World Cancer Research Fund International

CUP Continuous Update Project

Analysing research on cancer prevention and survival

Diet, nutrition, physical activity and **Breast Cancer Survivors**

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WORLD CANCER RESEARCH FUND INTERNATIONAL

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 though 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)

World Cancer Research Fund International's Continuous Update Project 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 Continuous Update Project is produced in partnership with the American Institute for Cancer Research, World Cancer Research Fund UK, World Cancer Research Fund NL and World Cancer Research Fund HK.

The findings from the Continuous Update Project are used to update our Recommendations for Cancer Prevention, ensuring 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 evaluate and interpret the evidence to make conclusions based on the body of scientific evidence. Their conclusions form the basis for reviewing and, where necessary, revising our Recommendations for Cancer Prevention.

A review of the Recommendations for Cancer Prevention is expected to be published in 2017, once an analysis of all of the cancers being assessed has been conducted. So far, new CUP reports have been published on the updated evidence for breast, colorectal, pancreatic, endometrial and ovarian cancers.

This report is based on the findings of the CUP Breast Cancer Survivors Systematic Literature Review (SLR) and the CUP Expert Panel discussion in June 2013. For further details please see the full Continuous Update Project Breast Cancer Survivors SLR 2014 (**www.wcrf.org/sites/default/files/Breast-Cancer-Survivors-SLR-2014.pdf**).

HOW TO CITE THIS REPORT

World Cancer Research Fund International. Continuous Update Project Report: Diet, Nutrition, Physical Activity, and Breast Cancer Survivors. 2014. Available at: **www.wcrf.org/sites/default/files/Breast-Cancer-Survivors-2014-Report.pdf**

EXECUTIVE SUMMARY

Background and context

Although there is a widely held perception that breast cancer is an issue only for the western world, the reality is that it is the most common cancer in women both in the developed and the developing world. Indeed, the incidence of breast cancer is rising in the developing world because of increased life expectancy, urbanisation, and the adoption of western lifestyles [1].

As early diagnosis and treatments for breast cancer improve, women are not only surviving the disease – they are surviving for longer. Investigating whether lifestyle factors could play a role in improving survival rates is also becoming increasingly important.

Understanding the science behind surviving breast cancer, however, is a relatively new area of research, but there is growing evidence that lifestyle choices may help to reduce the risk of having another diagnosis of breast cancer or dying from the disease.

World Cancer Research Fund International's Continuous Update Project report on breast cancer survivors is the most rigorous, systematic, global analysis of the scientific research currently available on breast cancer survivors, and how certain lifestyle factors affect how likely it is that a person will survive after developing the disease.

The report is the latest from our Continuous Update Project - the world's largest source of scientific research on cancer prevention and survivorship through diet, weight and physical activity. The research builds on our 2007 Expert Report on the links between lifestyle and cancer. At that time the research on surviving cancer was even more limited than it is today, and there was insufficient evidence to make recommendations specific to cancer survivors. However, there was enough evidence to conclude that cancer survivors should in general follow the recommendations for cancer prevention (see our Cancer Prevention Recommendations at wcrf.org).

Seven years on, we present World Cancer Research Fund International's first systematic analysis of global research focusing specifically on surviving breast cancer. In this section we offer an overview of that work and the scientific findings and conclusions made by the independent panel of experts who analysed the research.

How the research was conducted

The report specifically focuses on:

- female breast cancer survivors who are living with a diagnosis of cancer, including those who have recovered from the disease;
- the link between diet, weight, physical activity and the likelihood of female breast cancer survivors dying from breast cancer, second primary breast cancer (i.e. a new cancer occurring in the same breast after treatment or in the opposite breast), or any other disease.

Breast cancer survivors are defined in the report as women who have received a diagnosis of breast cancer – from the point of diagnosis, through and after treatment.

For the report, the global scientific research on diet, weight, physical activity and female breast cancer survivors was gathered and analysed, and then independently assessed by a panel of leading international scientists in order to draw conclusions about surviving breast cancer and reducing the risk of a second primary breast cancer.

The total number of women in the 85 studies reviewed was 164,416; and the total number of deaths in the studies came to 42,572.

Findings

The Continuous Update Project's independent panel of scientists concluded that because of limitations in either the design or execution of much of the research that exists, the evidence is still not strong enough to make specific recommendations for breast cancer survivors. However, there are indications of links between better survival after breast cancer and:

- a healthy body weight
- being physically active
- eating foods containing fibre
- eating foods containing soy
- a lower intake of total fat and, in particular, saturated fat.

Body weight

- Results show that there is a link between having a healthy BMI - both before and after diagnosis - and surviving breast cancer. However there are other factors that might explain why women who are overweight or obese have a greater risk of dying from the disease, so more research is needed to investigate these links.
- While there is no strong evidence about the link between body weight and *surviving* breast cancer, there is strong evidence from our analysis of research into other cancers which shows that being overweight or obese increases the risk of *developing* eight cancers; bowel, womb (endometrial), oesophageal, kidney, pancreatic, ovarian, gallbladder and post-menopausal breast cancer.

Physical activity

- Evidence shows that women who are physically active - both before and after diagnosis - have a greater chance of surviving breast cancer. Other factors may explain this link, so further research is needed to investigate the reason for the association.

Diet

Diet may also play a role in surviving a breast cancer diagnosis, but there are relatively few studies on diet and survival after breast cancer. The studies that are available indicate:

- Women who eat more foods containing fibre - both before and after diagnosis – may have a lower risk of dying from breast cancer.
- Breast cancer survivors who eat more foods containing soy *after* diagnosis may have a lower risk of dying from the disease.
- Women consuming a diet high in fat and saturated fat *before* developing the disease may have an increased risk of dying *following* a diagnosis of breast cancer.

More research is needed to investigate these links in order to confirm whether these foods affect survival after breast cancer.

Recommendations

1. After treatment for breast cancer our advice, if it fits with the specific medical advice given, is to follow our Cancer Prevention Recommendations (available at wcrf.org), which include eating a healthy diet, being physically active and maintaining a healthy weight.

2. More and better scientific research is needed in order to make specific recommendations for breast cancer survivors.

References

1. World Health Organisation. Breast Cancer: prevention and control. 2014; Available from: **www.who.int/cancer/detection/breastcancer/en/index.html**

DIET, NUTRITION, PHYSICAL ACTIVITY AND BREAST CANCER SURVIVAL (BY TIMEFRAME)

	Timing of exposure assessment	BEFORE DIAGNOSIS		LESS THAN 12 MONTHS AFTER DIAGNOSIS		12 MONTHS OR MORE AFTER DIAGNOSIS	
		DECREASES RISK	INCREASES RISK	DECREASES RISK	INCREASES RISK	DECREASES RISK	INCREASES RISK
		Exposure Outcome	Exposure Outcome	Exposure Outcome	Exposure Outcome	Exposure Outcome	Exposure Outcome
STRONG EVIDENCE	Convincing						
STRONG EVIDENCE	Probable						
LIMITED EVIDENCE	Limited-suggestive	Physical activity All mortality, BC mortality Foods containing fibre All mortality	Body fatness All mortality, BC mortality[2], 2nd BC Total fat All mortality Saturated fatty acids All mortality		Body fatness All mortality, BC mortality[2], 2nd BC	Physical activity All mortality Foods containing fibre All mortality Foods containing soy All mortality	Body fatness All mortality
LIMITED EVIDENCE	Limited-no conclusion[1]	Fruits, vegetables, foods containing folate, foods containing soy, carbohydrate, glycaemic index, glycaemic load, protein, dietary supplements, alcoholic drinks, dietary patterns, underweight, body fatness (premenopause), adult attained height, energy intake		Foods containing fibre, carbohydrate, protein, total fat, saturated fatty acids, alcoholic drinks, physical activity, underweight, body fatness (premenopause), adult attained height, energy intake		Fruits, vegetables, foods containing fibre, foods containing folate, foods containing soy, carbohydrate, glycaemic index, glycaemic load, protein, total fat, saturated fatty acids, alcoholic drinks, dietary patterns, physical activity, body fatness, underweight, height, energy intake	
STRONG EVIDENCE	Substantial effect on risk unlikely						

All mortality, All cause mortality; BC mortality, breast cancer mortality; 2nd BC, Second primary breast cancer
STRONG: Evidence strong enough to support a judgement of a convincing or probable causal relationship and generally justify making recommendations
LIMITED: Evidence that is too limited to justify making specific recommendations
1 Includes various exposure-outcome combinations where evidence was available but too limited to draw conclusions. For more details of the outcomes related to the exposures listed here, see the full Breast Cancer Survivors SLR
2 Postmenopause only

DIET, NUTRITION, PHYSICAL ACTIVITY AND BREAST CANCER SURVIVAL (BY OUTCOME)

	Outcome	ALL CAUSE MORTALITY		BREAST CANCER MORTALITY		SECOND PRIMARY BREAST CANCER	
		DECREASED RISK	INCREASED RISK	DECREASED RISK	INCREASED RISK	DECREASED RISK	INCREASED RISK
		Exposure Timeframe	Exposure Timeframe	Exposure Timeframe	Exposure Timeframe	Exposure Timeframe	Exposure Timeframe
STRONG EVIDENCE	Convincing						
STRONG EVIDENCE	Probable						
LIMITED EVIDENCE	Limited-suggestive	Physical activity Before diagnosis, ≥12 months after diagnosis Foods containing fibre Before diagnosis, ≥12 months after diagnosis Foods containing soy ≥12 months after diagnosis	Body fatness Before diagnosis, <12 months after diagnosis, ≥12 months after diagnosis Total fat Before diagnosis Saturated fatty acids Before diagnosis	Physical activity Before diagnosis	Body fatness[1] Before diagnosis, <12 months after diagnosis		Body fatness Before diagnosis, <12 months after diagnosis
STRONG EVIDENCE	Substantial effect on risk unlikely						

STRONG: Evidence strong enough to support a judgement of a convincing or probable causal relationship and generally justify making recommendations
LIMITED: Evidence that is too limited to justify making specific recommendations
1 Post menopause only

CUP Continuous Update Project

1. Summary of panel judgements

Despite the increasing amount of evidence available, limitations in study design or execution restrict the ability to ascribe causality to observed associations. The Panel was unable to draw firm conclusions on the effect of diet, nutrition (including body composition), or physical activity in women with a diagnosis of breast cancer, specifically in relation to the reduction of mortality (from breast cancer or any other cause) or of a second primary breast cancer. The following sections summarise the Panel's judgements on exposures measured before diagnosis, within a year of diagnosis, or a year or more after diagnosis, in relation to all-cause mortality, breast cancer mortality, and second primary breast cancer.

