World Cancer Research Fund International
Continuous Update Project Report

Systematic review on diet, nutrition, physical activity and survival and second cancers in breast cancer survivors

Analysing research on cancer prevention and survival

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Background

A. Second expert report and CUP reports on cancer survivors

The Panel of Experts for the 2007 WCRF/AICR report concluded that the available evidence from clinical trials on nutrition and physical activity, and cancer prognosis was limited and could not support specific recommendations for cancer survivors.

The ongoing review in the CUP review differs from the Systematic Literature Review commissioned for the 2007 WCRF/AICR report in two main aspects. First, all cancer sites were included in the 2007 SLR on cancer survivors, whereas the ongoing CUP review is restricted to studies on **breast cancer survivors**. Second, the SLR for 2007 WCRF/AICR Report was an SLR of randomised controlled trials, supplemented with a narrative review of observational studies, whereas the CUP will systematically review randomised controlled trials and observational longitudinal studies.

The review is conducted by the CUP team at Imperial College with the collaboration of Darren Greenwood (University of Leeds), Statistical advisor for the CUP and Tim Reeves, Research Support Librarian of the Medicine Central Library, Imperial College London, and under the coordination of Rachel Thompson (WCRF).

B. Modifications to the study protocol

The protocol for the CUP review on breast cancer survivors was prepared by the Imperial College Team. Advice was provided by a committee commissioned by WCRF. The protocol and the list of members of the Cancer Survivors Protocol Development Committee are in Annex 1.

A preliminary report of the CUP review on breast cancer survivors was discussed by the CUP Panel on June 13th 2012. Anne McTiernan led the discussion. The Panel indicated aspects related to the quality of the individual studies and recommended to add these to the tables in the report. The Panel also recommended to simplify the review.

The modifications to the protocol are detailed below:

a. Inclusion criteria (inclusion and exclusion criteria are in Annex 1 of this review)

The endpoints that will be considered in the review are total mortality, cause-specific mortality, in particular breast cancer mortality and cardiovascular disease mortality and second primary breast cancer.

Breast cancer recurrence, long-term treatment side effects and quality of life are not included as endpoints of the review. The reason is that accurate assessment of recurrences and long-term treatment side-effects requires access to medical records. Although randomised trials based on clinical series often have access to medical records, most often other studies and in particular, observational studies don't have complete access to medical records and rely on self-reported assessment, which is often unreliable. Finally, the definition used for recurrence varied across studies.

Quality of life is not included in the review. Summarising the results is not feasible due to the lack of evidence on the comparability of the extensive variety of instruments applied to assess quality of life in the existing studies.

b. Timeframe of exposure assessment

The timeframe of exposure assessment indicated in the protocol as "during therapy" was modified to "less than 12 months after diagnosis". This category includes studies in which exposure was assessed when some participants had not started treatment, some were under treatment and some have finished the treatment. These studies collected information in a timeframe shorter than a year from diagnosis. The information on the treatment status was included in the tables when it was provided in the papers.

c. Assessment of susceptibility to bias

In addition to the dimensions indicated in the protocol, the tables will include other study characteristics that may influence the results, as suggested by the CUP Panel:

- Time between breast cancer diagnosis and study recruitment
- Stage at cancer diagnosis
- Hormone receptor status
- Treatments and adherence
- Calendar period of breast cancer diagnosis

d. Statistical analysis

The protocol indicates that only dose-response meta-analyses will be conducted. However, high vs low meta-analyses had been included in this review for the following reasons:

For some exposures, only highest vs. lowest comparisons were possible.

The number of studies was low for some exposures and endpoints and no dose-response was reported in the papers. The highest vs lowest meta-analysis, conducted with the original data, can be useful for comparison with the dose-response meta-analysis where slopes had been derived by the review team from categorical data.

C. Results of the search

The WCRF database for breast cancer survivors was created at Imperial College and has been updated with results of studies published until 30th June 2012 (there was not a database from the SLR for 2007 WCRF/AICR report).

A total of 213 articles on mortality or second primary cancer as endpoints have been identified by the search. The flow chart of the search is in **Figure 1**. The distribution of articles by intervention/exposures according to study design is in **Table 1**.

