was observed.

Table 2: Summary of CUP 2017 meta-analyses and published pooled analysis[1] of breast cancer by hormone receptor type – non-starchy vegetables

Analysis	Increment/ contrast	RR (95% CI)	I^2	No. Studies	No. Cases
CUP Breast Cancer SLR 2017	Per 200 g/day				
	ER–PR–	0.79 (0.63–0.98)	39%		3,950
	ER+PR+	0.89 (0.79–1.01)	0%	3	1,229
	ER+PR–	0.96 (0.81–1.13)	37%		1,346
The Pooling Project 2013 [41][2]	Incidence Quintile 5 vs. Quintile 1				
	ER–	0.82 (0.74–0.90)	-		
	ER+	1.04 (0.97–1.11)	-	20	34,526
	PR–	0.94 (0.84–1.03)	-		
	PR+	1.02 (0.96–1.10)	-		
	Per 300 g/day				
	ER–	0.88 (0.81–0.95)	-		

[1] Pooled analysis not included in the CUP meta-analysis.

[2] Adjusted for ethnicity, family history of breast cancer, personal history of benign breast disease, alcohol consumption, smoking status, education, physical activity, age at menarche, body mass index, height, oral contraceptive use, menopausal status, energy intake, combination between parity and age of first birth.

Mechanisms

Note: In the future, a full review of mechanisms for this exposure will form part of a larger review of mechanisms (see ***Section 6.1*** *on page 18 in this report).*

A possible protective effect of bioactive components in vegetables may be more detectable in the less hormonally dependent ER– tumours than in ER+ tumours, where the effect of oestrogens might obscure a smaller effect from vegetables. Epidermal growth factor receptor tends to be overexpressed in ER– breast tumours. Phytochemicals found in vegetables have been suggested to reduce the level of epidermal growth factor receptor, which may, in turn, reduce the risk of developing ER– breast cancer [41].

CUP Panel's conclusion:

The evidence was limited but generally consistent. There was no evidence of a significant dose-response relationship. However, when stratified by hormone receptor status, the CUP analysis observed a significant inverse association for ER– breast cancers and not for other hormone receptor types. This finding was supported by results from a published pooled analysis which also reported a significant inverse association for ER– breast cancers only. There is evidence of plausible mechanisms operating in humans.

The CUP Panel concluded the following:

The evidence suggesting that consumption of non-starchy vegetables decreases the risk of oestrogen-receptor-negative (ER–) breast cancer (unspecified) is limited.

7.2 Foods containing carotenoids

(Also see CUP Breast SLR 2017: Sections 5.5.1.2.2, 5.5.1.2.3, 5.5.2, 5.5.2.1 and 5.5.2.3)

The following section includes dietary carotenoids as well as circulating carotenoids. Considering measurement error in studies estimating carotenoid intake, the bioavailability of carotenoids from different foods, and individual differences in absorption and metabolism, circulating carotenoids as biomarkers of intake may be better indicators of underlying carotenoid exposure.

Breast cancer (unspecified)

The CUP identified studies on dietary beta-carotene and circulating beta-carotene, alpha-carotene, total carotenoids, lutein, beta-cryptoxanthin and lycopene. Dose-response meta-analysis was possible on all of these exposures; the results are presented in **Table 3**. For dietary beta-carotene, all studies identified in the CUP were superseded by a published pooled analysis [44], and so no dose-response analysis was conducted for the CUP – results from the published pooled analysis are presented in the table. Results for other dietary carotenoids by hormone receptor status were also available from the published pooled analysis [44] (see **Table 4**).

Significant inverse associations were observed for circulating beta-carotene, total carotenoids and lutein. No significant associations were observed for circulating alpha-carotene, beta-cryptoxanthin and lycopene, but results for these exposures were all in the direction of an inverse association.

Table 3: Summary of CUP 2017 meta-analyses for carotenoid exposures and breast cancer (unspecified)

	Total no. studies identified in the CUP (publications)[1]	Results of CUP dose-response meta-analyses for breast cancer (unspecified)				
		Increment	RR (95% CI)	I^2	No. Studies	No. Cases
Dietary beta-carotene[2]	24 (16)	Per 5000 µg/day	1.00 (0.98-1.02)	0%	18[2]	3,055
Circulating beta-carotene	13 (19)	Per 50 µg/dL	0.78 (0.66-0.92)	0%	11	3,558
Circulating alpha-carotene	11 (17)	Per 10 µg/dL	0.90 (0.77–1.05)	0%	10	3,506
Circulating total carotenoids	9 (11)	Per 100 µg/dL	0.82 (0.71–0.96)	0%	9	3,407
Circulating lutein	7 (5)	Per 25 µg/dL	0.72 (0.55–0.93)	0%	7	1,296
Circulating beta-cryptoxanthin	11 (14)	Per 15 µg/dL	0.87 (0.68–1.11)	59%	10	3,517
Circulating lycopene	11 (16)	Per 25 µg/dL	0.90 (0.70–1.16)	39%	10	3,506

[1] For references, see CUP Breast SLR 2017.

[2] Summary estimate from pooled analysis [44] – no dose-response analysis conducted for the CUP as all studies were superseded by the pooled analysis.

In the 2005 SLR, dose-response meta-analyses reported a significant inverse association only for circulating lycopene (RR 0.86 (95% CI 0.77–0.96) per 10 micrograms per decilitre for two studies) – no significant associations were reported for circulating alpha-carotene and beta-carotene, or dietary beta-carotene. No meta-analyses were conducted in the 2005 or 2008 SLR for circulating total carotenoids, lutein and beta-cryptoxanthin.

Published pooled analyses and meta-analyses

One published pooled analysis of eight cohort studies [45] reported on most of the carotenoid-related exposures included in the CUP. This pooled analysis was included in the CUP dose-response meta-analyses for all exposures except circulating lutein.

Another published pooled analysis identified by the CUP [44] reported no association for 5000 micrograms of dietary beta-carotene per day (see **Table 3**). This pooled analysis superseded all studies identified in the CUP, and no CUP dose-response analysis was necessary for dietary beta-carotene.

One other published meta-analysis [46], with results from the CUP, was identified by the CUP. It reported on all of the carotenoid exposures.

For further details of the published pooled analyses and meta-analysis, see relevant sections in the CUP Breast SLR 2017.

Hormone receptor status

Two published pooled analyses [44, 45] and other individual studies [47–49] have reported on carotenoid exposures and breast cancer risk by hormone receptor status. The results from the published pooled analyses are presented in **Table 4**.

Results indicated overall a stronger association with ER– breast cancers, with significant associations reported for dietary beta-carotene, dietary alpha-carotene, dietary lutein/zeaxanthin, circulating alpha-carotene and circulating beta-carotene, and a borderline significant association for dietary beta-cryptoxanthin.

In addition to the results presented in the table, the EPIC study [47] showed significant inverse associations in ER– breast cancers for circulating alpha-carotene and beta-carotene only, and in ER+ breast cancers for circulating lutein only, and no differences by hormone receptor status for circulating total carotenoids, beta-cryptoxanthin and lycopene.

Table 4: Summary of results from pooled analyses for breast cancer risk by hormone receptor status (statistically significant or borderline significant findings are presented in bold text) – all carotenoid exposures

Exposure	Study	ER Status	RR (95% CI)	Increment/ Contrast
Dietary beta-carotene	Pooling project [44]	ER–	0.84 (0.77–0.93)	Quintile 5 vs. Quintile 1
			0.93 (0.88–0.99)	Per 5000 µg/d
		ER+	1.04 (0.98–1.10)	Quintile 5 vs. Quintile 1
			1.02 (0.99–1.05)	Per 5000 µg/d
Dietary alpha-carotene	Pooling project [44]	ER–	0.87 (0.78–0.97)	Per 5000 µg/d
		ER+	1.04 (0.99–1.09)	Per 5000 µg/d
Dietary beta-cryptoxanthin	Pooling project [44]	ER–	0.90 (0.81–1.00)	Per 5000 µg/d
		ER+	0.96 (0.92–1.00)	Per 5000 µg/d
Dietary lutein/ zeaxanthin	Pooling project [44]	ER–	0.87 (0.79–0.95)	Per 5000 µg/d
		ER+	1.00 (0.93–1.08)	Per 5000 µg/d
Dietary lycopene	Pooling project [44]	ER–	0.92 (0.83–1.02)	Per 5000 µg/d
		ER+	0.99 (0.94–1.04)	Per 5000 µg/d
Circulating alpha-carotene	Pooling project [44]	ER–	0.61 (0.40–0.93)	Quintile 5 vs. Quintile 1
		ER+	0.85 (0.65–1.12)	Quintile 5 vs. Quintile 1
Circulating beta-carotene	Pooling project [44]	ER–	0.52 (0.36–0.77)	Quintile 5 vs. Quintile 1
		ER+	0.83 (0.66–1.04)	Quintile 5 vs. Quintile 1
Circulating total carotenoids	Pooling project [44]	ER–	0.81 (0.56–1.16)	Quintile 5 vs. Quintile 1
		ER+	0.86 (0.69–1.07)	Quintile 5 vs. Quintile 1
Circulating beta-cryptoxanthin	Pooling project [44]	ER–	1.03 (0.69–1.53)	Quintile 5 vs. Quintile 1
		ER+	1.09 (0.86–1.39)	Quintile 5 vs. Quintile 1
Circulating lycopene	Pooling project [44]	ER–	0.95 (0.66–1.38)	Quintile 5 vs. Quintile 1
		ER+	0.83 (0.60-1.15)	Quintile 5 vs. Quintile 1

Mechanisms

Note: In the future, a full review of mechanisms for this exposure will form part of a larger review of mechanisms (see ***Section 6.1*** *on page 18 in this report).*

Carotenoids are found in a diverse array of fruits and vegetables. Blood and tissue concentrations show only modest correlation with estimated intake due to many variables, including host genetics impacting absorption and metabolism as well as food processing and cooking methods. Serum and tissue carotenoids may serve as a surrogate marker for a diverse diet rich in an array of bioactive phytochemicals derived from fruits and vegetables that may act synergistically to reduce breast cancer risk [46]. Alpha-carotene, beta-carotene, and beta-cryptoxanthin are pro-vitamin A carotenoids and can be metabolised to retinol, which may in turn have an impact on many relevant nuclear receptor pathways involved in carcinogenesis. The systemic and breast metabolism of carotenoids may have an impact on processes related to cell growth, differentiation and apoptosis, thereby altering the carcinogenic process [44]. However, some evidence suggests that carotenoids may have a direct impact on breast carcinogenesis. Carotenoids have antioxidant properties and may quench reactive oxygen and various free radicals, providing protection against DNA damage [50].

Carotenoids have also demonstrated anticarcinogenic properties in laboratory-based studies with breast cancer cells in culture and in rodent models, including improved gap-junction communication and enhanced immune system functioning.

CUP Panel's conclusion:

The evidence for breast cancer (unspecified) was limited but generally consistent, and there was evidence of an inverse dose-response relationship for several carotenoid-related exposures, including circulating beta-carotene, total carotenoids and lutein. Inverse associations were also observed for circulating alpha-carotene, beta-cryptoxanthin and lycopene, but these were not significant. Results from two published pooled analyses (one of which was included in the CUP analysis for most exposures) overall supported the CUP findings. The Panel also notes the evidence suggesting that the association is stronger for ER– breast cancers. There is evidence of plausible mechanisms operating in humans. The CUP Panel concluded the following:

The evidence suggesting that consumption of foods containing carotenoids decreases the risk of breast cancer (unspecified) is limited.

7.3 Dairy products

(Also see CUP Breast SLR 2017: Section 2.7)

Premenopausal breast cancer

The CUP identified five new or updated studies (five publications) [23, 35, 51–53], giving a total of 13 studies (eight publications) reviewing the evidence for dairy products and premenopausal breast cancer (for a full list of references, see CUP Breast SLR 2017 Tables 75 and 76).

Three of five studies showed inverse associations when comparing the highest and the lowest categories, one of which was significant (see CUP Breast SLR 2017 Figure 109). The other studies reported non-significant positive associations.

Seven studies were included in the dose-response meta-analysis for premenopausal breast cancer (*n* = 2,862 cases), which showed a statistically significant 5 per cent decreased risk per 200 grams of dairy products per day (RR 0.95 (95% CI 0.92–0.99); see CUP Breast SLR 2017 Figure 111). No heterogeneity was observed (I^2 = 0%).

Dose-response meta-analyses for premenopausal breast cancer by geographical location showed a borderline significant decreased risk in European and North American studies (RR 0.96 (95% CI 0.91–1.00) and RR 0.94 (95% CI 0.88–1.00); see CUP Breast SLR 2017 Figure 116).

One pooled analysis of eight studies [54] was excluded from the CUP analyses because it reported separate results for dairy fluids and solids.

Most studies adjusted for multiple confounders, including age, reproductive factors, BMI and alcohol consumption. Two studies [23, 55] did not adjust for alcohol intake.

No analysis by menopausal status was conducted in the 2005 or 2008 SLR.

Published pooled analyses and meta-analyses

One published pooled analysis of eight cohort studies [54] and one published meta-analysis of five cohort studies [56] on dairy products and premenopausal breast cancer risk were identified in the CUP Breast SLR 2017. The pooled analysis reported no significant association for dairy fluids or solids per 100 grams per day. The published meta-analysis reported a significant inverse association when comparing the highest versus the lowest categories of intake. Results from the published pooled and meta-analysis are presented in **Table 5**.

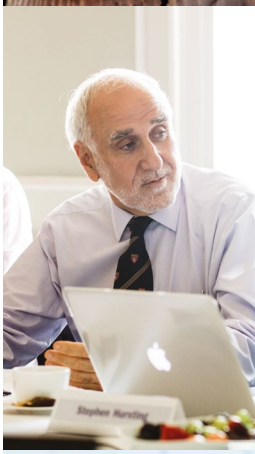
Table 5: Summary of CUP 2017 meta-analysis, published pooled analysis[1] and meta-analysis of premenopausal breast cancer – dairy products

Analysis	Increment/ contrast	RR (95% CI)	I^2	No. Studies	No. Cases
CUP Breast Cancer SLR 2017	Per 200 g/day	0.95 (0.92–0.99)	0%	7	2,862
Published pooled analysis (not included in the CUP analysis)					
The Pooling Project 2002[2] [54][3]	Total dairy fluids, per 100 g/day	0.96 (0.90–1.02)	-	8	7,379
	Total dairy solids, per 100 g/day	0.87 (0.68–1.11)	-		
Published meta-analysis					
Dong et al., 2011 [56]	Highest vs. lowest	0.79 (0.63–0.99)	50%	5	~2,137

[1] Pooled analysis not included in the CUP meta-analysis.

[2] The Nurses' Health Study [57] was the only study included in the CUP meta-analysis.

[3] Adjusted for age at menarche, parity, age at birth of first child, oral contraceptive use, history of benign breast disease, family history of breast cancer, menopausal status, BMI, hormone therapy use, smoking status, education, height, alcohol intake, total energy intake.



Other dairy exposures

The CUP Breast SLR 2017 identified five studies on total milk and premenopausal breast cancer. All five studies (*n* = 3,293 cases) were included in the dose-response meta-analysis and showed no significant association for 200 grams of milk per day (RR 0.97 (95% CI 0.88–1.06); I^2 = 51%) (for further information, see Figure 122 and Section 2.7.1 of the CUP Breast SLR 2017).

Postmenopausal breast cancer

For postmenopausal breast cancer, no significant associations were observed in eight studies on dairy products (RR per 200 g/day 0.97 (95% CI 0.93–1.01), I^2 = 39%) or six studies on total milk (RR per 200 g/day 1.01 (95% CI 0.97–1.04), I^2 = 40%) (see CUP Breast SLR 2017 Figures 112 and 123). Hence no further information is provided here.

Mechanisms

Note: In the future, a full review of mechanisms for this exposure will form part of a larger review of mechanisms (see ***Section 6.1*** *on page 18 in this report).*

Dairy products are a major source of dietary calcium, which may have a protective effect. Information on mechanisms for calcium can be found in Section 7.4 of this report.

CUP Panel's conclusion:

For premenopausal breast cancer, the evidence for consumption of dairy products was limited but generally consistent. The dose-response meta-analysis of seven studies showed a significant decreased risk of premenopausal breast cancer with higher consumption of dairy products; however, the pooled analysis of eight studies (excluded from the CUP analysis because it reported fluid and solid intake separately) reported no significant associations. In addition, no significant associations were observed for total milk in either the CUP analyses or other published meta-analysis. There is evidence of plausible mechanisms operating in humans.

For postmenopausal breast cancer, the evidence for an association was considered to be limited, and no conclusion was possible.

The CUP Panel concluded the following:

The evidence suggesting that consumption of dairy products decreases the risk of premenopausal breast cancer is limited.

7.4 Diets high in calcium

(Also see CUP Breast SLR 2017: Section 5.6.3)

Premenopausal breast cancer

The CUP identified five new or updated studies (five publications) [51–53, 58, 59], giving a total of six studies (six publications) reviewing the evidence for diets high in calcium and premenopausal breast cancer (for a full list of references, see CUP Breast SLR 2017 Tables 401 and 402).

All six studies reporting on premenopausal breast cancer showed inverse associations when comparing the highest and the lowest categories, two of which were significant (see CUP Breast SLR 2017 Figure 474).

Five studies were included in the dose-response meta-analysis for premenopausal breast cancer (n = 2,980 cases), which showed a statistically significant 13 per cent decreased risk per 300 milligrams of dietary calcium per day (RR 0.87 (95% CI 0.76–0.99); see CUP Breast SLR 2017 Figure 475). High heterogeneity was observed (I^2 = 67%). There was evidence of small study bias with Egger's test (p = 0.01). Visual inspection of the funnel plot showed asymmetry, with one small study [51] reporting an association stronger than expected (see CUP Breast SLR 2017 Figure 476). In influence analysis, the association was no longer significant when either the Norwegian Women and Cancer study [53], the SU.VI.MAX study [51] or the Nurses' Health Study [57] were excluded from the analysis.

All studies adjusted for age, alcohol intake, BMI and reproductive factors.

No analysis by menopausal status was conducted in the 2005 or 2008 SLR.

Published pooled analyses and meta-analyses

No pooled or published meta-analysis was identified on diets high in calcium and premenopausal breast cancer.

Postmenopausal breast cancer

The CUP identified five new or updated studies (five publications) [51–53, 58, 59], giving a total of seven studies (seven publications) reviewing the evidence for diets high in calcium and postmenopausal breast cancer (for a full list of references, see CUP Breast SLR 2017 Tables 405 and 406).

Six of the seven studies reporting on postmenopausal breast cancer showed inverse associations when comparing the highest and the lowest categories, one of which was significant, and the other study reported a non-significant positive association (see CUP Breast SLR 2017 Figure 478).

Six studies were included in the dose-response meta-analysis for postmenopausal breast cancer (*n* = 10,137 cases), which showed a statistically significant 4 per cent decreased risk per 300 milligrams of dietary calcium per day (RR 0.96 (95% CI 0.94–0.99); see CUP Breast SLR 2017 Figure 479). No heterogeneity was observed (I^2 = 0%).

All studies were adjusted for main risk factors.

No analysis by menopausal status was conducted in the 2005 or 2008 SLR.

Published pooled analyses and meta-analyses

No pooled or published meta-analysis was identified on diets high in calcium and postmenopausal breast cancer.

Mechanisms

Note: In the future, a full review of mechanisms for this exposure will form part of a larger review of mechanisms (see ***Section 6.1*** *on page 18 in this report).*

Calcium is the most abundant mineral in the body. Intracellular calcium is a pervasive second messenger acting on many cellular functions, including cell growth, and calcium has a potentially important role in carcinogenesis by regulating cell proliferation, differentiation and apoptosis [60]. Calcium homeostasis is carefully regulated to maintain constant serum and tissue concentrations. The endocrine system involving parathyroid hormone and calcitonin, coupled with vitamin D intake and metabolism, orchestrates calcium status to ensure the health of bone and other tissues during periods of variable calcium intake.

Laboratory studies have suggested hypotheses whereby variations in calcium intake and metabolism may have an impact on cancer, though direct mechanisms have not been established in humans. In rodent models, dietary calcium can reduce fat-induced mammary cell proliferation [61], perhaps by maintaining optimal intracellular calcium concentrations, reducing proliferation of cancer cells and maintaining differentiation.

CUP Panel's conclusions:

For both premenopausal and postmenopausal breast cancer, the evidence for diets high in calcium was limited but generally consistent. The dose-response meta-analyses of six (premenopausal) and seven (postmenopausal) studies both showed a significant decreased risk of those breast cancers with higher consumption of dietary calcium.

The CUP Panel concluded the following:

The evidence suggesting that diets high in calcium decrease the risk of premenopausal breast cancer is limited.

The evidence suggesting that diets high in calcium decrease the risk of postmenopausal breast cancer is limited.

7.5 Alcoholic drinks

(Also see CUP Breast SLR 2017: Section 5.4.1)

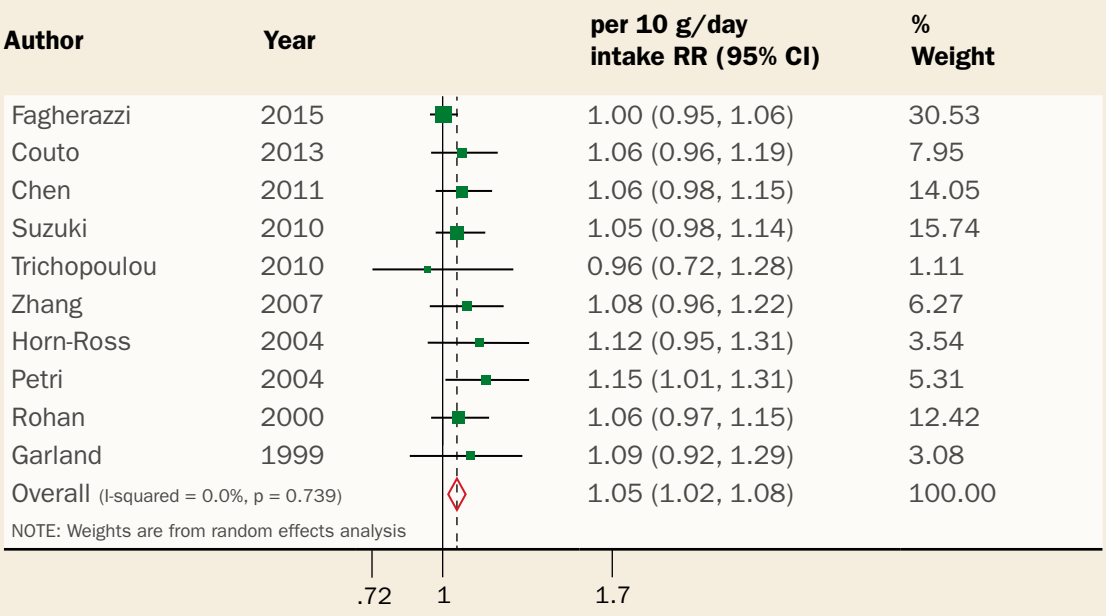
Premenopausal breast cancer

The CUP identified eight new or updated studies (eight publications) [23, 35, 62–67], giving a total of 16 studies (17 publications) reviewing the evidence for alcohol (as ethanol) and premenopausal breast cancer (for a full list of references, see CUP Breast SLR 2017 Tables 260 and 261). A pooled analysis of 15 cohort studies [68] on premenopausal breast cancer was identified after the CUP search and was included in an additional analysis combining the pooled analysis with non-overlapping studies from the CUP.

Eight of nine studies reporting on premenopausal breast cancer showed positive associations when comparing the highest and the lowest categories of alcohol intake, two of which were significant and two of which were borderline significant. The other study reported a non-significant inverse association (see CUP Breast SLR 2017 Figure 329).

Ten studies were included in the dose-response meta-analysis for premenopausal breast cancer (n = 4,227 cases), which showed a statistically significant 5 per cent increased risk per 10 grams of ethanol per day (RR 1.05 (95% CI 1.02–1.08); see **Figure 1**, CUP Breast SLR 2017 Figure 330). No heterogeneity was observed (I^2 = 0%).

Figure 1: Dose-response meta-analysis of alcohol (as ethanol) and premenopausal breast cancer, per 10 grams per day



Dose-response meta-analyses for premenopausal breast cancer by geographical location showed a statistically significant increased risk in North American studies only (RR 1.07 (95% CI 1.02–1.12), I^2 = 0%; see CUP Breast SLR 2017 Figure 333). The results for Asia and Europe were non-significant but in the same direction.

One study [69] was not included in any of the CUP analyses as it did not report sufficient data.

Most studies adjusted for the main risk factors.

The CUP findings are similar to the dose-response meta-analysis in the 2005 SLR, which also reported a significant increased risk of premenopausal breast cancer (RR 1.09 (95% CI 1.01–1.17) per 10 g/day ethanol for five studies) with moderate heterogeneity observed.

Published pooled analyses and meta-analyses

One published pooled analysis of 15 cohort studies on premenopausal breast cancer and alcohol intake [68] was identified in the CUP Breast SLR 2017, reporting no significant association for 10 grams of alcohol per day and no differences by hormone receptor status. The pooled analysis was published after the end of the CUP search but was included in a separate CUP meta-analysis which showed no significant association. Results from the CUP and the published pooled analysis are presented in **Table 6**.

Table 6: Summary of CUP 2017 meta-analyses and published pooled analysis[1] of premenopausal breast cancer – alcohol (as ethanol)

Analysis	Increment	RR (95% CI)	I^2	No. Studies	No. Cases
CUP Breast Cancer SLR 2017	Per 10 g/day	1.05 (1.02–1.08)	0%	10	4,227
The Pooling Project 2016[2] [68][3]	Per 10 g/day	1.03 (0.99–1.08)	-	15	3,730
CUP additional analysis: Pooled analysis of The Pooling Project studies [68] combined with three non-overlapping studies from the CUP [23, 67, 70]	Per 10 g/day	1.03 (0.99–1.07)	19%	18	4,426

[1] Pooled analysis not included in the CUP meta-analysis.

[2] Published after the CUP SLR 2017 search.

[3] Adjusted for age, energy intake, ethnicity, education, BMI, height, physical activity, smoking status, age at menarche, parity and age at birth of first child, oral contraceptive use, family history of breast cancer, personal history of benign breast disease.

Other alcohol exposures

The CUP Breast SLR 2017 identified three studies on premenopausal breast cancer and alcohol intake (as ethanol) from beer, wine and spirits. A significant increased risk was only observed for alcohol intake from beer. Results are presented in **Table 7** (for further information, see also Sections 5.4.1.1, 5.4.1.2 and 5.4.1.3 of the CUP Breast SLR 2017).

Table 7: Summary of CUP 2017 dose-response meta-analyses of premenopausal breast cancer – alcohol (as ethanol) from beer, wine and spirits

Analysis	Increment	RR (95% CI)	I^2	No. Studies	No. Cases
Beer	Per 10 g/day	1.32 (1.06–1.64)	0%	3	818
Wine	Per 10 g/day	1.17 (0.79–1.73)	74%	3	818
Spirits	Per 10 g/day	1.10 (0.92–1.30)	0%	3	818

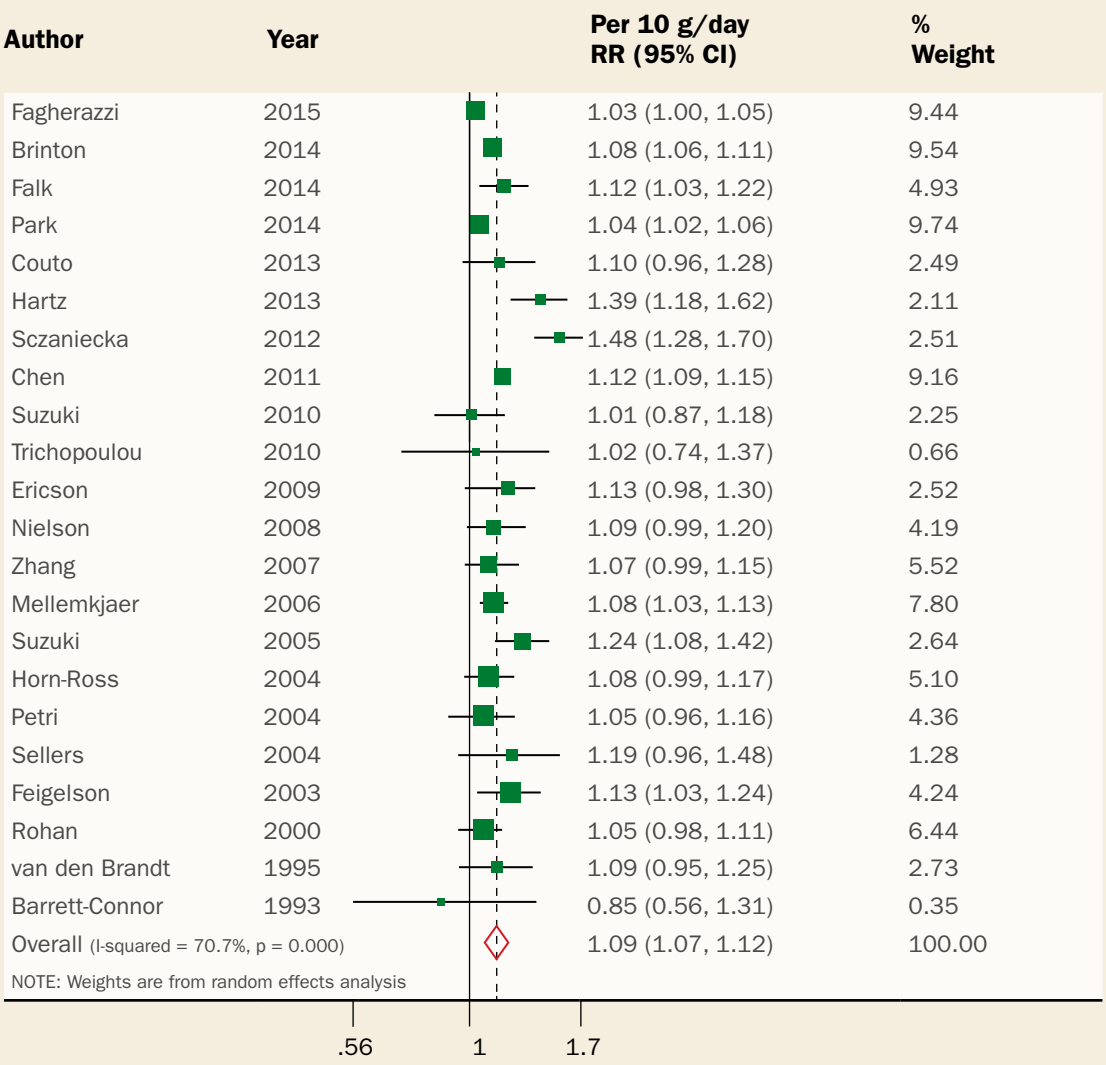
Postmenopausal breast cancer

The CUP identified 21 new or updated studies (40 publications) [23, 35, 62–67, 71–102], giving a total of 34 studies (62 publications) reviewing the evidence for alcohol (as ethanol) and postmenopausal breast cancer (for a full list of references, see CUP Breast SLR 2017 Tables 264 and 265). A pooled analysis of 20 cohort studies [68] on postmenopausal breast cancer was identified after the CUP search and was included in an additional analysis combining the pooled analysis with non-overlapping studies from the CUP.