The Panel judges that:

- **In relation to all cause mortality, the evidence suggesting that:**

  A higher consumption of foods containing fibre before or 12 months or more after a diagnosis of primary breast cancer reduces risk is limited.

  A higher consumption of foods containing soy 12 months or more after a diagnosis of primary breast cancer reduces risk is limited.

  Consuming a diet higher in total fat before a diagnosis of primary breast cancer increases risk is limited.

  Consuming a diet higher in saturated fatty acids before a diagnosis of primary breast cancer increases risk is limited.

  Being physically active before or 12 months or more after a diagnosis of primary breast cancer increases risk is limited.

  Greater body fatness before, less than 12 months after, or 12 months or more after, a diagnosis of primary breast cancer increases risk is limited.

- **In relation to breast cancer mortality, the evidence suggesting that:**

  Being physically active before a diagnosis of primary breast cancer reduces risk is limited.

  Greater body fatness before, or less than 12 months after a diagnosis of postmenopausal primary breast cancer increases risk is limited.

- **In relation to second primary breast cancer, the evidence suggesting that:**

  Greater body fatness before, or less than 12 months after a diagnosis of primary breast cancer increases risk is limited.

For other outcomes/timing of exposure assessment combinations related to the above exposures, the evidence was either absent or too limited to draw any conclusions. The Panel judgements (by timeframe and outcome) are shown in the matrices on page 6.

2. Definitions

The term ‘breast cancer survivors’ denotes women who have received a diagnosis of cancer, from the point of diagnosis, through and after treatment.

The definition of ‘breast cancer survivor’ here does not include people living with a diagnosis of a benign tumour, or tumours defined as premalignant.

3. Incidence and prevalence of breast cancer

The current World Health Organisation classification of tumours of the breast recognises more than 20 different subtypes [1]. Breast cancers may be classified according to histopathological characteristics, for example invasive (or infiltrating) ductal carcinoma or invasive lobular carcinoma, or molecular receptor status (for example for oestrogen, progesterone or HER2), or both. Less common types of breast cancer include inflammatory breast cancer, Paget disease of the nipple, phyllodes tumour, and angiosarcoma. Although rare (less than 1 per cent of cases [2]), breast cancer can occur in men, but it is not included in this report.

Depending on the size and type of the tumour, extent of any spread, and patient preference, treatment usually comprises breast conserving surgery or mastectomy. Underarm lymph nodes may also be removed and evaluated during surgery in order to assess if the tumour has spread. Surgery may be accompanied by adjuvant therapy (radiotherapy, chemotherapy, hormonal or HER targeted therapy) [3]. Even for similar type or grade of breast cancer responses to therapy or long term outcome may differ between patients [3].

The Continuous Update Project (CUP) report on Breast Cancer [4] provided a comprehensive analysis of the relationship between diet, nutrition (including body composition), physical activity, and breast cancer risk (see box 1 for further information).

Breast cancer is the most frequently diagnosed cancer (excluding non-melanoma skin cancers) among women in 140 of 180 countries worldwide. Between 2008 and 2012 breast cancer incidence increased by 20%, while mortality has increased by 14% [5]. In the US, it is estimated that there are currently 3.1 million breast cancer survivors [6].

Overall survival rates for breast cancer vary world wide, but in general survival rates have improved. This is because the majority of breast cancer cases are diagnosed at an earlier and localised stage, and improved surgery and adjuvant tailored treatment regimes are available. In many countries the 5-year survival rate for women diagnosed with Stage I/II (only spread to tissues or nodes under the arm) breast cancer is 80-90%. If it has reached the distant stage (spread to distant lymph nodes or organs) the survival rate falls to 24% [7]. The five-year prevalence of breast cancer[1] per 100,000 is 665 in Western Europe, 745 in North America, and 170 in Eastern Asia [5].

Box 1.

Several factors have been shown to increase or decrease risk of first occurrence of breast cancer (see appendix 1). These factors have also been examined in relation to their effect on outcomes (all cause mortality, breast cancer mortality and second primary breast cancer) after breast cancer is diagnosed. There are additional considerations that must be taken into account for observational studies of breast cancer survivors, in whom randomised controlled trials would provide the strongest evidence. Therefore new criteria for judgement were developed for categorising the strength of evidence for causality in breast cancer survivors. In addition any exposure may have different effects on incidence of breast cancer and outcome after breast cancer diagnosis.

4 INTERPRETATION OF THE EVIDENCE

4.1 General

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

4.2 Specific

Considerations specific to breast cancer survivors

Timeframe

The timeframes of exposure assessment used were; before primary breast cancer diagnosis; less than 12 months after diagnosis of primary breast cancer; and 12 months or more after diagnosis of primary breast cancer. These timeframes take into account exposure assessment at various stages of treatment - those who have not started, those undergoing treatment, and those who have finished treatment.

[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.

Treatment

Treatment varies by breast tumour type and spread, and patient characteristics. The type and amount of treatment can have a greater effect on survival than most exposures related to diet, nutrition, and physical activity, and is likely a confounding factor. In the United States, for example, access to treatments varies by socio-economic status, as does diet and physical activity, so an apparent diet-survival relationship may be confounded by the type of treatment received. This also pertains to stage at diagnosis but stage is more easily ascertained in studies and is thus easier to control for than treatment information.

Given the rise in rates of obesity, the practice of limiting doses in overweight and obese patients may negatively influence the quality of care and outcomes for overweight or obese women. The American Society of Clinical Oncology (ASCO) set recommendations in 2012 that full weight-based chemotherapy doses be used in the treatment of obese patients with cancer.

Weight gain is common in individuals treated with chemotherapy [8], especially when steroids are also administered or if premature menopause is induced in previously premenopausal women. During treatment, sarcopenia (loss of muscle mass) is often accompanied by a gain of adipose tissue.

Time periods and changes in treatments

Due to improved knowledge regarding tumour type, new treatment regimens have changed the expected effect of treatment and thus breast cancer mortality. For example, 15-20% of breast cancer cases are now known to be positive for HER2. Treatment regimens vary according to time periods, country, and socio-economic status within countries.

Reverse causation

An exposure being studied may be a result of the diagnosis (or treatment), and not the other way around. For example, it is hard to differentiate between intentional and unintentional weight loss, difficult to assess the impact of therapy on weight gain, and difficult to accurately measure or recall weight prior to the development of disease.

Mortality and breast cancer subtype

Pre-existing disease, and some specific subtypes of breast cancer (such as breast cancer negative for oestrogen, progesterone and HER2 receptors), are more likely to lead to early recurrence or death, conventionally defined as occurring within the first two years after diagnosis. If a survivor cohort is assembled a long time after diagnosis, such women at high risk for mortality may not be included. Furthermore, advances in treatment coupled with earlier diagnosis have led to longer survival beyond five years, up to 10 years and beyond. Therefore, it is important to consider survival in terms both of the cancer subtype, as well as of the time point after diagnosis when data collection occurs and follow-up begins.

Randomised Controlled Trials (RCTs) and cohort data

Well-conducted RCTs may provide strong evidence; however patients included in RCTs may not be representative of the wider population of breast cancer survivors. Survivors who do not enter RCTs may be sicker, have different lifestyles and could have lower survival rates. Cohort studies with large numbers of cases and a high response to follow-up may have better generalisability. However, in order to provide strong evidence cohort data must be fully adjusted for potential confounders such as tumour type, type of treatment, amount of treatment received, and the dissemination of disease, and this is not always possible.

Criteria for grading evidence for breast cancer survivors

The Panel discussed the approach to be used for reviewing the evidence for breast cancer survivors during 2012. The evidence for breast cancer survivors comes mostly from cohort and follow up studies with few RCTs, and there is a complex set of outcomes including quality of life, recurrence, and mortality. For the Second Expert Report in 2007, there were no existing systems for assessing the quality of evidence. Grading of Recommendations Assessment, Development and Evaluation (GRADE) is now widely used as a recognised way of assessing and grading quality of evidence for making recommendations in healthcare settings. However, the use of GRADE does not translate directly to the context of this review. Possible options were presented for grading the evidence for breast cancer survivors. The Panel agreed to use the features of GRADE that were appropriate but adapt others to be more in line with the CUP principles and methodology for other cancer sites. In addition, it was agreed that the same terminology of probable, convincing and limited suggestive used in the Second Expert Report should be used to describe the evidence for breast cancer survivors in relation to likely causal effects. See Appendix 2 for further information on the criteria for grading evidence for breast cancer survivors.

5. Methodology

The protocol was developed by the research team at Imperial College London based on advice from the Cancer Survivors Protocol Development Committee.

The outcomes included in the Breast Cancer Survivors Systematic Literature Review (SLR) 2013 are all cause mortality, cause specific breast cancer mortality, second primary breast cancer, cardiovascular disease mortality, mortality not related to breast cancer, second primary endometrial cancer, second primary colorectal cancer, and second primary ovarian cancer. This report is limited to all cause mortality, cause specific breast cancer mortality, and second primary breast cancer. Breast cancer recurrence, long-term treatment side effects and quality of life are not included as endpoints in this review, because accurate assessment of these requires access to medical records. Although randomised clinical trials often have access to medical records, most other studies, and in particular cohort studies, often do not have such access and rely on self-reported assessment, which is often unreliable. Also, the definition for recurrence varies across studies. Quality of life is not included in the review as summarising the results is not feasible. This is due to lack of evidence on the comparability of the extensive variety of instruments applied to assess quality of life in the existing studies.