Figure 1 Flow chart of the search on breast cancer survivors (Last searched on 30th June 2012)

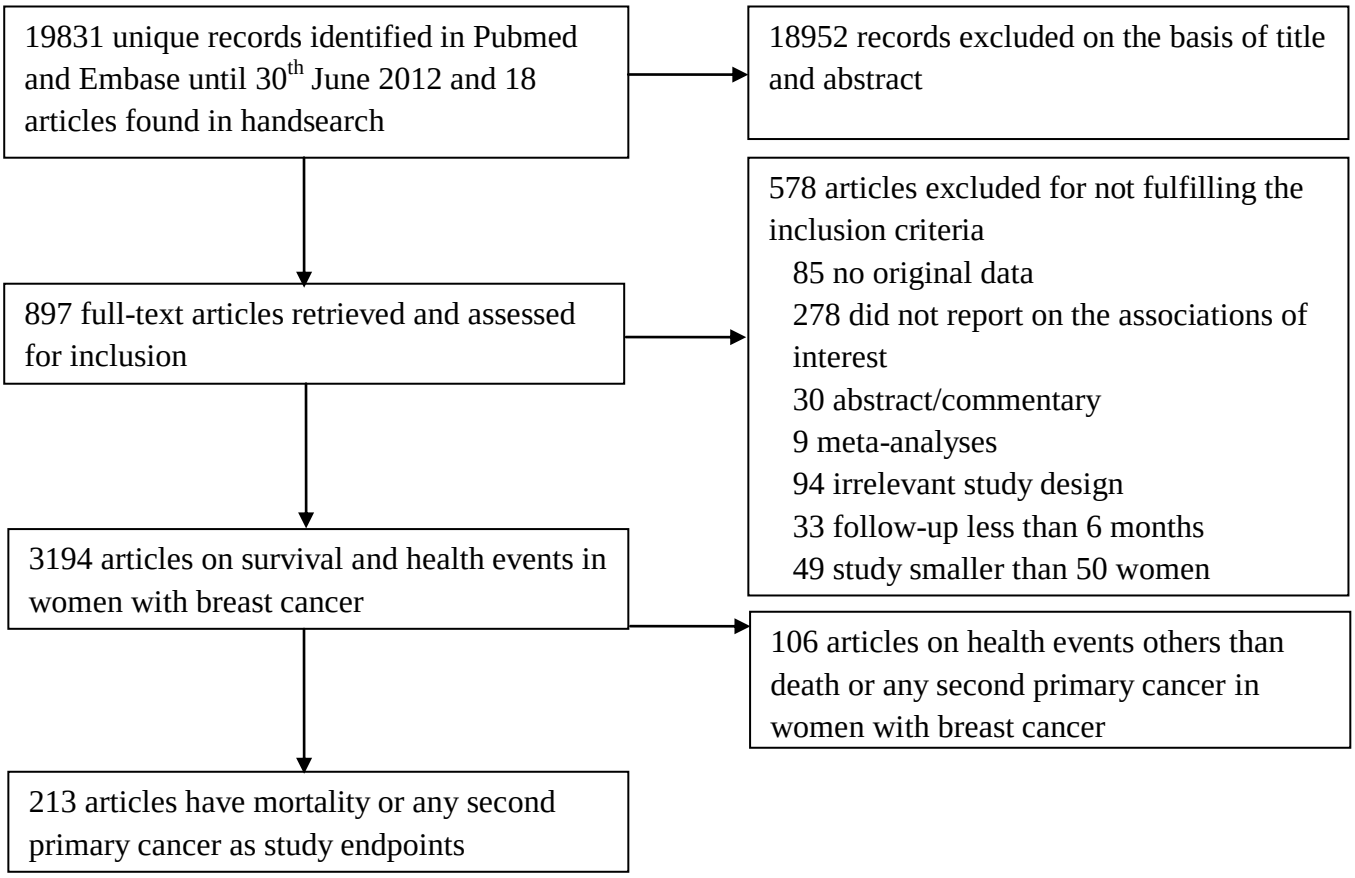


Table 1 Number of studies on breast cancer survivors by intervention/before, less than 12 months after, and 12 months or more after diagnosis exposure and outcome with more than 3 studies for any relevant outcome during the search period

Before diagnosis exposures are exposures refer to the period before cancer diagnosis. less than 12 months after diagnosis refers to the period at or around cancer diagnosis, and usually before cancer treatment. 12 months or more after diagnosis refers to the period after cancer diagnosis.