Of 20 of the new or updated studies, all but one showed a positive association when comparing the highest and the lowest categories of alcohol intake, 11 of which were significant. The other study reported a non-significant inverse association (see CUP Breast SLR 2017 Figure 335).

Twenty-two studies were included in the dose-response meta-analysis for postmenopausal breast cancer (*n* = 35,221 cases), which showed a statistically significant 9 per cent increased risk per 10 grams of ethanol per day (RR 1.09 (95% CI 1.07–1.12); see **Figure 2**, CUP Breast SLR 2017 Figure 336). High heterogeneity was observed (I^2 = 71%). There was evidence of small study bias from Egger's test (p = 0.05), with two studies [91, 93] appearing as outliers (see CUP Breast SLR 2017 Figure 338).

Figure 2: Dose-response meta-analysis of alcohol (as ethanol) and postmenopausal breast cancer, per 10 grams per day



Dose-response meta-analyses for postmenopausal breast cancer by geographical location showed a statistically significant increased risk in European and North American studies only (see **Table 8** and CUP Breast SLR 2017 Figure 340). When stratified by hormone therapy use, significant positive associations were observed for current hormone therapy users and never users, and when stratified by hormone receptor status, significant positive associations were observed for ER+PR+ and ER+PR– (see **Table 8** and CUP Breast SLR 2017 Figures 345 and 344 respectively). Significant increased risk also remained in studies adjusted for age, BMI and reproductive factors (RR 1.08 (95% CI 1.05–1.10)).

Table 8: Summary of CUP 2017 stratified dose-response meta-analyses of postmenopausal breast cancer – alcohol (as ethanol)

Analysis	Increment	RR (95% CI)	I^2	No. Studies
GEOGRAPHICAL LOCATION				
Europe	Per 10 g/day	1.08 (1.04–1.12)	41%	9
North America	Per 10 g/day	1.11 (1.07–1.15)	79%	12
HORMONE THERAPY USE				
Current users	Per 10 g/day	1.12 (1.09–1.16)	0%	5
Ever users	Per 10 g/day	1.07 (0.98–1.18)	0%	2
Former users	Per 10 g/day	1.07 (0.82–1.39)	76%	2
Never users	Per 10 g/day	1.04 (1.02–1.07)	0%	6
Former/never users	Per 10 g/day	1.12 (1.00–1.24)	16%	3
HORMONE RECEPTOR STATUS				
ER+PR+	Per 10 g/day	1.06 (1.03–1.09)	61%	6
ER+PR–	Per 10 g/day	1.12 (1.01–1.24)	76%	5
ER–PR–	Per 10 g/day	1.02 (0.98–1.06)	10%	6

Three studies [69, 103, 104] and three pooled analyses (two with one non-overlapping study [88, 101] and one with two non-overlapping studies [102]) were not included in any of the CUP analyses as they reported insufficient data.

Most studies adjusted for the main risk factors.

The CUP findings are similar to the dose-response meta-analysis in the 2005 SLR, which also reported a significant increased risk of postmenopausal breast cancer (RR 1.08 (95% CI 1.05–1.10) per 10 g/day for 11 studies) with moderate heterogeneity observed.

Published pooled analyses and meta-analyses

Four published pooled analyses on postmenopausal breast cancer [68, 88, 101, 102] were identified in the CUP Breast SLR 2017. These were not included in the CUP dose-response meta-analysis. The most recent pooled analysis [68] reported a significant positive association for 10 grams of alcohol per day. It was not included in the main CUP analysis because it was published after the end of the CUP search, but was included in a separate CUP meta-analysis which showed no significant association for postmenopausal breast cancer (see **Table 9**). The second pooled analysis [102] found a significant positive association and the third pooled analysis [88] reported a significant positive association in both nulliparous and parous women. The fourth pooled analysis [101] (not shown in table) reported a significant positive association in non-users of hormone therapy, and no significant association in current users of hormone therapy in a highest versus lowest analysis. Results from the CUP and the published pooled analyses are presented in **Table 9**.

Table 9: Summary of CUP 2017 meta-analyses and published pooled analyses[1] of postmenopausal breast cancer – alcohol (as ethanol)

Analysis	Increment/ contrast	RR (95% CI)	I^2	No. Studies	No. Cases
CUP Breast SLR 2017	Per 10 g/day	1.09 (1.07–1.12)	71%	22	35,221
The Pooling Project 2016[2,3] [68]	Per 10 g/day	1.09 (1.07–1.11)	-	20	25,411
UK Dietary Cohort Consortium [102][4]	Per 10 g/day	1.09 (1.01–1.18)	-	4	656
National Cancer Institute studies [88][5]	≥7 drinks/week vs. none				
	Nulliparous women, postmenopausal	1.30 (1.11–1.52)	-		1,501
	Parous women aged <25 years at first birth	1.22 (1.11–1.35)	-	4	4,719
	Parous women aged ≥25 years at first birth	1.33 (1.19–1.50)	-		2,856
CUP additional analysis: Pooled analysis of The Pooling Project studies [68] combined with nine non-overlapping studies from the CUP [23, 67, 70, 71, 77, 79, 91, 93, 105]	Per 10 g/day	1.11 (1.06–1.16)	81%	29	33,415

[1] Pooled analysis not included in the CUP meta-analysis.

[2] Published after the CUP 2017 SLR search.

[3] Age, energy intake, ethnicity, education, BMI, height, physical activity, smoking status, age at menarche, hormone therapy use, parity and age at birth of first child, oral contraceptive use, family history of breast cancer, personal history of benign breast disease.

[4] Age, parity, height, weight, hormone therapy use at date of food diary completion, physical activity, total energy intake, folate intake, menopausal status, smoking, education level.

[5] Age, hormone therapy use, BMI, history of benign breast disease, age at menarche, age at natural menopause, ever/never use of oral contraceptive.

Other alcohol exposures

The CUP Breast SLR 2017 identified 10 studies on postmenopausal breast cancer and alcohol intake (as ethanol) from beer, wine and spirits. A significant increased risk was observed only for alcohol intake from wine. Results are presented in **Table 10** (for further information, see also Sections 5.4.1.1, 5.4.1.2 and 5.4.1.3 of the CUP Breast SLR 2017).

Table 10: Summary of CUP 2017 dose-response meta-analyses of postmenopausal breast cancer – alcohol (as ethanol) from beer, wine and spirits

Analysis	Increment	RR (95% CI)	I^2	No. Studies	No. Cases
Beer	Per 10 g/day	1.06 (0.94–1.21)	66%	7	7,798
Wine	Per 10 g/day	1.12 (1.08–1.17)	0%	6	3,913
Spirits	Per 10 g/day	1.05 (0.93–1.17)	73%	7	7,798

Mechanisms

Note: This is adapted from section 4.8 of the Second Expert Report. An updated review of mechanisms for this exposure will form part of a larger review of mechanisms (see ***Section 6.1*** *on page 18 in this report).*

The mechanisms whereby alcohol may act to influence breast cancer risk in humans remain uncertain and are likely complex. It is possible that this relationship occurs in part because the dietary patterns of consumers of alcohol may differ from those of people who do not consume alcohol. Heavy alcohol consumers have demonstrated inadequate intake in several essential nutrients, which may make the host susceptible to carcinogenesis via a multitude of mechanisms. For example, folate-containing foods are consumed more sparsely by those with high alcohol intake, and folate is involved in DNA methylation that may be dysregulated in breast carcinogenesis. In the pooled analysis of prospective cohort studies [68], low total folate intake was significantly positively associated with ER+ and PR+ breast cancer risk. Some prospective cohort studies [64, 67], but not all [81, 97, 106], reported that alcohol intake in combination with low folate status is associated with higher breast cancer risk. In rodent studies, alcohol has also been demonstrated to alter carotenoid and retinoid metabolism, with potential adverse effects on cellular growth, cellular differentiation and susceptibility to carcinogenesis [107].

In addition, the effects of alcohol may be mediated through impacts on bioactive lipid metabolism, including the production of prostaglandins, lipid peroxidation and the generation of free-radical oxygen species. Alcohol also acts as a solvent, potentially enhancing penetration of carcinogens into cells.

Alcohol is metabolised principally by the liver, but also in breast tissue, to acetaldehyde, potentially producing reactive oxygen species (ROS) associated with DNA damage and initiating the cancer cascade [108].

Alcohol may have significant impacts upon endocrine and growth factor networks that affect breast carcinogenesis. For example, in some studies alcohol may increase circulating levels of oestrogen, which could affect susceptibility to transformation or promote cancer growth [109]. Many recent prospective cohort studies have reported stronger positive associations of alcohol intake with ER+PR+ [67, 86, 98, 110], ER+ and PR+ [98]. A pooled analysis [68] reported stronger positive associations with ER+ and PR+ breast cancer for alcohol intakes above 15 grams per day.

The risk of cancer for alcohol drinkers may be modulated by genetic factors, such as variants in genes for alcohol metabolism, folate and methionine metabolism, and DNA repair [111]. Genetic polymorphisms for ethanol metabolism genes such as alcohol dehydrogenase (ADH) and CYP2E1 have been shown to affect breast cancer risk [107]. It is likely that a multitude of genetic factors will be linked to alcohol metabolism or to altering the sensitivity of the breast to carcinogenic stimuli over the life cycle. In addition, alcohol consumption is graded by the International Agency for Research on Cancer (IARC) as carcinogenic to humans (Group 1) [112].

CUP Panel's conclusions:

For premenopausal breast cancer, the evidence was generally consistent and the dose response meta-analysis showed a significant increased risk with increasing alcohol consumption. No heterogeneity was observed. A pooled analysis found no significant association for premenopausal breast cancer; when combined with non-overlapping studies from the CUP, an increased risk was found but was not significant. No threshold for alcohol intake was identified. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded the following:

Consumption of alcoholic drinks is probably a cause of premenopausal breast cancer.

For postmenopausal breast cancer, the evidence again was generally consistent, and the dose-response meta-analysis showed a significant increased risk with increasing alcohol consumption. Significant findings were shown for Europe and North America, for current and never users of hormone therapy, and for hormone receptor status ER+PR+ and ER+PR–. The CUP finding was supported by four published pooled analyses, and when the most recent pooled analysis was combined with non-overlapping studies from the CUP, the association remained significant. No threshold for alcohol intake was identified. There is robust evidence for mechanisms operating in humans.

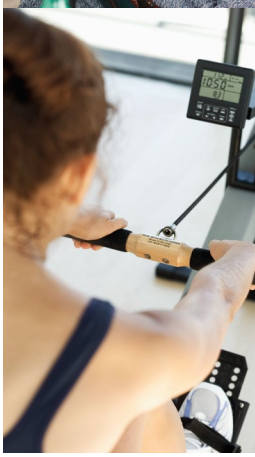
The CUP Panel concluded the following:

Consumption of alcoholic drinks is a convincing cause of postmenopausal breast cancer.

7.6 Physical activity

(Also see CUP Breast SLR 2017: **Section 6.1***)*

A variety of measures were used to collect the data on physical activity, so it was not possible to conduct dose-response meta-analysis on all physical activity domains. Study results were therefore summarised for the highest compared with the lowest physical activity category. For recreational physical activity, the number of studies reported in comparable measurement unit (MET-hour/week and minutes/day, respectively) were sufficient, and dose-response meta-analyses were conducted.



Premenopausal breast cancer

The CUP identified three new or updated studies (five publications) [113–117], giving a total of four studies (six publications) reviewing the evidence for total physical activity and premenopausal breast cancer (for a full list of references, see CUP Breast SLR 2017 Tables 436 and 437).

In a meta-analysis of all four studies comparing the highest with the lowest level of total physical activity (*n* = 1,837 cases), no significant association was observed (RR 0.93 (95% CI 0.79–1.08); see CUP Breast SLR 2017 Figure 488). No heterogeneity was observed (I^2 = 0%).

Three studies [114, 115, 117] were adjusted for age, BMI, alcohol intake and reproductive factors. One study [118] did not adjust for alcohol intake.

No meta-analysis for total physical activity was conducted in the 2005 or 2008 SLR.

Published pooled analyses and meta-analyses

One published meta-analysis on premenopausal breast cancer [119] was identified in the CUP Breast SLR 2017, showing a significant inverse association when comparing the highest versus the lowest levels of activity. Results from the CUP and the published meta-analysis are presented in **Table 11**.

Table 11: Summary of CUP 2017 meta-analysis and published meta-analysis of premenopausal breast cancer – total physical activity

Analysis	Contrast	RR (95% CI)	I^2	No. Studies	No. Cases
CUP Breast SLR 2017	Highest vs. lowest	0.93 (0.79–1.08)	0%	4	1,834
Wu et al., 2013 [119]	Highest vs. lowest	0.77 (0.69–0.86)	15%	6	2,258

Other physical activity exposures

The CUP Breast SLR 2017 also identified studies on premenopausal breast cancer and occupational physical activity and recreational physical activity. No significant associations were observed. The CUP analyses for these physical activity exposures are presented in **Table 12** (for references and further information, see also Sections 6.1.1.1 and 6.1.1.2 of the CUP Breast SLR 2017).

Table 12: Summary of CUP 2017 meta-analyses of premenopausal breast cancer – other physical activity exposures

Analysis	Increment/ contrast	RR (95% CI)	I^2	No. Studies	No. Cases
Occupational	Highest vs. lowest	0.82 (0.59–1.15)	76%	6	4,494
Recreational	Per 10 MET-hr/week	0.96 (0.90–1.03)	69%	3	2,331
	Highest vs. lowest	0.93 (0.74–1.16)	59%	10	>3,901

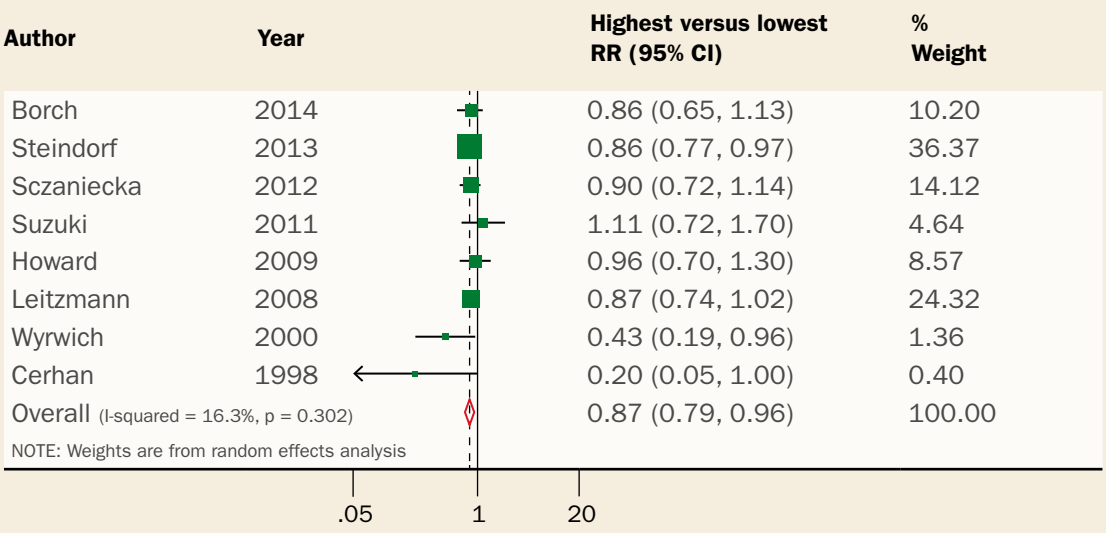
*Note: Vigorous activity is covered separately in **Section 7.7** of this report.*

Postmenopausal breast cancer

The CUP identified seven new or updated studies (11 publications) [91, 96, 113–117, 120–123], giving a total of nine studies (13 publications) reviewing the evidence for total physical activity and postmenopausal breast cancer (for a full list of references, see CUP Breast SLR 2017 Tables 441 and 442).

In a meta-analysis analysis of eight studies comparing the highest with the lowest level of total physical activity (*n* = 11,798 cases), a statistically significant 13 per cent decreased risk was observed (RR 0.87 (95% CI 0.79–0.96); see **Figure 3**, CUP Breast SLR 2017 Figure 489). Low heterogeneity was observed (I^2 = 16%).

Figure 3: Highest versus lowest meta-analysis of total physical activity and postmenopausal breast cancer



One study was excluded from the CUP analyses as it reported on a subgroup of white women only [121].

Five studies adjusted for age, BMI, alcohol intake, reproductive factors and hormone therapy use [114, 115, 117, 120, 122]. One study adjusted for age only [91].

No meta-analysis for total physical activity was conducted in the 2005 or 2008 SLR.

Published pooled analyses and meta-analyses

One published meta-analysis on postmenopausal breast cancer [119] was identified in the CUP Breast SLR 2017, showing a significant inverse association when comparing the highest versus the lowest levels of activity. Results from the CUP and the published meta-analysis are presented in **Table 13**.

Table 13: Summary of CUP 2017 meta-analysis and published meta-analysis of postmenopausal breast cancer – total physical activity

Analysis	Contrast	RR (95% CI)	I^2	No. Studies	No. Cases
CUP Breast SLR 2017	Highest vs. lowest	0.87 (0.79–0.96)	16%	8	11,798
Wu et al., 2013 [119]	Highest vs. lowest	0.87 (0.87–0.92)	15%	17	32,623

Other physical activity exposures

The CUP Breast SLR 2017 also identified studies on postmenopausal breast cancer and occupational physical activity, recreational physical activity and walking. Significant inverse associations were observed for occupational and recreational physical activity. The CUP analyses for these physical activity exposures are presented in **Table 14** (for references and further information, see also Sections 6.1.1.1 and 6.1.1.2 of the CUP Breast SLR 2017).

Table 14: Summary of CUP 2017 meta-analyses of postmenopausal breast cancer – other physical activity exposures

Analysis	Increment/ contrast	RR (95% CI)	I^2	No. Studies	No. Cases
Occupational	Highest vs. lowest	0.89 (0.83–0.96)	0%	8	22,352
Recreational	Per 10 MET-hr/week	0.98 (0.97–0.99)	0%	5	18,486
	Highest vs. lowest	0.87 (0.81–0.94)	37%	17	>24,253
Walking	Highest vs. lowest	0.94 (0.86–1.04)	0%	4	7,300

*Note: Vigorous activity is covered separately in **Section 7.7** on pages 45–48 of this report.*

In the 2005 SLR, a meta-analysis of cohort data on recreational physical activity showed a 3 per cent decreased risk of postmenopausal breast cancer per 7 MET-hours per week (RR 0.97 (95% CI 0.95–0.99)).

Mechanisms

*Note: This is adapted from section 7.10.5.3 of the Second Expert Report. An updated review of mechanisms for this exposure will form part of a larger review of mechanisms (see **Section 6.1** on page 18 in this report).*

Physical activity is proposed to modify the risk of breast cancer through several hypothesised mechanisms.

Increased physical activity can decrease body fat overall and in specific areas including subcutaneous, visceral and liver fat, thereby altering a multitude of endocrine and growth factor profiles that may affect susceptibility to cancer. For example, physical activity improves insulin sensitivity and reduces fasting insulin and C-peptide levels, a pattern associated with reduced risk [124].

Increased lifetime exposure to oestrogens (for example, early menarche, late age at menopause, first birth after the age of 30) or through individual variation in oestrogen levels, is associated with a greater risk of breast cancer in both premenopausal and postmenopausal women. Physical activity has been shown to decrease levels of oestrogens and androgens in postmenopausal women, and some trials have also shown decreases in circulating oestrogens, increased menstrual cycle length and decreased ovulation in premenopausal women with a high level of physical activity.

In addition, physical activity has been shown to have immunomodulatory effects, with some studies showing improvements in biomarkers of the innate and acquired immune response, which may have implications for promoting the surveillance and elimination of cancer cells [124, 125]. Physically active individuals who exercise outdoors are also likely to have higher sunlight exposure and consequently increased vitamin D, which may influence cancer risk [126].

In conclusion, physical activity of various types, duration and intensity has a multitude of physiological effects that may affect, through diverse mechanisms, the risk of breast cancer. Additional studies are necessary to define key interactions with genetics and other environmental variables, such as diet, to elucidate mechanisms of action during key phases of the life cycle.

CUP Panel's conclusions:

For premenopausal breast cancer, the evidence for total physical activity was limited but generally consistent with most studies reporting an inverse association. In a meta-analysis of four studies comparing the highest versus the lowest levels of physical activity, no significant association was observed for premenopausal breast cancer (no heterogeneity observed). However, the CUP SLR 2017 identified one published meta-analysis of six studies (more studies than the CUP) which showed a significant inverse association when comparing the highest and lowest levels of physical activity, with low heterogeneity. No significant associations were observed for occupational physical activity or recreational physical activity, although generally the evidence supports an effect in the direction of an inverse association. There is evidence for plausible mechanisms operating in humans.

The CUP Panel concluded the following:

The evidence suggesting that total physical activity decreases the risk of premenopausal breast cancer is limited.

For postmenopausal breast cancer, the evidence was generally consistent and the meta-analysis of eight studies comparing the highest versus the lowest levels of activity showed a significant decreased risk with increasing levels of physical activity, with low heterogeneity. Significant inverse associations were also observed for occupational physical activity and recreational physical activity (no heterogeneity), but not for walking. In addition, in support of the CUP finding, one published meta-analysis also reported a significant decreased risk of postmenopausal breast cancer for the highest versus the lowest comparison, with low heterogeneity. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded the following:

Total physical activity probably protects against postmenopausal breast cancer.

7.7 Vigorous physical activity

(Also see CUP Breast SLR 2017: Section 6.1.3)

For vigorous physical activity, the number of studies reported in comparable measurement units (MET-hour/week and minutes/day, respectively) were sufficient and dose-response meta-analyses were conducted.

Premenopausal breast cancer

The CUP identified five new or updated studies [114, 127–130], giving a total of six studies (seven publications) reviewing the evidence for vigorous physical activity and premenopausal breast cancer (for a full list of references, see CUP Breast SLR 2017 Tables 495 and 496).

In a meta-analysis of six studies comparing the highest with the lowest level of vigorous physical activity (*n* = 4,452 cases), a statistically significant 17 per cent decreased risk was observed (RR 0.83 (95% CI 0.73–0.95); see **Figure 4**, CUP Breast SLR 2017 Figure 514). Low heterogeneity was observed (I^2 = 17%). A dose-response meta-analysis of three studies (*n* = 1,473 cases) showed no significant association per 30 minutes of vigorous physical activity per day (RR 0.91 (95% CI 0.83–1.01), I^2 = 0%) (see **Figure 5**, CUP Breast SLR 2017 Figure 515). No meta-analysis for vigorous physical activity was conducted in the 2005 or 2008 SLR.

Figure 4: Highest versus lowest meta-analysis of vigorous physical activity and premenopausal breast cancer

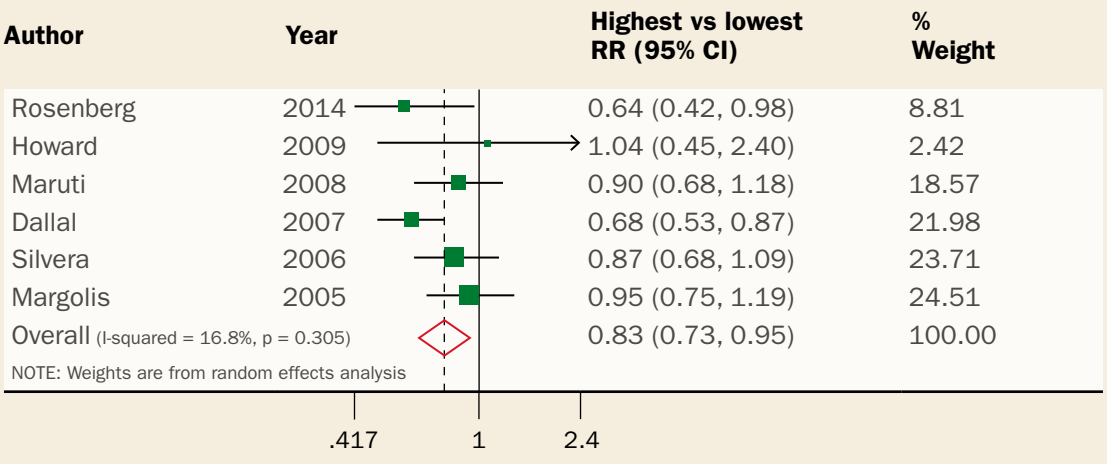
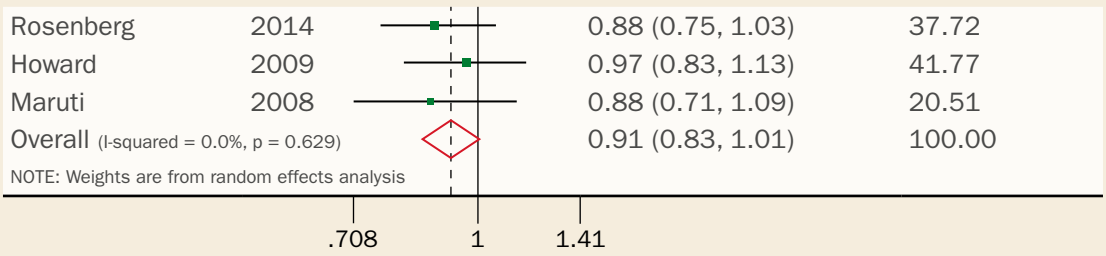


Figure 5: Dose-response meta-analysis of vigorous physical activity and premenopausal breast cancer, per 30 minutes per day



All except two studies [129, 130] adjusted for age, BMI, alcohol intake and reproductive factors.

No analysis was conducted in the 2005 or 2008 SLR.

Published pooled analyses and meta-analyses

No pooled or published meta-analysis was identified on vigorous physical activity and premenopausal breast cancer.

Postmenopausal breast cancer

The CUP identified eight new or updated studies (11 publications) [92, 99, 114, 120, 127, 128, 130–134], giving a total of 12 studies (15 publications) reviewing the evidence for vigorous physical activity and postmenopausal breast cancer (for a full list of references, see CUP Breast SLR 2017 Tables 499 and 500).

In a meta-analysis of 11 studies comparing the highest with the lowest level of vigorous physical activity (*n* = 20,171 cases), a statistically significant 10 per cent decreased risk was observed (RR 0.90 (95% CI 0.85–0.95); see **Figure 6**, CUP Breast SLR 2017 Figure 517). No heterogeneity was observed (I^2 = 0%). A dose-response meta-analysis of three studies (*n* = 3,293 cases) showed no significant association per 30 minutes of vigorous physical activity per day (RR 0.94 (95% CI 0.86–1.02), I^2 = 0%) (see **Figure 7**, CUP Breast SLR 2017 Figure 518).

Figure 6: Highest versus lowest meta-analysis of vigorous physical activity and postmenopausal breast cancer

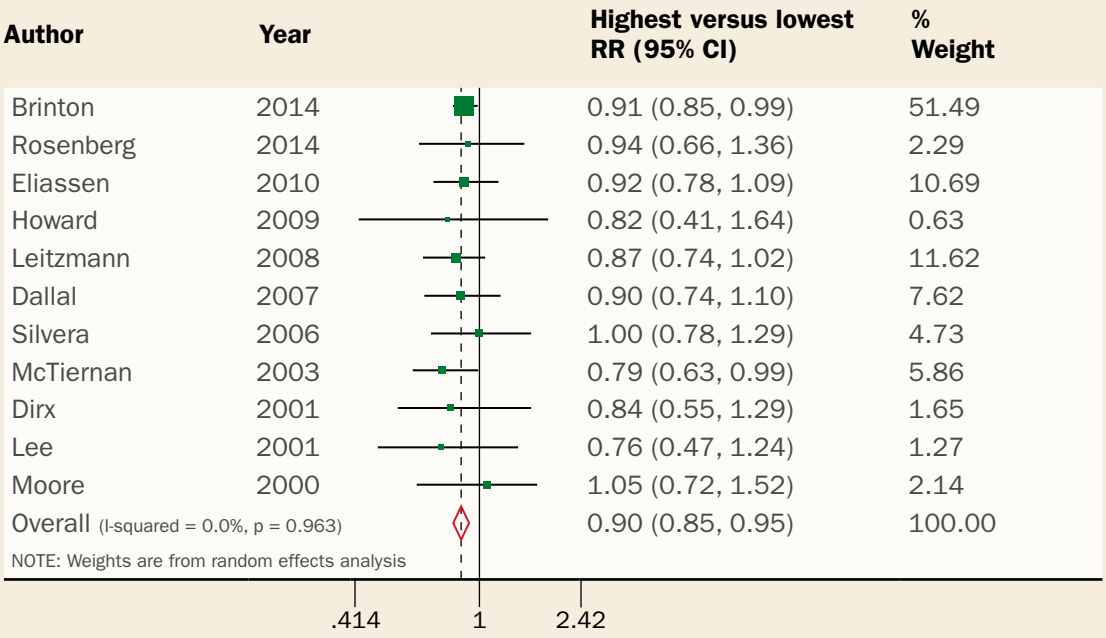
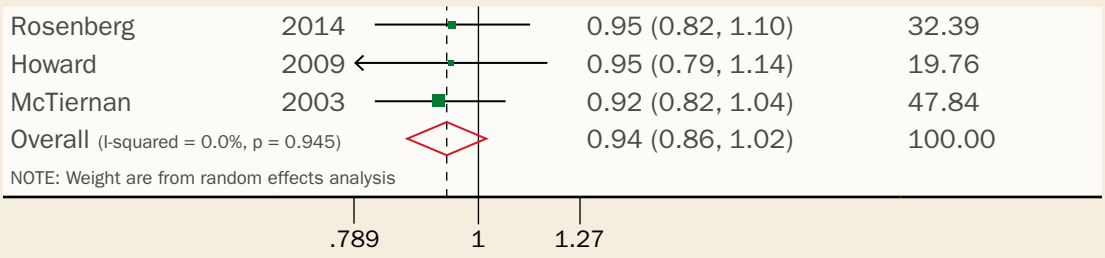


Figure 7: Dose-response meta-analysis of vigorous physical activity and postmenopausal breast cancer, per 30 minutes per day



One study [134] was excluded from the CUP analyses as it reported on subtypes of breast cancer only.

All but three studies [130, 135, 136] adjusted for age, BMI, alcohol intake and reproductive factors. One study [137] was not further adjusted for hormone therapy use.

No meta-analysis for vigorous physical activity was conducted in the 2005 or 2008 SLR.

Published pooled analyses and meta-analyses

No pooled or published meta-analysis was identified on vigorous physical activity and postmenopausal breast cancer.

Mechanisms

Note: In the future, a full review of mechanisms for this exposure will form part of a larger review of mechanisms (see ***Section 6.1*** *on page 18 in this report).*

Information on mechanisms for physical activity can be found in Section 7.6 of this report.