The study populations included are pre and postmenopausal women with a diagnosis of in situ or invasive breast cancer. Studies included reported primary, secondary or ancillary analyses of randomised controlled trials or cohort studies on associations between food, nutrition, weight control, nutrition-related complementary medicine, physical activity and outcomes in breast cancer survivors. Included randomised trials had to have at least 50 participants and a follow-up of at least 6 months. Follow-up of breast cancer cases from cohorts and case-control studies were also included (see appendix 2 for further information).

The literature search was conducted using Medline, EMBASE, and the Cochrane Library CENTRAL and included RCTs or follow up studies. Publications in foreign languages were not included. Published meta-analyses and pooled analyses are included in the SLR as a comparison with the CUP findings.

The Breast Cancer Survivors SLR included studies published up to 30 June 2012. For more information on methodology please see the full Breast Cancer Survivors SLR 2013 (**www.wcrf.org/sites/default/files/Breast-Cancer-Survivors-SLR-2014.pdf**)

6. Evidence and judgements

In general, there was a lack of evidence from RCTs and pooled analyses. Additionally, it was not clear to what extent individual studies have fully adjusted for potential confounders such as the tumour type, type of treatment, amount of treatment received, and dissemination of disease.

6.1 Foods containing fibre

(Also see Breast Cancer Survivors SLR 2013: Section 4.3)

FOODS CONTAINING FIBRE			
		DECREASES RISK	
		Timing of exposure assessment	Outcome
STRONG EVIDENCE	Convincing		
	Probable		
LIMITED EVIDENCE	Limited-suggestive	Before diagnosis	All cause mortality
		≥12 months after diagnosis	All cause mortality
STRONG EVIDENCE	Substantial effect on risk unlikely		

The following sections summarise the evidence identified by the CUP on consumption of foods containing fibre before a diagnosis of primary breast cancer and 12 months or more after diagnosis of primary breast cancer.

Before primary breast cancer diagnosis

The CUP identified three follow-up studies on consumption of foods containing fibre *before* a diagnosis of primary breast cancer and subsequent *all cause mortality* [9-11].

For ***all cause mortality***, two studies reported a significant inverse association when comparing the highest versus the lowest categories of intake (see Breast Cancer Survivors SLR 2013 figure 36).

All three studies identified were included in the dose-response meta-analysis (n = 443), which showed a statistically significant 32% decreased risk per 10 g per day (RR 0.68 (95% CI 0.55-0.84)) (see Breast Cancer Survivors SLR 2013 figure 37). No heterogeneity was observed.

Two of the studies reported on postmenopausal women only [9, 10] and the results were the same when the meta-analysis was restricted to women with postmenopausal breast cancer (RR 0.69 (95% CI 0.55-0.86); n = 297; I^2 = 5.7%) (see Breast Cancer Survivors SLR 2013 figure 39).

All three studies assessed patients' pre-diagnosis diet after cancer was diagnosed. One study only included 26 deaths and adjusted for fewer factors than the other two studies.

12 months or more after diagnosis of primary breast cancer

The CUP identified four follow-up studies on consumption of foods containing fibre *12 months or more after* a diagnosis of primary breast cancer and subsequent *all cause mortality* [12-15].

For ***all cause mortality***, three studies reported a non-significant inverse association when comparing the highest versus the lowest categories of intake (see Breast Cancer Survivors SLR 2013 figure 40).

Three of the four studies identified in the CUP were included in the dose-response meta-analysis (*n* = 1,092), which showed a statistically significant 12% decreased risk per 10 g per day (RR 0.88 (95% CI 0.78-0.99)) (see Breast Cancer Survivors SLR 2013 figure 41). No heterogeneity was observed.

One study was not included in the CUP analysis due to insufficient data.

All studies included more than 100 deaths. All of the studies reported on pre and postmenopausal women, but it was not possible to conduct a meta-analysis stratified by menopausal status.

CUP Panel's conclusions

The evidence was sparse but generally consistent. Overall, there was a significant inverse association between consumption of foods containing fibre and all cause mortality. The CUP Panel concluded:

Before a diagnosis of primary breast cancer

All cause mortality: The evidence is limited but consistent. The evidence suggesting that a higher consumption of foods containing fibre *before* a diagnosis of primary breast cancer reduces risk of *all cause mortality* is limited.

12 months or more after a diagnosis of primary breast cancer

All cause mortality: The evidence is limited but consistent. The evidence suggesting that a higher consumption of foods containing fibre *12 months or more after* diagnosis of primary breast cancer reduces risk of *all cause mortality* is limited.

6.2 Foods containing soy

(Also see Breast Cancer Survivors SLR 2013: Section 4.6 and 4.10)

FOOD CONTAINING SOY			
		DECREASES RISK	
		Timing of exposure assessment	Outcome
STRONG EVIDENCE	Convincing		
	Probable		
LIMITED EVIDENCE	Limited-suggestive	≥12 months after diagnosis	All cause mortality
STRONG EVIDENCE	Substantial effect on risk unlikely		

The following sections summarise the evidence identified by the CUP on foods containing soy consumed 12 months or more after a diagnosis of primary breast cancer.

12 months or more after diagnosis of primary breast cancer

The CUP identified three follow up studies on isoflavone intake *12 months or more after* a diagnosis of primary breast cancer *and all cause mortality* [16-18], and two on soy protein intake and all cause mortality [17, 18].

For *isoflavone intake*, one study reported a significant inverse association when comparing the highest versus the lowest category of intake, and two reported a non-significant inverse association (see Breast Cancer Survivors SLR 2013 figure 65).

All three studies identified were included in the dose-response meta-analysis (n = 794), which showed no significant association (RR 0.91 (95% CI 0.83-1.00)) per 10 mg per day (see Breast Cancer Survivors SLR 2013 figure 66). There was evidence of substantial heterogeneity (I^2 = 67.7%) largely due to size of effect.

Two of the three studies had more than 100 deaths. Two of the studies were from China and one was from the United States. All of the studies reported on pre and postmenopausal women, but it was not possible to conduct a meta-analysis stratified by menopausal status.

For *soy protein* both studies reported a significant inverse association for soy protein intake above 13 g per day and were included in the isoflavone dose-response meta-analysis.

Published pooled analysis

The results from one published pooled analysis on intake of isoflavones and breast cancer survival was identified in the Breast Cancer Survivors SLR 2013 [19]. The pooled study reported no significant association between consuming at least 10 mg isoflavones per day compared to less than 4 mg per day and all cause mortality (HR 0.87 (95% CI 0.70-1.10)). There was no significant interaction with menopausal status.

CUP Panel's conclusions

The evidence was sparse and generally consistent, and is suggestive of an inverse relationship between consumption of foods containing soy and all cause mortality.
The CUP Panel concluded:

All cause mortality: The evidence is limited but generally consistent. The evidence suggesting that a higher consumption foods containing soy *12 months or more after* a diagnosis of primary breast cancer reduces risk of *all cause mortality* is limited.

6.3 Total fat

(Also see Breast Cancer Survivors SLR 2013: Section 4.4 and 6.2)

		TOTAL FAT	
		INCREASES RISK	
		Timing of exposure assessment	Outcome
STRONG EVIDENCE	Convincing		
	Probable		
LIMITED EVIDENCE	Limited-suggestive	Before diagnosis	All cause mortality
STRONG EVIDENCE	Substantial effect on risk unlikely		

The following sections summarise the evidence identified by the CUP on total fat before a diagnosis of primary breast cancer.

Before primary breast cancer diagnosis

The CUP identified seven follow up studies on total fat intake *before* a diagnosis of primary breast cancer and subsequent *all cause mortality* [10, 11, 13, 20-23]. Three of these studies also reported on per cent of energy intake from fat and *all cause mortality* [10, 11, 23].

For *total fat intake* (g per day), three studies reported comparing the highest versus the lowest intake, two studies showed a significant positive association, and one a non-significant inverse association (see Breast Cancer Survivors SLR 2013 figure 46).

Four of the seven identified studies were included in the dose-response meta-analysis (n = 178), which showed a significant 19% increased risk per 10 g per day (RR 1.19 (95% CI 1.01-1.41)) (see Breast Cancer Survivors SLR 2013 figure 47). There was evidence of substantial heterogeneity (I^2 = 82.0%) largely due to size of effect.

Five of the studies assessed patients' pre-diagnosis diet after cancer was diagnosed. Six of the studies included pre and postmenopausal women; and one included postmenopausal women only.

Two studies were not included in the CUP analysis due to insufficient information.

For *per cent energy from fat*, two studies reported a significant positive association comparing the highest versus lowest intake (no figure available).

All three studies identified were included in the dose-response meta-analysis (n = 178), which showed a significant 82% increased risk per 10 per cent energy from fat (RR 1.82 (95% CI 1.41-2.36)) (see Breast Cancer Survivors SLR 2013 figure 82). No heterogeneity was observed.

Two of the three studies identified assessed patients' pre-diagnosis diet after cancer was diagnosed, and all three included pre and postmenopausal women. All three studies also reported on total fat (g per day).

CUP Panel's conclusions

The evidence was sparse and generally consistent. Overall, there was a significant positive association between fat intake and all cause mortality. The CUP Panel concluded:

All cause mortality: The evidence is limited but generally consistent. The evidence suggesting that consuming a diet higher in total fat *before* a diagnosis of primary breast cancer increases risk of *all cause mortality* is limited.

6.4 Saturated fatty acids

(Also see Breast Cancer Survivors SLR 2013: Section 4.5)

		SATURATED FATTY ACIDS	
		INCREASES RISK	
		Timing of exposure assessment	Outcome
STRONG EVIDENCE	Convincing		
	Probable		
LIMITED EVIDENCE	Limited-suggestive	Before diagnosis	All cause mortality
STRONG EVIDENCE	Substantial effect on risk unlikely		

The following sections summarise the evidence identified by the CUP on intake of saturated fatty acids before a diagnosis of primary breast cancer.