C1. Randomised trials

	Outcome		
Intervention/Exposure	Total mortality	Breast cancer mortality	Second primary breast cancer
Dietary patterns	2		

C2. Observational studies

Studies in which exposure was assessed before breast cancer diagnosis

Exposure	Total mortality	Breast cancer mortality	Second primary breast cancer
Dietary patterns	2	2	
Breastfeeding	2		1
Fruit and vegetables	2	1	
Vegetables	4	1	
Fruits	4	2	
Alcohol	9	5	
Carbohydrate	4	1	
Fibre	3	2	
Total fat	7	4	
Saturated fat	4	1	
Protein	5	1	
Dietary beta-carotene	3		
Dietary Vitamin C	3		
Total folate	3	1	
Dietary folate	4	2	
Multivitamin supplement	1	2	
Isoflavones	3		
Physical activity	9	8	
Total energy Intake	4	2	
Percentage energy from fat	3	2	
BMI	23	24	3

Weight	6	4	1
Waist circumference	1		
Hips circumference	1	1	
Waist to hip ratio	1		
Height	4	4	1

Studies in which exposure was assessed less than 12 months after breast cancer diagnosis

Exposure	Total mortality	Breast cancer mortality	Second primary breast cancer
Breastfeeding	3		
Alcohol	2	3	2
Carbohydrate		1	
Fibre		1	
Total fat		1	
Saturated fat		1	
Protein		1	
Physical activity		1	
Total energy intake		1	
Percentage energy from fat		1	
BMI	42	19	8
Weight	9	6	3
Waist circumference	3		
Hips circumference	2		
Waist-hip-ratio	4	2	
Height	2	1	2

Studies in which exposure was assessed 12 months or more after breast cancer diagnosis

Exposure	Total mortality	Breast cancer mortality	Second primary breast cancer
Dietary patterns	4	4	
Fruit and vegetables	1	1	
Vegetables	2	2	
Fruits	2	1	
Alcohol	7	3	5
Carbohydrate	4	3	
Fibre	4	3	
Total fat	4	4	
Saturated fat	2	2	
Protein	2	2	

Lycopene	3		
Vitamin C from supplement	2	2	
Vitamin E from supplement	3		
Total folate	2		
Dietary folate	1		
Mutlivitamin supplement	3	1	
Isoflavones	3	1	1
Physical activity	8	4	
Total energy intake	3	2	
Percentage energy from fat	2	1	
BMI	5	2	
Weight	1		
Weight gain	15	6	
Weight loss	9	3	
Height	1		

Results from randomised controlled trials

Two randomised controlled trials on total mortality were identified (Chlebowski, 2006; Pierce, 2007b). Both studies, the Women's Intervention Nutrition Study (WINS) and the Women's Healthy Eating and Living (WHEL) Randomised Controlled Trial were dietary intervention trials.

WINS aimed at reducing dietary fat intake to 15% of total energy intake (Chlebowski, 2006). A goal plan based on energy intake needed to maintain weight was given to each individual in the intervention group. No counseling on weight reduction was provided. The comparison group received minimal dietary counseling. In this study, 2437 women (age 48-79 years) with early stage, resected breast cancer receiving conventional cancer management were accrued between 1994 and 2001, and follow-up until 2003 (median 60 months follow-up). In the intervention group (n = 975), 45 participants were lost and 170 participants withdrew. In the comparison group (n = 1462), 66 participants were lost and 106 participants withdrew.

Mean dietary fat intake was lower in the intervention group relative to the comparison group after 60 months (intervention minus comparison group at 60 months = -19.0g/day (95% CI -22.1 to -16.0; $p < 0.0001$)). Similar differences were observed for percentage energy from fat. Energy intake was lower and dietary fibre was slightly higher in the intervention group. Women in the intervention group were also on average 6 pounds lower in weight than in the comparison group at year 5 ($p = 0.005$).

There was no difference in overall survival comparing intervention with comparison groups (HR 0.89 (95% CI 0.65-1.21); stratified log-rank test $p = 0.56$). Only 15 and 19 deaths without breast cancer recurrence were reported respectively in the groups. The primary endpoint of the study was relapse-free survival, for which the HR was 0.76 (95% CI 0.60-0.98), stratified log-rank test $p = 0.077$, $p = 0.034$ for adjusted Cox model analysis, 277 events.