CUP Panel's conclusions:

For premenopausal breast cancer, the evidence for vigorous physical activity was generally consistent, and the meta-analysis of six studies comparing the highest versus the lowest levels of activity showed a significant decreased risk with increasing levels of activity, with low heterogeneity observed. A dose-response meta-analysis of fewer studies observed no significant association, although the effect was in the direction of an inverse association. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded the following:

Vigorous physical activity probably protects against premenopausal breast cancer.

For postmenopausal breast cancer, evidence was generally consistent and the meta-analysis of 11 studies comparing the highest versus the lowest levels of activity showed a significant decreased risk with increasing levels of vigorous physical activity, with no heterogeneity observed. A dose-response meta-analysis of fewer studies observed no significant association, although the effect was in the direction of an inverse association. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded the following:

Vigorous physical activity probably protects against postmenopausal breast cancer.

7.8 Body fatness in young adulthood

(Also see CUP Breast SLR 2017: Section 8.1.1)

Body fatness in young adulthood is marked by BMI and based on data available for participants aged between about 18 and 30 years. Sufficient data were available for the Panel to undertake a separate review of the evidence for body fatness in young adulthood in addition to that carried out for overall body fatness (see **Section 7.9** on pages 53–75 in this report).

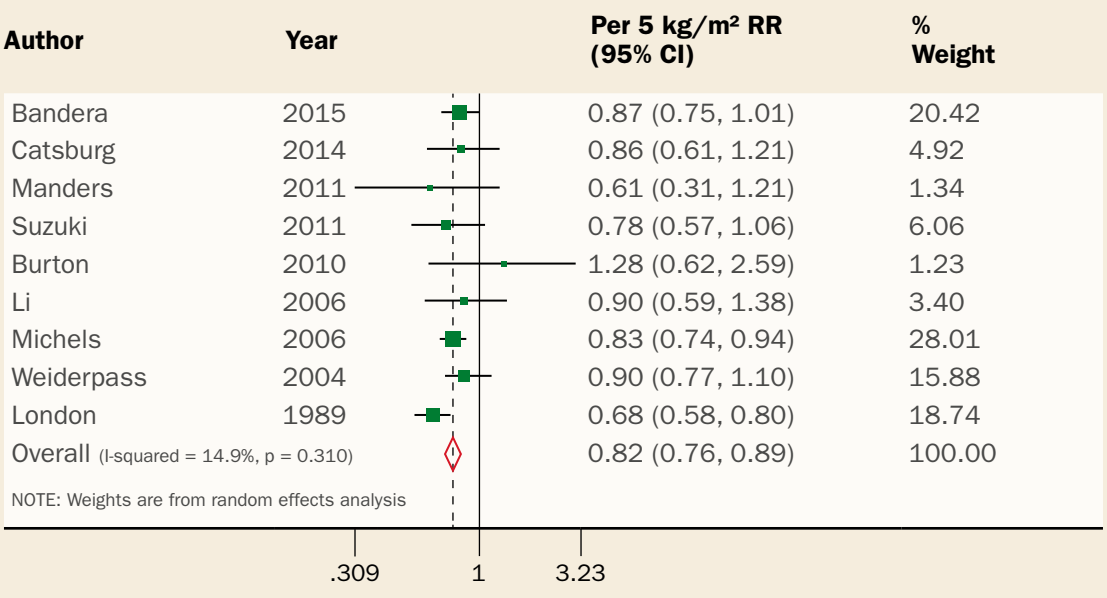
Body mass index

Premenopausal breast cancer

The CUP identified 10 new or updated studies (eight publications) [138–145], giving a total of 12 studies (12 publications) reviewing the evidence for BMI in young adulthood (aged between about 18 and 30 years) and premenopausal breast cancer (for a full list of references, see CUP Breast SLR 2017 Tables 544 and 545). This included one pooled analysis of three studies [145] which included one cohort study and two case-control studies (results were not reported separately by study type).

All 12 studies (including one pooled analysis) were included in the dose-response meta-analysis for premenopausal breast cancer (n = 4,953 cases), which showed a statistically significant 18 per cent decreased risk per 5 kg/m^2 (RR 0.82 (95% CI 0.76–0.89); see **Figure 8**, CUP Breast SLR 2017 Figure 569). Low heterogeneity was observed (I^2 = 15%). When the pooled study [145] that included one cohort and two case-control studies was excluded, the association remained significant (RR 0.81 (95% CI 0.73–0.89)).

Figure 8: Dose-response meta-analysis of BMI in young adulthood and premenopausal breast cancer, per 5 kg/m^2



Dose-response meta-analyses for premenopausal breast cancer by geographical location showed a statistically significant decreased risk in North American studies only (RR 0.80 (95% CI 0.71–0.90); see CUP Breast SLR 2017 Figure 571). The significant inverse association remained in studies adjusted for age, alcohol intake and reproductive factors (RR 0.77 (95% CI 0.70–0.85)), and in studies adjusted for weight change or adult BMI/ waist–hip ratio (RR 0.85 (95% CI 0.79–0.92)).

Most studies adjusted for major risk factors. Some studies [139, 141, 145, 146] did not adjust for alcohol consumption.

No analysis by menopausal status was conducted in the 2005 or 2008 SLR.

Published pooled analyses and meta-analyses

One published pooled analysis was identified on BMI in young adulthood and premenopausal breast cancer [145], reporting no significant association for the highest versus the lowest categories of BMI in young adulthood. This pooled analysis was included in the CUP dose-response meta-analysis.

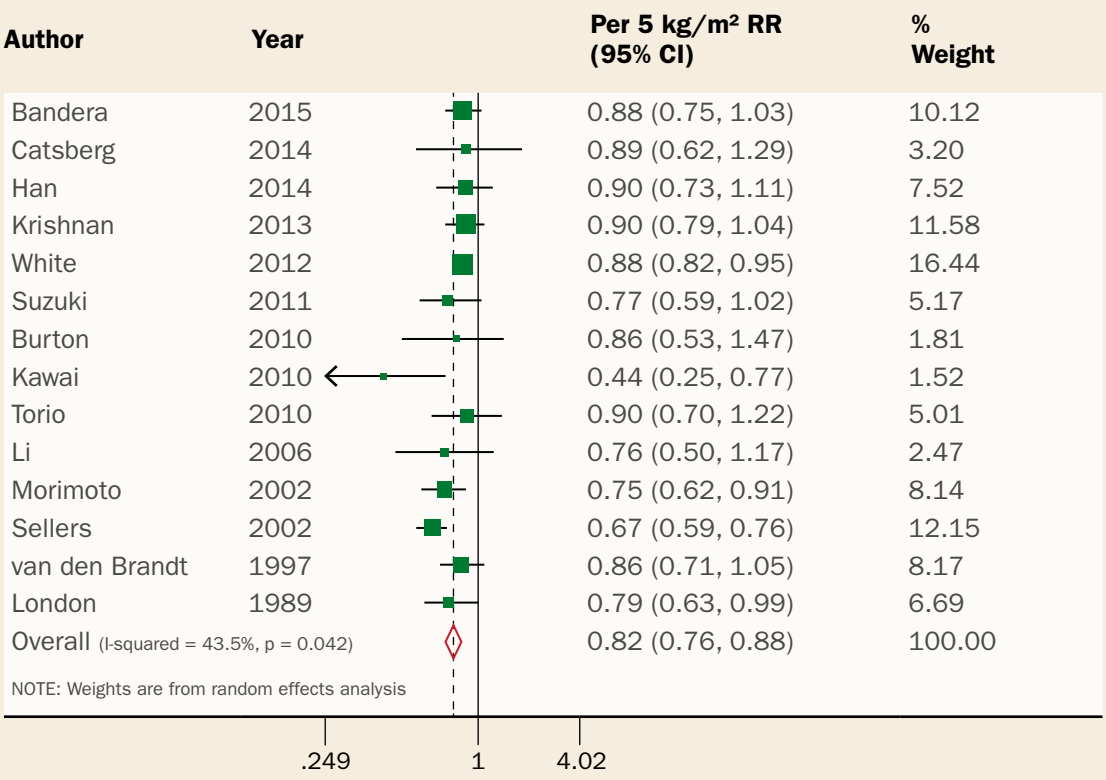
Postmenopausal breast cancer

The CUP identified 18 new or updated studies (16 publications) [87, 134, 139–145, 147–153], giving a total of 21 studies (24 publications) reviewing the evidence for BMI in young adulthood (aged between about 18 and 30 years) and postmenopausal breast cancer (for a full list of references, see CUP Breast SLR 2017 Tables 548 and 549). This included one pooled analysis of four studies [145] which included two cohort studies and two case-control studies (results were not reported separately by study type).

All 17 studies reporting on postmenopausal breast cancer showed inverse associations when comparing the highest and the lowest categories of BMI in young adulthood; five of 19 estimates were significant (see CUP Breast SLR 2017 Figure 573).

Seventeen studies (including one pooled analysis) were included in the dose-response meta-analysis for postmenopausal breast cancer (*n* = 10,229 cases), which showed a statistically significant 18 per cent decreased risk per 5 kg/m^2 (RR 0.82 (95% CI 0.76–0.88); see **Figure 9**, CUP Breast SLR 2017 Figure 574). Moderate heterogeneity was observed (I^2 = 44%). When the pooled study [145] that included two cohort and two case-control studies was excluded, the association remained significant (RR 0.81 (95% CI 0.75–0.88)).

Figure 9: Dose-response meta-analysis of BMI in young adulthood and postmenopausal breast cancer, per 5 kg/m²



Dose-response meta-analyses for postmenopausal breast cancer by geographical location showed a statistically significant decreased risk in North American studies and Asian studies (RR 0.82 (95% CI 0.75–0.90) and RR 0.68 (95% CI 0.51–0.92) respectively, see CUP Breast SLR 2017 Figure 576). The significant inverse association remained in studies adjusted for age, alcohol intake and reproductive factors (RR 0.81 (95% CI 0.74–0.88)), and in studies adjusted for weight change or adult BMI/waist-hip ratio (RR 0.76 (95% CI 0.64–0.91)).

Two studies were not included in any of the CUP analyses because they reported by hormone receptor status [134, 144].

Most studies adjusted for major risk factors. Some studies [139, 141, 145, 146] did not adjust for alcohol consumption.

No analysis by menopausal status was conducted in the 2005 or 2008 SLR.

Published pooled analyses and meta-analyses

One published pooled analysis was identified on BMI in young adulthood and postmenopausal breast cancer [145], reporting no significant association for the highest versus the lowest categories of BMI in young adulthood. This pooled analysis was included in the CUP dose-response meta-analysis.

Mechanisms

Note: In the future, a full review of mechanisms for this exposure will form part of a larger review of mechanisms (see ***Section 6.1*** *on page 18 in this report).*

Body fatness in childhood and adolescence is inversely related to the risk of premenopausal breast cancer as well as postmenopausal breast cancer, suggesting a long-term effect of body fatness at young age on breast cancer risk later in life. These findings contrast with the higher risk of breast cancer among postmenopausal women with greater body fatness throughout adulthood.

Early life, including childhood and adolescence, is hypothesized to be a critical window for breast tumorigenesis. This is a period of rapid growth and development with high rates of mammary gland tissue proliferation during puberty which may increase susceptibility to molecular damage and may explain why particular exposures may be important for breast cancer risk later in life. Body fatness during childhood has been associated with slower adolescent growth, whereas peak height growth velocity as a measure of adolescent growth is associated with an increased risk of breast cancer [154]. Insulin-like growth factor (IGF)-I, the main mediator of growth hormone activity, is an established positive risk factor for breast cancer [155] but may be lower among women who had greater body fatness in childhood and adolescence [156]. Sex hormones may also partly explain the inverse relation between early life adiposity and breast cancer risk. Adipose tissue-derived oestrogen in overweight adolescents may induce early breast differentiation and render the breast tissue less susceptible to tumorigenesis, as has been demonstrated in animal models [157]. Obese young women are also more likely to experience anovulation and therefore lower levels of ovarian hormones such as progesterone and lower peaking of oestradiol [158]. On the other hand, body fatness in pre-adolescent and adolescent girls is related to higher insulin (6) and androgen levels and lower sex-hormone-binding globulin concentrations [159], which would likely increase breast cancer risk. Overall, the mechanisms underlying the inverse association of early life body fatness and breast cancer risk are complex and not well-delineated.

CUP Panel's conclusions:

For premenopausal and postmenopausal breast cancer, the evidence was generally consistent and the dose response meta-analyses showed a significant decreased risk with increasing BMI in young adulthood. Low to moderate heterogeneity was observed. For both premenopausal and postmenopausal breast cancer, significant findings were observed in North American studies, and also for Asian studies in postmenopausal women. The association remained significant for both premenopausal and postmenopausal breast cancer when adjusted for age, alcohol and reproductive factors, and when adjusted for weight change or adult BMI/waist–hip ratio. There is evidence of plausible mechanisms operating in humans.

The CUP Panel concluded the following:

Greater body fatness in young women (aged about 18 to 30 years) (marked by BMI) probably protects against premenopausal breast cancer.

Greater body fatness in young women (aged about 18 to 30 years) (marked by BMI) probably protects against postmenopausal breast cancer.

7.9 Body fatness

(Also see CUP Breast SLR 2017: Sections 8.1.1, 8.2.1 and 8.2.3)

Note: Sufficient data were available for the Panel to undertake a separate review of the evidence for body fatness in young adulthood (aged about 18 to 30 years) (see ***Section 7.8*** *on pages 49–53 in this report).*

The Panel interpreted BMI together with measures of waist circumference and waist–hip ratio as indicating interrelated aspects of body fatness and fat distribution. The evidence for these exposures is presented and followed by an overall conclusion that incorporates all of these.

Anthropometric measures are imperfect and cannot distinguish reliably between lean and fat, between total and abdominal fat, or between visceral and subcutaneous fat. Increases in body weight during adulthood depend on accumulation of fat more than of lean tissue, and therefore any such change may better reflect fatness than adult weight itself.

Premenopausal breast cancer

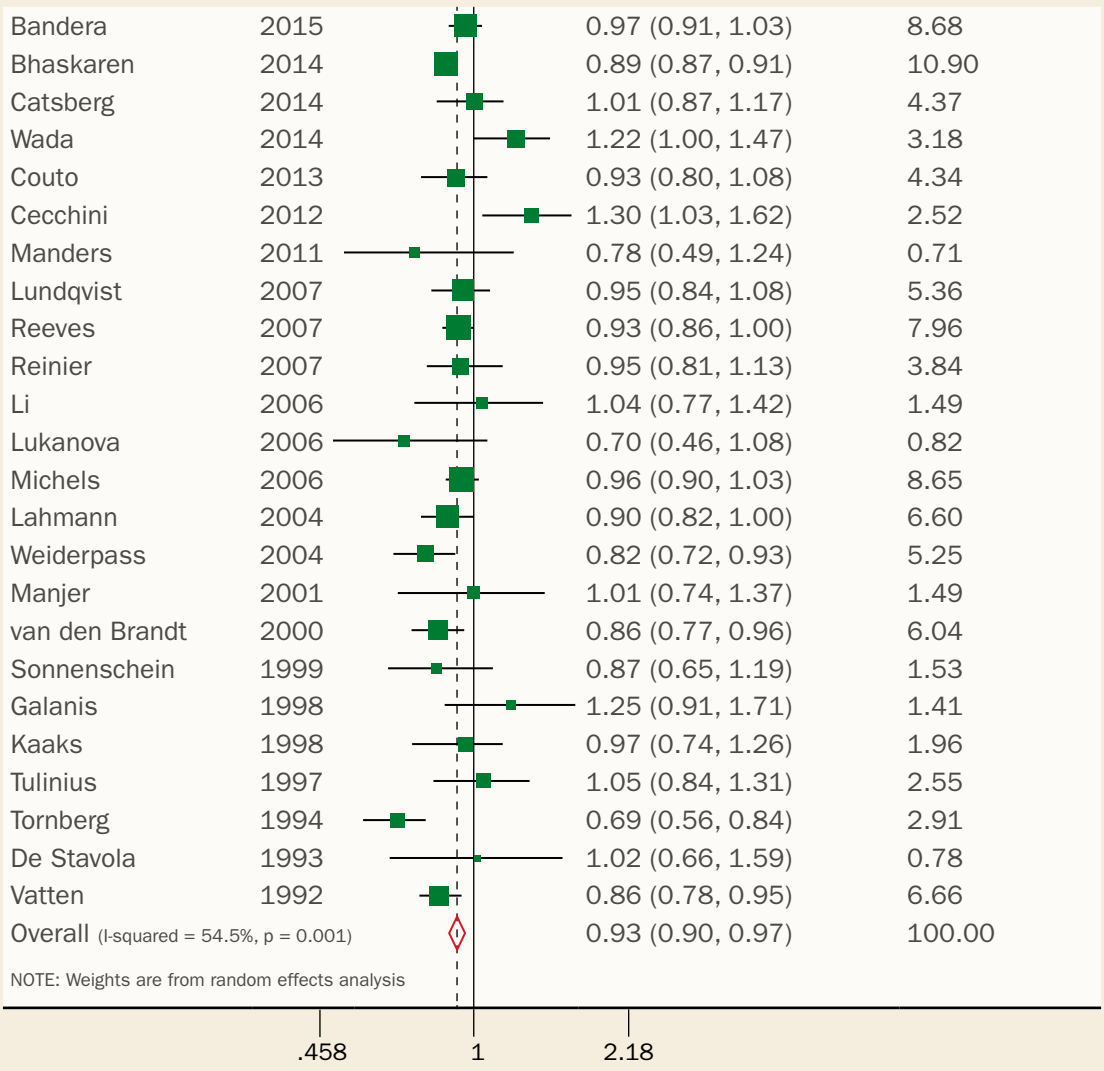
Body mass index

The CUP identified 113 new or updated studies (33 publications) [35, 127, 138–145, 160–182], giving a total of 128 studies (57 publications) reviewing the evidence for BMI and premenopausal breast cancer (for a full list of references, see CUP Breast SLR 2017 Tables 528 and 529).

Of 23 estimates (26 studies) for premenopausal breast cancer, 14 showed an inverse association (seven significant) when comparing the highest and the lowest categories of BMI, three reported no effect (RR = 1.00) and the remaining studies reported a positive association, one of which was significant (see CUP Breast SLR 2017 Figure 534). Three pooled analyses [145, 170, 183] also reported inverse associations for the highest versus the lowest comparisons, one of which was significant and one borderline significant, and another pooled analysis [180] reported a significant positive association. In addition, a pooled analysis and one other study [164, 169] reporting on premenopausal breast cancer mortality also showed non-significant inverse associations when comparing the highest and the lowest categories of BMI, and another pooled analysis [170] reported a non-significant positive association (see CUP Breast SLR 2017 Figure 542).

Thirty-seven studies (including three pooled analyses) were included in the dose-response meta-analysis for premenopausal breast cancer (*n* = 16,371 cases), which showed a statistically significant 7 per cent decreased risk per 5 kg/m^2 for all incidence and mortality studies combined (RR 0.93 (95% CI 0.90–0.97)) (see **Figure 10**, CUP Breast SLR 2017 Figure 535). High heterogeneity was observed (I^2 = 55%), which could be explained partly by geographical locations of the cohorts.

Figure 10: Dose-response meta-analysis of BMI and premenopausal breast cancer, per 5 kg/m²



Dose-response meta-analyses for premenopausal breast cancer by geographical location showed a statistically significant decreased risk in European studies only (see **Table 15** and CUP Breast SLR 2017 Figure 537), and the significant inverse association also remained in studies that measured participants' height and weight (see CUP Breast SLR 2017 Figure 538). The association became non-significant when restricted to only invasive breast cancer, studies that involved breast or mammography screening and studies that adjusted for confounders (age, alcohol intake and reproductive factors) (results not shown in table; see CUP Breast SLR 2017 for more information). When stratified by hormone receptor type, non-significant associations were also observed (see **Table 15**).

Table 15: Summary of CUP 2017 stratified dose-response meta-analyses of premenopausal breast cancer – BMI

Analysis	Increment	RR (95% CI)	I^2	No. Studies
GEOGRAPHICAL LOCATION				
Europe	Per 5 kg/m²	0.89 (0.86–0.92)	11%	17
North America	Per 5 kg/m²	0.97 (0.91–1.03)	40%	11
Asia	Per 5 kg/m²	1.16 (0.99–1.37)	0%	9
HORMONE RECEPTOR STATUS				
ER+	Per 5 kg/m²	1.02 (0.90–1.15)	68%	7
ER–	Per 5 kg/m²	1.01 (0.94–1.08)	0%	7

In a separate meta-analysis of the 36 studies on premenopausal breast cancer mortality (including a pooled analysis of 35 studies) (*n* = 545), no effect was observed (RR 1.00 (95% CI 0.73–1.38)) with evidence of high heterogeneity (I^2 = 75%) (see CUP Breast SLR 2017 Figure 543).

Four studies were not included in any of the CUP analyses. One reported mean comparisons only [69], one included exposures on proxy BMI [167], one included BMI at a younger age [141] and one reported on specific cancer types not included in the CUP analyses [177].

Fifteen of the studies (including studies from two pooled analyses) [35, 144, 164, 180, 183, 184] simultaneously adjusted for age, alcohol intake and reproductive factors.

The CUP findings are similar to the dose-response meta-analysis in the 2005 SLR, which also reported a significant decreased risk of premenopausal breast cancer (RR 0.94 (95% CI 0.92–0.95) per 2 kg/m² for 14 studies) with moderate heterogeneity observed.

Published pooled analyses and meta-analyses

Seven published pooled analyses [145, 166, 169, 170, 172, 180, 183] and six published meta-analyses [185–190] on BMI and premenopausal breast cancer risk were identified in the CUP Breast SLR 2017. Four of the pooled analyses [145, 166, 180, 183] were included in the CUP dose-response meta-analyses. One of these reported no association per 5 kg/m² [145], one reported a borderline significant positive association [180], one reported a significant inverse association [183] and one showed a significant positive association for mortality per 5 kg/m² [166]. Results from the other published pooled analyses and meta-analyses are presented in **Table 16**.

Table 16: Summary of CUP 2017 meta-analysis, and published pooled analyses[1] and meta-analyses of premenopausal breast cancer – BMI

Analysis	Increment/ contrast	RR (95% CI)	I^2	No. Studies	No. Cases
CUP Breast Cancer SLR 2017	Per 5 kg/m²				
	Incidence	0.93 (0.90–0.97)	55%	37	16,371
	Mortality	1.00 (0.73–1.38)	75%	36	545
Published pooled analyses (not included in the CUP analysis)					
Breast Cancer Association Consortium Studies (BCAC) [172][2]	>30 vs. <25kg/m² Incidence, invasive breast cancer			12	
	ER+	0.81 (0.69-0.95)	-		10,900
	ER–	1.10 (0.92-1.30)	-		3,895
The Metabolic Syndrome and Cancer Project (Me-Can) [170][3]	>31.7 vs. <20kg/m²			6	3,043
	Incidence	0.70 (0.57–0.85)	-		
	Mortality	1.22 (0.64–2.31)	-		
Asia-Pacific Cohort Studies Collaboration (APCSC) [169][4]	Mortality 30–60 vs. 18.5–24.9kg/m²	0.93 (0.42–2.09)	-	35	324 Breast cancer (unspecified)
	Per 5 kg/m²	1.13 (0.97–1.33)	-		
Published meta-analyses[5,6]					
Munsell, 2014 [190]	Incidence				
	25–29.9 vs. <25kg/m²	0.99 (0.92–1.07)	47%	6	4,469
	≥30 vs. <25kg/m²	0.72 (0.55–0.94)	77%		
Xia, 2014 [189]	Incidence				
	Per 5 kg/m²	0.99 (0.98–1.00)	-	12	4,699
Cheraghi, 2012 [186]	Incidence				
	Overweight vs. normal	1.01 (0.77–1.31)	72%	4	564
	Obese vs. normal	0.91 (0.71–1.18)	34%		
Suzuki, 2009 [185]	Per 5 kg/m²				
	ER+PR+	0.90 (0.82–0.99)	-	4	1,720

[1] Pooled analyses not included in the CUP meta-analysis.

[2] Adjusted for age, study, age at menarche, nulliparity, age at birth of first child.

[3] Adjusted for year of birth, age at measurement, smoking, stratified for cohort.

[4] Adjusted for attained age, smoking status, stratified by study.

[5] All cohort studies identified were included in the CUP 2017 analyses, apart from Barlow, 2006 [191], which was identified in Cheraghi, 2012 [186], as this study from the Breast Cancer Surveillance Consortium estimated the risk of developing breast cancer within a year of mammography screening.

[6] Pierobon, 2013 [187] and Amadou, 2013 [188] are not included in the table as they included cohort and case-control studies.

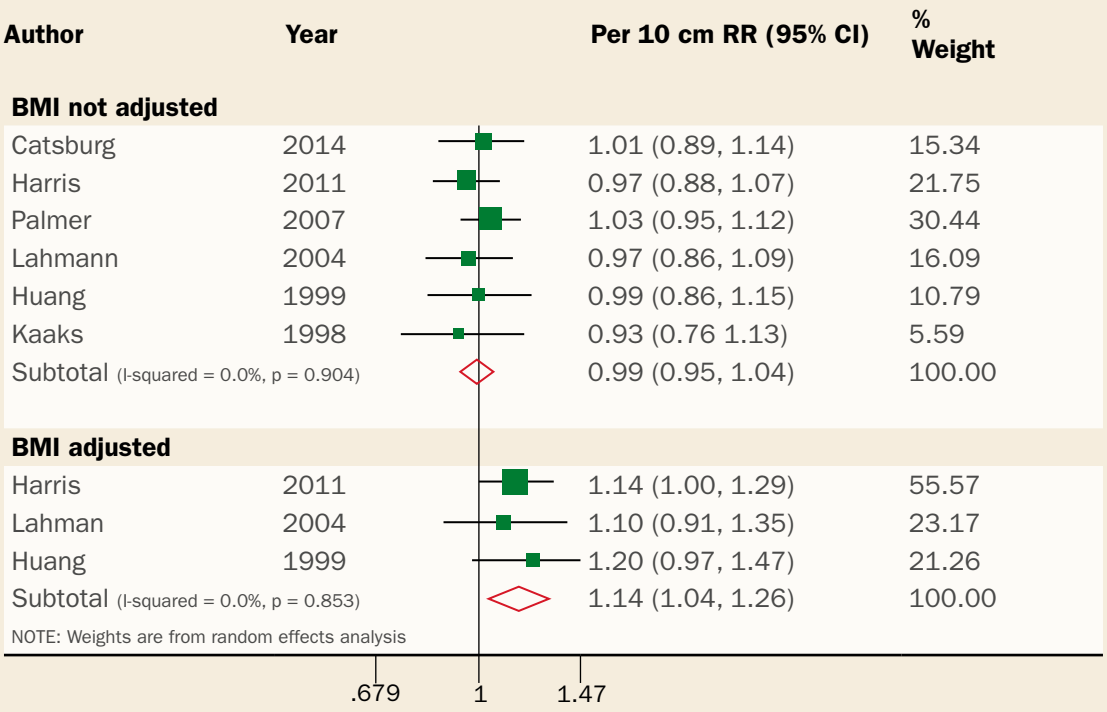
Waist circumference

The CUP identified four new or updated studies (six publications) [140, 144, 161, 173, 175, 192], giving a total of six studies (nine publications) reviewing the evidence for waist circumference and premenopausal breast cancer (for a full list of references, see CUP Breast SLR 2017 Tables 575 and 576).

Most studies reporting on premenopausal breast cancer that had not been adjusted for BMI showed inverse associations when comparing the highest and the lowest categories of waist circumference, none of which were significant, and all the studies that adjusted for BMI showed positive associations, one of which was significant (see CUP Breast SLR 2017 Figure 601).

Six studies were included in the dose-response meta-analysis for premenopausal breast cancer (BMI unadjusted) (*n* = 2,423 cases), which showed no significant association per 10 cm (RR 0.99 (95% CI 0.95–1.04); see **Figure 11**, CUP Breast SLR 2017 Figure 602). No heterogeneity was observed (I^2 = 0%). However, when the study that contributed the largest weight (56%) in the analysis [173] was excluded, the association became borderline significant (RR 1.15 (95% CI 1.00–1.32)). In another dose-response meta-analysis of the three studies adjusting for BMI (*n* = 1,291), a statistically significant 14 per cent increased risk per 10 cm was observed (RR 1.14 (95% CI 1.04–1.26)), with no evidence of heterogeneity (I^2 = 0%). A non-linear dose-response analysis showed evidence of non-linearity (p = <0.01). The curve showed an initial increase in risk of premenopausal breast cancer with an increase of waist circumference that started to drop again after 80 cm (see CUP Breast SLR 2017 Figure 604 and Table 577).

Figure 11: Dose-response meta-analysis of waist circumference and premenopausal breast cancer, per 10cm



Most studies adjusted for age, alcohol intake and reproductive factors. Two studies [140, 193] did not adjust for alcohol intake. Not all studies reported results with and without BMI adjustment.

No analysis for premenopausal breast cancer and waist circumference was conducted in the 2005 SLR. In dose-response meta-analyses for the CUP in 2008, no significant association was observed for studies not adjusted for BMI (RR 0.97 (95% CI 0.90–1.05) per 8 cm for four studies) and a borderline significant positive association was observed for studies adjusted for BMI (RR 1.12 (95% CI 1.00–1.25) per 8 cm for two studies).

Published pooled analyses and meta-analyses

One published meta-analysis of cohort and case-control studies on premenopausal breast cancer [188] was identified in the CUP Breast SLR 2017, showing no significant association per 10 centimetres of waist circumference.