Before primary breast cancer diagnosis

The CUP identified four follow up studies on intake of saturated fatty acids *before* a diagnosis of primary breast cancer and *all cause mortality* [10, 11, 21, 23].

For ***all cause mortality***, two reported a significant positive association when comparing the highest versus the lowest categories of intake (No figure available).

Three of the four studies identified were included in the dose-response meta-analysis (n = 178), which showed a statistically significant 66% increased risk per 10 g per day (RR 1.66 (95% CI 1.26-2.19)) (see Breast Cancer Survivors SLR 2013 figure 54). There was evidence of moderate heterogeneity (I^2 = 31.8%).

None of the studies had more than 100 deaths. Two of the three studies assessed patients' before diagnosis diet after cancer was diagnosed. One study included pre and postmenopausal women, the other two included postmenopausal women only.

One study was not included in the CUP analysis due to insufficient data.

CUP Panel's conclusions

The evidence was sparse and generally consistent. Overall, there was a significant positive association between intake of saturated fatty acids and all cause mortality. The CUP Panel concluded:

All cause mortality: The evidence is limited but generally consistent. The evidence suggesting that consuming a diet higher in saturated fatty acids *before* a diagnosis of primary breast cancer increases risk of *all cause mortality* is limited.

6.5 Physical activity

(Also see Breast Cancer Survivors SLR 2013: Section 5)

PHYSICAL ACTIVITY			
		DECREASES RISK	
		Timing of exposure assessment	Outcome
STRONG EVIDENCE	Convincing		
	Probable		
LIMITED EVIDENCE	Limited-suggestive	Before diagnosis	All cause mortality Breast cancer mortality
		≥12 months after diagnosis	All cause mortality
STRONG EVIDENCE	Substantial effect on risk unlikely		

The following sections summarise the evidence identified by the CUP on physical activity before a diagnosis of primary breast cancer and 12 months or more after a diagnosis of primary breast cancer.

Before primary breast cancer diagnosis

The CUP identified nine follow-up studies on physical activity assessed *before* a diagnosis of primary breast cancer and *all cause mortality* [20, 24-31], and eight studies on physical activity *assessed before a* diagnosis of primary breast cancer and *breast cancer mortality* [20, 25, 26, 28-32].

For ***all cause mortality,*** two studies reported on total physical activity and eight studies reported on recreational physical activity (one study reported on both exposures).

For *total physical activity,* both studies reported a non-significant inverse association when comparing the highest versus the lowest activity levels (see Breast Cancer Survivors SLR 2013 figure 68). No dose-response meta-analysis was possible.

Both studies had more than 100 deaths, included pre and postmenopausal women, and were from North America. Follow up times were 6 and 8.3 years.

For *recreational activity*, seven studies reported an inverse association when comparing the highest versus the lowest activity levels, four of which were statistically significant (see Breast Cancer Survivors SLR 2013 figure 68). The other study reported no association (RR 1.00). No dose-response meta-analysis was possible.

All eight studies included pre and postmenopausal women except one that included premenopausal women only. Five studies were from North America and three were from Europe. Follow-up time in most studies was between 5 and 10 years and most studies carried out assessment of physical activity prior to diagnosis.

For ***breast cancer mortality***, two studies reported on total physical activity and seven studies reported on recreational physical activity (one study reported on both exposures).

For *total physical activity,* both studies showed a non-significant inverse association when comparing the highest versus the lowest activity levels (see Breast Cancer Survivors SLR 2013 figure 76). No dose-response meta-analysis was possible.

Both studies had more than 100 deaths, included pre and postmenopausal women, and were from North America. Follow up times were 6 and 8.3 years.

For *recreational physical activity,* all seven studies compared the highest versus the lowest levels of activity, five reported a non-significant inverse association, of which two were statistically significant, and two studies reported a non-significant positive association (see Breast Cancer Survivors SLR 2013 figure 76). Again, no dose-response meta-analysis was possible.

All studies included pre and postmenopausal women, except one that included only premenopausal women. Four studies were from North America and three were from Europe. All studies reported more than 100 deaths, and follow-up time in most studies was between 5 and 12 years.

12 months or more after diagnosis of primary breast cancer

The CUP identified eight follow-up studies on physical activity *12 months or more after* a diagnosis of primary breast cancer and *all cause mortality* as the outcome [25, 27, 33-38].

For ***all cause mortality***, three studies reported on total physical activity and five studies reported on recreational physical activity (no study reported on both exposures).

For *total physical activity* all three studies reported an inverse association when comparing the highest versus the lowest activity levels, one of which was statistically significant (see Breast Cancer Survivors SLR 2013 figure 69).

All three studies on total physical activity were included in a dose-response meta-analysis (n = 514), which showed a non-significant decreased risk of all cause mortality per 10 Metabolic Equivalent per Task (MET)-hours per week (RR 0.90 (95% CI 0.79-1.03)) with evidence of high heterogeneity (I^2 = 78.7%) (see Breast Cancer Survivors SLR 2013 figure 70).

All studies included pre and postmenopausal women, and reported more than 100 deaths, and were from the United States. Follow up time ranged from 6 to 7 years.

For *recreational activity* all five studies reported an inverse association when comparing the highest versus the lowest activity levels, four of which were statistically significant (see Breast Cancer Survivors SLR 2013 figure 69).

All five studies on recreational physical activity were included in a dose-response meta-analysis (n = 2,337), which showed a statistically significant 19% decreased risk of all cause mortality per 10 MET-hours per week (RR 0.81 (95% CI 0.73-0.90)) and again with evidence of high heterogeneity (I^2 = 63.8%) (see Breast Cancer Survivors SLR 2013 figure 72), mainly due to size of effect.

For stratification by menopausal status showed a significant decreased risk for postmenopausal women (n = 902; 4 studies) but not for premenopausal women (n = 225; 2 studies) (RRs 0.74 (95% CI 0.59-0.93) and 0.76 (95% CI 0.49-1.19) per 10 MET-hours per week, respectively) (see Breast Cancer Survivors SLR 2013 figure 75). There was evidence of moderate (I^2 = 42.3%) and high (I^2 = 73.6%) heterogeneity in pre and postmenopausal women, respectively.

Three studies included pre and postmenopausal women and two included only postmenopausal women. Three studies were from the United States, one from China and one from Germany. All studies reported more than 100 deaths, and follow up time ranged from 4 to 8 years.

Published pooled analysis

Results are consistent with the After Breast Cancer Pooling Project which reported a 27% significant decreased risk of mortality by engaging in at least 10 MET-hours per week compared to less than 10 MET-hours per week [39].

CUP Panel's conclusions

The evidence was generally consistent showing an inverse association between physical activity and all cause mortality and breast cancer mortality. It was not clear to what extent individual studies have fully adjusted for potential confounders such as the tumour type, type of treatment, amount of treatment received, and the dissemination of the disease. The CUP Panel concluded:

Before a diagnosis of primary breast cancer

All cause mortality: The evidence is limited but generally consistent. The evidence suggesting that being physical active *before* a diagnosis of primary breast cancer reduces risk of *all cause mortality* is limited.

Breast cancer mortality: The evidence is limited but generally consistent. The evidence suggesting that being physical active *before* a diagnosis of primary breast cancer reduces risk of *breast cancer mortality* is limited.

12 months or more after a diagnosis of primary breast cancer

All cause mortality: There is ample evidence from follow-up studies, which is generally consistent and there is evidence of a dose-response relationship. However, the possibility of confounding cannot be excluded and there is no evidence from randomised controlled trials. The evidence suggesting that being physically active *12 months or more after* a diagnosis of primary breast cancer reduces risk of *all cause mortality* is limited.

6.6 Body fatness

(Also see Breast Cancer Survivors SLR 2013: Section 7.1, 7.6, 7.7 and 7.8)

BODY FATNESS

		INCREASES RISK	
		Timing of exposure assessment	Outcome
STRONG EVIDENCE	Convincing		
	Probable		
LIMITED EVIDENCE	Limited-suggestive	Before diagnosis	All cause mortality Breast cancer mortality[1] Second primary breast cancer
		<12 months after diagnosis	All cause mortality Breast cancer mortality[1] Second primary breast cancer
		≥12 months after diagnosis	All cause mortality
STRONG EVIDENCE	Substantial effect on risk unlikely		

1 Postmenopausal only

The following sections summarise the evidence identified by the CUP on body fatness before a diagnosis of primary breast cancer, less than 12 months after a diagnosis of primary breast cancer, and 12 months or more after a diagnosis of primary breast cancer.

The Panel interpreted body mass index (BMI), waist and hip circumference and waist-hip ratio as measures of body fatness. The Panel is aware that these anthropometrical measures are imperfect and cannot distinguish between lean mass and fat mass.

Before primary breast cancer diagnosis

The CUP identified 23 follow up studies on body fatness *before* a diagnosis of primary breast cancer and *all cause mortality* [13, 20, 22, 23, 26, 28, 29, 35, 40-58], 25 studies on body fatness and *breast cancer mortality* [20, 23, 26, 28, 29, 32, 40, 41, 44, 46-48, 52, 58-69], and three studies on body fatness and *second primary breast cancer* [70-72].

For ***all cause mortality,*** 23 studies reported on BMI, one of which also reported on waist and hip circumference, and waist-hip ratio.

For *BMI*, 20 studies reported a positive association of which 13 were statistically significant when comparing highest versus lowest groups (see Breast Cancer Survivors SLR 2013 figure 84).

Fourteen of the 23 studies identified in the CUP were included in the dose-response meta-analysis (n = 6,261), which showed a statistically significant 17% increased risk per 5 kg/m^2 (RR 1.17 (95% CI 1.13-1.21)) (see **figure 1** (Breast Cancer Survivors SLR 2013 figure 88)). There was evidence of low heterogeneity (I^2 = 13%). Egger's test for publication bias was significant (p = 0.04), which may be explained by two small studies that reported strong positive associations (see Breast Cancer Survivors SLR 2013 figure 89). There was no evidence of a strong influence from any one study.