The WHEL Study promoted a dietary pattern that was high in vegetables (daily intake of 5 servings plus 16 oz of vegetable juice), fruit (3 servings/day) and fibre (30 g/day) and low in fat (15-20% of energy intake that was kept isocaloric) in the intervention group (n = 1537) (Pierce, 2007b). The comparison group (n = 1551) received 5-A-Day dietary advice. Participants (age 18-70 years, n = 3088) of this trial were women with early-stage breast cancer, diagnosed within the past 4 years, had surgery and received treatment. Study recruitment was between 1995 and 2000 and participants were followed until 2006 (mean 7.3 years follow-up), during which 16 participants were lost and 22 participants withdrew consent from the intervention group, and 8 participants were lost and 19 participants withdrew consent from the comparison group.

At four years, statistically significant between group differences in mean consumption of vegetables (+65%), fruit (+25%), fibre (+30%) and energy from fat (-13%) (all $p < 0.001$) were observed. Mean energy intake and body weight differed by less than 80 kcal/day and 1 kg respectively between the groups at any study time point. Average body weight in the intervention group was 73.5 kg at baseline and increased to 74.1 kg after 72 months. Body weight in the comparison group remained similar (73.3 kg and 73.7 kg respectively).

There were 315 deaths from any cause (155 and 160 deaths in the intervention and comparison groups respectively). More than 80% were due to breast cancer. Adjusted HR for survival in the intervention group versus the comparison group was 0.91 (95% CI 0.72-1.15; $p = 0.43$). When stratified by hormone receptor status, the HRs were 0.92, 1.03, 1.08, and 1.13 for ER+/PR+, ER+/PR-, ER-/PR+, ER-/PR- breast cancer respectively ($p_{interaction} = 0.88$). All results were statistically non-signficant.

There were 518 breast cancer events (recurrence or second primary cancer) (256 and 262 in the intervention and comparison groups, respectively). Adjusted HR for disease-free survival was 0.96 (95% CI 0.80-1.14). When stratified by hormone receptor status, the HRs were 0.95, 0.97, 0.89, and 1.14 for ER+/PR+, ER+/PR-, ER-/PR+, ER-/PR- breast cancer respectively ($p_{interaction} = 0.85$). All results were statistically non-signficant.