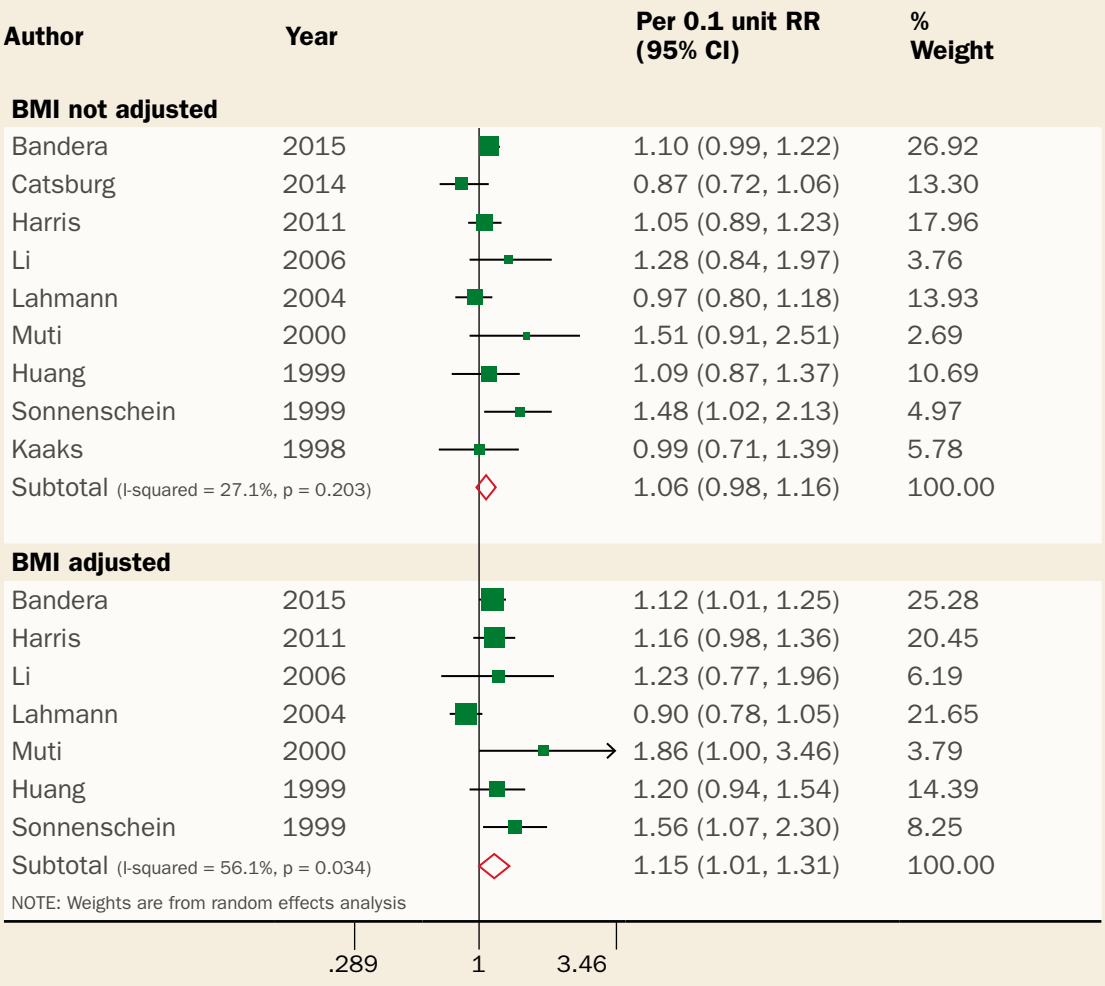
Waist–hip ratio

The CUP identified seven new or updated studies (seven publications) [139, 140, 144, 145, 161, 173, 175], giving a total of 11 studies (12 publications) reviewing the evidence for waist–hip ratio and premenopausal breast cancer (for a full list of references, see CUP Breast SLR 2017 Tables 588 and 589). This included one pooled analysis of three studies [145] (one cohort study and two case-control studies, results were not reported separately by study type).

Of eight individual studies reporting on premenopausal breast cancer that had not been adjusted for BMI, four showed non-significant positive associations, three showed non-significant inverse associations and one showed no effect (RR = 1.00) when comparing the highest and the lowest categories of waist–hip ratio. All six studies adjusted for BMI showed positive associations, one of which was significant and one borderline significant (see CUP Breast SLR 2017 Figure 614). The pooled analysis of three studies showed a non-significant positive association for studies adjusted and not adjusted for BMI.

Eleven studies (including one pooled analysis) were included in the dose-response meta-analysis for premenopausal breast cancer (BMI unadjusted) (*n* = 3,465 cases), which showed no significant association per 0.1 unit (RR 1.06 (95% CI 0.98–1.16); see **Figure 12**, CUP Breast SLR 2017 Figure 615). Low heterogeneity was observed (I^2 = 27%). However, the association became significant when one study (13 per cent weighting) [173] was excluded (RR 1.09 (95% CI 1.02–1.17)). A dose-response meta-analysis of the nine studies adjusting for BMI (*n* = 2,722) showed a statistically significant 15 per cent increased risk per 0.1 unit (RR 1.15 (95% CI 1.01–1.31)), with high heterogeneity (I^2 = 56%).

Figure 12: Dose-response meta-analysis of waist-hip ratio and premenopausal breast cancer, per 0.1 unit



Significant positive associations for BMI adjusted waist–hip ratio were observed only in studies from North America (RR 1.06 (95% CI 1.07–1.26)), with self-reported waist and hip measurement (RR 1.14 (95% CI 1.05–1.24)) (see CUP Breast SLR 2017 Figures 617 and 618 respectively). For both BMI-adjusted and -unadjusted studies, the association was significant without adjustment for confounders (age, alcohol intake and reproductive factors) (RR 1.28 (95% CI 1.04–1.59) and RR 1.15 (95% CI 1.02–1.29) respectively).

All studies adjusted for most major confounding factors, but most studies did not adjust for alcohol consumption. Two studies did not adjust for BMI [144, 193].

No analysis for premenopausal breast cancer and waist–hip ratio was conducted in the 2005 SLR. In dose-response meta-analyses for the CUP in 2008, no significant associations were observed per 0.1 unit for studies both adjusted and unadjusted for BMI (RR 1.24 (95% CI 0.91–1.67) for four studies and RR 1.07 (95% CI 0.90–1.26) for six studies respectively).

Published pooled analyses and meta-analyses

One published pooled analysis was identified in the CUP Breast SLR 2017 [145] and was included in the CUP dose-response meta-analysis. One published meta-analysis of cohort and case-control studies on premenopausal breast cancer [188] was identified, showing a significant positive association with waist–hip ratio per 0.1 unit.

Postmenopausal breast cancer

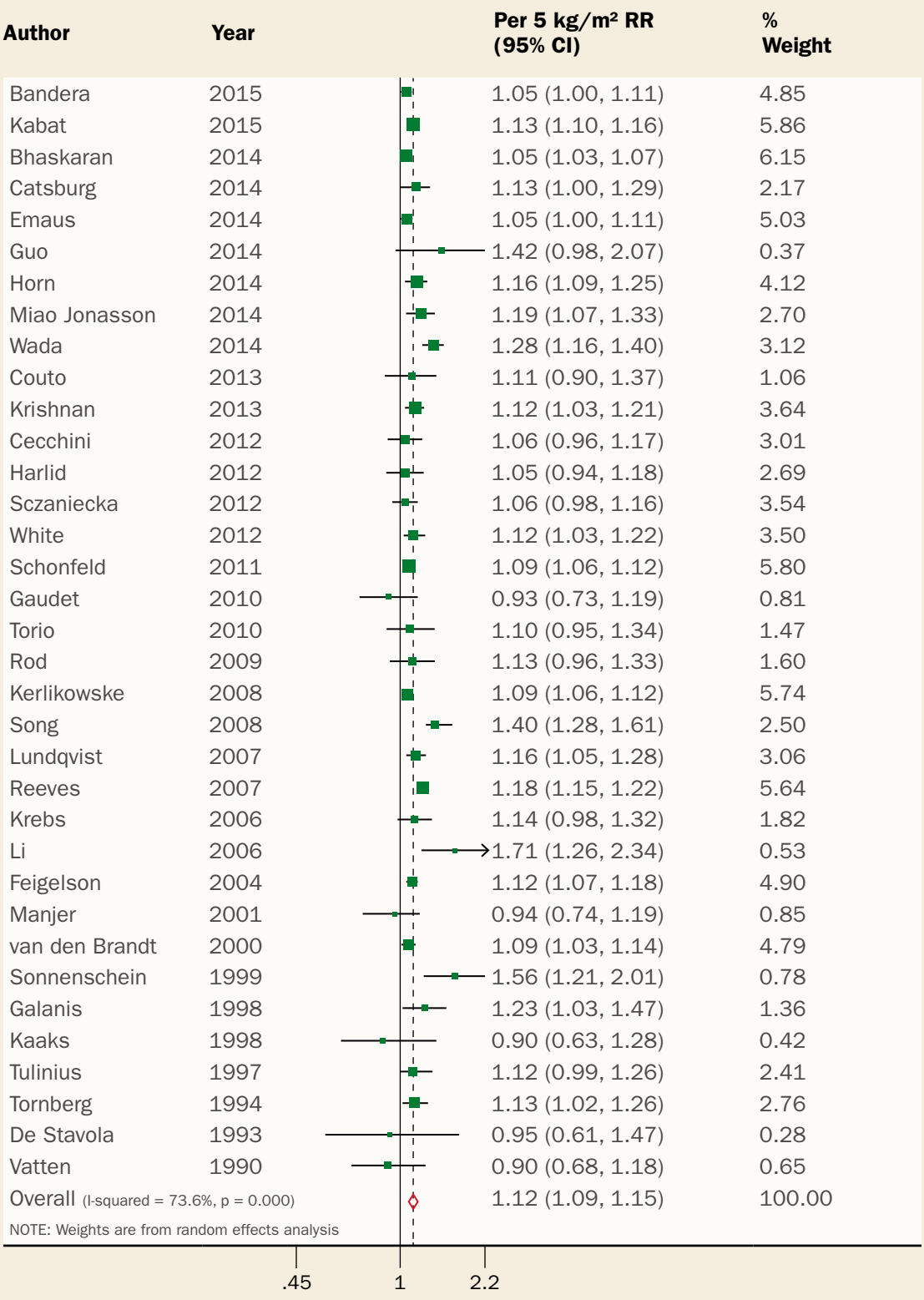
Body mass index

The CUP identified 143 new or updated studies (87 publications) [33, 35, 71, 73–76, 80, 87, 88, 91, 92, 94–96, 99, 123, 127, 134, 139–145, 147–152, 160–172, 174–181, 194–227], giving a total of 156 studies (131 publications) reviewing the evidence for BMI and postmenopausal breast cancer (for a full list of references, see CUP Breast SLR 2017 Tables 535 and 536).

Of 36 estimates (from 34 studies) for postmenopausal breast cancer, 30 showed a positive association (15 significant and three borderline significant) when comparing the highest and the lowest categories of BMI, and the remaining studies reported an inverse association, six of which were significant (see CUP Breast SLR 2017 Figure 545). Five pooled analyses [88, 145, 166, 170, 183] also reported positive associations for the highest versus the lowest comparisons, two of which were significant and one significant only in participants less than 25 years of age at the birth of the first child. In addition, a pooled analysis and five other studies reporting on postmenopausal breast cancer mortality [164, 169, 214, 228, 229] also showed positive associations (four significant) when comparing the highest and the lowest categories of BMI, and another pooled analysis [170] reported a non-significant inverse association (see CUP Breast SLR 2017 Figure 560).

Fifty-six studies (including four pooled analyses) were included in the dose-response meta-analysis for postmenopausal breast cancer (*n* = 80,404 cases), which showed a statistically significant 12 per cent increased risk per 5 kg/m^2 for all incidence and mortality studies combined (RR 1.12 (95% CI 1.09–1.15)) (see **Figure 13**, CUP Breast SLR 2017 Figure 546). High heterogeneity was observed (I^2 = 74%), which could be explained partly by geographical locations of the cohorts. There was evidence of small study bias with Egger's test (p = 0.03). Visual inspection of the funnel plot showed more large-sized studies published positive associations (see CUP Breast SLR 2017 Figure 547).

Figure 13: Dose-response meta-analysis of BMI and postmenopausal breast cancer, per 5 kg/m²



Dose-response meta-analyses for postmenopausal breast cancer by geographical location showed a statistically significant increased risk in North American and European studies, and a stronger association in Asian studies (see **Table 17** and CUP Breast SLR 2017 Figure 548). When stratified by hormone therapy use and breast cancer subtype, significant positive associations were observed only among never users of hormone therapy or never/former users (see **Table 17** CUP Breast SLR 2017 Figure 552). BMI was significantly positively associated with ER+ breast cancer, PR+ breast cancer and ER+PR+ breast cancer, but not ER– or other joint hormone-receptor-defined breast cancers (see **Table 17** and CUP Breast SLR 2017 Figures 554 and 556). Stratified analyses of other factors, including anthropometric measurement methods, study type, confounder adjustment, publication year, number of cases and range of BMI in studies, showed significant positive associations of similar magnitude (results not shown in table; see CUP Breast SLR 2017 Tables 531, 532, 533 and Figures 549 and 550).

Table 17: Summary of CUP 2017 stratified dose-response meta-analyses of postmenopausal breast cancer – BMI

Analysis	Increment	RR (95% CI)	I^2	No. Studies
GEOGRAPHICAL LOCATION				
Europe	Per 5 kg/m²	1.10 (1.06–1.15)	75%	19
North America	Per 5 kg/m²	1.10 (1.08–1.12)	30%	25
Asia	Per 5 kg/m²	1.37 (1.24–1.50)	27%	11
HORMONE RECEPTOR STATUS				
ER+	Per 5 kg/m²	1.17 (1.09–1.25)	91%	14
ER–	Per 5 kg/m²	1.00 (0.95–1.06)	7%	13
PR+	Per 5 kg/m²	1.47 (1.36–1.60)	0%	5
PR–	Per 5 kg/m²	1.05 (0.93–1.18)	0%	5
ER+PR+	Per 5 kg/m²	1.29 (1.19–1.40)	78%	9
ER+PR–	Per 5 kg/m²	0.94 (0.87–1.01)	0%	6
ER–PR–	Per 5 kg/m²	0.96 (0.87–1.06)	33%	9
HORMONE THERAPY USE				
Current	Per 5 kg/m²	0.98 (0.90–1.06)	69%	5
Ever	Per 5 kg/m²	1.01 (0.96–1.06)	0%	13
Never	Per 5 kg/m²	1.16 (1.10–1.23)	72%	15
Never/former	Per 5 kg/m²	1.20 (1.15–1.25)	0%	4

In a separate meta-analysis of the 38 studies on postmenopausal breast cancer mortality (including a pooled analysis of 35 studies) (*n* = 4,131), a significant positive association was also observed (RR 1.20 (95% CI 1.13–1.27)) with evidence of moderate heterogeneity (I^2 = 49%) (see CUP Breast SLR 2017 Figure 561).

Twenty studies including three individual studies [69, 141, 167] and two pooled analyses [172, 227] were not included in any of the CUP analyses.

About half of the studies were simultaneously adjusted for age, alcohol intake, reproductive factors and hormone therapy use.

The CUP findings are similar to the dose-response meta-analysis in the 2005 SLR, which also reported a significant increased risk of postmenopausal breast cancer (RR 1.03 (95% CI 1.01–1.04) per 2 kg/m^2 for 17 studies) with high heterogeneity observed.

Published pooled analyses and meta-analyses

Nine published pooled analyses [88, 145, 166, 169, 170, 172, 180, 183, 227] and six published meta-analyses [185-187, 189, 190, 230] on BMI and postmenopausal breast cancer risk were identified in the CUP Breast SLR 2017. Five of the pooled analyses were included in the CUP dose-response meta-analyses [88, 145, 166, 180, 183]; four of these showed significant or borderline significant positive associations per 5 kg/m^2 [88, 145, 180, 183] and the other (mortality only) [166] also showed a significant positive association per 5 kg/m^2. Results from the other published pooled and meta-analyses are presented in **Table 18**.

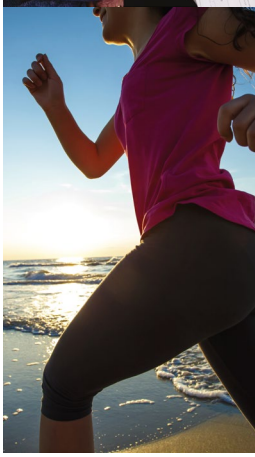


Table 18: Summary of CUP 2017 meta-analysis, and published pooled analyses[1] and meta-analyses of postmenopausal breast cancer – BMI

Analysis	Increment	RR (95% CI)	I^2	No. Studies	No. Cases
CUP Breast Cancer SLR 2017	Per 5 kg/m² Incidence Mortality	 1.12 (1.09–1.15) 1.20 (1.13–1.27)	 74% 49%	 56 38	 80,404 4,131
Published pooled analyses (not included in the CUP analysis)					
Breast Cancer Association Consortium Studies (BCAC) [172][2]	≥30 vs. ≤25 kg/m² Incidence invasive breast cancer ER+ ER–	BMI did not significantly modify the association	-	12	
The Metabolic Syndrome and Cancer Project (Me-Can) [170][3]	≥31.7 vs. ≤20 kg/m² Incidence Mortality	 0.87 (0.71–1.07) 0.92 (0.66–1.27)	 - -	 6	 1,106 219
Asia-Pacific Cohort Studies Collaboration (APCSC)[169][4]	Mortality 30–60 vs. 18.5–24.9 kg/m² Per 5 kg/m²	 1.63 (1.13–2.35) 1.19 (1.03–1.38)	 - -	 35	 324 Breast cancer (unspecified)
Published meta-analyses[5,6]					
Munsell, 2014 [190]	Incidence 25–29.9 vs. <25kg/m² >30 vs. <25 kg/m²	 1.13 (1.09–1.18) 1.20 (1.11–1.31)	 6% 64%	 12	 16,180
Xia, 2014 [189][7]	Incidence 25 vs. 21.75 kg/m² ≥30 vs. 21.75 kg/m² 35 vs. 21.75 kg/m²	 1.02 (0.98–1.06) 1.12 (1.01–1.24) 1.26 (1.07–1.50)	 - - -	 25 estimates from 20 prospective studies and 1 pooled analysis of cohorts	 22,809
Cheraghi, 2012 [186][8]	Incidence Overweight vs. normal	 1.12 (1.06–1.18)	 56%	 8	 9,878

[1] Pooled analyses not included in the CUP meta-analysis.

[2] Adjusted for age, study, age at menarche, nulliparity, age at first birth.

[3] Adjusted for year of birth, age at measurement, smoking, stratified for cohort.

[4] Adjusted for attained age, smoking status, stratified by study.

[5] All cohorts and RCTs identified were included in the CUP 2017 analyses unless otherwise specified.

[6] Pierobon, 2013 [187], Esposito, 2013 [230] and Suzuki, 2009 [185] are not included in the table as they included cohort and case-control studies.

[7] Four studies (Cecchini, 2012, P-1; Cecchini, 2012, STAR; Opdahl, 2011; Li, 2006) [139, 176, 216] included in Xia, 2014 [189] had insufficient BMI categories and one study (Canchola, 2012) [150] reported results only by hormone receptor subtype; these studies were not included in the non-linear analysis of the CUP 2017 analyses (36 studies, 13 studies not in Xia, 2014 [189]).

[8] Two studies included in Cheraghi, 2012 [186] were not included in the CUP 2017 analyses. Barlow, 2006 (Breast Cancer Surveillance Consortium) [191] estimated the risk of developing breast cancer within a year of mammography screening and no relevant data could be found in Lee, 2006 [231].

Waist circumference

The CUP identified 21 new or updated studies (25 publications) [71, 134, 140, 144, 147, 150, 161, 175, 192, 194, 198, 205, 210, 218, 220, 221, 224–227, 232–236], giving a total of 27 studies (39 publications) reviewing the evidence for waist circumference and postmenopausal breast cancer (for a full list of references, see CUP Breast SLR 2017 Tables 580 and 581).

All 11 studies reporting on postmenopausal breast cancer that had not been adjusted for BMI showed positive associations when comparing the highest and the lowest categories of waist circumference, six of which were significant. Of five studies that adjusted for BMI, most of these showed positive associations, one of which was significant (see CUP Breast SLR 2017 Figure 606).

Eleven studies were included in the dose-response meta-analysis for postmenopausal breast cancer (BMI unadjusted) (*n* = 14,033 cases), which showed a statistically significant 11 per cent increased risk per 10 cm (RR 1.11 (95% CI 1.09–1.13); see **Figure 14**, CUP Breast SLR 2017 Figure 607). No heterogeneity was observed (I^2 = 0%). A meta-analysis of the five studies adjusting for BMI (*n* = 12,022) showed a statistically significant 6 per cent increased risk per 10 cm (RR 1.06 (95% CI 1.01–1.12)), with evidence of high heterogeneity (I^2 = 72%). A non-linear dose-response analysis showed evidence of non-linearity (p = 0.02); however, the curve showed an almost linear increase in risk of postmenopausal breast cancer with an increase in waist circumference (see **Figure 15**, CUP Breast SLR 2017 Figure 612 and Table 582).

Figure 14: Dose-response meta-analysis of waist circumference and postmenopausal breast cancer, per 10 centimetres

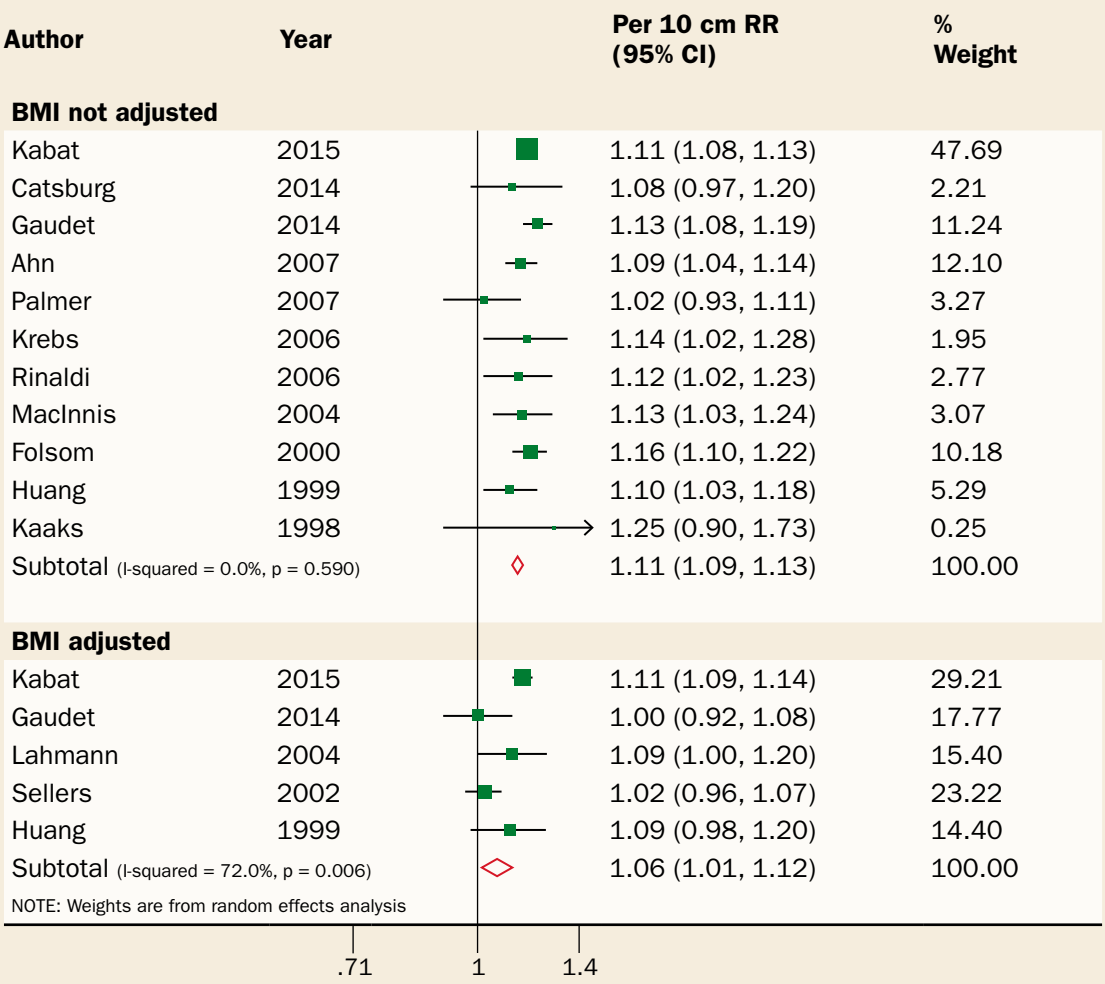
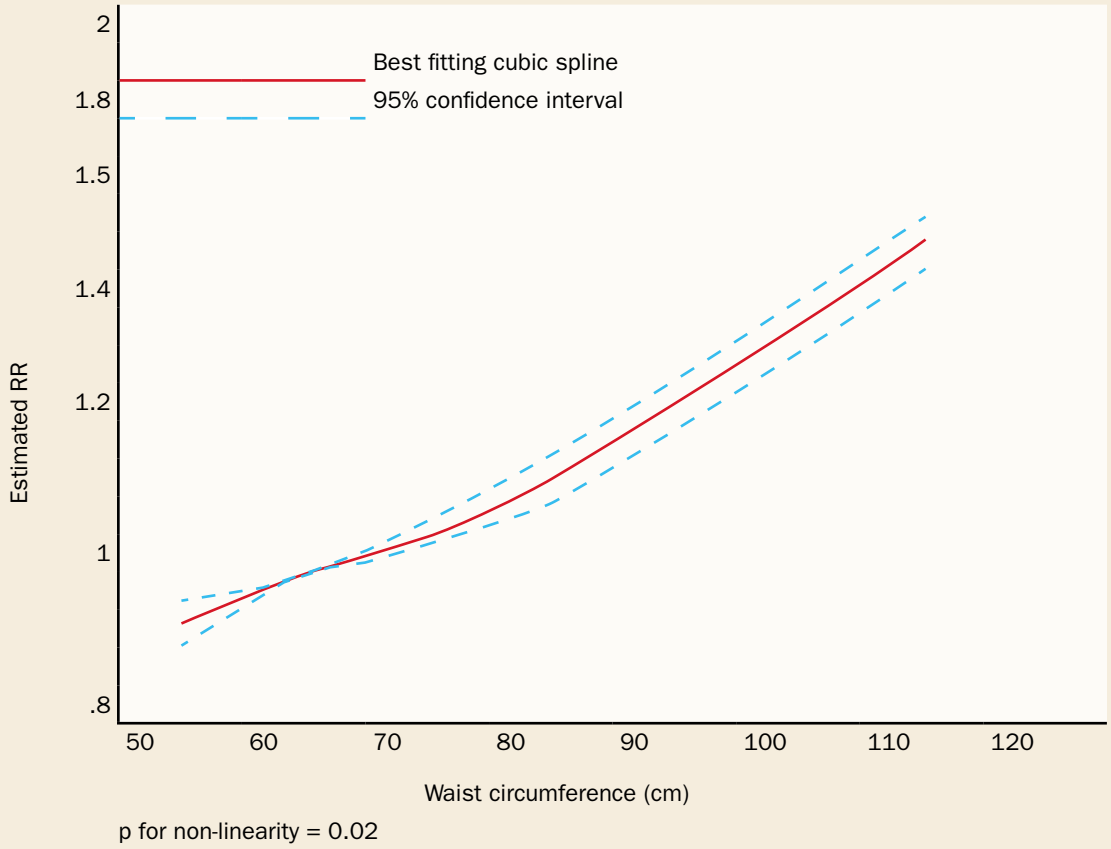


Figure 15: Non-linear dose-response meta-analysis of waist circumference and postmenopausal breast cancer

Non-linear relation between waist circumference and postmenopausal breast cancer



The significant association remained (in studies not adjusted for BMI) when stratified by geographical location (RR 1.11 (95% CI 1.09–1.13) in North American studies and RR 1.13 (95% CI 1.03–1.24) in European studies) (see CUP Breast SLR 2017 Figures 609 and 610). It also remained in studies adjusted for age, alcohol intake, reproductive factors and hormone therapy use (RR 1.11 (95% CI 1.09–1.13)).

Ten studies (including studies from one pooled analysis) were not included in any of the CUP analyses because they did not report sufficient data [227, 235].

About half of the studies simultaneously adjusted for age, alcohol intake, reproductive factors and hormone therapy use.

In the 2005 SLR, a dose-response meta-analysis showed a borderline significant increased risk of postmenopausal breast cancer (RR 1.05 (95% CI 1.00–1.10) per 8 cm for four studies) with no heterogeneity observed.

Published pooled analyses and meta-analyses

One published pooled analysis on postmenopausal breast cancer [227] showing a significant positive association per 1 SD was identified in the CUP Breast SLR 2017. The pooled analysis was not included in the CUP dose-response meta-analysis. Results from the CUP and the published pooled analysis are presented in **Table 19**.

Table 19: Summary of CUP 2017 meta-analysis and published pooled analysis[1] of postmenopausal breast cancer – waist circumference

Analysis	Increment	RR (95% CI)	I^2	No. Studies	No. Cases
CUP Breast SLR 2017	Per 10 cm BMI unadjusted	1.11 (1.09–1.13)	0%	11	14,033
	BMI adjusted	1.06 (1.01–1.12)	72%	5	12,022
ANZDCC [227] [2]	Per 1 SD	1.06 (1.01–1.12)	-	10	1,323

[1] Pooled analysis not included in the CUP meta-analysis.
[2] Adjusted for smoking status, education, cohort, age as timescale in model.

Waist–hip ratio

The CUP identified 23 new or updated studies (16 publications) [71, 94, 134, 139, 140, 144, 145, 147, 161, 175, 194, 198, 218, 220, 225, 226], giving a total of 29 studies (36 publications) reviewing the evidence for waist–hip ratio and postmenopausal breast cancer (for a full list of references, see CUP Breast SLR 2017 Tables 592 and 593). This included one pooled analysis of four studies [145] (two cohort studies and two case-control studies; results were not reported separately by study type).

Of 14 studies reporting on postmenopausal breast cancer that had not been adjusted for BMI, most showed positive associations when comparing the highest and the lowest categories of waist–hip ratio, six of which were significant. Of six studies that adjusted for BMI, four showed positive associations, one of which was significant (see CUP Breast SLR 2017 Figure 620). The pooled analysis of four studies showed a significant positive association for both studies adjusted and not adjusted for BMI.

Eighteen studies (including one pooled analysis) were included in the dose-response meta-analysis for postmenopausal breast cancer (BMI unadjusted) (*n* = 15,643 cases), which showed a significant positive association per 0.1 unit (RR 1.10 (95% CI 1.05–1.16); see **Figure 16**, CUP Breast SLR 2017 Figure 621). High heterogeneity was observed (I^2 = 60%). A dose-response meta-analysis of 10 studies adjusting for BMI (*n* = 5,700) showed no significant association (RR 1.06 (95% CI 0.99–1.15) per 0.1 unit), with moderate heterogeneity observed (I^2 = 41%). A non-linear dose-response analysis showed evidence of non-linearity (p = <0.01). The curve showed an increase in risk of postmenopausal breast cancer with the increase in waist–hip ratio, which became steeper after 0.8 units (see **Figure 17**, CUP Breast SLR 2017 Figure 626 and Table 594).