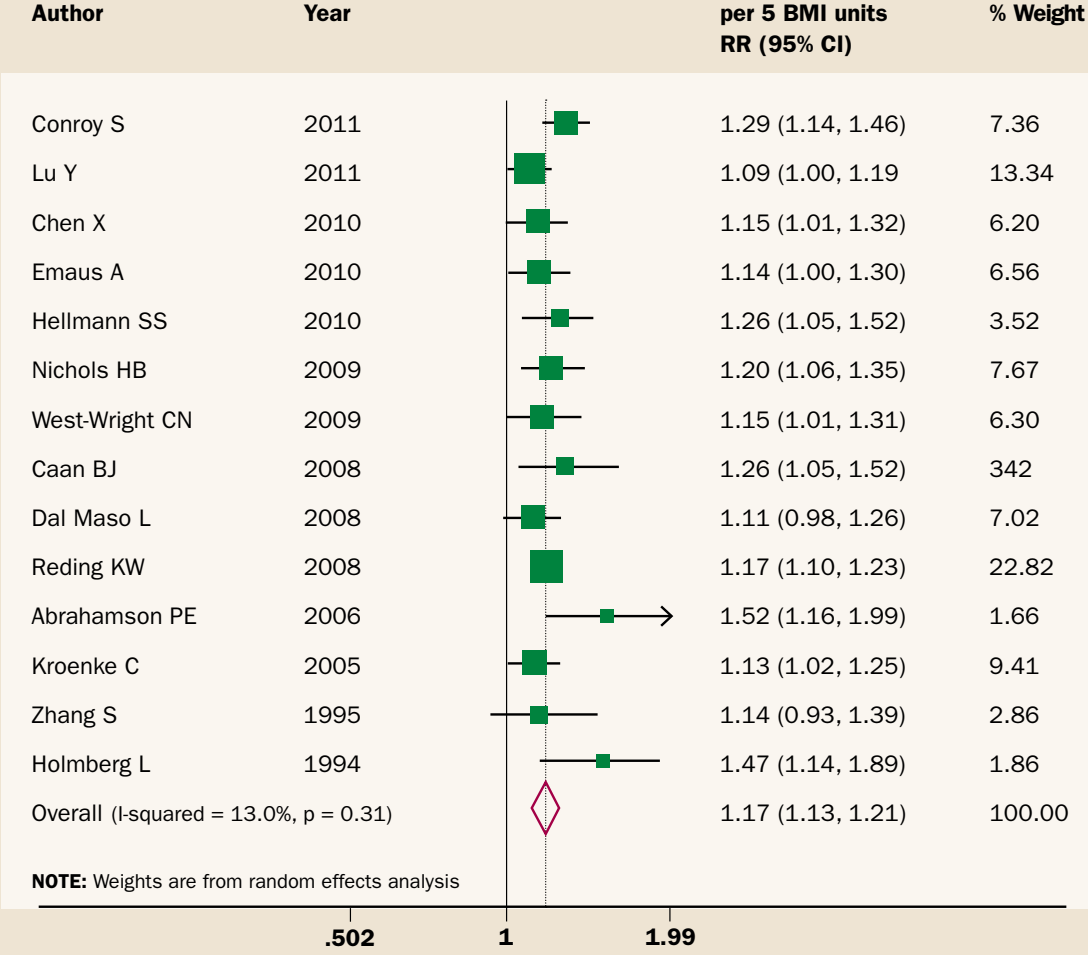
Stratification by menopausal status, showed a statistically significant increased risk for premenopausal and postmenopausal women. There was evidence of non-linearity (p < 0.001). A non-linear dose-response meta-analysis of all data, including those from the underweight patients, showed a slight J-shape relation (see Breast Cancer Survivors SLR 2013 figure 92).

Four studies included postmenopausal women only and two included premenopausal women only, with the remaining 18 including both pre and postmenopausal women. Two studies had less than 100 deaths, and follow up times ranged between 3 to 25 years.

Three studies were not included in the CUP analysis due to one reporting unadjusted results, and two reporting insufficient data.

For *waist and hip circumference*, and *waist-hip ratio* all studies reported a non-significant positive association. No meta-analysis was possible for waist and hip circumference, and waist-hip ratio.

Figure 1. Linear dose-response meta-analysis of BMI before primary breast cancer diagnosis and all cause mortality



Published pooled analysis

Results are consistent with the After Breast Cancer Pooling Project, which reported a 17% significant increased risk of all cause mortality for obese women, when compared with normal weight women [73]. An increased risk was observed when stratified by menopausal status, for postmenopausal women (RR 1.16 (95% CI 1.01-1.33)).

For ***breast cancer mortality***, 25 studies reported on BMI, one of which also reported on hip circumference.

For *BMI*, 21 studies compared highest versus lowest groups, 19 reported a positive association, of which 12 were statistically significant, and two a non-significant inverse association when comparing highest versus lowest groups (see Breast Cancer Survivors SLR figure 109).

Seventeen of the 25 studies identified were included in the dose-response meta-analysis for BMI (*n* = 6,634), which showed a statistically significant increased risk of 18% per 5 kg/m^2 (RR 1.18 (95% CI 1.11-1.24)) (see Breast Cancer Survivors SLR 2013 figure 113). There was evidence of moderate heterogeneity (I^2 = 47.8%).

Stratification by menopausal status showed an increased risk, which was statistically significant in postmenopausal (RR 1.15 (95% CI 1.05-1.25); I^2 = 53.6%; 7 studies) but not premenopausal women (RR 1.12 (0.92-1.35); I^2 = 72.3%; 5 studies).

Four studies were not included in the CUP analysis, two due to unadjusted results and two due to insufficient data.

For *hip circumference*, no risk estimate was reported, and no meta-analysis was carried out.

Published pooled analysis

Results are not consistent with the After Breast Cancer Pooling Project, which reported no significant association between breast cancer mortality in overweight (RR 1.04 (95% CI 0.92-1.18)) and obese women (RR 1.10 (95% CI 0.95-1.28)), when compared with normal weight women [73].

For ***second primary breast cancer***, three studies reported on BMI, two showed a significant positive association and one a non-significant inverse association comparing the highest versus lowest groups (see Breast Cancer Survivors SLR figure 126).

All three of the studies identified were included in the dose-response meta-analysis (*n* = 701), which showed a statistically significant increased risk of 21% per 5 kg/m^2 (RR 1.21 (95% CI 1.04-1.40)) (see Breast Cancer Survivors SLR 2013 figure 127). There was evidence of low heterogeneity (I^2 = 20.8%).

One study was on premenopausal only, while the other two included pre and postmenopausal women. All but one study included more than 100 cases, and all studies were carried out in the United States.

Less than 12 months after diagnosis of primary breast cancer

The CUP identified 45 follow up studies on body fatness less than 12 months after a diagnosis of primary breast cancer and *all cause mortality* as the outcome [11, 20, 42, 51, 74-113], 20 studies on body fatness and *breast cancer mortality* as the outcome [12, 20, 76, 78, 79, 85-87, 89, 92, 97, 100, 114-123], and eight studies on body fatness and *second primary breast cancer* as the outcome [87, 97, 124-129].

For ***all cause mortality,*** 44 studies reported on BMI, three of which also reported on waist circumference, two on hip circumference, and three on waist-hip ratio. One study reported on waist-hip ratio only.

For *BMI*, 26 studies compared highest versus lowest groups, 22 reported a positive association, of which 14 were statistically significant, and four reported an inverse association, of which one was statistically significant.

Ten of the 44 studies identified were included in the dose-response meta-analysis (*n* = 5,875), which showed a statistically significant increased risk of 11% per 5 kg/m^2 (RR 1.11 (95% CI 1.06-1.17)) (see **figure 2** (Breast Cancer Survivors SLR 2013 figure 97)). There was evidence of substantial heterogeneity (I^2 = 60.5%). There was evidence of non-linearity (p = 0.02). A non-linear dose-response meta-analysis of all data, including those from the underweight patients, showed a slight J-shape relation (see Breast Cancer Survivors SLR 2013 figure 104).

All of the 10 included studies reported over 100 deaths and included pre and postmenopausal women. Follow up time was between 4 and 14 years.

Fifteen studies were not included in the CUP analysis due to five reporting unadjusted results, and ten reporting insufficient data.

For *waist circumference*, all three studies reported a positive association when comparing the highest versus the lowest groups, one of which was statistically significant (see Breast Cancer Survivors SLR figure 149).

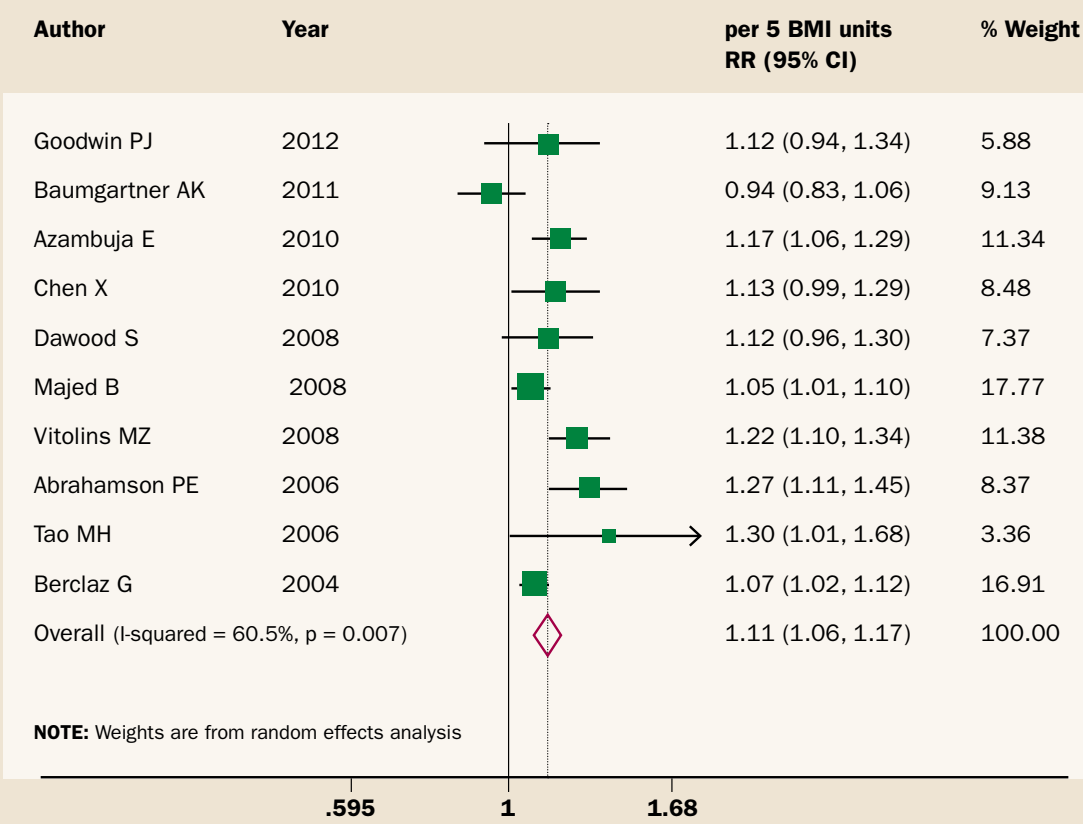
All three studies were included in the dose-response meta-analysis (*n* = 664), which showed no significant association per 10 cm (RR 1.21 (95% CI 0.97-1.49)) (see Breast Cancer Survivors SLR 2013 figure 150).