Table 2 Table of randomised controlled trial of dietary intervention

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Intervention /control Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Chlebowski RT (2006)	Women's Intervention Nutrition Study (WINS) United States	1994-2001	Randomised controlled trial of dietary intervention	2437 participants Overall age ranged from 48-79 years Respectively for intervention and comparison groups: mean age 58.6 and 58.5 years; race/ethnicity 84.7 and 84.5% white; 65.3% and 64.0% used menopausal hormone therapy before	60 months	Invasive breast cancer Respectively for intervention and comparison groups: 54.5 and 54.5% cancer stage I, 32.0 and 31.9% stage IIA, 10.5 and 9.6% stage IIB, 3.1 and 4.0% stage IIIA	Respectively for intervention and comparison groups (among those with data): 79.0 and 81.3% ER positive, 21.0 and 18.7% ER negative, 69.6 and 69.4% PR positive, 29.1 and 29.9% PR negative Respectively for intervention and comparison groups (among those with data): 73.1 and 72.9% node negative	Respectively for intervention and comparison groups (among those with data): 35.5 and 29.9% mastectomy, 64.5 and 70.1% breast conserving surgery, 68.7 and 70.5% radiation therapy, 47.7 and 47.4% tamoxifen alone, 38.5 and 38.0% tamoxifen plus chemotherapy, 13.9 and 14.6% chemotherapy alone therapies	45 participants from the interventional group, 66 participants from the comparison group	Intervention: Individual fat gram goal to reduce percentage calories from fat to adequacy, counselled by registered dieticians Controls: Written information on general dietary guidelines, counselled on nutritional adequacy for vitamin and mineral intake	2437 participants; 975 in intervention and 1462 controls; 96 and 181 relapse events respectively (primary outcome); 15 and 19 deaths without breast cancer recurrence (secondary outcome)		Intervention vs control Overall Overall ER positive ER negative PR positive PR negative ER+/PR+ ER+/PR- ER-/PR+ ER-/PR-	Total mortality: 0.89 (0.65-1.21) Relapse-free survival: 0.76 (0.60-0.98) 0.85 (0.63-1.14) 0.58 (0.37-0.91) 0.83 (0.59-1.15) 0.54 (0.35-0.83) 0.83 (0.58-1.17) 0.73 (0.37-1.46) 0.57 (0.17-1.87) 0.44 (0.25-0.77)	Nodal status, systemic adjuvant therapy, tumor size, and mastectomy
Pierce JP (2007b)	Women's Healthy Eating and Living (WHEL) Randomised Trial	Trial recruitment: 1995-2000, Trial follow-up: Until 2006	Randomised controlled trial of dietary intervention	3088 participants Overall age ranged from 18-70 years Respectively for intervention and comparison groups: mean age 53.3 and 53.0 years; race/ethnicity 85% and 85.6% white; 69.4 and 65.3% ever antiestrogen use	7.3 years	Invasive breast cancer diagnosed within past 4 years Respectively for intervention and comparison groups: 38.1 and 39.1% cancer stage I, 57.0 and 55.9% stage II, 4.9 and 5.0% stage IIIA	Respectively for intervention and comparison groups: 62.1 and 61.1% ER+/PR+, 12.8 and 10.9% ER+/PR-, 3.4 and 5.0% ER-/PR+, 19.5 and 20.6% ER-/PR- Respectively for intervention and comparison groups: 57.2 and 57.8% node negative	Respectively for intervention and comparison groups: 52.8 and 51.6% mastectomy, 47.2 and 48.4% breast-sparing surgery, 61 and 62% radiation, 71.2 and 68.6% adjuvant chemotherapy	16 participants from the interventional group, 8 participants from the comparison group	Intervention: Promoted daily targets of 5 vegetable servings plus 16 oz of vegetable juice; 3 fruit servings; 30 g of fibre; and 15% to 20% of energy intake from fat Controls: Advised to follow the US Department of Agriculture 5-A-Day diet	3088 participants; 1537 in intervention and 1551 controls; 256 and 262 recurrence or new primary cancer respectively; 155 and 160 deaths from any causes (all primary outcomes)		Intervention vs control Overall ER+/PR+ ER+/PR- ER-/PR+ ER-/PR- Overall ER+/PR+ ER+/PR- ER-/PR+ ER-/PR-	Total mortality: 0.91 (0.72-1.15) 0.92 (0.68-1.26) 1.03 (0.57-1.85) 1.08 (0.41-2.83) 1.13 (0.74-1.73) P for interaction = 0.88 Disease-free survival: 0.96 (0.80-1.14) 0.95 (0.76-1.20) 0.97 (0.60-1.56) 0.89 (0.42-1.88) 1.14 (0.80-1.61)	Stratified by tumor stage, age, and clinical site; adjusted for antiestrogen use, oophorectomy status

														P for interaction = 0.85	

Results from observational studies by exposure.

For each exposure, the review will show first the results for total mortality as outcome, followed by studies on breast cancer related mortality (abbreviated as breast cancer mortality), cardiovascular disease mortality, mortality not related to breast cancer, and second primary cancers, second primary breast cancer and cancer-specific second cancers as endpoints.

Within each outcome, the results will be presented according to timeframe of exposure assessment: pre-diagnosis (before primary breast cancer diagnosis), at diagnosis (less than 12 months after diagnosis of primary breast cancer) and post diagnosis (12 months or more after diagnosis of primary cancer).

Dose-response meta-analyses were conducted when three or more articles presented enough information, highest vs. lowest meta-analysis are also shown for comparison. Each section starts with a table summarising the results of the meta-analysis for each outcome and exposure timeframe.

1 Patterns of diet

Overall, four observational studies were identified.

This section differs from other sections in the report in that endpoints will be presented together in the same section. This is because of the low number of studies identified. For the same reason, no meta-analysis was possible. The evidence is presented in text and tables.

Main results

Dietary patterns derived “a posteriori”

Two studies investigated “a posteriori” dietary patterns. The Nurses’ Health Study (Kroenke, 2005) reported on before and 12 months or more after-diagnosis diet. The Life after Cancer Epidemiology Study (Kwan, 2009) reported on diet 12 months or more after diagnosis of primary breast cancer. Dietary patterns were derived using factor analysis.

In the two studies (Kroenke, 2005; Kwan, 2009), a “western” and a “prudent” pattern were identified. In the Nurses’ Health Story (Kroenke, 2005), a higher score of the prudent pattern was described as a diet pattern with higher amounts of fruit, vegetables, whole grains, and low-fat dairy products, higher amounts of protein and fibre, lower amounts of trans-unsaturated and saturated fats and a lower glycaemic load. A higher western diet pattern score indicated a diet with higher amounts of

refined grains, processed meat, red meat, high-fat dairy, and desserts, less protein and fibre, higher trans- and saturated fats, and higher glycaemic load.