Figure 16: Dose-response meta-analysis of waist-hip ratio and postmenopausal breast cancer, per 0.1 unit

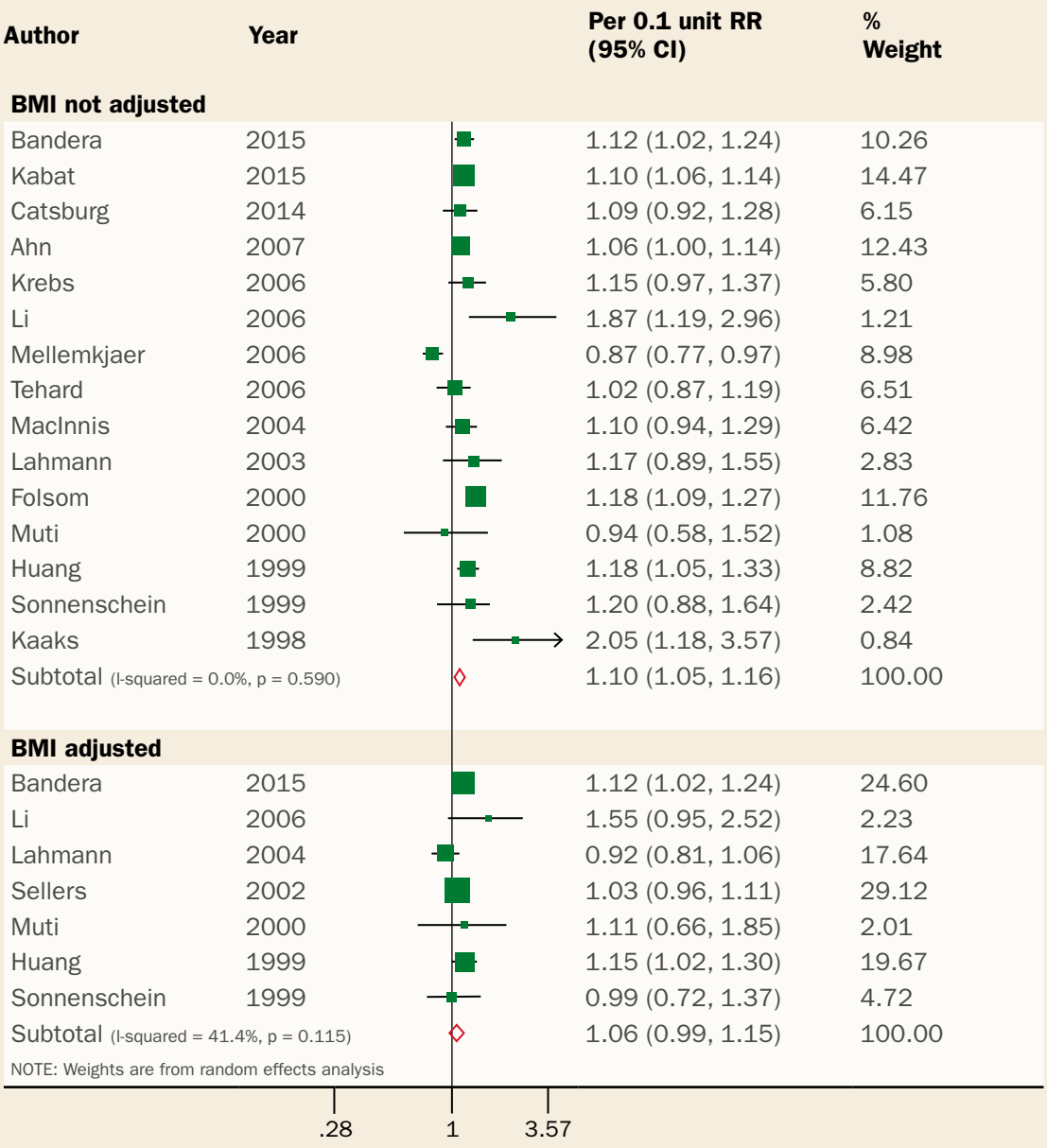
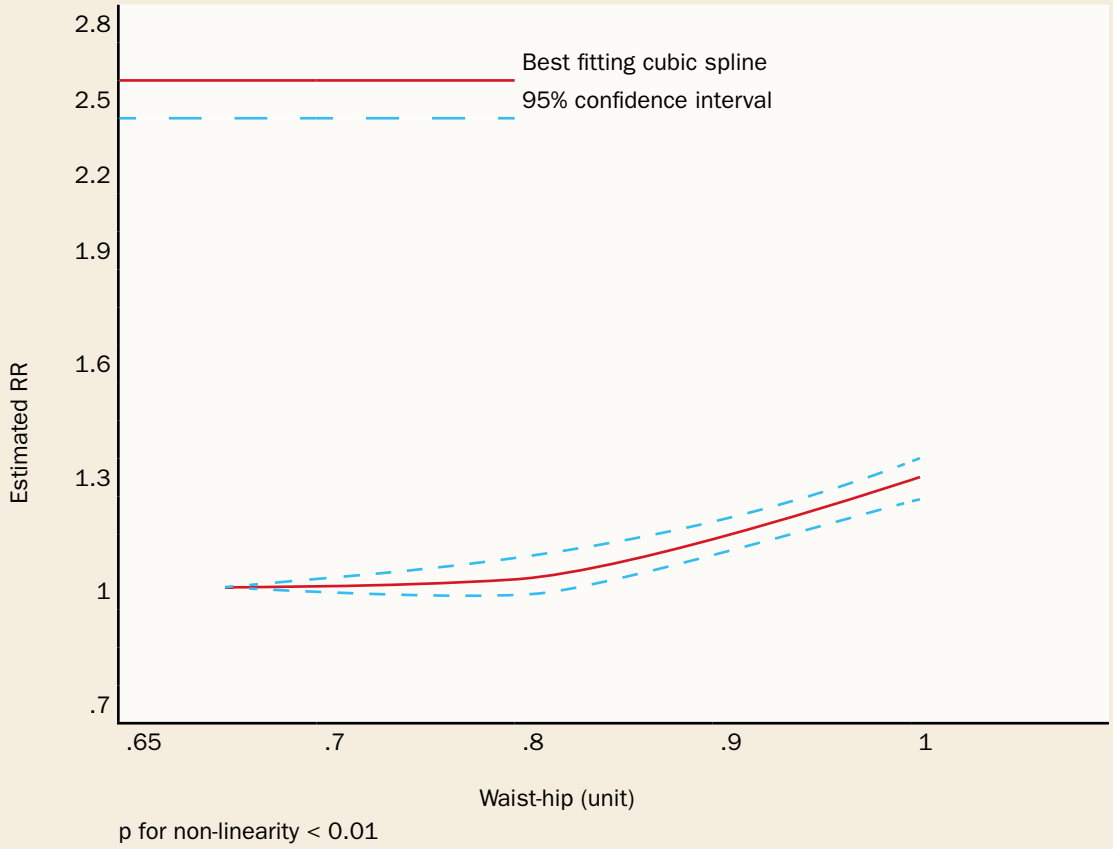


Figure 17: Non-linear dose-response meta-analysis of waist–hip ratio and postmenopausal breast cancer



Significant positive associations for BMI-adjusted waist–hip ratio were observed only in studies from North America, with self-reported waist and hip measurements (see **Table 20** and CUP Breast SLR 2017 Figures 623 and 624 respectively) and without simultaneous adjustment for age, alcohol, reproductive factors and hormone therapy use. For studies unadjusted for BMI, the association became significant in stratified analyses for North American studies, self-reported waist and hip measurements, and again without adjustment for age, alcohol, reproductive factors and hormone therapy use (see CUP Breast SLR 2017 Figures 623 and 624 respectively).

Table 20: Summary of CUP 2017 stratified dose-response meta-analyses of postmenopausal breast cancer – waist–hip ratio

Analysis	Increment	RR (95% CI)	I^2	No. Studies
GEOGRAPHICAL LOCATION				
Europe				
BMI adjusted	Per 0.1 unit	0.93 (0.82–1.06)	0%	2
BMI unadjusted	Per 0.1 unit	1.05 (0.87–1.28)	69%	5
North America				
BMI adjusted	Per 0.1 unit	1.08 (1.02–1.15)	11%	7
BMI unadjusted	Per 0.1 unit	1.11 (1.08–1.14)	0%	11
ANTHROPOMETRIC ASSESSMENT METHOD				
Self-reported				
BMI adjusted	Per 0.1 unit	1.09 (1.02–1.17)	36%	6
BMI unadjusted	Per 0.1 unit	1.12 (1.06–1.19)	43%	10
Measured				
BMI adjusted	Per 0.1 unit	1.02 (0.85–1.23)	31%	4
BMI unadjusted	Per 0.1 unit	1.09 (0.98–1.21)	69%	8

Ten studies were not included in any of the CUP analyses, an individual study [237] and nine non-overlapping studies from the pooled analysis [227], as there were not sufficient data.

About half the studies did not adjust for BMI or alcohol intake.

No analysis for postmenopausal breast cancer and waist–hip ratio was conducted in the 2005 SLR. In dose-response meta-analyses for the CUP in 2008, no significant association was observed per 0.1 unit for five studies adjusted for BMI (RR 1.03 (95% CI 0.95–1.12)) and a borderline significant positive association was observed for 11 studies not adjusted for BMI (RR 1.09 (95% CI 1.00–1.19)).

Published pooled analyses and meta-analyses

Two published pooled analyses on postmenopausal breast cancer [145, 227] were identified in the CUP Breast SLR 2017. The most recent pooled analysis [145] showed a significant positive association for the highest versus the lowest categories of waist–hip ratio and was included in the CUP dose-response meta-analysis. The other pooled analysis [227] reported no significant association per 1 SD and was not included in the CUP meta-analysis as it reported insufficient data. Results from the CUP and the published pooled analysis are presented in **Table 21**.

Table 21: Summary of CUP 2017 meta-analysis and published pooled analysis[1] of postmenopausal breast cancer – waist–hip ratio

Analysis	Increment	RR (95% CI)	I^2	No. Studies	No. Cases
CUP Breast SLR 2017	Per 0.1 unit	1.10 (1.05–1.16)	60%	18	15,643
ANZDCC [227][2]	Per 1 SD	1.06 (0.95–1.07)	-	10	1,323

[1] Pooled analysis not included in the CUP meta-analysis.
[2] Adjusted for smoking status, education, cohort, age as timescale in model.

Mechanisms

*Note: This is adapted from Chapter 2 and Section 6.1 of the Second Expert Report. An updated review of mechanisms for this exposure will form part of a larger review of mechanisms (see **Section 6.1** on page 18 in this report).*

A challenge for understanding mechanisms of action for various measures of body fatness and breast cancer risk is the apparent protective impact for premenopausal breast cancer and enhancement of risk for postmenopausal breast cancer. Although much remains to be elucidated, this finding may imply fundamental differences in the aetiology, confounded by complex interactions between diet, physical activity and genetics.

There is no single well-established mechanism through which body fatness may prevent premenopausal breast cancer. One possible mechanism is that the increased adipose tissue–derived oestrogen concentrations or other endocrine factors in overweight children and adolescents could induce changes in the breast tissue that reduces susceptibility to carcinogenesis [238]. For example, anovulation and abnormal hormone profiles are associated with obesity [158]. It is also critical to consider that attained adult height is a risk factor for premenopausal breast cancer (see **Section 7.11** on pages 80–84 in this report), a process that is in part genetic but strongly impacted by childhood and adolescent nutrition as well as physical activity.

Various measures of body fatness, including weight, BMI and waist circumference, are associated with increased postmenopausal breast cancer risk. An imbalance between energy intake and expenditure, leading to excess body fatness, is a complex and diverse process at the interface between dietary composition and pattern, appetite, and metabolism and energy expenditure from physical activity. These processes have a multitude of biological impacts on the host that may alter the risk of breast cancer.

Body fatness directly affects concentrations of many circulating hormones such as insulin, insulin-like growth factors, oestrogens, multiple adipokines and growth factors, creating an environment that may encourage breast carcinogenesis [239]. Insulin and leptin are elevated in obese people and can promote the growth of cancer cells.

In addition, insulin resistance is increased, in particular by abdominal fatness, and the pancreas compensates by increasing insulin production. Sex steroid hormones, including oestrogens, androgens and progesterone, are likely to play a role in obesity and cancer. Indeed, after the menopause, adipose tissue is the major source of endogenous oestrogen.

In recent years, studies have implicated obesity as associated with a low-grade chronic inflammatory state. Obese adipose tissue is characterised by infiltration of immune competent cells and may activate both local and systemic inflammatory pathways. These may be particularly relevant to the breast, where adipose tissue and the breast epithelium are in intimate association. Adipocytes (fat cells) can produce pro-inflammatory factors, and obese individuals have elevated concentrations of circulating cytokines such as tumour necrosis factor (TNF)-alpha, interleukin (IL)-6 and C-reactive protein, compared with lean people, as well as of leptin, which also appears to have pro-inflammatory activity. The activation of inflammatory cascades is one process that may predispose to carcinogenesis [240].

CUP Panel's conclusions:

For premenopausal breast cancer, the evidence for BMI was consistent and the dose response meta-analysis showed a significant decreased risk with increasing BMI. No effect was observed for BMI and premenopausal breast cancer mortality. Four pooled analyses identified by the CUP on BMI were included in the dose-response meta-analysis. No significant associations were observed for waist circumference and waist–hip ratio, although significant positive associations were observed after adjusting for BMI. There is evidence of plausible mechanisms operating in humans. Although overall the evidence for body fatness indicates a decreased risk of premenopausal breast cancer, the Panel notes that breast cancer diagnosed after the menopause is much more common and that the decreased risk of premenopausal breast cancer would be outweighed by an increased risk of postmenopausal breast cancer.

The CUP Panel concluded the following:

Greater body fatness in women before the menopause (marked by BMI, waist circumference and waist–hip ratio) probably protects against premenopausal breast cancer.

For postmenopausal breast cancer, the evidence for BMI was consistent and the dose response meta-analyses showed a significant increased risk, with increasing BMI for studies on both incidence and mortality. Stratification by geographical location showed significant positive associations with BMI in all groups, with a stronger effect observed in Asian studies. Significant positive associations were limited to hormone therapy never users, and never/former users. BMI was also significantly positively associated with ER+ or ER+PR+ breast cancer and PR+ breast cancer. Results from nine published pooled analyses overall supported the CUP finding, and five were included in the CUP dose-

response meta-analyses. Most of the other published meta-analyses also supported the CUP finding, reporting significant positive associations for BMI in high versus low comparisons and/or continuous estimates. The evidence for waist circumference and waist–hip ratio was also generally consistent, with dose-response meta-analyses showing significant positive associations, and these associations were generally supported by other published pooled analyses and meta-analyses. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded the following:

Greater body fatness throughout adulthood (marked by BMI, waist circumference and waist–hip ratio) is a convincing cause of postmenopausal breast cancer.

7.10 Adult weight gain

(Also see CUP Breast SLR 2017: Section 8.1.6)

Premenopausal breast cancer

For premenopausal breast cancer, no significant association was observed for weight gain in adults (RR per 5 kg (RR 0.99 (95% CI 0.96–1.03), I^2 = 13% for five studies) (see CUP Breast SLR 2017 Figure 580). Hence no further information is provided here.

Postmenopausal breast cancer

The CUP identified 16 new or updated studies (19 publications) [93, 139, 140, 143, 144, 147, 149–153, 171, 179, 198, 226, 241–244], giving a total of 22 studies (34 publications) reviewing the evidence for adult weight gain and postmenopausal breast cancer (for a full list of references, see CUP Breast SLR 2017 Tables 563 and 564).

Of 19 studies (22 estimates) reporting on postmenopausal breast cancer, most showed positive associations when comparing the highest and the lowest categories of adult weight gain; nine of the 22 estimates were significant. Two of the 19 studies reported a non-significant inverse association (see CUP Breast SLR 2017 Figure 586).

Fifteen studies were included in the dose-response meta-analysis for postmenopausal breast cancer (*n* = 16,600 cases), which showed a statistically significant 6 per cent increased risk per 5 kilograms (RR 1.06 (95% CI 1.05–1.08); see **Figure 18**, CUP Breast SLR 2017 Figure 587). Moderate heterogeneity was observed (I^2 = 38%). A non-linear dose-response analysis showed evidence of non-linearity (p = 0.04), although postmenopausal breast cancer risk appeared to increase linearly with increasing weight gain (see **Figure 19**, CUP Breast SLR 2017 Figure 595 and Table 565).

Figure 18: Dose-response meta-analysis of adult weight gain and postmenopausal breast cancer, per 5 kg

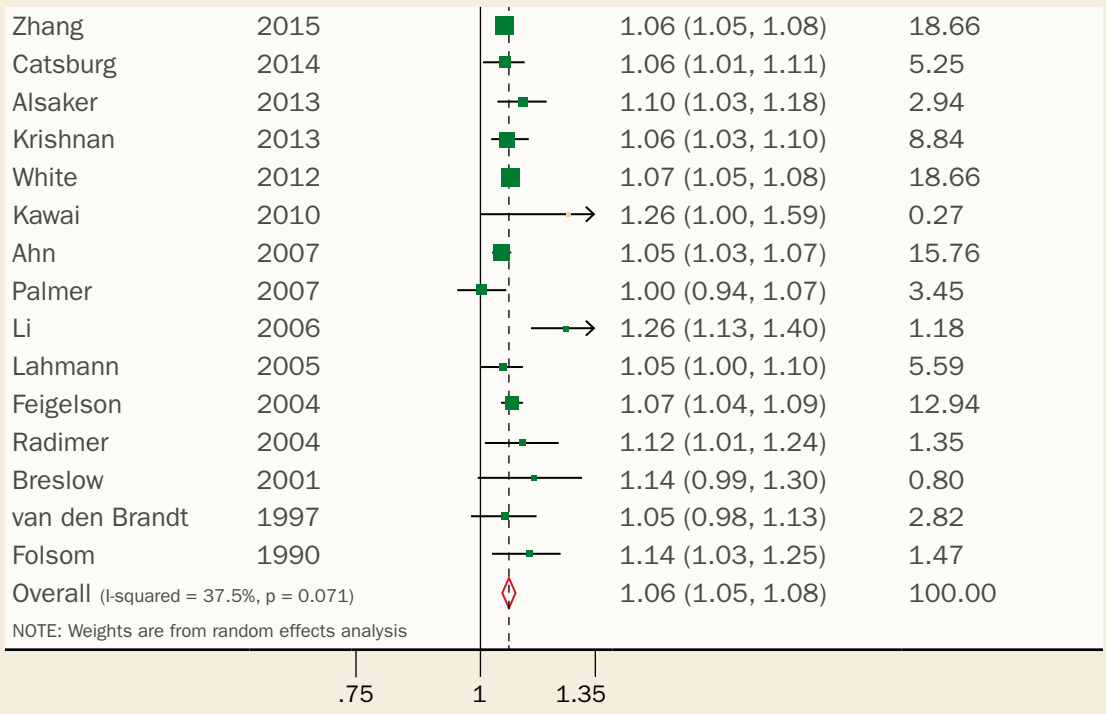
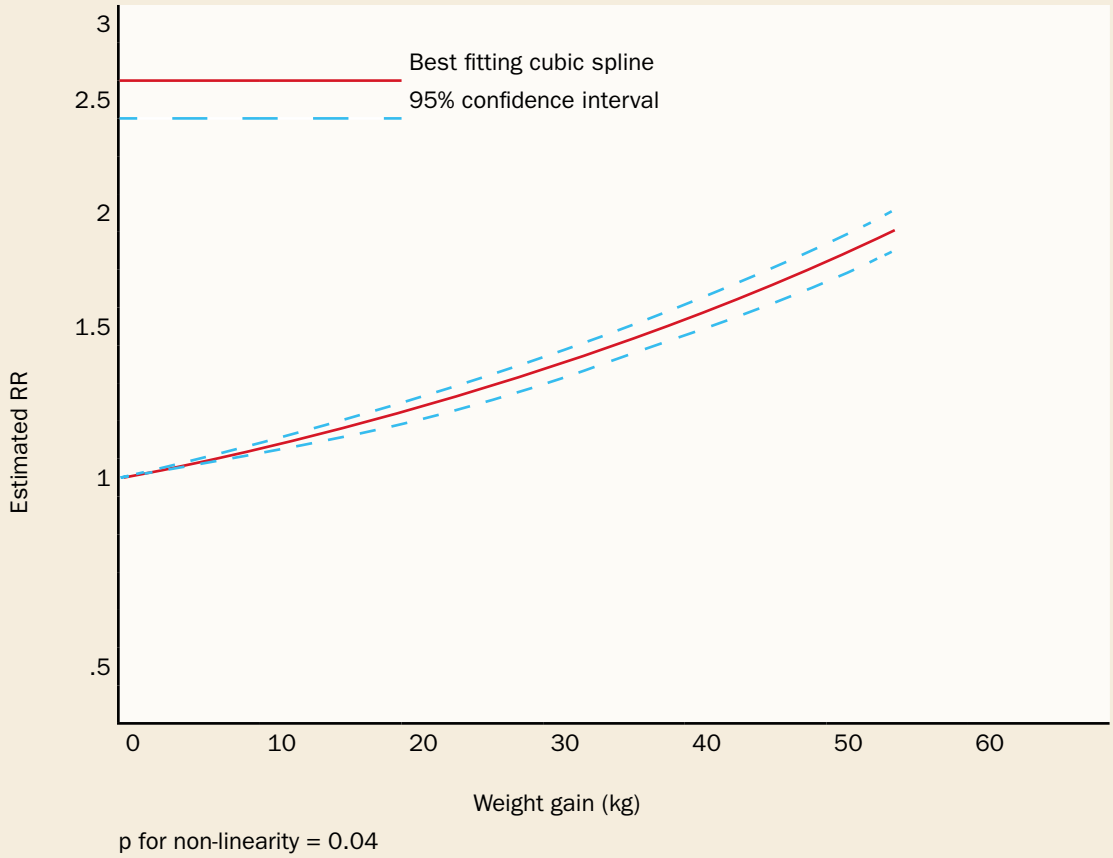


Figure 19: Non-linear dose-response meta-analysis of weight gain and postmenopausal breast cancer

Non-linear relation between weight gain and postmenopausal breast cancer



Dose-response meta-analysis for postmenopausal breast cancer by geographical location showed a statistically significant increased risk in North American and European studies, and a stronger association in Asian studies (see **Table 22** and CUP Breast SLR 2017 Figure 589). When stratified by joint hormone receptor status a significant positive association was observed for ER+PR+ breast cancer, but not ER+PR– or ER–PR– breast cancers in postmenopausal women. The significant association also remained in never users of hormone therapy use and never/former users (see **Table 22**). The significant positive association also remained in studies adjusted for age, alcohol intake and reproductive factors (RR 1.08 (95% CI 1.03–1.13)) (result not shown in table).

Table 22: Summary of CUP 2017 stratified dose-response meta-analyses of postmenopausal breast cancer – adult weight gain

Analysis	Increment	RR (95% CI)	I^2	No. Studies
GEOGRAPHICAL LOCATION				
Europe	Per 5 kg	1.06 (1.03–1.10)	0%	3
North America	Per 5 kg	1.06 (1.05–1.07)	19%	9
Asia	Per 5 kg	1.26 (1.14–1.39)	0%	2
HORMONE RECEPTOR STATUS				
ER+PR+	Per 5 kg	1.13 (1.04–1.22)	91%	5
ER+PR–	Per 5 kg	1.00 (0.95–1.04)	0%	3
ER–PR–	Per 5 kg	1.02 (0.98–1.06)	4%	5
HORMONE THERAPY USE				
Current	Per 5 kg	1.00 (0.98–1.03)	19%	3
Ever	Per 5 kg	1.08 (1.00–1.16)	44%	3
Never	Per 5 kg	1.06 (1.03–1.09)	0%	4
Never/former	Per 5 kg	1.09 (1.07–1.12)	37%	3

One study [93] was not included in any of the CUP analyses because it did not report sufficient data.

Most studies adjusted for major risk factors.

The CUP findings are similar to the dose-response meta-analysis in the 2005 SLR, which also reported a significant increased risk of postmenopausal breast cancer (RR 1.03 (95% CI 1.02–1.04) per 5 kg for four studies) with moderate heterogeneity observed.

Published pooled analyses and meta-analyses

Two published meta-analyses on adult weight gain and postmenopausal breast cancer [245, 246] were identified in the CUP Breast SLR 2017. The most recent meta-analysis [245] reported significant positive associations for non-users and low users of hormone therapy, and no association for users of hormone therapy. The other published meta-analysis [246] reported significant positive associations for joint hormone receptor types ER+PR+ and ER–PR– postmenopausal breast cancers (not shown in table). Results from the CUP and the published meta-analyses are presented in **Table 23**.

Table 23: Summary of CUP 2017 meta-analysis and published meta-analysis[1] of postmenopausal breast cancer – adult weight gain

Analysis	Increment/ Contrast	RR (95% CI)	I^2	No. Studies	No. Cases
CUP Breast SLR 2017	Per 5 kg	1.06 (1.05–1.08)	38%	15	16,600
Keum 2015 [245]	No or low hormone therapy users: Per 5 kg Highest vs. lowest	 1.11 (1.08–1.13) 1.75 (1.54–2.00)	 22% 0%	7	4,750
	No use of hormone therapy: Per 5 kg Highest vs. lowest	 1.11 (1.08–1.13) 1.83 (1.58–2.13)	 39% 0%	5	
	Hormone therapy users: Per 5 kg Highest vs. lowest	 1.01 (0.99–1.02) 1.14 (1.00–1.30)	 0% 0%	4	

[1] Vrieling, 2010 [246] not included in the table as it included mainly case-control studies.
Note: All cohort studies were included in the CUP 2017 analyses.

Mechanisms

*Note: In the future, a full review of mechanisms for this exposure will form part of a larger review of mechanisms (see **Section 6.1** on page 18 in this report).*

Information on mechanisms for body fatness can be found in **Section 7.9** on pages 73–74 of this report.

CUP Panel's conclusions:

For premenopausal breast cancer, the evidence for an association was considered to be limited, and no conclusion was possible.

For postmenopausal breast cancer, the evidence was generally consistent and the dose response meta-analysis showed a significant increased risk with increasing weight gain in adulthood. Moderate heterogeneity was observed. Further analysis showed evidence of non-linearity, although the risk appeared to increase linearly with increasing weight gain. The significant association remained in never users of hormone therapy and never/former users, and ER+PR+ postmenopausal breast cancer. The significant association also remained when stratified by geographical location and when adjusted for age, alcohol and reproductive factors. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded the following:

Greater weight gain in adulthood is a convincing cause of postmenopausal breast cancer.

7.11 Adult attained height

(Also see CUP Breast SLR 2017: Section 8.3.1)

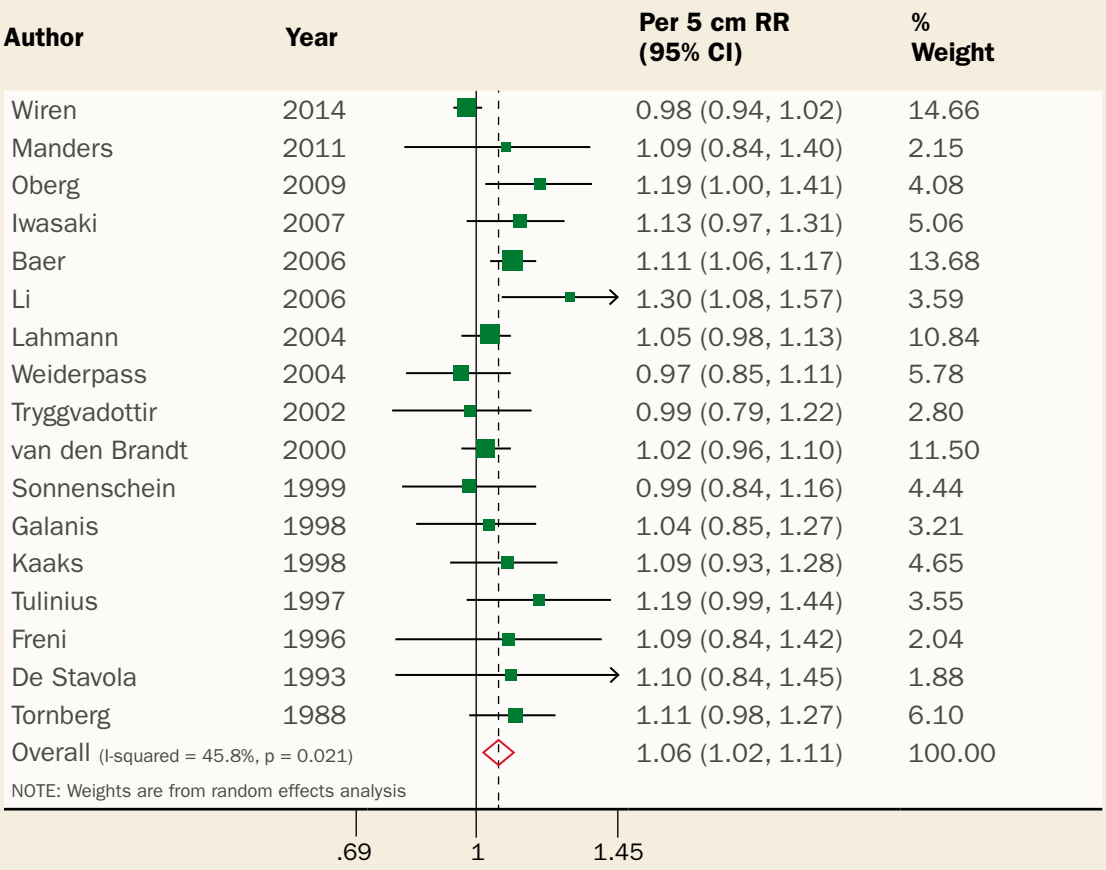
Premenopausal breast cancer

The CUP identified 15 new or updated studies (12 publications) [139, 143, 161, 165, 175, 177, 247–252] giving a total of 29 studies (33 publications) reviewing the evidence for adult attained height and premenopausal breast cancer (for a full list of references, see CUP Breast SLR 2017 Tables 603 and 604).

Of 20 studies reporting on premenopausal breast cancer, most showed positive associations when comparing the highest and the lowest categories of adult attained height, four of which were significant. One study reported no effect (RR = 1.00) and three studies reported a non-significant inverse association (see CUP Breast SLR 2017 Figure 635).

Twenty-six studies (including two pooled analyses) were included in the dose-response meta-analysis for premenopausal breast cancer (*n* = 6,479 cases), which showed a statistically significant 6 per cent increased risk per 5 centimetres (RR 1.06 (95% CI 1.02–1.11); see **Figure 20**, CUP Breast SLR 2017 Figure 636). Moderate heterogeneity was observed (I^2 = 46%).

Figure 20: Dose-response meta-analysis of adult attained height and premenopausal breast cancer, per 5 centimetres



Dose-response meta-analyses for premenopausal breast cancer by geographical location showed a statistically significant increased risk in North American and Asian studies (see **Table 24** and CUP Breast SLR 2017 Figure 638). The significant association also remained in studies adjusted for age, alcohol intake and reproductive factors (RR 1.07 (95% CI 1.03–1.12)).

Table 24: Summary of CUP 2017 stratified dose-response meta-analyses of premenopausal breast cancer – adult attained height

Analysis	Increment	RR (95% CI)	I^2	No. Studies
GEOGRAPHICAL LOCATION				
Europe	Per 5 cm	1.04 (0.99–1.09)	27%	17
North America	Per 5 cm	1.08 (1.03–1.12)	0%	6
Asia	Per 5 cm	1.20 (1.04–1.37)	26%	3

Two studies [177, 253] were not included in any of the CUP analyses because they did not report sufficient data or reported on subtypes of breast cancer.

Most studies did not simultaneously adjust for age, alcohol intake and reproductive factors.

The CUP findings are similar to the dose-response meta-analysis in the 2005 SLR, which also reported a significant increased risk of premenopausal breast cancer for adult attained height (RR 1.09 (95% CI 1.05–1.14) per 5 cm for 11 studies), with low heterogeneity observed.

Published pooled analyses and meta-analyses

Two published pooled analyses were identified on adult attained height and premenopausal breast cancer [183, 252], and both were included in the CUP dose-response meta-analysis. Neither reported a significant association (per 5 cm), with one in the direction of a positive association [183] and the other in the direction of an inverse association [252]. One other published meta-analysis of cohort and case-control studies was identified in the CUP SLR 2017 [188], and this reported a significant positive association for premenopausal breast cancer per 10-centimetre increase in height.