For *waist-hip ratio*, all four studies reported a positive association when comparing the highest versus the lowest groups, two of which were statistically significant (see Breast Cancer Survivors SLR figure 152).

All four of the studies were included in the dose-response meta-analysis (*n* = 1,475), which showed a statistically significant increased risk of 31% per 0.1 unit (RR 1.31 (95% CI 1.17-1.48)) (Breast Cancer Survivors SLR 2013 figure 153). No heterogeneity was observed. All studies included pre and postmenopausal women.

No dose-response analysis was carried out on hip circumference.

Figure 2. Linear dose-response meta-analysis of BMI less than 12 months after diagnosis of primary breast cancer and all cause mortality



For ***breast cancer mortality,*** 20 studies reported on BMI, and two on waist-hip ratio.

For *BMI,* 11 studies compared highest versus lowest groups, 10 reported a positive association, of which six were significant, and one reported a non-significant inverse association (see Breast Cancer Survivors SLR 2013 figure 117).

Five of the 20 studies identified were included in the dose-response meta-analysis (*n* = 1,918), which showed a statistically significant increased risk of 18% per 5 kg/m^2 (RR 1.18 (95% CI 1.11-1.25)) (see Breast Cancer Survivors SLR 2013 figure 121). No heterogeneity was observed.

All studies included pre and postmenopausal women, except one that reported on postmenopausal only. All but three included more than 100 deaths. Follow up time in most studies was greater than 4 years.

Six studies were not included in the CUP analysis, three due to unadjusted results and three due to insufficient data.

For *waist-hip ratio*, one study reported a non-significant positive association; the other study reported a significant positive association in postmenopausal women and a non-significant positive association in premenopausal women. No meta-analysis was carried out.

For ***second primary breast cancer***, eight studies reported on BMI, all compared highest versus lowest groups, seven reported a positive association, of which one was significant, and one reported a non-significant inverse association.

Seven of the eight studies identified in the CUP were included in the dose-response meta-analysis (*n* = 3,186), which showed a statistically significant increased risk of 13% per 5 kg/m^2 (RR 1.13 (95% CI 1.06-1.21)) (see Breast Cancer Survivors SLR 2013 figure 130). There was evidence of low heterogeneity (I^2 = 15.2%).

All studies included pre and postmenopausal women, and more than 100 cases. Follow up time in most studies was greater than 3 years. Anthropometrical data were either taken from medical records or self-reported.

12 months or more after diagnosis of primary breast cancer

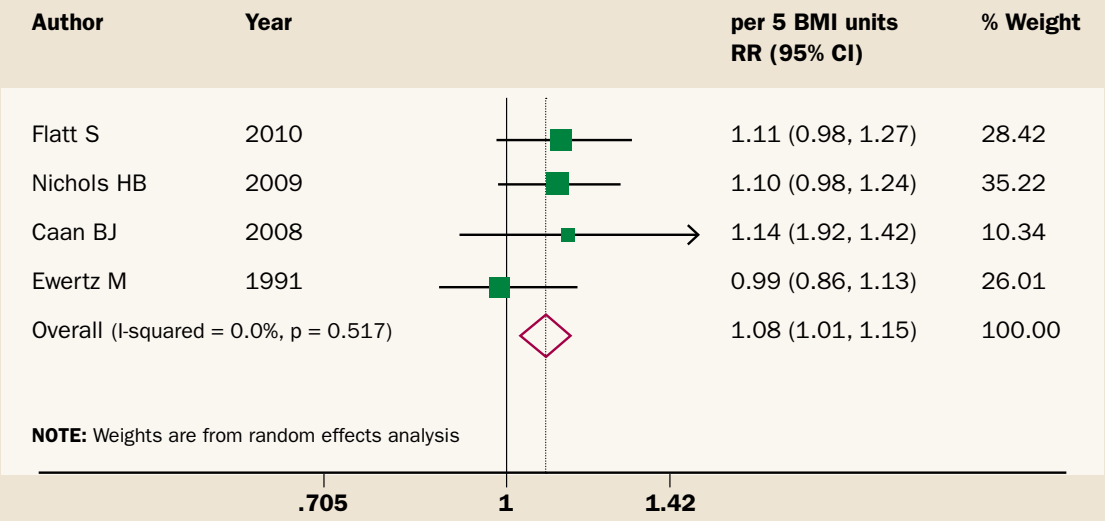
The CUP identified five follow up studies on body fatness *12 months or more* after a diagnosis of primary breast cancer and *all cause mortality* as the outcome [44, 48, 130-134].

For *all cause mortality*, four of the five studies reported a non-significant positive association when comparing the highest versus the lowest, and the other reported a non-significant inverse association (see Breast Cancer Survivors SLR 2013 figure 105).

Four of the five studies identified were included in the dose-response meta-analysis (*n* = 1,703), which showed a statistically significant 8% increased risk per 5 kg/m^2 (RR 1.08 (95% CI 1.01-1.15)) (see **figure 3** (Breast Cancer Survivors SLR 2013 figure 107)). No heterogeneity was observed.

All five studies included pre and postmenopausal women and included more than 100 deaths. Follow up time in most studies was greater than 6 years.

Figure 3. Linear dose-response meta-analysis of BMI 12 months or more after diagnosis of primary breast cancer and all cause mortality



CUP Panel's conclusions

There is generally consistent evidence of a positive association between greater body fatness (which the CUP Panel interprets to be marked by BMI) and all cause mortality, breast cancer mortality and development of second primary breast cancer. However, it is not clear to what extent individual studies have fully adjusted for potential confounders such as the tumour type, type of treatment, amount of treatment received, and the dissemination of the disease. The evidence on waist circumference, hip circumference and waist-hip ratio was consistent with that of BMI, but was limited. The CUP Panel therefore concluded:

Before a diagnosis of primary breast cancer

All cause mortality: The evidence is substantial, consistent, and shows evidence of a dose-response relationship, but the possibility of confounding cannot be excluded. The evidence suggesting that greater body fatness *before* a diagnosis of primary breast cancer reduces risk of *all cause mortality* is limited.

Breast cancer mortality: The evidence is substantial, generally consistent, and shows evidence of a dose-response relationship, but the possibility of confounding cannot be excluded. The evidence suggesting that greater body fatness *before* a diagnosis of postmenopausal primary breast cancer reduces risk of *breast cancer mortality* is limited.

Second primary breast cancer: **The evidence is limited and there is some inconsistency. The evidence suggesting that greater body fatness *before* a diagnosis of primary breast cancer reduces risk of a *second primary breast cancer* is limited.**

Less than 12 months after a diagnosis of primary breast cancer

All cause mortality: **The evidence is substantial, generally consistent, and shows evidence of a dose-response relationship, but the possibility of confounding cannot be excluded. The evidence suggesting that greater body fatness *less than 12 months after* a diagnosis of primary breast cancer reduces risk of *all cause mortality* is limited.**

Breast cancer mortality: **The evidence is substantial, consistent, and shows evidence of a dose-response relationship, but the possibility of confounding cannot be excluded. The evidence suggesting that greater body fatness *less than 12 months after* a diagnosis of postmenopausal primary breast cancer reduces risk of *breast cancer mortality* is limited.**

Second primary breast cancer: **The evidence is substantial, generally consistent, and shows evidence of a dose-response relationship, but the possibility of confounding cannot be excluded. The evidence suggesting that greater body fatness *less than 12 months after* a diagnosis of primary breast cancer reduces risk of *second primary breast cancer* is limited**

12 months or more after a diagnosis of primary breast cancer

All cause mortality: **The evidence is substantial, generally consistent, and shows some evidence of a dose-response relationship, but the possibility of confounding factors cannot be excluded. The evidence suggesting that greater body fatness *12 months or more after* a diagnosis of primary breast cancer reduces risk of *all cause mortality* is limited.**

6.7 Other

Other exposures were evaluated. However, data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. For data on survival in underweight patients versus normal weight patients, the Panel was unable to make a conclusive judgement, as it was not clear if weight had been lost unintentionally or intentionally. The list of exposures judged as 'limited-no conclusion' is summarised in the matrix on page 6.

7. Conclusions

The Recommendations for cancer survivors will be reviewed in 2017 as part of the review of the Recommendations for Cancer Prevention. The CUP Panel will review the evidence relating to breast cancer survivors again after 2017.

The CUP Panel judges that:

- **In relation to *all cause mortality*, the evidence suggesting that:**

  A higher consumption of foods containing fibre *before* or *12 months or more after* a diagnosis of primary breast cancer reduces risk is limited.

  A higher consumption of foods containing soy *12 months or more after* a diagnosis of primary breast cancer reduces risk is limited.

  Consuming a diet higher in total fat *before* a diagnosis of primary breast cancer increases risk is limited.

  Consuming a diet higher in saturated fatty acids *before* a diagnosis of primary breast cancer increases risk is limited.

  Being physically active *before* or *12 months or more after* a diagnosis of primary breast cancer increases risk is limited.

  Greater body fatness *before*, *less than 12 months after*, or *12 months or more after*, a diagnosis of primary breast cancer increases risk is limited.

- **In relation to *breast cancer mortality*, the evidence suggesting that:**

  Being physically active *before* a diagnosis of primary breast cancer reduces risk is limited.

  Greater body fatness *before*, or *less than 12 months after* a diagnosis of postmenopausal primary breast cancer increases risk is limited.

- **In relation to second primary breast cancer, the evidence suggesting that:**

  Greater body fatness *before,* or *less than 12 months after* a diagnosis of primary breast cancer increases risk is limited.

Acknowledgements

Panel Members

CHAIR - **Alan Jackson** CBE MD FRCP FRCPath FRCPCH FAfN
University of Southampton
Southampton, UK

Elisa Bandera MD PhD
Rutgers Cancer Institute of New Jersey
New Brunswick, NJ, USA

Steven Clinton MD PhD
The Ohio State University
Columbus, OH, USA

Edward Giovannucci MD ScD
Harvard School of Public Health
Boston, MA, USA

Stephen Hursting PhD MPH
University of North Carolina at Chapel Hill
Chapel Hill, NC, USA

Michael Leitzmann MD DrPH
Regensburg University
Regensburg, Germany

Anne McTiernan MD PhD
Fred Hutchinson Cancer Research Center
Seattle, WA, USA

Hilary Powers PhD RNutr
University of Sheffield
Sheffield, UK

Inger Thune MD
Oslo University Hospital and University of Tromsø
Norway

Ricardo Uauy MD PhD
Instituto de Nutrición y Technología de los Alimentos
Santiago, Chile

Observers

Elio Riboli MD ScM MPH
Imperial College London
London, UK

Isabelle Romieu MD MPH ScD
International Agency for Research on Cancer
Lyon, France

Research team

Teresa Norat PhD
Principal Investigator
Imperial College London
London, UK

Doris Chan
Research Associate
Imperial College London
London, UK

Ana Rita Vieira
Research Associate
Imperial College London
London, UK

Dagfinn Aune
Research Associate
Imperial College London
London, UK

Deborah Navarro-Rosenblatt
Research Associate
Imperial College London
London, UK

Snieguole Vingeliene
Research Associate
Imperial College London
London, UK

Leila Abar
Research Associate
Imperial College London
London, UK

Rui Vieira
Data Manager
Imperial College London
London, UK
Until September 2012

Darren Greenwood PhD
Statistical Advisor
Senior Lecturer in Biostatistics
University of Leeds
Leeds, UK
Advisor to ICL for the protocol development meeting

Cancer survivors protocol development committee

CHAIR – **Lawrence H Kushi** ScD
Kaiser Permanente,
Oakland CA, USA

Marie-Christine Boutron-Ruault
MD, PhD
INSERM, E3N-EPIC Group
Institut Gustave Roussy
Villejuif, France

Bas Bueno-de-Mesquita MD MPH PhD
National Institute for Public Health
Bilthoven, The Netherlands

Josette Chor PhD MBBS FHKAM
School of Public Health and Primary Care
Chinese University of Hong Kong, Hong Kong

Wendy Demark-Wahnefried PhD RD
University of Alabama at Birmingham
Comprehensive Cancer Centre
Birmingham AL, USA

Michelle Harvie PhD RD
University of Manchester, UK

WCRF Executive

Kate Allen PhD
Executive Director, Science & Public Affairs
WCRF International

Deirdre McGinley-Gieser
Senior Vice President for Programs
AICR

Secretariat

HEAD - **Rachel Thompson** PhD RNutr
Head of Research Interpretation
WCRF International

Susan Higginbotham PhD RD
Vice President of Research
AICR

Rachel Marklew RNutr
Science Programme Manager
(Communications)
WCRF International
Until February 2014

Amy Mullee PhD
Science Programme Manager
(Research Interpretation)
WCRF International
From January 2014

Martin Wiseman FRCP FRCPath FAfN
Medical and Scientific Adviser
WCRF International

Giota Mitrou PhD
Head of Research Funding and
Science Activities
WCRF International

Abbreviations

BMI	Body mass index
CUP	Continuous Update Project
GRADE	Grading of Recommendation Assessment, Development and Evaluation
RCT	Randomised Controlled Trial
RR	Relative Risk
SLR	Systematic literature review
n	Number of cases

Glossary

Adjustment
A statistical tool for taking into account the effect of known confounders.

Bias
In epidemiology, 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 design or analysis.

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

Carcinoma
Malignant tumour derived from epithelial cells, usually with the ability to spread into the surrounding tissue (invasion) and produce secondary tumours (metastases).

Carcinoma in situ
The first stage of carcinoma in which the malignant tumour has not spread beyond the epithelium.

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 past or recent history of an exposure such as smoking, genetic profile, alcohol consumption, or dietary intake is associated with the risk of disease.

Cohort study
A study of a (usually large) group of people whose characteristics are recorded at recruitment (and sometimes later), 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 to 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 in one study may be expressed as 10 (95% CI 5–15). This means that in this particular analysis, 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, within a specific epidemiological study, that is associated with an exposure, is also a risk factor for the disease, and is not in the causal pathway from the exposure to the disease. If not adjusted for, 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 (controlled) in studies, might make coffee drinking appear falsely as a possible cause of lung cancer.

Confounding factor (see confounder)

Dietary fibre
Constituents of plant cell walls that are not digested in the small intestine. Several methods of analysis are used, which identify different components. The many constituents that are variously included in the definitions have different chemical and physiological features that are not easily defined under a single term. The different analytical methods do not generally characterise the physiological impact of foods or diets. Non-starch polysaccharides are a consistent feature and are fermented by colonic bacteria to produce energy and short chain fatty acids including butyrate. The term dietary fibre is increasingly seen as a concept describing a particular aspect of some dietary patterns.

Egger's test
A statistical test for small study effects such as publication bias.

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.

Fatty acid
A carboxylic acid with a carbon chain of varying length, which may be either saturated (no double bonds) or unsaturated (one or more double bonds). Three fatty acids attached to a glycerol backbone make up a triglyceride, the usual form of fat in foods and adipose tissue.

Forest plot
A simple visual representation of the amount of variation between the results of the individual studies in a meta-analysis. Their construction begins with plotting the observed exposure effect of each individual study, which is represented as the centre of a square. Horizontal lines run through this to show the 95% confidence interval. Different sized squares may be plotted for each of the individual studies, the size of the box increasing with the size of the study and the weight that it takes in the analysis. The overall summary estimate of effect and its confidence interval can also be added to the bottom of this plot, if appropriate, and this is represented as a diamond. The centre of the diamond is the pooled summary estimate and the horizontal tips are the confidence intervals.

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.

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

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.

Lesion
A general term for any abnormality of cells or tissues, including those due to cancerous change.

Malignant
A tumour with the capacity to spread to surrounding tissue or to other sites in the body.

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

Metabolic equivalent (MET)
One MET equals the resting metabolic rate, measured as the rate of oxygen consumption, which is approximately 3.5 millilitres of oxygen per kilogram body weight per minute. Equivalent to physical activity ratio.

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.

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

Peer review
The scrutiny of scientific papers by one or more suitably qualified scientists.

Physical activity
Any movement using skeletal muscles.

Pooled analysis (see pooling)

Pooling

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

Publication bias

A bias in the overall balance of evidence in the published literature due to selective publication. Not all studies carried out are published, and those that are may differ from those that are not. Publication bias can be tested for with either Begg's or Egger's tests.

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. Neither investigators nor subjects usually know to which condition they have been randomised; this is called 'double-blinding'.

Relative risk (RR)

The ratio of the rate of disease or death among people exposed to a factor, compared to the rate among the unexposed, usually used in cohort studies.

Saturated fatty acids

Fatty acids that do not contain any double bonds.

Socioeconomic status

A combined product of social and economic status reflecting education level, personal wealth, class, and associated factors.

Statistical significance

The probability that any observed result might not have occurred by chance. In most epidemiologic work, a study result whose probability is less than 5% ($p < 0.05$) is considered sufficiently unlikely to have occurred by chance to justify the designation '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 circumference ratio

A measure of body shape indicating fat distribution.

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Appendix 1 - Breast Cancer Prevention 2010 report matrices

FOOD, NUTRITION, PHYSICAL ACTIVITY AND BREAST CANCER (PREMENOPAUSE) 2010

	DECREASES RISK	INCREASES RISK
Convincing	**Lactation**	**Alcoholic drinks**
Probable	**Body fatness**	**Adult attained height[1]** **Greater birth weight**
Limited - suggestive	**Physical activity[2]**	
Limited - no conclusion	Dietary fibre; vegetables and fruits; soya and soya products; meat; fish; milk and dairy products; total fat; folate; vitamin D; calcium; glycaemic index; dietary patterns; adult weight gain; abdominal fatness	
Substantial effect on risk unlikely	None identified	

1 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.13 – Second Expert Report).

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

FOOD, NUTRITION, PHYSICAL ACTIVITY AND BREAST CANCER (POSTMENOPAUSE) 2010

	DECREASES RISK	INCREASES RISK
Convincing	**Lactation**	**Alcoholic drinks** **Body fatness** **Adult attained height[1]**
Probable	**Physical activity[2]**	**Abdominal fatness** **Adult weight gain**
Limited - suggestive		**Total fat**
Limited - no conclusion	Dietary fibre; vegetables and fruits; soya and soya products; meat; fish; milk and dairy products; folate; vitamin D; calcium; selenium; glycaemic index; dietary patterns; birth weight; energy intake	
Substantial effect on risk unlikely	None identified	

1 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.13 – Second Expert Report).