Postmenopausal breast cancer

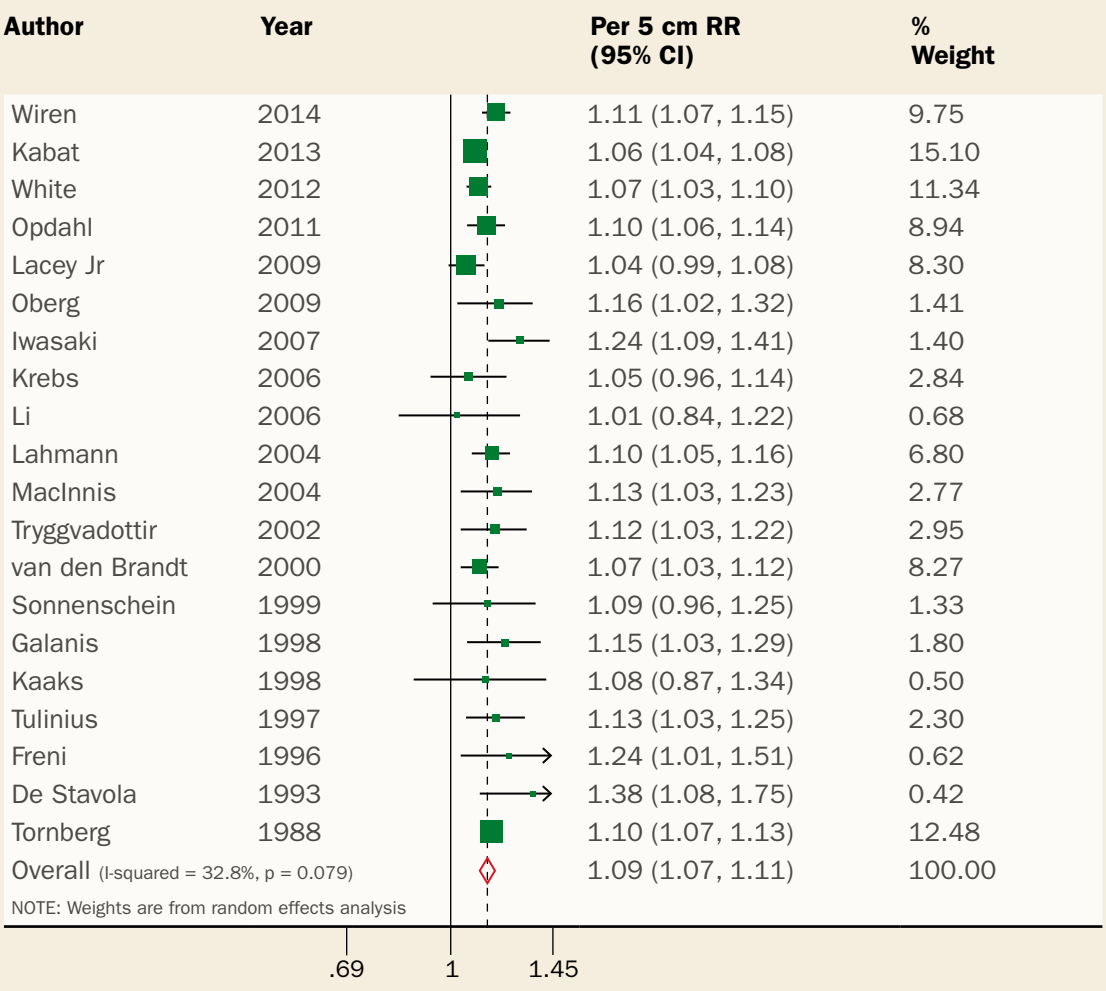
The CUP identified 22 new or updated studies (24 publications) [92, 139, 143, 150, 151, 161, 165, 175, 177, 196, 198, 205, 208, 216, 217, 219, 223, 248–252, 254, 255], giving a total of 41 studies (57 publications) reviewing the evidence for adult attained height and postmenopausal breast cancer (for a full list of references, see CUP Breast SLR 2017 Tables 607 and 608).

Of 20 estimates from 21 studies reporting on postmenopausal breast cancer, most showed positive associations when comparing the highest and the lowest categories of adult attained height, eight of which were significant and three of which were borderline

significant. A pooled analysis [183] also reported a non-significant positive association, and one other study reported a non-significant inverse association (see CUP Breast SLR 2017 Figure 641).

Thirty-three studies (including two pooled analyses) were included in the dose-response meta-analysis for postmenopausal breast cancer (*n* = 24,975 cases), which showed a statistically significant 9 per cent increased risk per 5 centimetres (RR 1.09 (95% CI 1.07–1.11); see **Figure 21**, CUP Breast SLR 2017 Figure 642). Moderate heterogeneity was observed (I^2 = 33%). In a dose-response meta-analysis of seven studies on postmenopausal breast cancer mortality (*n* = 3,181 cases), a statistically significant 8 per cent increased risk per 5-centimetre increase in height was observed (RR 1.08 (95% CI 1.05–1.11), I^2 = 0%; see CUP Breast SLR 2017 Figure 646).

Figure 21: Dose-response meta-analysis of adult attained height and postmenopausal breast cancer, per 5cm



Dose-response meta-analyses for postmenopausal breast cancer by geographical location showed a statistically significant increased risk in North American and European studies (see **Table 25** and CUP Breast SLR 2017 Figure 644). The significant positive association remained in studies adjusted for age, alcohol intake and reproductive factors (RR 1.08 (95% CI 1.06–1.10)).

Table 25: Summary of CUP 2017 stratified dose-response meta-analyses of postmenopausal breast cancer – adult attained height

Analysis	Increment	RR (95% CI)	I^2	No. Studies
GEOGRAPHICAL LOCATION				
Europe	Per 5 cm	1.10 (1.08–1.12)	5%	18
North America	Per 5 cm	1.06 (1.04–1.08)	0%	11
Asia	Per 5 cm	1.13 (0.93–1.38)	68%	3

Five studies were not included in any of the CUP analyses [92, 105, 150, 177, 253].

Fewer than half of the studies simultaneously adjusted for age, alcohol intake and reproductive factors.

The CUP findings are similar to the dose-response meta-analysis in the 2005 SLR, which also reported a significant increased risk of postmenopausal breast cancer for adult attained height (RR 1.11 (95% CI 1.09–1.13) per 5 cm for 15 studies) with no heterogeneity observed.

Published pooled analyses and meta-analyses

Two published pooled analyses were identified on adult attained height and postmenopausal breast cancer [183, 252], and both were included in the CUP dose-response meta-analysis. Both pooled analyses reported an overall significant positive association for height (per 5 cm), and one [252] also reported a borderline significant positive association for height and postmenopausal breast cancer mortality.

Mechanisms

*Note: This section is adapted from Chapter 2 and Section 6.2 of the Second Expert Report. An updated review of mechanisms for this exposure will form part of a larger review of mechanisms (see **Section 6.1** on page 18 in this report).*

Adult height is related to inheritance as well as the rate of growth during fetal development and childhood [256, 257]. Clearly, health and nutrition status in childhood affect the age of sexual maturity, a known risk factor for breast cancer. Growth and breast development are orchestrated by a vast array of hormonal and growth factor signalling pathways that appear to influence the risk of breast carcinogenesis. Many of these mechanisms, such as early-life nutrition affecting body composition, altered circulating and free hormone profiles, can modulate the rate of tissue growth and sexual maturation. It is therefore plausible that nutritional factors that affect height could also

influence cancer risk. Specific tissues in taller people are exposed to higher levels of insulin, pituitary-derived growth hormone and IGFs. Therefore, adult attained height may serve as a marker of an aggregated fetal and childhood experience and is clearly also a surrogate for important nutritional exposures. These affect several hormonal and metabolic axes, which may influence breast cancer risk.

CUP Panel's conclusions:

For premenopausal breast cancer, the evidence was consistent and the dose-response meta-analysis showed a significant increased risk with increasing height in adulthood. The significant association also remained when stratified by geographical location, except for European countries, and also when adjusted for age, alcohol and reproductive factors. Two published pooled analyses were identified, both showing no significant association, and were included in the CUP dose-response meta-analysis. The CUP finding was similar to the 2005 SLR but included more than double the number of studies. There is also robust evidence for mechanisms operating in humans.

The CUP Panel concluded the following:

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

For postmenopausal breast cancer, the evidence was consistent and the dose-response meta-analyses showed a significant increased risk with increasing height in adulthood for both studies on incidence and mortality. The significant association also remained when stratified by geographical location, except for Asian studies, and also when adjusted for age, alcohol and reproductive factors. Two published pooled analyses also showing significant positive associations were identified and included in the CUP dose-response meta-analysis. The finding was similar to that of the 2005 SLR but included more than double the number of studies. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded the following:

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

7.12 Birthweight

(Also see CUP Breast SLR 2017: Section 8.4.1)

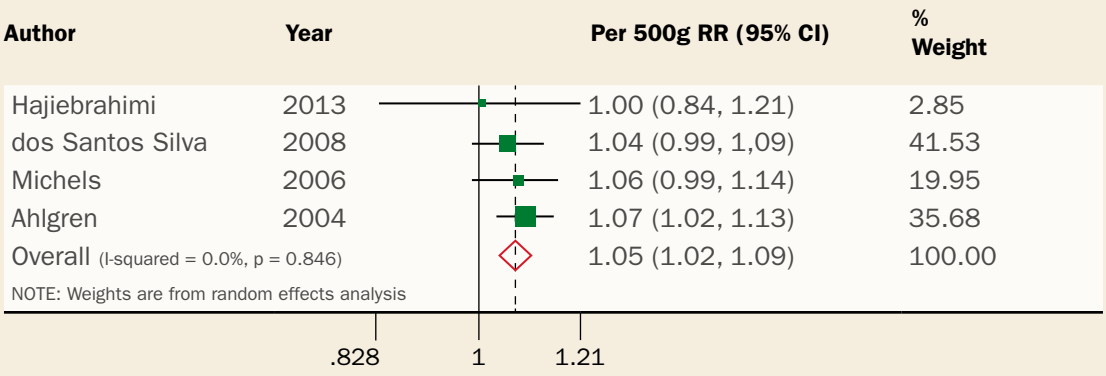
Premenopausal breast cancer

The CUP identified 15 new or updated studies (four publications) [248, 258–260], giving a total of 25 studies (12 publications) reviewing the evidence for birthweight and premenopausal breast cancer (for a full list of references, see CUP Breast SLR 2017 Tables 618 and 619). This included a study with pooled data from premenopausal women in 13 studies [259] including eight cohort studies and five case-control studies (results by study type were not available).

Two studies reporting on premenopausal breast cancer showed non-significant positive associations when comparing the highest and the lowest categories of birthweight. A pooled analysis [259] also reported non-significant positive associations apart from studies that used parental recalls, where a non-significant inverse association was observed (see CUP Breast SLR 2017 Figure 654).

Sixteen studies (including one pooled analysis) were included in the dose-response meta-analysis for premenopausal breast cancer (n = >3,135 cases), which showed a statistically significant 5 per cent increased risk per 500 grams of birthweight (RR 1.05 (95% CI 1.02–1.09); see **Figure 22**, CUP Breast SLR 2017 Figure 655). No heterogeneity was observed (I^2 = 0%).

Figure 22: Dose-response meta-analysis of birthweight and premenopausal breast cancer, per 500 grams



One study was not included in any of the CUP analyses because the paper included another study that overlapped with the pooled analysis [261].

Not all studies adjusted for age, alcohol intake, reproductive factors and adult BMI.

The CUP findings are similar to the dose-response meta-analysis in the 2005 SLR, which also reported a significant increased risk of premenopausal breast cancer for birthweight (RR 1.08 (95% CI 1.04–1.13) per 1 kg for four studies) with high heterogeneity observed.

Published pooled analyses and meta-analyses

One published pooled analysis was identified on birthweight and premenopausal breast cancer [259], reporting no significant association overall, and this was included in the CUP dose-response meta-analysis. One other published meta-analysis of cohort and case-control studies was identified in the CUP SLR 2017 [262], and this reported no significant association for premenopausal breast cancer when comparing the highest versus the lowest categories of birthweight.

Postmenopausal breast cancer

For postmenopausal breast cancer, no effect was observed for birthweight (RR per 500 grams 1.00 (95% CI 0.98–1.02), I^2 = 0% for 14 studies) (see CUP Breast SLR 2017 Figure 658). Hence no further information is provided.

Mechanisms

Note: This is adapted from Chapter 2 and Section 6.2.1.1 of the Second Expert Report. An updated review of mechanisms for this exposure will form part of a larger review of mechanisms (see ***Section 6.1*** *on page 18 in this report).*

Birthweight is dependent upon genetic determinants, as well as factors affecting maternal health and nutrition. There are many hypothesised mechanisms, such as long-term programming of hormonal systems, through which birthweight could plausibly increase cancer risk. Greater birthweight raises circulating maternal oestrogen levels and may increase insulin-like growth factor (IGF)-1 activity; low birthweight raises fetal and maternal levels of IGF-1 binding protein. The action of both oestrogens and IGF-1 are thought to be important in fetal growth and mammary gland development and play a central, synergistic role in the initiation and promotion of breast cancer [263]. Yet, how these hormonal environments affect fetal breast development and the risk of cancer remains uncertain. Animal experiments also provide evidence that exposure to oestrogens and other variables during fetal and early postnatal development affect the risk of mammary cancers [264].

CUP Panel's conclusion:

For premenopausal breast cancer, the evidence was generally consistent and the dose response meta-analysis showed a significant increased risk with increasing birthweight. No heterogeneity was observed. One published pooled analysis reporting no significant association was identified and included in the CUP dose-response meta-analysis. One other published meta-analysis reported no significant association for premenopausal breast cancer. There is robust evidence for mechanisms operating in humans.

For postmenopausal breast cancer, the evidence for an association was considered to be limited, and no conclusion was possible.

The CUP Panel concluded the following:

The factors that lead to greater birthweight, or its consequences, are probably a cause of premenopausal breast cancer.

7.13 Lactation

(Also see CUP Breast SLR 2017: Section 1.6.1)

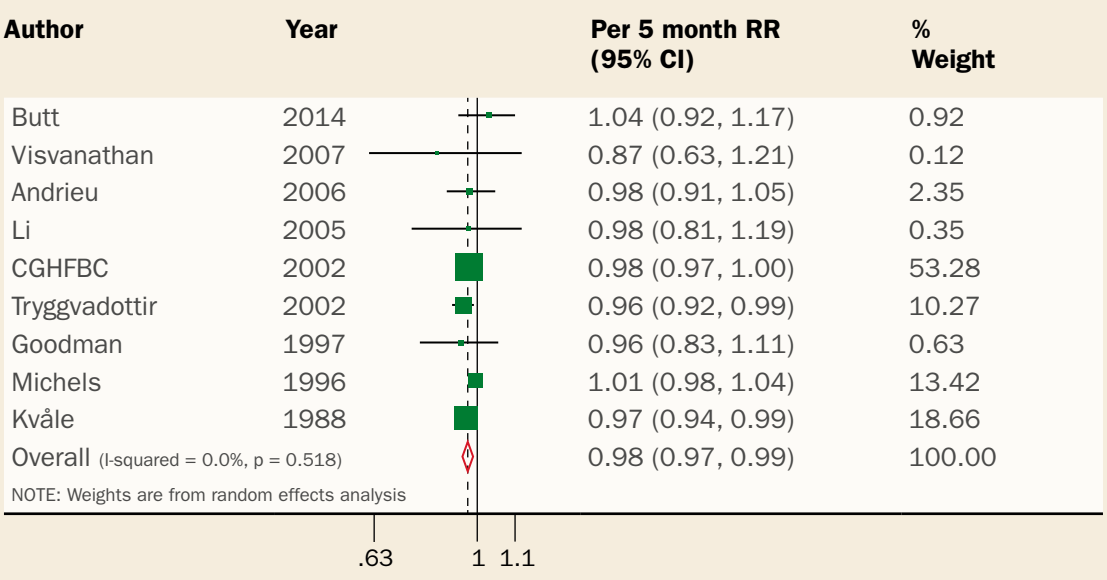
Breast cancer (unspecified)

The CUP identified nine new or updated studies (nine publications) [62, 265–272], giving a total of 18 studies (17 publications) reviewing the evidence for lactation and breast cancer (unspecified) (for a full list of references, see CUP Breast SLR 2017 Tables 15 and 16).

Of 11 studies reporting on breast cancer (unspecified), almost half showed inverse associations when comparing the highest and lowest categories of lactation, one of which was significant and one of which was borderline significant. The remaining studies showed non-significant positive associations apart from one study which showed no effect (RR = 1.00). A pooled analysis of five studies reported a borderline significant inverse association (see CUP Breast SLR 2017 Figure 18).

Thirteen studies (including one pooled analysis) were included in the dose-response meta-analysis for breast cancer (unspecified) (*n* = 11,610 cases), which showed a statistically significant 2 per cent decreased risk per five-month increase of breastfeeding duration (RR 0.98 (95% CI 0.97–0.99); see **Figure 23**, CUP Breast SLR 2017 Figure 19). No heterogeneity was observed (I^2 = 0%).

Figure 23: Dose-response meta-analysis of lactation and breast cancer (unspecified), per 5-month increase in breastfeeding duration



A separate dose-response meta-analysis of four studies reporting on premenopausal breast cancer (*n* = 1,321) reported no significant association for a five-month increase in breastfeeding duration (RR 0.95 (95% CI 0.89–1.01)) with high heterogeneity observed (I^2 = 63%) (see CUP Breast SLR 2017 Figure 22). Another dose-response meta-analysis of five studies reporting on postmenopausal breast cancer (*n* = 7,359) showed no effect (RR 1.00 (95% CI 0.99–1.02)) with low heterogeneity observed (I^2 = 5%) (see CUP Breast SLR 2017 Figure 25).

For breast cancer (unspecified), one study [268] was not included in any of the CUP analyses because it reported only on tumour receptor status.

Only one study did not adjust for main risk factors [62].

The CUP finding is stronger than that reported in the 2005 SLR, which reported a borderline significant decreased risk of breast cancer (unspecified) per five months duration of breastfeeding (RR 0.98 (95% CI 0.97–1.00) for four studies) with no heterogeneity observed. The CUP Breast SLR 2017 included more than three times the number of studies and cases breast cancer than the 2005 SLR.

Published pooled analyses and meta-analyses

One published pooled analysis [273] and two published meta-analyses [274, 275] on lactation and breast cancer risk were identified in the CUP Breast SLR 2017. The published pooled analysis, which was included in the CUP dose-response meta-analysis, reported a significant inverse association per six months of life, and a 4.6 per cent risk reduction per 12-month increment [273]. Results from the CUP and published meta-analyses are presented in **Table 26**.

Table 26: Summary of CUP 2017 meta-analysis, published pooled analysis[1] and meta-analyses of breast cancer (unspecified) – lactation

Analysis	Increment/ Contrast	RR (95% CI)	I^2	No. Studies	No. Cases
CUP Breast SLR 2017	Per 5-month duration	0.98 (0.97–0.99)	0%	13	11,610
Published meta-analyses					
Islami, 2015 [275]	Ever vs. never ER–PR– Triple negative ER+PR+ ER+ and/or PR+	 0.84 (0.72–0.97) 0.73 (0.62–0.87) 1.00 (0.90–1.10) 0.97 (0.88–1.07)	 50% 0% 54% 78%	 7 3 4 7	>1,777
Zhou, 2015 [274]	Highest vs. lowest	1.00 (0.91–1.08)	0%	3	3,849

[1] Pooled analysis not included in the CUP meta-analysis.

Note: All cohort studies from Islami 2015 [275], and Zhou 2015 [274], were included in the CUP 2017 analyses.

Mechanisms

Note: This is adapted from Section 6.3 of the Second Expert Report. An updated review of mechanisms for this exposure will form part of a larger review of mechanisms (see ***Section 6.1*** *on page 18 in this report).*

The mechanisms through which lactation or breastfeeding may influence cancer risk are several. Lactation induces a unique hormonal pattern along with an associated period of amenorrhea and infertility. This decreases lifetime exposure to menstrual cycles and therefore alters hormone levels, particularly androgens, which can influence cancer risk (see box 2.4 in the Second Expert Report). Increased levels of sex steroids are strongly associated with risk of postmenopausal breast cancers [276]. Perhaps lactation also induces epigenetic changes that exert a lasting impact on risk of carcinogenesis. In addition, the strong exfoliation of breast tissue during the process of lactation, and the massive epithelial apoptosis at the end of lactation, could decrease risk by elimination of cells with potential DNA damage.

CUP Panel's conclusions:

The dose response meta-analysis showed a significant decreased risk with increasing duration of breastfeeding studies that included pre- and postmenopausal breast cancers, and no heterogeneity was observed. An inverse association, although not significant, was observed in the limited number of studies in premenopausal breast cancer, and no association was observed for postmenopausal breast cancers. One pooled analysis reporting a significant inverse association for breast cancer overall was included in the CUP dose-response meta-analysis. Two other published meta-analyses were identified, one of which reported significant inverse associations for ER–PR– and triple negative breast cancer. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded the following:

Lactation probably protects against breast cancer (unspecified).

7.14 Other

Other exposures were evaluated, but data were either of too low quality or too inconsistent, or the number of studies too few to allow conclusions to be reached. The list of exposures judged as 'limited – no conclusion' is summarised in the matrices on pages 8-9.

The evidence for total dietary fat, previously judged as 'limited – suggestive increases risk' for postmenopausal breast cancer in the Second Expert Report [1], was less consistent, and the Panel could not draw any conclusions from the updated evidence.

Evidence for the following exposures, previously judged as 'limited – no conclusion' in the Second Expert Report, remains unchanged after updating the analyses with new data

identified in the CUP Breast SLR 2017: dietary fibre, non-starchy vegetables (ER+ breast cancers), fruits, soy and soya products, red and processed meat, poultry, fish, coffee, tea, carbohydrate, glycaemic index, folate, vitamin D, isoflavones, dietary patterns, energy intake.

The following exposures, for which evidence also was previously too limited to draw conclusions in the Second Expert Report and not updated as part of the CUP, remain 'limited-no conclusion': cereal grains and their products, potatoes, pulses (legumes), eggs, fats and oils, vegetable fat, fatty acid composition, trans fatty acids, cholesterol, sugar (sucrose), other sugars, sugary foods and drinks, starch, protein, vitamin A, riboflavin, vitamin B6, vitamin B12, vitamin C, vitamin E, iron, selenium, dichlorodiphenyldichloroethylene, dichlorodiphenyltrichloroethane, dieldrin, hexachlorobenzene, hexachlorocyclohexane, trans-nonachlor, polychlorinated biphenyls, culturally defined diets, birth length, being breastfed.

In addition, evidence for the following exposures, for which no judgement was made in the Second Expert Report, is too limited to draw any conclusions: acrylamide, glycaemic load, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, calcium supplements, phytoestrogens, sedentary behaviour.

8. Comparison with the Second Expert Report

Breast cancer in women of unspecified menopausal age, premenopausal women and postmenopausal women were reviewed separately where possible, as in the 2007 Second Expert Report [1]. Evidence from additional cohort studies identified in the Continuous Update Project was generally consistent with that reviewed as part of the Second Expert Report, and much of the new evidence related to body fatness (including body fatness in young adulthood), adult weight gain, alcohol and vigorous physical activity. The increase in the amount and quality of the evidence enabled some exposures to be reviewed by hormone receptor status.

9. Conclusions

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

Premenopausal breast cancer

Convincing evidence

Adult attained height: Developmental factors leading to greater linear growth (marked by adult attained height) are a convincing cause of premenopausal breast cancer.

Probable evidence

Vigorous physical activity: Vigorous physical activity probably protects against premenopausal breast cancer.

Body fatness: Greater body fatness in women before the menopause (marked by BMI, waist circumference and waist–hip ratio) probably protects against premenopausal breast cancer.

Body fatness in young adulthood: Greater body fatness in young women (aged about 18 to 30 years) (marked by BMI) probably protects against premenopausal breast cancer.

Lactation: Lactation probably protects against breast cancer (unspecified).

Alcoholic drinks: Consumption of alcoholic drinks is probably a cause of premenopausal breast cancer.

Birthweight: The factors that lead to greater birthweight, or its consequences, are probably a cause of premenopausal breast cancer.

Limited – suggestive evidence

Non-starchy vegetables: The evidence suggesting that consumption of non-starchy vegetables decreases the risk of oestrogen-receptor-negative (ER–) breast cancer (unspecified) is limited.

Dairy products: The evidence suggesting that consumption of dairy products decreases the risk of premenopausal breast cancer is limited.

Foods containing carotenoids: The evidence suggesting that consumption of foods containing carotenoids decreases the risk of breast cancer (unspecified) is limited.

Diets high in calcium: The evidence suggesting that diets high in calcium decrease the risk of premenopausal breast cancer is limited.

Total physical activity: The evidence suggesting that being physically active decreases the risk of premenopausal breast cancer is limited.

Postmenopausal breast cancer

Convincing evidence

Alcoholic drinks: Consumption of alcoholic drinks is a convincing cause of postmenopausal breast cancer.

Body fatness: Greater body fatness throughout adulthood (marked by BMI, waist circumference and waist–hip ratio) is a convincing cause of postmenopausal breast cancer.

Adult weight gain: Greater weight gain in adulthood is a convincing cause of postmenopausal breast cancer.

Adult attained height: Developmental factors leading to greater linear growth (marked by adult attained height) are a convincing cause of postmenopausal breast cancer.

Probable evidence

Total (including vigorous) physical activity: Being physically active (including vigorous physical activity) probably protects against postmenopausal breast cancer.

Body fatness in young adulthood: Greater body fatness in young women (aged about 18 to 30 years) (marked by BMI) probably protects against postmenopausal breast cancer.

Lactation: Lactation probably protects against breast cancer (unspecified).

Limited – suggestive evidence

Non-starchy vegetables: The evidence suggesting that consumption of non-starchy vegetables decreases the risk of oestrogen-receptor-negative (ER–) breast cancer (unspecified) is limited.

Foods containing carotenoids: The evidence suggesting that consumption of foods containing carotenoids decreases the risk of breast cancer (unspecified) is limited.

Diets high in calcium: The evidence suggesting that diets high in calcium decrease the risk of postmenopausal breast cancer is limited.

For a full description of the definitions of, and criteria for, the terminology of ‘convincing’, ‘probable’, ‘limited – suggestive’, ‘limited – no conclusion’ and ‘substantial effect on risk unlikely’, see the Appendix on page 114. The CUP database is being continually updated for all cancers. The Cancer Prevention Recommendations will be reviewed in 2017 when the Panel has reviewed the conclusions for the other cancers.

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Abbreviations

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

Glossary

Adjustment

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

Androgen

Any masculinising sex hormone, such as testosterone.

Anthropometric measures

Measures of body dimensions.

Antioxidant

A molecule that inhibits the oxidation of other molecules. Oxidation is a chemical reaction involving the loss of electrons, which can produce free radicals. In turn, these radicals can start chain reactions, which can cause damage or death to cells (see free radicals).

Apoptosis

The death of cells which occurs as a normal and controlled part of the cell cycle.

Bias

In epidemiology, consistent deviation of an observed result from the true value in a particular direction (systematic error) due to factors pertaining to the observer or to study type or analysis (see selection bias).

Biomarkers

A naturally occurring molecule, gene, or characteristic by which a particular pathological or physiological process can be identified.

Body mass index (BMI)

Body weight expressed in kilograms divided by the square of height expressed in metres (BMI = kg/m^2). Provides an indirect measure of body fatness. Also known as Quetelet's Index.

Carcinogenesis

The initiation of cancer formation.

Carotenoids

Any of a class of mainly yellow, orange, or red fat-soluble pigments, including carotenoids, which give colour to plant parts such as ripe tomatoes.

Case-control study

An epidemiological study in which the participants are chosen based on their disease or condition (cases) or lack of it (controls), to test whether distant or recent history of an exposure such as smoking, genetic profile, alcohol consumption or dietary intake is associated with the risk of disease.

Cell differentiation

The process of development of cells to take on the structural and functional characteristics specific to a particular tissue. Also, the degree to which tumour cells have the structure or function of the tissue from which the tumour arose. Tumours can be described as well, moderately or poorly differentiated: well-differentiated tumours appear similar to the cells of the tissue in which they arose; poorly differentiated tumours do not. The degree of differentiation may have prognostic significance.

Cell proliferation

An increase in the number of cells as a result of increased cell division.

Chronic

Describing a condition or disease that is persistent or long lasting.

Cohort study

A study of a (usually large) group of people whose characteristics are recorded at recruitment (and sometimes later) and followed up for a period of time during which outcomes of interest are noted. Differences in the frequency of outcomes (such as disease) within the cohort are calculated in relation to different levels of exposure to factors of interest – for example, smoking, alcohol consumption, diet and exercise. Differences in the likelihood of a particular outcome are presented as the relative risk, comparing one level of exposure with another.

Confidence interval (CI)

A measure of the uncertainty in an estimate, usually reported as 95% confidence interval (CI), which is the range of values within which there is a 95% chance that the true value lies. For example, the effect of smoking on the relative risk of lung cancer may be expressed as 10 (95% CI 5–15). This means that the estimate of the relative risk was calculated as 10, and that there is a 95% chance that the true value lies between 5 and 15.

Confounder

A variable that is associated both with an exposure and a disease but is not in the causal pathway from the exposure to the disease. If not adjusted for within a specific epidemiological study, this factor may distort the apparent exposure–disease relationship. An example is that smoking is related both to coffee drinking and to risk of lung cancer, and thus unless accounted for (adjusted) in studies, might make coffee drinking appear falsely as a cause of lung cancer.

Cytokines

Cell-signalling molecules that aid cell-to-cell communication in immune responses and stimulate the movement of cells toward sites of inflammation, infection and trauma.

Deoxyribonucleic acid (DNA)

The double-stranded, helical molecular chain found within the nucleus of each cell, which carries the genetic information.

DNA methylation

A process by which methyl groups are added to DNA. DNA methylation is one of several epigenetic mechanisms that regulate gene expression.

Dose-response

A term derived from pharmacology that describes the degree to which an effect changes as the level of an exposure changes, for instance, intake of a drug or food (see Second Expert Report Box 3.2).

Effect modifier

Effect modification (or effect-measure modification) occurs when the effect of an exposure differs according to levels of another variable (the modifier).

Endogenous

Substances and processes that originate from within an organism, tissue or cell.

Exposure

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

Free radicals

An atom or group of atoms that have one or more unpaired electrons. A prominent feature of radicals is that they have high chemical reactivity, which explains their normal biological activities and how they inflict damage on cells. There are many types of radicals, but those of most importance in biological systems are derived from oxygen and known collectively as reactive oxygen species.

Heterogeneity

A measure of difference between the results of different studies addressing a similar question. In meta-analysis, the degree of heterogeneity may be calculated statistically using the I^2 test.

High-income countries

As defined by the World Bank, countries with a gross average annual national product of more than an agreed figure per head (in 2006 this was more than US$10,726). This term is more precise than, and used in preference to, ‘economically developed countries’.

Hormone

A substance secreted by specialised cells that affects the structure and/or function of cells or tissues in another part of the body.

Hormone receptor status

Hormone receptors are proteins found in and on breast or other cells that respond to circulating hormones and influence cell structure or function. A cancer is called oestrogen-receptor-positive (ER+) if it has receptors for oestrogen, and oestrogen-receptor-negative (ER–) if it does not have the receptors for oestrogen.

Hormone therapy

Treatment with oestrogens and progesterones with the aim of alleviating menopausal symptoms or osteoporosis. Also known as hormone replacement therapy.

Immune response

The production of antibodies or specialised cells in response to foreign proteins or other substances.

Incidence rates

The number of new cases of a condition appearing during a specified period of time expressed relative to the size of the population; for example, 60 new cases of breast cancer per 100,000 women per year.

Inflammation

The immunologic response of tissues to injury or infection. Inflammation is characterised by accumulation of white blood cells that produce several bioactive chemicals (cytokines), causing redness, pain, heat and swelling.

Insulin-like growth factor (IGF)

Polypeptides with high sequence similarity to insulin. IGFs are part of a complex system that cells use to communicate with their physiologic environment.

Interleukin-6

A cytokine involved in inflammation and infection responses and also in the regulation of metabolic, regenerative and neural processes.

Lactation

The production and secretion of milk by the mammary glands.

Lipid peroxidation

The oxidative degradation of lipids. It is the process in which free radicals ‘steal’ electrons from the lipids in cell membranes, resulting in cell damage.

Low-income countries

As defined by the World Bank, countries with a gross average annual national product of less than an agreed figure per head (in 2006, this was US$875). This term is more precise than, and used in preference to, ‘economically developing countries’.

Menarche

The start of menstruation.

Menopause

The cessation of menstruation.

Meta-analysis

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

Mutation

A permanent change of the nucleotide sequence of the genome (an organism's complete set of DNA).

Nested case-control study

A case-control study in which cases and controls are drawn from the population of a cohort study; often used for studies of prospectively collected information or biological samples.

Odds ratio

A measure of the risk of an outcome such as cancer, associated with an exposure of interest, used in case-control studies; approximately equivalent to relative risk.

Oestrogen

The principal female sex hormone, produced mainly by the ovaries during reproductive life, and also by adipose tissue.

p53

A protein central to regulation of cell growth. Mutations of the p53 gene are important causes of cancer.

Pathogenesis

The origin and development of disease. The mechanisms by which causal factors increase the risk of disease.

Polymorphisms

Common variations (in more than 1 per cent of the population) in the DNA sequence of a gene.

Pooled analysis

In epidemiology, a type of study in which original individual-level data from two or more original studies are obtained, combined and re-analysed.

Progesterone

Female sex hormone, produced mainly by the ovaries during reproductive life and by the placenta during pregnancy.

Prostaglandins

A group of physiologically active lipid compounds having diverse hormone-like effects in animals.

Randomised controlled trial (RCT)

A study in which a comparison is made between one intervention (often a treatment or prevention strategy) and another (control). Sometimes the control group receives an inactive agent (a placebo). Groups are randomised to one intervention or the other, so that any difference in outcome between the two groups can be ascribed with confidence to the intervention. Sometimes, neither investigators nor subjects know to which intervention they have been randomised; this is called 'double-blinding'.

Relative risk (RR)

The ratio of the rate of an outcome (e.g., disease (incidence) or death (mortality)) among people exposed to a factor, to the rate among the unexposed, usually used in cohort studies.

Selection bias

Bias arising from the procedures used to select study participants and from factors influencing participation.

Statistical significance

The probability that any observed result has or has not occurred by chance. Conventionally, a probability of less than 5 per cent ($p < 0.05$) that a study result has occurred by chance is considered 'statistically significant' (see confidence interval).

Systematic literature review (SLR)

A means of compiling and assessing published evidence that addresses a scientific question with a predefined protocol and transparent methods.

Waist–hip ratio (WHR)

A measure of body shape indicating central (abdominal) fat distribution.

References

1. World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. **wcrf.org/int/research-we-fund/continuous-update-project-cup/second-expert-report**. 2007.
2. Ferlay J, Soerjomataram I, Ervik M, *et al*. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11. 2015.
3. McPherson K, Steel CM and Dixon JM. ABC of breast diseases. Breast cancer epidemiology, risk factors and genetics. *BMJ* 2000; 321: 624–8.
4. Putti TC, El-Rehim DM, Rakha EA, *et al*. Estrogen receptor-negative breast carcinomas: a review of morphology and immunophenotypical analysis. *Mod Pathol* 2005; 18: 26–35.
5. International Agency for Research on Cancer. Combined Estrogen-Progestogen Contraceptives. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* 2012; 100A: 283–317.
6. Sainsbury JR, Anderson TJ and Morgan DA. ABC of breast diseases: breast cancer. *BMJ* 2000; 321: 745–50.
7. American Cancer Society. Cancer Facts & Figures 2014, American Cancer Society: Atlanta. 2014.
8. *Holland-Frei Cancer Medicine*. 6th ed. Ed. P.R. Kufe DW, Weichselbaum RR, Bast Jr RC, Gansler TS, Holland JF, Frei III E. Hamilton, Ontario: BC Decker. 2003.
9. Kong Y, Yang L, Tang H, *et al*. A nation-wide multicenter retrospective study of the epidemiological, pathological and clinical characteristics of breast cancer in situ in Chinese women in 1999–2008. *PLoS One* 2013; 8: e81055.
10. Lippman ME, Dickson RB, Gelmann EP, *et al*. Growth regulation of human breast carcinoma occurs through regulated growth factor secretion. *J Cell Biochem* 1987; 35: 1–16.
11. Murray PA, Barrett-Lee P, Travers M, *et al*. The prognostic significance of transforming growth factors in human breast cancer. *Br J Cancer* 1993; 67: 1408–12.
12. Pharoah PD, Day NE, Duffy S, *et al*. Family history and the risk of breast cancer: a systematic review and meta-analysis. *Int J Cancer* 1997; 71: 800–9.
13. Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. *Lancet* 2001; 358: 1389–99.
14. Kharazmi E, Chen T, Narod S, *et al*. Effect of multiplicity, laterality and age at onset of breast cancer on familial risk of breast cancer: a nationwide prospective cohort study. *Breast Cancer Res Treat* 2014; 144: 185–92.
15. International Agency for Research on Cancer. World Cancer Report 2008. Ed. Boyle P, Levin B. Lyon. 2008.
16. MacMahon B. General Motors Cancer Research Prizewinners Laureates Lectures. Charles S. Mott Prize. Reproduction and cancer of the breast. *Cancer* 1993; 71: 3185–8.
17. Berkey CS, Gardner JD, Frazier AL, *et al*. Relation of childhood diet and body size to menarche and adolescent growth in girls. *Am J Epidemiol* 2000; 152: 446–52.
18. Modan B, Chetrit A, Alfandary E, *et al*. Increased risk of breast cancer after low-dose irradiation. *Lancet* 1989; 1: 629–31.
19. Ronckers CM, Erdmann CA and Land CE. Radiation and breast cancer: a review of current evidence. *Breast Cancer Res* 2005; 7: 21–32.
20. Reeves GK, Beral V, Green J, *et al*. Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. *Lancet Oncol* 2006; 7: 910–8.
21. Fung TT, Hu FB, McCullough ML, *et al*. Diet quality is associated with the risk of estrogen receptor-negative breast cancer in postmenopausal women. *J Nutr* 2006; 136: 466–72.
22. Sonestedt E, Borgquist S, Ericson U, *et al*. Plant foods and oestrogen receptor alpha- and beta-defined breast cancer: observations from the Malmo Diet and Cancer cohort. *Carcinogenesis* 2008; 29: 2203–9a.
23. Trichopoulou A, Bamia C, Lagiou P, *et al*. Conformity to traditional Mediterranean diet and breast cancer risk in the Greek EPIC (European Prospective Investigation into Cancer and Nutrition) cohort. *Am J Clin Nutr* 2010; 92: 620–5.

24. George SM, Park Y, Leitzmann MF, *et al*. Fruit and vegetable intake and risk of cancer: a prospective cohort study. *Am J Clin Nutr* 2009; 89: 347–53a.
25. Jayalekshmi P, Varughese SC, Kalavathi S, *et al*. A nested case-control study of female breast cancer in Karunagappally cohort in Kerala, India. *Asian Pac J Cancer Prev* 2009; 10: 241–6.
26. Butler LM, Wu AH, Wang R, *et al*. A vegetable-fruit-soy dietary pattern protects against breast cancer among postmenopausal Singapore Chinese women. *Am J Clin Nutr* 2010; 91: 1013–9.
27. Brasky TM, Lampe JW, Potter JD, *et al*. Specialty supplements and breast cancer risk in the VITamins And Lifestyle (VITAL) Cohort. *Cancer Epidemiol Biomarkers Prev* 2010; 19: 1696–708.
28. Boggs DA, Palmer JR, Wise LA, *et al*. Fruit and vegetable intake in relation to risk of breast cancer in the Black Women's Health Study. *Am J Epidemiol* 2010; 172: 1268–79a.
29. Lof M, Sandin S, Lagiou P, *et al.* Fruit and vegetable intake and risk of cancer in the Swedish women's lifestyle and health cohort. *Cancer Causes Control* 2011; 22: 283–9.
30. Fung TT, Hu FB, Hankinson SE, *et al*. Low-carbohydrate diets, dietary approaches to stop hypertension-style diets and the risk of postmenopausal breast cancer. *Am J Epidemiol* 2011; 174: 652–60.
31. Masala G, Assedi M, Bendinelli B, *et al*. Fruit and vegetables consumption and breast cancer risk: the EPIC Italy study. *Breast Cancer Res Treat* 2012; 132: 1127–36.
32. Fung TT, Chiuve SE, Willett WC, *et al*. Intake of specific fruits and vegetables in relation to risk of estrogen receptor-negative breast cancer among postmenopausal women. *Breast Cancer Res Treat* 2013; 138: 925–30.
33. Suzuki R, Iwasaki M, Hara A, *et al.* Fruit and vegetable intake and breast cancer risk defined by estrogen and progesterone receptor status: the Japan Public Health CentER–based Prospective Study. *Cancer Causes Control* 2013; 24: 2117–28.
34. Buckland G, Travier N, Cottet V, *et al.* Adherence to the Mediterranean diet and risk of breast cancer in the European Prospective Investigation into Cancer and Nutrition cohort study. *Int J Cancer* 2013; 132: 2918–27.
35. Couto E, Sandin S, Lof M, *et al*. Mediterranean dietary pattern and risk of breast cancer. *PLoS One* 2013; 8: e55374.
36. Wie GA, Cho YA, Kang HH, *et al*. Red meat consumption is associated with an increased overall cancer risk: a prospective cohort study in Korea. *Br J Nutr* 2014; 112: 238–47.
37. Makarem N, Lin Y, Bandera EV, *et al*. Concordance with World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) guidelines for cancer prevention and obesity-related cancer risk in the Framingham Offspring cohort (1991–2008). *Cancer Causes Control* 2015; 26: 277–86.
38. Emaus MJ, Peeters PH, Bakker MF, *et al*. Vegetable and fruit consumption and the risk of hormone receptor-defined breast cancer in the EPIC cohort. *Am J Clin Nutr* 2016; 103: 168–77.
39. Frazier AL, Li L, Cho E, *et al*. Adolescent diet and risk of breast cancer. *Cancer Causes Control* 2004; 15: 73–82.
40. Smith-Warner SA, Spiegelman D, Yaun SS, *et al*. Intake of fruits and vegetables and risk of breast cancer: a pooled analysis of cohort studies. *JAMA* 2001; 285: 769–76a.
41. Jung S, Spiegelman D, Baglietto L, *et al*. Fruit and vegetable intake and risk of breast cancer by hormone receptor status. *J Natl Cancer Inst* 2013; 105: 219–36.
42. Aune D, Chan DS, Vieira AR, *et al*. Fruits, vegetables and breast cancer risk: a systematic review and meta-analysis of prospective studies. *Breast Cancer Res Treat* 2012; 134: 479–93.
43. Shibata A, Paganini-Hill A, Ross RK, *et al*. Intake of vegetables, fruits, beta-carotene, vitamin C and vitamin supplements and cancer incidence among the elderly: a prospective study. *Br J Cancer* 1992; 66: 673–9.
44. Zhang X, Spiegelman D, Baglietto L, *et al*. Carotenoid intakes and risk of breast cancer defined by estrogen receptor and progesterone receptor status: a pooled analysis of 18 prospective cohort studies. *Am J Clin Nutr* 2012; 95: 713–25.
45. Eliassen AH, Hendrickson SJ, Brinton LA, *et al*. Circulating carotenoids and risk of breast cancer: pooled analysis of eight prospective studies. *J Natl Cancer Inst* 2012; 104: 1905–16.
46. Aune D, Chan DS, Vieira AR, *et al*. Dietary compared with blood concentrations of carotenoids and breast cancer risk: a systematic review and meta-analysis of prospective studies. *Am J Clin Nutr* 2012; 96: 356–73.

47. Bakker MF, Peeters PH, Klaasen VM, *et al*. Plasma carotenoids, vitamin C, tocopherols, and retinol and the risk of breast cancer in the European Prospective Investigation into Cancer and Nutrition cohort. *Am J Clin Nutr* 2016; 103: 454–64.

48. Sisti JS, Lindstrom S, Kraft P, *et al*. Premenopausal plasma carotenoids, fluorescent oxidation products and subsequent breast cancer risk in the nurses' health studies. *Breast Cancer Res Treat* 2015; 151: 415–25.

49. Eliassen AH, Liao X, Rosner B, *et al*. Plasma carotenoids and risk of breast cancer over 20 y of follow-up. *Am J Clin Nutr* 2015; 101: 1197–205.

50. Elliott R. Mechanisms of genomic and non-genomic actions of carotenoids. *Biochim Biophys Acta* 2005; 1740: 147–54.

51. Kesse-Guyot E, Bertrais S, Duperray B, *et al*. Dairy products, calcium and the risk of breast cancer: results of the French SU.VI.MAX prospective study. *Ann Nutr Metab* 2007; 51: 139–45.

52. Lin J, Manson JE, Lee IM, *et al*. Intakes of calcium and vitamin D and breast cancer risk in women. *Arch Intern Med* 2007; 167: 1050–9.

53. Hjartaker A, Thoresen M, Engeset D, *et al*. Dairy consumption and calcium intake and risk of breast cancer in a prospective cohort: the Norwegian Women and Cancer study. *Cancer Causes Control* 2010; 21: 1875–85.

54. Missmer SA, Smith-Warner SA, Spiegelman D, *et al*. Meat and dairy food consumption and breast cancer: a pooled analysis of cohort studies. *Int J Epidemiol* 2002; 31: 78–85.

55. Li W, Ray RM, Lampe JW, *et al*. Dietary and other risk factors in women having fibrocystic breast conditions with and without concurrent breast cancer: a nested case-control study in Shanghai, China. *Int J Cancer* 2005; 115: 981–93.

56. Dong JY, Zhang L, He K, *et al*. Dairy consumption and risk of breast cancer: a meta-analysis of prospective cohort studies. *Breast Cancer Res Treat* 2011; 127: 23–31.

57. Shin MH, Holmes MD, Hankinson SE, *et al*. Intake of dairy products, calcium, and vitamin D and risk of breast cancer. *J Natl Cancer Inst* 2002; 94: 1301–11.

58. Larsson SC, Bergkvist L and Wolk A. Long-term dietary calcium intake and breast cancer risk in a prospective cohort of women. *Am J Clin Nutr* 2009; 89: 277–82d.

59. Abbas S, Linseisen J, Rohrmann S, *et al*. Dietary intake of vitamin D and calcium and breast cancer risk in the European Prospective Investigation into Cancer and Nutrition. *Nutr Cancer* 2013; 65: 178–87.

60. Cui Y and Rohan TE. Vitamin D, calcium, and breast cancer risk: a review. *Cancer Epidemiol Biomarkers Prev* 2006; 15: 1427–37.

61. Jacobson EA, James KA, Newmark HL, *et al*. Effects of dietary fat, calcium and vitamin D on growth and mammary tumorigenesis induced by 7,12-dimethylbenz(a)anthracene in female Sprague-Dawley rats. *Cancer Res* 1989; 49: 6300–3.

62. Visvanathan K, Crum RM, Strickland PT, *et al*. Alcohol dehydrogenase genetic polymorphisms, low-to-moderate alcohol consumption and risk of breast cancer. *Alcohol Clin Exp Res* 2007; 31: 467–76.

63. Zhang SM, Lee IM, Manson JE, *et al*. Alcohol consumption and breast cancer risk in the Women's Health Study. *Am J Epidemiol* 2007; 165: 667–76.

64. Suzuki R, Iwasaki M, Inoue M, *et al.* Alcohol consumption-associated breast cancer incidence and potential effect modifiers: the Japan Public Health Center–based Prospective Study. *Int J Cancer* 2010; 127: 685–95.

65. Chen WY, Rosner B, Hankinson SE, *et al*. Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. *JAMA* 2011; 306: 1884–90.

66. Kawai M, Minami Y, Kakizaki M, *et al*. Alcohol consumption and breast cancer risk in Japanese women: the Miyagi Cohort study. *Breast Cancer Res Treat* 2011; 128: 817–25.

67. Fagherazzi G, Vilier A, Boutron-Ruault MC, *et al*. Alcohol consumption and breast cancer risk subtypes in the E3N-EPIC cohort. *Eur J Cancer Prev* 2015; 24: 209–14.

68. Jung S, Wang M, Anderson K, *et al*. Alcohol consumption and breast cancer risk by estrogen receptor status: in a pooled analysis of 20 studies. *Int J Epidemiol* 2016; 45: 916–28.

69. Rissanen H, Knekt P, Jarvinen R, *et al*. Serum fatty acids and breast cancer incidence. *Nutr Cancer* 2003; 45: 168–75.

70. Petri AL, Tjonneland A, Gamborg M, *et al*. Alcohol intake, type of beverage, and risk of breast cancer in pre- and postmenopausal women. *Alcohol Clin Exp Res* 2004; 28: 1084–90.

71. Mellemkjaer L, Bigaard J, Tjonneland A, *et al.* Body composition and breast cancer in postmenopausal women: a Danish prospective cohort study. *Obesity (Silver Spring)* 2006; 14: 1854–62.

72. Stolzenberg-Solomon RZ, Chang SC, Leitzmann MF, *et al.* Folate intake, alcohol use and postmenopausal breast cancer risk in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. *Am J Clin Nutr* 2006; 83: 895–904.

73. Ravn-Haren G, Olsen A, Tjonneland A, *et al*. Associations between GPX1 Pro198Leu polymorphism, erythrocyte GPX activity, alcohol consumption and breast cancer risk in a prospective cohort study. *Carcinogenesis* 2006; 27: 820–5.

74. Vogel U, Christensen J, Nexo BA, *et al.* Peroxisome proliferator-activated [corrected] receptor-gamma2 [corrected] Pro12Ala, interaction with alcohol intake and NSAID use, in relation to risk of breast cancer in a prospective study of Danes. *Carcinogenesis* 2007; 28: 427–34.

75. Ericson U, Sonestedt E, Gullberg B, *et al*. High folate intake is associated with lower breast cancer incidence in postmenopausal women in the Malmo Diet and Cancer cohort. *Am J Clin Nutr* 2007; 86: 434–43.

76. Chlebowski RT, Anderson GL, Lane DS, *et al*. Predicting risk of breast cancer in postmenopausal women by hormone receptor status. *J Natl Cancer Inst* 2007; 99: 1695–705.

77. Nielsen NR and Gronbaek M. Interactions between intakes of alcohol and postmenopausal hormones on risk of breast cancer. *Int J Cancer* 2008; 122: 1109–13.

78. Sonestedt E, Ericson U, Gullberg B, *et al*. Do both heterocyclic amines and omega-6 polyunsaturated fatty acids contribute to the incidence of breast cancer in postmenopausal women of the Malmo diet and cancer cohort? *Int J Cancer* 2008; 123: 1637–43b.

79. Ericson U, Sonestedt E, Ivarsson MI, *et al*. Folate intake, methylenetetrahydrofolate reductase polymorphisms and breast cancer risk in women from the Malmo Diet and Cancer cohort. *Cancer Epidemiol Biomarkers Prev* 2009; 18: 1101–10.

80. Rod NH, Hansen AM, Nielsen J, *et al.* Low-risk factor profile, estrogen levels and breast cancer risk among postmenopausal women. *Int J Cancer* 2009; 124: 1935–40.

81. Maruti SS, Ulrich CM and White E. Folate and one-carbon metabolism nutrients from supplements and diet in relation to breast cancer risk. *Am J Clin Nutr* 2009; 89: 624–33.

82. Lew JQ, Freedman ND, Leitzmann MF, *et al*. Alcohol and risk of breast cancer by histologic type and hormone receptor status in postmenopausal women: the NIH-AARP Diet and Health Study. *Am J Epidemiol* 2009; 170: 308–17.

83. Duffy CM, Assaf A, Cyr M, *et al*. Alcohol and folate intake and breast cancer risk in the WHI Observational Study. *Breast Cancer Res Treat* 2009; 116: 551–62.

84. Allen NE, Beral V, Casabonne D, *et al*. Moderate alcohol intake and cancer incidence in women. *J Natl Cancer Inst* 2009; 101: 296–305.

85. Stevens VL, McCullough ML, Sun J, *et al*. Folate and other one-carbon metabolism-related nutrients and risk of postmenopausal breast cancer in the Cancer Prevention Study II Nutrition Cohort. *Am J Clin Nutr* 2010; 91: 1708–15.

86. Li CI, Chlebowski RT, Freiberg M, *et al*. Alcohol consumption and risk of postmenopausal breast cancer by subtype: the women's health initiative observational study. *J Natl Cancer Inst* 2010; 102: 1422–31.

87. Kotsopoulos J, Chen WY, Gates MA, *et al*. Risk factors for ductal and lobular breast cancer: results from the nurses' health study. *Breast Cancer Res* 2010; 12: R106.

88. Schonfeld SJ, Pfeiffer RM, Lacey JV, Jr. *et al*. Hormone-related risk factors and postmenopausal breast cancer among nulliparous versus parous women: an aggregated study. *Am J Epidemiol* 2011; 173: 509–17.

89. Kabat GC, Kim M, Phipps AI, *et al*. Smoking and alcohol consumption in relation to risk of triple-negative breast cancer in a cohort of postmenopausal women. *Cancer Causes Control* 2011; 22: 775–83.

90. Horn-Ross PL, Canchola AJ, Bernstein L, *et al*. Alcohol consumption and breast cancer risk among postmenopausal women following the cessation of hormone therapy use: the California Teachers Study. *Cancer Epidemiol Biomarkers Prev* 2012; 21: 2006–13.

91. Sczaniecka AK, Brasky TM, Lampe JW, *et al*. Dietary intake of specific fatty acids and breast cancer risk among postmenopausal women in the VITAL cohort. *Nutr Cancer* 2012; 64: 1131–42.

92. Nyante SJ, Dallal CM, Gierach GL, *et al*. Risk factors for specific histopathological types of postmenopausal breast cancer in the NIH-AARP Diet and Health Study. *Am J Epidemiol* 2013; 178: 359–71.

93. Hartz AJ and He T. Cohort study of risk factors for breast cancer in postmenopausal women. *Epidemiol Health* 2013; 35: e2013003.

94. Poynter JN, Inoue-Choi M, Ross JA, *et al.* Reproductive, lifestyle and anthropometric risk factors for cancer in elderly women. *Cancer Epidemiol Biomarkers Prev* 2013; 22: 681–7.

95. Loft S, Olsen A, Moller P, *et al*. Association between 8-oxo-7,8-dihydro-2'-deoxyguanosine excretion and risk of postmenopausal breast cancer: nested case-control study. *Cancer Epidemiol Biomarkers Prev* 2013; 22: 1289–96.

96. Hastert TA, Beresford SA, Patterson RE, *et al*. Adherence to WCRF/AICR cancer prevention recommendations and risk of postmenopausal breast cancer. *Cancer Epidemiol Biomarkers Prev* 2013; 22: 1498–508.

97. Park SY, Kolonel LN, Lim U, *et al*. Alcohol consumption and breast cancer risk among women from five ethnic groups with light to moderate intakes: the Multiethnic Cohort Study. *Int J Cancer* 2014; 134: 1504–10.

98. Falk RT, Maas P, Schairer C, *et al*. Alcohol and risk of breast cancer in postmenopausal women: an analysis of etiological heterogeneity by multiple tumor characteristics. *Am J Epidemiol* 2014; 180: 705–17.

99. Brinton LA, Smith L, Gierach GL, *et al*. Breast cancer risk in older women: results from the NIH-AARP Diet and Health Study. *Cancer Causes Control* 2014; 25: 843–57.

100. Hippisley-Cox J and Coupland C. Development and validation of risk prediction algorithms to estimate future risk of common cancers in men and women: prospective cohort study. *BMJ Open* 2015; 5: e007825.

101. Hvidtfeldt UA, Tjonneland A, Keiding N, *et al*. Risk of breast cancer in relation to combined effects of hormone therapy, body mass index, and alcohol use, by hormone-receptor status. *Epidemiology* 2015; 26: 353–61.

102. Keogh RH, Park JY, White IR, *et al*. Estimating the alcohol-breast cancer association: a comparison of diet diaries, FFQs and combined measurements. *Eur J Epidemiol* 2012; 27: 547–59.

103. Hiatt RA, Klatsky AL and Armstrong MA. Alcohol consumption and the risk of breast cancer in a prepaid health plan. *Cancer Res* 1988; 48: 2284–7a.

104. Pike MC, Kolonel LN, Henderson BE, *et al*. Breast cancer in a multiethnic cohort in Hawaii and Los Angeles: risk factor-adjusted incidence in Japanese equals and in Hawaiians exceeds that in whites. *Cancer Epidemiol Biomarkers Prev* 2002; 11: 795–800.

105. Barrett-Connor E and Friedlander NJ. Dietary fat, calories and the risk of breast cancer in postmenopausal women: a prospective population-based study. *J Am Coll Nutr* 1993; 12: 390–9.

106. Larsson SC, Bergkvist L and Wolk A. Folate intake and risk of breast cancer by estrogen and progesterone receptor status in a Swedish cohort. *Cancer Epidemiol Biomarkers Prev* 2008; 17: 3444–9.

107. Dumitrescu RG and Shields PG. The etiology of alcohol-induced breast cancer. *Alcohol* 2005; 35: 213–25.

108. International Agency for Research on Cancer. Personal habits and indoor combustions. *IARC Monogr Eval Carcinog Risks Hum* 2012; 100E: 373–499.

109. Singletary KW and Gapstur SM. Alcohol and breast cancer: review of epidemiologic and experimental evidence and potential mechanisms. *JAMA* 2001; 286: 2143–51.

110. Romieu I, Scoccianti C, Chajes V, *et al*. Alcohol intake and breast cancer in the European prospective investigation into cancer and nutrition. *Int J Cancer* 2015; 137: 1921–30.

111. Boffetta P and Hashibe M. Alcohol and cancer. *Lancet Oncol* 2006; 7: 149–56.

112. International Agency for Research on Cancer. Consumption of alcoholic beverages. In: The Evaluation of Carconogenic Risks to Humans. IARC Monogr no 100E monographs.iarc.fr/ENG/Monographs/vol100E/. 2012.

113. Lahmann PH, Friedenreich C, Schuit AJ, *et al*. Physical activity and breast cancer risk: the European Prospective Investigation into Cancer and Nutrition. *Cancer Epidemiol Biomarkers Prev* 2007; 16: 36–42.

114. Howard RA, Leitzmann MF, Linet MS, *et al*. Physical activity and breast cancer risk among pre- and postmenopausal women in the U.S. Radiologic Technologists cohort. *Cancer Causes Control* 2009; 20: 323–33.

115. Suzuki R, Iwasaki M, Yamamoto S, *et al*. Leisure-time physical activity and breast cancer risk defined by estrogen and progesterone receptor status – the Japan Public Health Center–based Prospective Study. *Prev Med* 2011; 52: 227–33a.

116. Steindorf K, Ritte R, Tjonneland A, *et al*. Prospective study on physical activity and risk of in situ breast cancer. *Cancer Epidemiol Biomarkers Prev* 2012; 21: 2209–19.

117. Steindorf K, Ritte R, Eomois PP, *et al*. Physical activity and risk of breast cancer overall and by hormone receptor status: the European prospective investigation into cancer and nutrition. *Int J Cancer* 2013; 132: 1667–78.

118. Lee SY, Kim MT, Kim SW, *et al*. Effect of lifetime lactation on breast cancer risk: a Korean women's cohort study. *Int J Cancer* 2003; 105: 390–3.

119. Wu Y, Zhang D and Kang S. Physical activity and risk of breast cancer: a meta-analysis of prospective studies. *Breast Cancer Res Treat* 2013; 137: 869–82.

120. Leitzmann MF, Moore SC, Peters TM, *et al*. Prospective study of physical activity and risk of postmenopausal breast cancer. *Breast Cancer Res* 2008; 10: R92.

121. Cohen SS, Matthews CE, Bradshaw PT, *et al*. Sedentary behavior, physical activity and likelihood of breast cancer among black and white women: a report from the Southern Community Cohort Study. *Cancer Prev Res (Phila)* 2013; 6: 566–76.

122. Borch KB, Lund E, Braaten T, *et al*. Physical activity and the risk of postmenopausal breast cancer – the Norwegian Women and Cancer Study. *J Negat Results Biomed* 2014; 13: 3.

123. McKenzie F, Ferrari P, Freisling H, *et al*. Healthy lifestyle and risk of breast cancer among postmenopausal women in the European Prospective Investigation into Cancer and Nutrition cohort study. *Int J Cancer* 2015; 136: 2640–8.

124. McTiernan A. Mechanisms linking physical activity with cancer. *Nat Rev Cancer* 2008; 8: 205–11.

125. Friedenreich CM, Neilson HK and Lynch BM. State of the epidemiological evidence on physical activity and cancer prevention. *Eur J Cancer* 2010; 46: 2593–604

126. Deeb KK, Trump DL and Johnson CS. Vitamin D signalling pathways in cancer: potential for anticancer therapeutics. *Nat Rev Cancer* 2007; 7: 684–700.

127. Silvera SA, Jain M, Howe GR, *et al*. Energy balance and breast cancer risk: a prospective cohort study. *Breast Cancer Res Treat* 2006; 97: 97–106.

128. Dallal CM, Sullivan-Halley J, Ross RK, *et al*. Long-term recreational physical activity and risk of invasive and in situ breast cancer: the California teachers study. *Arch Intern Med* 2007; 167: 408–15.

129. Maruti SS, Willett WC, Feskanich D, *et al*. A prospective study of age-specific physical activity and premenopausal breast cancer. *J Natl Cancer Inst* 2008; 100: 728–37b.

130. Rosenberg L, Palmer JR, Bethea TN, *et al*. A prospective study of physical activity and breast cancer incidence in African-American women. *Cancer Epidemiol Biomarkers Prev* 2014; 23: 2522–31.

131. Peters TM, Moore SC, Gierach GL, *et al.* Intensity and timing of physical activity in relation to postmenopausal breast cancer risk: the prospective NIH-AARP diet and health study. *BMC Cancer* 2009; 9: 349b.