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

Appendix 2 - Criteria for grading evidence for Breast Cancer Survivors

A. The criteria

The grades are 'convincing', 'probable', 'limited-suggestive', 'limited-no conclusion', and 'substantial effect on risk unlikely.' The Panel's recommendations for Breast Cancer Survivors will be made using evidence for a that is judged to demonstrate a 'convincing' or 'probable' causal effect, or 'substantial effect on risk unlikely'.

CONVINCING (requires RCT evidence)

These criteria are for evidence strong enough to support a judgment of a convincing effect or causal relationship, which justifies goals and recommendations designed to reduce second primary breast cancer occurrence and mortality.

1. Evidence of an effect from a meta-analysis of RCTs or at least two well-designed independent RCTs

a) No substantial unexplained heterogeneity
b) No evidence of publication bias
c) Note: strong and plausible mechanistic evidence is desirable but not required

PROBABLE

These criteria are for evidence strong enough to support a judgment of a probable effect or causal relationship, which would generally justify goals and recommendations designed to reduce second primary breast cancer occurrence and mortality. Note: 'Well-designed' cohort studies must demonstrate adequate control for potential confounders including the type of tumour, type of treatment, amount of treatment received, and the dissemination of the disease.

1. Evidence of an effect from a meta-analysis of RCTs or two well-designed RCTs

a) Some unexplained heterogeneity allowed
b) No evidence of publication bias
c) Note: strong and plausible mechanistic evidence is desirable but not required

OR

2. Evidence of an effect from one well-designed RCT and one well-designed cohort study

a) No unexplained heterogeneity
b) No evidence of publication bias
c) Strong and plausible mechanistic evidence

OR

3. Evidence from at least one well-designed pooled analysis of follow-up studies

a) No unexplained heterogeneity
b) No evidence of publication bias
c) Strong and plausible mechanistic evidence

OR

4. Evidence from at least two independent well-designed follow-up studies

d) No unexplained heterogeneity
e) No evidence of publication bias
f) Strong and plausible mechanistic evidence

LIMITED SUGGESTIVE

These criteria are for evidence that is too limited to permit a probable or convincing judgement, but where there is evidence suggestive of a direction of effect. The evidence may have methodological flaws, or be limited in amount, but shows a generally consistent direction of effect. This level of evidence would not be used to justify making specific recommendations.

Evidence from RCTs

1. Evidence from a meta-analysis of RCTs or at least two well-designed RCTs but the confidence interval may include the null

a) Some unexplained heterogeneity allowed
b) No evidence of publication bias
c) Strong and plausible mechanistic evidence is not required

OR

2. Evidence from one well-designed RCT but the confidence interval may include the null

a) No unexplained heterogeneity
b) No evidence of publication bias
c) Strong and plausible mechanistic evidence

OR

Evidence from pooled follow-up studies

3. Evidence of an effect from a pooled analysis of follow-up studies

a) Some unexplained heterogeneity allowed
b) No evidence of publication bias
c) Strong and plausible mechanistic evidence not required

OR

4. Evidence from a pooled analysis of follow-up studies but the confidence interval may include the null

a) Some unexplained heterogeneity allowed
b) No evidence of publication bias
c) Strong and plausible mechanistic evidence

OR

Evidence from follow-up studies

5. Evidence of an effect from at least one follow-up study

a) No unexplained heterogeneity
b) No evidence of publication bias
c) Strong and plausible mechanistic evidence

OR

6. Evidence of an effect from at least two follow-up studies

a) No unexplained heterogeneity
b) No evidence of publication bias
c) Strong and plausible mechanistic evidence not required

OR

7. Evidence from at least two follow-up studies but the confidence interval may include the null

a) Some unexplained heterogeneity allowed
b) No evidence of publication bias
c) Strong and plausible mechanistic evidence

LIMITED – NO CONCLUSION (any of the following)

Evidence is so limited that no firm conclusions can be made. Evidence may be judged 'limited-no conclusion' for any of the following reasons:

- Too few studies available
- Inconsistency of direction of effect
- Poor quality of studies

SUBSTANTIAL EFFECT ON RISK UNLIKELY

Evidence is strong enough to support a judgement that a particular exposure is unlikely to have a substantial effect or causal relation to a cancer outcome. The evidence should be robust enough to be unlikely to be modified in the foreseeable future. Note: evidence of absence of an effect is required for each time frame being studied (before diagnosis, less than 12 months after diagnosis, and 12 months or more after diagnosis). All of the following are required: (Note: 'Well-designed' cohort studies must demonstrate adequate control for potential confounders including the type of tumour, type of treatment, amount of treatment received, and the dissemination of the disease).

- Evidence of the absence of an effect (a summary estimate close to 1.0) from any of the following:

a) a meta-analysis of RCTs
b) at least two well-designed independent RCTs
c) a well-designed pooled analysis of follow-up studies
d) at least two well-designed1 follow-up studies

- No substantial unexplained heterogeneity
- Absence of a dose response relationship (in follow-up studies)
- Absence of strong and plausible mechanistic evidence

SPECIAL UPGRADING FACTORS

- 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 (a relative risk of 2.0 or more, or 0.5 or less, depending on the unit of exposure), after appropriate control for confounders.
- Evidence from appropriately controlled experiments demonstrating one or more plausible and specific mechanisms
- All plausible known residual confounders or biases including reverse causation would reduce a demonstrated effect, or suggest a spurious effect when results show no effect. Special considerations important for evidence for breast cancer survivors include the following potential confounding variables - the type of tumour, type of treatment, amount of treatment received, and the dissemination of the disease.

B. Background

The following study designs are included in the protocol for the Systematic Literature Review being conducted for studies of breast cancer survivors

1. Follow up of breast cancer cases from case-control studies
2. Follow up of breast cancer cases from cohort studies
3. Cohort studies of cancer survivors
4. Ancillary analyses from randomised controlled trials (RCTs)
5. RCTs with follow up of at least 6 months*
6. Published meta-analyses and pooled analyses are searched for by the team at Imperial College London and included in the Systematic Literature Reviews (SLRs) but are not entered into the database.

Study designs 1-4 are all referred to as "follow up studies" in the grading criteria.

* 6 months was set with regard to quality of life which is included in the original protocol but not the 2012 SLR. For outcomes included in the 2012 SLR two years is more appropriate. It is important to note that women with some types of breast cancer can survive decades, and therefore follow-up may need to be much longer than two years depending on the type of breast cancers studied.

Study designs not included in the above list are excluded.

Please note: grading criteria are to be applied within each timeframe of exposure assessment for each exposure and outcome. The timeframes are (1) before primary breast cancer diagnosis, (2) less than 12 months after diagnosis of primary breast cancer diagnosis and (3) 12 months or more after diagnosis of primary breast cancer.

The outcomes included in the Systematic Literature Review Continuous Update Project Report from Imperial College London are:

1. Total mortality
2. Breast cancer mortality
3. Second primary breast cancer

No other outcomes are being addressed at this time.

C. Special considerations to take into account when grading breast cancer survivor evidence:

1. ***What treatments have the cohort members had?*** Treatment varies by breast tumour type and patient characteristics. The type and amount of treatment can have greater effect on survival than most exposures related to diet, nutrition, and physical activity, and there is likely confounding factor. In the United States, for example, access to treatments varies by economics, as does diet and physical activity, so an apparent diet-survival relationship may be confounded by the type of treatment received. This also pertains to stage at diagnosis but stage is more easily ascertained in studies and is thus easier to control for than treatment information.

2. ***Healthy cohort effect.*** Some types of breast cancer recur early and cause early mortality. If a survivor cohort is assembled a long time after diagnosis, women at high risk for mortality may not be included. This has happened in some cohorts already (including the HEAL study), and in any trial that included persons diagnosed in the more distant past (for example the WHEL study). This is particularly important for some types of cancer (such as breast cancer negative for oestrogen and progesterone receptors and HER2).

3. ***Time periods and changes in treatments.*** Due to improved knowledge regarding tumour type, new treatment regimens have changed the expected effect of treatment and thus breast cancer mortality. For example, 15-20% of breast cancer cases are now known to be positive for HER2. Treatment regimens vary according to time periods, country, and socio-economic status within countries.

4. ***Early mortality vs. late mortality.*** For most breast cancer types, independent of tumor type, early recurrence is that occurring within the first 2 years (possible due to already metastatic disease not responding to adjuvant treatment). Thereafter, 10-year and, to a lesser extent, 5-year breast cancer survival should be discussed. This underlines the importance of understanding breast cancer as a chronic disease with longer expected survival time.

D. Special considerations regarding RCTs and breast cancer survivor studies

1. A greater weight is placed on RCTs versus follow-up studies for the grading criteria for cancer survivors compared with the grading criteria for cancer incidence because of the greater possibility and difficulty correcting for confounding in observational studies. Evidence of an effect from a meta-analysis of RCTs or at least two well-designed independent RCTs is required for evidence to be judged 'convincing'.

2. RCTs can also determine adverse effects. Most treatment trials include careful attention to adverse effects, and that needs to be addressed for nutrition/physical activity/weight change trials also.

3. When good quality data from RCTs are available, strong and plausible mechanistic evidence is desirable, but is not required, for evidence to be judged 'convincing'.

4. RCT evidence is not required for evidence to be judged 'probable' but strong and plausible mechanistic evidence is required if there is not good RCT evidence, and the observational data need to be fully adjusted for potential confounders such as the tumour type, type of treatment, amount of treatment received, and the dissemination of the disease.

5. The evidence is stronger when there are similar results from different designs (e.g RCT and cohort). Also, for some exposures such as alcohol, RCT evidence may never be available.

6. RCT evidence may have good internal validity if it is well conducted; however patients included in RCTs may not be representative of the wider population of breast cancer survivors. Survivors who do not enter RCTs may be sicker and have different lifestyles and could have lower survival. In terms of generalisability, more weight should be put on cohort studies with large numbers of cases and a high response to follow-up.

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World Cancer Research Fund International

World Cancer Research Fund International
Second Floor
22 Bedford Square
London WC1B 3HH
United Kingdom

Tel: +44 (0) 20 7343 4200
Fax: +44 (0) 20 7343 4220
Email: international@wcrf.org

www.wcrf.org