132. Peters TM, Schatzkin A, Gierach GL, *et al*. Physical activity and postmenopausal breast cancer risk in the NIH-AARP diet and health study. *Cancer Epidemiol Biomarkers Prev* 2009; 18: 289–96a.

133. Eliassen AH, Hankinson SE, Rosner B, *et al*. Physical activity and risk of breast cancer among postmenopausal women. *Arch Intern Med* 2010; 170: 1758–64.

134. Phipps AI, Chlebowski RT, Prentice R, *et al*. Body size, physical activity, and risk of triple-negative and estrogen receptor-positive breast cancer. *Cancer Epidemiol Biomarkers Prev* 2011; 20: 454–63.

135. Dirx MJ, Voorrips LE, Goldbohm RA, *et al*. Baseline recreational physical activity, history of sports participation, and postmenopausal breast carcinoma risk in the Netherlands Cohort Study. *Cancer* 2001; 92: 1638–49.

136. Moore DB, Folsom AR, Mink PJ, *et al*. Physical activity and incidence of postmenopausal breast cancer. *Epidemiology* 2000; 11: 292–6.

137. Lee IM, Rexrode KM, Cook NR, *et al*. Physical activity and breast cancer risk: the Women's Health Study (United States). *Cancer Causes Control* 2001; 12: 137–45.

138. Michels KB, Terry KL and Willett WC. Longitudinal study on the role of body size in premenopausal breast cancer. *Arch Intern Med* 2006; 166: 2395–402a.

139. Li HL, Gao YT, Li Q, *et al*. [Anthropometry and female breast cancer: a prospective cohort study in urban Shanghai]. *Zhonghua Liu Xing Bing Xue Za Zhi* 2006; 27: 488–93.

140. Palmer JR, Adams-Campbell LL, Boggs DA, *et al*. A prospective study of body size and breast cancer in black women. *Cancer Epidemiol Biomarkers Prev* 2007; 16: 1795–802.

141. Burton A, Martin R, Galobardes B, *et al*. Young adulthood body mass index and risk of cancer in later adulthood: historical cohort study. *Cancer Causes Control* 2010; 21: 2069–77.

142. Suzuki R, Iwasaki M, Inoue M, *et al*. Body weight at age 20 years, subsequent weight change and breast cancer risk defined by estrogen and progesterone receptor status – the Japan public health center–based prospective study. *Int J Cancer* 2011; 129: 1214–24b.

143. Manders P, Pijpe A, Hooning MJ, *et al*. Body weight and risk of breast cancer in BRCA1/2 mutation carriers. *Breast Cancer Res Treat* 2011; 126: 193–202.

144. Catsburg C, Kirsh VA, Soskolne CL, *et al*. Associations between anthropometric characteristics, physical activity, and breast cancer risk in a Canadian cohort. *Breast Cancer Res Treat* 2014; 145: 545–52b.

145. Bandera EV, Chandran U, Hong CC, *et al*. Obesity, body fat distribution and risk of breast cancer subtypes in African American women participating in the AMBER Consortium. *Breast Cancer Res Treat* 2015; 150: 655–66.

146. Weiderpass E, Braaten T, Magnusson C, *et al*. A prospective study of body size in different periods of life and risk of premenopausal breast cancer. *Cancer Epidemiol Biomarkers Prev* 2004; 13: 1121–7.

147. Ahn J, Schatzkin A, Lacey JV, Jr., *et al*. Adiposity, adult weight change and postmenopausal breast cancer risk. *Arch Intern Med* 2007; 167: 2091–102.

148. Torio CM, Klassen AC, Curriero FC, *et al*. The modifying effect of social class on the relationship between body mass index and breast cancer incidence. *Am J Public Health* 2010; 100: 146–51.

149. Kawai M, Minami Y, Kuriyama S, *et al*. Adiposity, adult weight change and breast cancer risk in postmenopausal Japanese women: the Miyagi Cohort Study. *Br J Cancer* 2010; 103: 1443–7b.

150. Canchola AJ, Anton-Culver H, Bernstein L, *et al*. Body size and the risk of postmenopausal breast cancer subtypes in the California Teachers Study cohort. *Cancer Causes Control* 2012; 23: 473–85.

151. White KK, Park SY, Kolonel LN, *et al*. Body size and breast cancer risk: the Multiethnic Cohort. *Int J Cancer* 2012; 131: E705–E16.

152. Krishnan K, Bassett JK, MacInnis RJ, *et al*. Associations between weight in early adulthood, change in weight, and breast cancer risk in postmenopausal women. *Cancer Epidemiol Biomarkers Prev* 2013; 22: 1409–16.

153. Han X, Stevens J, Truesdale KP, *et al*. Body mass index at early adulthood, subsequent weight change and cancer incidence and mortality. *Int J Cancer* 2014; 135: 2900–9.

154. Berkey CS, Frazier AL, Gardner JD, *et al*. Adolescence and breast carcinoma risk. *Cancer* 1999; 85: 2400–9.

155. Key TJ, Appleby PN, Reeves GK, *et al.* Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3) and breast cancer risk: pooled individual data analysis of 17 prospective studies. *Lancet Oncol* 2010; 11: 530–42.

156. Poole EM, Tworoger SS, Hankinson SE, *et al*. Body size in early life and adult levels of insulin-like growth factor 1 and insulin-like growth factor binding protein 3. *Am J Epidemiol* 2011; 174: 642–51.

157. Grubbs CJ, Farnell DR, Hill DL, *et al*. Chemoprevention of N-nitroso-N-methylurea-induced mammary cancers by pretreatment with 17 beta-estradiol and progesterone. *J Natl Cancer Inst* 1985; 74: 927–31.

158. Pasquali R, Pelusi C, Genghini S, *et al*. Obesity and reproductive disorders in women. *Hum Reprod Update* 2003; 9: 359–72.

159. Baer HJ, Colditz GA, Willett WC, *et al*. Adiposity and sex hormones in girls. *Cancer Epidemiol Biomarkers Prev* 2007; 16: 1880–8.

160. Lukanova A, Bjor O, Kaaks R, *et al*. Body mass index and cancer: results from the Northern Sweden Health and Disease Cohort. *Int J Cancer* 2006; 118: 458–66.

161. Tehard B and Clavel-Chapelon F. Several anthropometric measurements and breast cancer risk: results of the E3N cohort study. *Int J Obes (Lond)* 2006; 30: 156–63.

162. Lundqvist E, Kaprio J, Verkasalo PK, *et al*. Co-twin control and cohort analyses of body mass index and height in relation to breast, prostate, ovarian, corpus uteri, colon and rectal cancer among Swedish and Finnish twins. *Int J Cancer* 2007; 121: 810–8.

163. Reinier KS, Vacek PM and Geller BM. Risk factors for breast carcinoma in situ versus invasive breast cancer in a prospective study of pre- and post-menopausal women. *Breast Cancer Res Treat* 2007; 103: 343–8.

164. Reeves GK, Pirie K, Beral V, *et al*. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ* 2007; 335: 1134.

165. Iwasaki M, Otani T, Inoue M, *et al*. Body size and risk for breast cancer in relation to estrogen and progesterone receptor status in Japan. *Ann Epidemiol* 2007; 17: 304–12b.

166. Whitlock G, Lewington S, Sherliker P, *et al*. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009; 373: 1083–96.

167. Davey SG, Sterne JA, Fraser A, *et al*. The association between BMI and mortality using offspring BMI as an indicator of own BMI: large intergenerational mortality study. *BMJ* 2009; 339: b5043.

168. Cust AE, Stocks T, Lukanova A, *et al*. The influence of overweight and insulin resistance on breast cancer risk and tumour stage at diagnosis: a prospective study. *Breast Cancer Res Treat* 2009; 113: 567–76.

169. Parr CL, Batty GD, Lam TH, *et al*. Body mass index and cancer mortality in the Asia-Pacific Cohort Studies Collaboration: pooled analyses of 424,519 participants. *Lancet Oncol* 2010; 11: 741–52.

170. Bjorge T, Lukanova A, Jonsson H, *et al*. Metabolic syndrome and breast cancer in the me-can (metabolic syndrome and cancer) project. *Cancer Epidemiol Biomarkers Prev* 2010; 19: 1737–45.

171. Wilson KM, Willett WC and Michels KB. Mothers' pre-pregnancy BMI and weight gain during pregnancy and risk of breast cancer in daughters. *Breast Cancer Res Treat* 2011; 130: 273–9.

172. Yang XR, Chang-Claude J, Goode EL, *et al*. Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. *J Natl Cancer Inst* 2011; 103: 250–63.

173. Harris HR, Willett WC, Terry KL, *et al*. Body fat distribution and risk of premenopausal breast cancer in the Nurses' Health Study II. *J Natl Cancer Inst* 2011; 103: 273–8b.

174. Ritte R, Lukanova A, Berrino F, *et al*. Adiposity, hormone replacement therapy use and breast cancer risk by age and hormone receptor status: a large prospective cohort study. *Breast Cancer Res* 2012; 14: R76.

175. Fagherazzi G, Chabbert-Buffet N, Fabre A *et al*. Hip circumference is associated with the risk of premenopausal ER–/PR– breast cancer. *Int J Obes (Lond)* 2012; 36: 431–9a.

176. Cecchini RS, Costantino JP, Cauley JA, *et al*. Body mass index and the risk for developing invasive breast cancer among high-risk women in NSABP P-1 and STAR breast cancer prevention trials. *Cancer Prev Res (Phila)* 2012; 5: 583–92.

177. Schairer C, Li Y, Frawley P, *et al*. Risk factors for inflammatory breast cancer and other invasive breast cancers. *J Natl Cancer Inst* 2013; 105: 1373–84.

178. Guo L, Li N, Wang G, *et al*. [Body mass index and cancer incidence: a prospective cohort study in northern China]. *Zhonghua Liu Xing Bing Xue Za Zhi* 2014; 35: 231–6.

179. Emaus MJ, van Gils CH, Bakker MF, *et al*. Weight change in middle adulthood and breast cancer risk in the EPIC-PANACEA study. *Int J Cancer* 2014; 135: 2887–99.

180. Wada K, Nagata C, Tamakoshi A, *et al*. Body mass index and breast cancer risk in Japan: a pooled analysis of eight population-based cohort studies. *Ann Oncol* 2014; 25: 519–24.

181. Bhaskaran K, Douglas I, Forbes H, *et al*. Body mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. *Lancet* 2014; 384: 755–65.

182. Harris HR, Tamimi RM, Willett WC, *et al*. Body size across the life course, mammographic density and risk of breast cancer. *Am J Epidemiol* 2011; 174: 909–18a.

183. van den Brandt PA, Spiegelman D, Yaun SS, *et al*. Pooled analysis of prospective cohort studies on height, weight and breast cancer risk. *Am J Epidemiol* 2000; 152: 514–27.

184. Lahmann PH, Hoffmann K, Allen N, *et al*. Body size and breast cancer risk: findings from the European Prospective Investigation into Cancer and Nutrition (EPIC). *Int J Cancer* 2004; 111: 762–71a.

185. Suzuki R, Orsini N, Saji S, *et al*. Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status – a meta-analysis. *Int J Cancer* 2009; 124: 698–712.

186. Cheraghi Z, Poorolajal J, Hashem T, *et al*. Effect of body mass index on breast cancer during premenopausal and postmenopausal periods: a meta-analysis. *PLoS One* 2012; 7: e51446.

187. Pierobon M and Frankenfeld CL. Obesity as a risk factor for triple-negative breast cancers: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2013; 137: 307–14.

188. Amadou A, Ferrari P, Muwonge R, *et al*. Overweight, obesity and risk of premenopausal breast cancer according to ethnicity: a systematic review and dose-response meta-analysis. *Obes Rev* 2013; 14: 665–78.

189. Xia X, Chen W, Li J, *et al*. Body mass index and risk of breast cancer: a nonlinear dose-response meta-analysis of prospective studies. *Sci Rep* 2014; 4: 7480.

190. Munsell MF, Sprague BL, Berry DA, *et al.* Body mass index and breast cancer risk according to postmenopausal estrogen-progestin use and hormone receptor status. *Epidemiol Rev* 2014; 36: 114–36.

191. Barlow WE, White E, Ballard-Barbash R, *et al*. Prospective breast cancer risk prediction model for women undergoing screening mammography. *J Natl Cancer Inst* 2006; 98: 1204–14.

192. Bosco JL, Palmer JR, Boggs DA, *et al*. Cardiometabolic factors and breast cancer risk in U.S. black women. *Breast Cancer Res Treat* 2012; 134: 1247–56.

193. Kaaks R, Van Noord PA, den Tonkelaar I, *et al*. Breast-cancer incidence in relation to height, weight and body-fat distribution in the Dutch "DOM" cohort. *Int J Cancer* 1998; 76: 647–51.

194. Rinaldi S, Key TJ, Peeters PH, *et al*. Anthropometric measures, endogenous sex steroids and breast cancer risk in postmenopausal women: a study within the EPIC cohort. *Int J Cancer* 2006; 118: 2832–9.

195. Modugno F, Kip KE, Cochrane B, *et al*. Obesity, hormone therapy, estrogen metabolism and risk of postmenopausal breast cancer. *Int J Cancer* 2006; 118: 1292–301.

196. Chang SC, Ziegler RG, Dunn B, *et al.* Association of energy intake and energy balance with postmenopausal breast cancer in the prostate, lung, colorectal and ovarian cancer screening trial. *Cancer Epidemiol Biomarkers Prev* 2006; 15: 334–41.

197. Suzuki R, Rylander–Rudqvist T, Ye W, *et al.* Body weight and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status among Swedish women: A prospective cohort study. *Int J Cancer* 2006; 119: 1683–9.

198. Krebs EE, Taylor BC, Cauley JA, *et al*. Measures of adiposity and risk of breast cancer in older postmenopausal women. *J Am Geriatr Soc* 2006; 54: 63–9.

199. Gallicchio L, McSorley MA, Newschaffer CJ, *et al*. Body mass, polymorphisms in obesity-related genes and the risk of developing breast cancer among women with benign breast disease. *Cancer Detect Prev* 2007; 31: 95–101.

200. Song YM, Sung J and Ha M. Obesity and risk of cancer in postmenopausal Korean women. *J Clin Oncol* 2008; 26: 3395–402.

201. Kerlikowske K, Walker R, Miglioretti DL, *et al*. Obesity, mammography use and accuracy, and advanced breast cancer risk. *J Natl Cancer Inst* 2008; 100: 1724–33.

202. Jee SH, Yun JE, Park EJ, *et al*. Body mass index and cancer risk in Korean men and women. *Int J Cancer* 2008; 123: 1892–6.

203. Setiawan VW, Monroe KR, Wilkens LR, *et al*. Breast cancer risk factors defined by estrogen and progesterone receptor status: the multiethnic cohort study. *Am J Epidemiol* 2009; 169: 1251–9.

204. Gunter MJ, Hoover DR, Yu H, *et al*. Insulin, insulin-like growth factor-I and risk of breast cancer in postmenopausal women. *J Natl Cancer Inst* 2009; 101: 48–60.

205. Borgquist S, Jirstrom K, Anagnostaki L, *et al*. Anthropometric factors in relation to different tumor biological subgroups of postmenopausal breast cancer. *Int J Cancer* 2009; 124: 402–11.

206. Prentice RL, Pettinger M, Tinker LF, *et al*. Regression calibration in nutritional epidemiology: example of fat density and total energy in relationship to postmenopausal breast cancer. *Am J Epidemiol* 2013; 178: 1663–72a.

207. Sue LY, Schairer C, Ma X, *et al*. Energy intake and risk of postmenopausal breast cancer: an expanded analysis in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) cohort. *Cancer Epidemiol Biomarkers Prev* 2009; 18: 2842–50.

208. Lacey JV, Jr., Kreimer AR, Buys SS, *et al*. Breast cancer epidemiology according to recognized breast cancer risk factors in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial Cohort. *BMC Cancer* 2009; 9: 84.

209. Gaudet MM, Falk RT, Gierach GL *et al*. Do adipokines underlie the association between known risk factors and breast cancer among a cohort of United States women? *Cancer Epidemiol* 2010; 34: 580–6.

210. Kabat GC, Kim M, Wactawski-Wende J, *et al*. Recreational physical activity, anthropometric factors and risk of ductal carcinoma in situ of the breast in a cohort of postmenopausal women. *Cancer Causes Control* 2010; 21: 2173–81.

211. Benzon LS, Vogel U, Christensen J, *et al*. Interaction between ADH1C Arg(272)Gln and alcohol intake in relation to breast cancer risk suggests that ethanol is the causal factor in alcohol related breast cancer. *Cancer Lett* 2010; 295: 191–7.

212. Andreotti G, Hou L, Beane Freeman LE, *et al*. Body mass index, agricultural pesticide use and cancer incidence in the Agricultural Health Study cohort. *Cancer Causes Control* 2010; 21: 1759–75.

213. Grenier D, Cooke AL, Lix L, *et al*. Bone mineral density and risk of postmenopausal breast cancer. *Breast Cancer Res Treat* 2011; 126: 679–86.

214. Bessonova L, Marshall SF, Ziogas A, *et al*. The association of body mass index with mortality in the California Teachers Study. *Int J Cancer* 2011; 129: 2492–501.

215. Vacek PM, Skelly JM and Geller BM. Breast cancer risk assessment in women aged 70 and older. *Breast Cancer Res Treat* 2011; 130: 291–9.

216. Opdahl S, Alsaker MD, Janszky I, *et al*. Joint effects of nulliparity and other breast cancer risk factors. *Br J Cancer* 2011; 105: 731–6.

217. Harlid S, Butt S, Ivarsson MI, *et al.* Interactive effect of genetic susceptibility with height, body mass index, and hormone replacement therapy on the risk of breast cancer. *BMC Womens Health* 2012; 12: 17.

218. Hartz A, He T and Rimm A. Comparison of adiposity measures as risk factors in postmenopausal women. *J Clin Endocrinol Metab* 2012; 97: 227–33.

219. Harlid S, Ivarsson MI, Butt S, *et al*. Combined effect of low-penetrant SNPs on breast cancer risk. *Br J Cancer* 2012; 106: 389–96.

220. Rohan TE, Heo M, Choi L, *et al*. Body fat and breast cancer risk in postmenopausal women: a longitudinal study. *J Cancer Epidemiol* 2013; 2013: 754815.

221. Gaudet MM, Patel AV, Teras LR, *et al*. Obesity-related markers and breast cancer in CPS-II Nutrition Cohort. *Int J Mol Epidemiol Genet* 2013; 4: 156–66.

222. Miao JJ, Cederholm J and Gudbjornsdottir S. Excess body weight and cancer risk in patients with type 2 diabetes who were registered in Swedish National Diabetes Register – register–based cohort study in Sweden. *PLoS One* 2014; 9: e105868.

223. Horn J, Alsaker MD, Opdahl S, *et al*. Anthropometric factors and risk of molecular breast cancer subtypes among postmenopausal Norwegian women. *Int J Cancer* 2014; 135: 2678-86b.

224. Gaudet MM, Carter BD, Patel AV, *et al*. Waist circumference, body mass index and postmenopausal breast cancer incidence in the Cancer Prevention Study-II Nutrition Cohort. *Cancer Causes Control* 2014; 25: 737–45.

225. Kabat GC, Xue X, Kamensky V, *et al*. Risk of breast, endometrial, colorectal, and renal cancers in postmenopausal women in association with a body shape index and other anthropometric measures. *Cancer Causes Control* 2015; 26: 219–29b.

226. Zhang X, Eliassen AH, Tamimi RM, *et al*. Adult body size and physical activity in relation to risk of breast cancer according to tumor androgen receptor status. *Cancer Epidemiol Biomarkers Prev* 2015; 24: 962–8.

227. Harding JL, Shaw JE, Anstey KJ, *et al*. Comparison of anthropometric measures as predictors of cancer incidence: A pooled collaborative analysis of 11 Australian cohorts. *Int J Cancer* 2015; 137: 1699–708.

228. Petrelli JM, Calle EE, Rodriguez C, *et al*. Body mass index, height, and postmenopausal breast cancer mortality in a prospective cohort of US women. *Cancer Causes Control* 2002; 13: 325–32.

229. Lin YS, Caffrey JL, Lin JW, *et al.* Increased risk of cancer mortality associated with cadmium exposures in older Americans with low zinc intake. *J Toxicol Environ Health A* 2013; 76: 1–15.

230. Esposito K, Chiodini P, Capuano A, *et al*. Metabolic syndrome and postmenopausal breast cancer: systematic review and meta-analysis. *Menopause* 2013; 20: 1301–9.

231. Lee S, Kolonel L, Wilkens L, *et al*. Postmenopausal hormone therapy and breast cancer risk: the Multiethnic Cohort. *Int J Cancer* 2006; 118: 1285–91.

232. Kabat GC, Kim M, Chlebowski RT, *et al*. A longitudinal study of the metabolic syndrome and risk of postmenopausal breast cancer. *Cancer Epidemiol Biomarkers Prev* 2009; 18: 2046–53b.

233. Agnoli C, Berrino F, Abagnato CA, *et al*. Metabolic syndrome and postmenopausal breast cancer in the ORDET cohort: a nested case-control study. *Nutr Metab Cardiovasc Dis* 2010; 20: 41–8.

234. Reeves KW, McLaughlin V, Fredman L, *et al*. Components of metabolic syndrome and risk of breast cancer by prognostic features in the study of osteoporotic fractures cohort. *Cancer Causes Control* 2012; 23: 1241–51.

235. Fourkala EO, Burnell M, Cox C, *et al*. Association of skirt size and postmenopausal breast cancer risk in older women: a cohort study within the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). *BMJ Open* 2014; 4: e005400.

236. Heo M, Kabat GC, Strickler HD, *et al*. Optimal cutoffs of obesity measures in relation to cancer risk in postmenopausal women in the Women's Health Initiative Study. *J Womens Health (Larchmt)* 2015; 24: 218–27.

237. Morimoto LM, White E, Chen Z, *et al*. Obesity, body size and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). *Cancer Causes Control* 2002; 13: 741–51.

238. Hilakivi-Clarke L, Forsen T, Eriksson JG, *et al*. Tallness and overweight during childhood have opposing effects on breast cancer risk. *Br J Cancer* 2001; 85: 1680–4.

239. De Pergola G and Silvestris F. Obesity as a major risk factor for cancer. *J Obes* 2013; 2013: 291546.

240. Calle EE and Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* 2004; 4: 579–91.

241. Feigelson HS, Patel AV, Teras LR, *et al*. Adult weight gain and histopathologic characteristics of breast cancer among postmenopausal women. *Cancer* 2006; 107: 12–21.

242. Eliassen AH, Colditz GA, Rosner B, *et al*. Adult weight change and risk of postmenopausal breast cancer. *JAMA* 2006; 296: 193–201.

243. Alsaker MD, Janszky I, Opdahl S, *et al*. Weight change in adulthood and risk of postmenopausal breast cancer: the HUNT study of Norway. *Br J Cancer* 2013; 109: 1310–7.

244. Rosner B, Eliassen AH, Toriola AT, *et al*. Short-term weight gain and breast cancer risk by hormone receptor classification among pre- and postmenopausal women. *Breast Cancer Res Treat* 2015; 150: 643–53.

245. Keum N, Greenwood DC, Lee DH, *et al*. Adult weight gain and adiposity-related cancers: a dose-response meta-analysis of prospective observational studies. *J Natl Cancer Inst* 2015; 107 (2): djv088

246. Vrieling A, Buck K, Kaaks R *et al*. Adult weight gain in relation to breast cancer risk by estrogen and progesterone receptor status: a meta-analysis. *Breast Cancer Res Treat* 2010; 123: 641–9.

247. Baer HJ, Rich-Edwards JW, Colditz GA, *et al*. Adult height, age at attained height and incidence of breast cancer in premenopausal women. *Int J Cancer* 2006; 119: 2231–5.

248. Oberg S, Cnattingius S, Sandin S, *et al*. Birth weight-breast cancer revisited: is the association confounded by familial factors? *Cancer Epidemiol Biomarkers Prev* 2009; 18: 2447–52.

249. Fagherazzi G, Vilier A, Boutron-Ruault MC, *et al*. Height, sitting height and leg length in relation with breast cancer risk in the E3N cohort. *Cancer Epidemiol Biomarkers Prev* 2012; 21: 1171–5b.

250. Ritte R, Lukanova A, Tjonneland A, *et al*. Height, age at menarche and risk of hormone receptor-positive and -negative breast cancer: a cohort study. *Int J Cancer* 2013; 132: 2619–29b.

251. Kabat GC, Heo M, Kamensky V, *et al*. Adult height in relation to risk of cancer in a cohort of Canadian women. *Int J Cancer* 2013; 132: 1125–32a.

252. Wiren S, Haggstrom C, Ulmer H, *et al.* Pooled cohort study on height and risk of cancer and cancer death. *Cancer Causes Control* 2014; 25: 151–9.

253. Palmer JR, Rao RS, Adams-Campbell LL, *et al*. Height and breast cancer risk: results from the Black Women's Health Study (United States). *Cancer Causes Control* 2001; 12: 343–8.

254. Mellemkjaer L, Christensen J, Frederiksen K, *et al*. Leg length, sitting height and postmenopausal breast cancer risk. *Br J Cancer* 2012; 107: 165–8.

255. Kabat GC, Anderson ML, Heo M, *et al*. Adult stature and risk of cancer at different anatomic sites in a cohort of postmenopausal women. *Cancer Epidemiol Biomarkers Prev* 2013; 22: 1353–63b.

256. Barker DJ and Thornburg KL. Placental programming of chronic diseases, cancer and lifespan: a review. *Placenta* 2013; 34: 841–5.

257. Rolland-Cachera MF. Rate of growth in early life: a predictor of later health? *Adv Exp Med Biol* 2005; 569: 35–9.

258. Michels KB, Xue F, Terry KL, *et al*. Longitudinal study of birthweight and the incidence of breast cancer in adulthood. *Carcinogenesis* 2006; 27: 2464–8b.

259. dos Santos Silva S, De Stavola B and McCormack V. Birth size and breast cancer risk: re-analysis of individual participant data from 32 studies. *PLoS Med* 2008; 5: e193.

260. Hajiebrahimi M, Bahmanyar S, Oberg S, *et al*. Breast cancer risk in opposite-sexed twins: influence of birth weight and co-twin birth weight. *J Natl Cancer Inst* 2013; 105: 1833–6.

261. Michels KB, Trichopoulos D, Robins JM, *et al*. Birthweight as a risk factor for breast cancer. *Lancet* 1996; 348: 1542–1546.

262. Xu X, Dailey AB, Peoples-Sheps M, *et al*. Birth weight as a risk factor for breast cancer: a meta-analysis of 18 epidemiological studies. *J Womens Health (Larchmt)* 2009; 18: 1169–78.

263. Innes K, Byers T and Schymura M. Birth characteristics and subsequent risk for breast cancer in very young women. *Am J Epidemiol* 2000; 152: 1121–8.

264. Hilakivi-Clarke L. Mechanisms by which high maternal fat intake during pregnancy increases breast cancer risk in female rodent offspring. *Breast Cancer Res Treat* 1997; 46: 199–214.

265. Andrieu N, Goldgar DE, Easton DF, *et al*. Pregnancies, breast-feeding and breast cancer risk in the International BRCA1/2 Carrier Cohort Study (IBCCS). *J Natl Cancer Inst* 2006; 98: 535–44.

266. Iwasaki M, Otani T, Inoue M, *et al*. Role and impact of menstrual and reproductive factors on breast cancer risk in Japan. *Eur J Cancer Prev* 2007; 16: 116–23a.

267. Kawai M, Minami Y, Kuriyama S, *et al*. Reproductive factors, exogenous female hormone use and breast cancer risk in Japanese: the Miyagi Cohort Study. *Cancer Causes Control* 2010; 21: 135–45a.

268. Palmer JR, Boggs DA, Wise LA, *et al*. Parity and lactation in relation to estrogen receptor negative breast cancer in African American women. *Cancer Epidemiol Biomarkers Prev* 2011; 20: 1883–91.

269. Tamimi RM, Colditz GA, Hazra A, *et al*. Traditional breast cancer risk factors in relation to molecular subtypes of breast cancer. *Breast Cancer Res Treat* 2012; 131: 159–67.

270. Ritte R, Tikk K, Lukanova A, *et al*. Reproductive factors and risk of hormone receptor positive and negative breast cancer: a cohort study. *BMC Cancer* 2013; 13: 584a.

271. Horn J, Opdahl S, Engstrom MJ, *et al*. Reproductive history and the risk of molecular breast cancer subtypes in a prospective study of Norwegian women. *Cancer Causes Control* 2014; 25: 881–9a.

272. Butt S, Borgquist S, Anagnostaki L, *et al*. Breastfeeding in relation to risk of different breast cancer characteristics. *BMC Res Notes* 2014; 7: 216.

273. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. *Lancet* 2002; 360: 187–95.

274. Zhou Y, Chen J, Li Q, *et al*. Association between breastfeeding and breast cancer risk: evidence from a meta-analysis. *Breastfeed Med* 2015; 10: 175–82.

275. Islami F, Liu Y, Jemal A, *et al*. Breastfeeding and breast cancer risk by receptor status – a systematic review and meta-analysis. *Ann Oncol* 2015; 26: 2398–407.

276. Key T, Appleby P, Barnes I, *et al*. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst* 2002; 94: 606–16.

Appendix - Criteria for grading evidence

(Adapted from Chapter 3 of the Second Expert Report [1])

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 (STRONG EVIDENCE)

This judgement is 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 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)

This judgement is 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 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

This judgement is for evidence that is too limited to permit a probable or convincing causal judgement but is 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 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 incidence of cancer; any exceptions to this require special explicit justification.

All 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 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 World Cancer Research Fund International website (www.wcrf.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, 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 as '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 it 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 as low as you can within the healthy range.

Move more
Be physically active for at least 30 minutes every day, and sit less.

Avoid high-calorie foods and sugary drinks
Limit high-calorie foods (particularly processed foods high in fat or added sugar, or low in fibre) and avoid sugary drinks.

Enjoy more grains, veg, fruit and beans
Eat a wide variety of whole grains, vegetables, fruit and pulses such as beans.

Limit red meat and avoid processed meat
Eat no more than 500g (cooked weight) a week of red meat, such as beef, pork and lamb. Eat little, if any, processed meat such as ham and bacon.

For cancer prevention, don't drink alcohol
For cancer prevention, it's best not to drink alcohol. If you do, limit alcoholic drinks and follow national guidelines.

Eat less salt, and avoid mouldy grains and cereals
Limit your salt intake to less than 6g (2.4g sodium) a day by adding less salt and eating less food processed with salt. Avoid mouldy grains and cereals as they may be contaminated by aflatoxins.

For cancer prevention, don't rely on supplements
Eat a healthy diet rather than relying on supplements to protect against cancer.

If you can, breastfeed your baby
If you can, breastfeed your baby for six months before adding other liquids and foods.

Cancer survivors should follow our Recommendations (where possible)
After cancer treatment, the best advice is to follow the Cancer Prevention Recommendations. Check with your health professional.

The Panel also emphasises the importance of not smoking and avoiding exposure to tobacco smoke.

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