In the Life After Cancer Epidemiology Study (Kwan, 2009) a higher prudent pattern describes higher intakes of fruits, vegetables, whole grains, and poultry. A higher western pattern described higher intakes of red and processed meats and refined grains.

Before diagnosis dietary patterns and all-cause mortality, mortality for breast cancer and for other causes

In the only study identified, the Nurses' Health Study (Kroenke, 2005), before diagnosis prudent diet was unrelated to all-cause mortality (414 deaths) and death from breast cancer (242 deaths). However, patients with a higher intake of the prudent dietary pattern had a lower risk of death from causes other than breast cancer (172 deaths). The results were not shown in the publication.

A higher score of western pattern was not associated to breast cancer mortality but it was related to increased all-cause mortality (HR 1.68; 95% CI 1.24-2.27) and mortality from causes other than breast cancer (HR 1.95; 95% CI 1.06-3.60).

Table 3 Table of studies on before diagnosis dietary pattern and all-cause mortality, mortality for breast cancer and for other causes

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status	Treatment info	Response rate	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Kroenke (2005)	Nurses' Health Study United States	Cancer diagnosis: 1982 - 1998, Follow-up until 2002	Cancer survivors of prospective cohort study of Nurses	2619 participants 30 - 55 years at baseline	Median 9 years	Not available	Not available	~60% Tamoxifen ~33% Chemotherapy ~ 24% Node positive ~82% ER+		Closest diet before diagnosis and cumulative average of diet before diagnosis FFQ (118 items)	414 deaths, 242 of breast cancer, and 172 from other causes	Family, postal authorities, National Death Index	Western dietary pattern Q5 vs Q1 Total mortality 1.68 (1.24 -2.27) p<0.01 Death from breast cancer 1.01 (0.59 - 1.72) Death from other causes 1.95 (1.06 -3.60) p=0.03 Prudent dietary pattern No association		Age , BMI, energy intake, smoking, physical activity, age at menarche, oral contraceptive use, birth index ,menopausal status and use of postmenopausal hormone therapy ,age at menopause , tamoxifen use, chemotherapy stage at diagnosis, time between dietary assessment and diagnosis

12 months or more after diagnosis dietary pattern and all-cause mortality

Prudent pattern was not related to all-cause mortality in the Nurses' Health Study (414 deaths) (Kroenke, 2005) whereas higher intake of prudent diet was related to a significantly lower risk of all-cause mortality in the Life After Cancer Epidemiology Study (Kwan, 2009) ($HR_{Q5\ vs\ Q1}$; 0.57; 95% CI 0.36-0.90; 226 deaths).

Western pattern was related to an increasing risk of overall death in the Nurses' Health Study ($HR_{Q5\ vs\ Q1}$ 1.53; 95% CI 1.03-2.29). The association was driven by the strong positive association of the western pattern with mortality from causes other than breast cancer (see below). The association was stronger in women with node-positive cancer (p value, test for interaction < 0.003 and < 0.005 respectively). In this study, none of individual food groups was related to survival outcomes (data not shown).

The association of western pattern with all-cause mortality showed a trend of borderline significance in the Life After Cancer Epidemiology Study ($HR_{Q5\ vs\ Q1}$;1.53 95% CI 0.93-2.54; p_{trend} = 0.05).

12 months or more after diagnosis dietary pattern and mortality for breast cancer

Prudent or western dietary patterns after diagnosis were not associated with death from breast cancer in the Nurses' Health Study (242 deaths) (Kroenke, 2005) nor in the Life After Cancer Epidemiology Study (128 deaths) (Kwan, 2009).

12 months or more after diagnosis dietary pattern and mortality for other causes

Prudent pattern was related to lower risk of mortality from causes other than breast cancer in both studies. The hazard ratios were 0.54 (95% CI 0.31-0.95; 172 deaths) in the Nurses' Health Study (Kroenke, 2005) and 0.35 (95% CI 0.17-0.73; 98 deaths) respectively.

In the two studies, western pattern was related to an increasing risk of death from causes other than breast cancer. The hazard ratios were 2.31 (95% CI 1.23-4.32; 172 deaths) in the Nurses' Health Study (Kroenke, 2005) and 2.15 (95% CI 0.97-4.77; p_{trend} = 0.02; 98 deaths) in the Life After Cancer Epidemiology Study.

Study quality

In the Nurses' Health Study (Kroenke, 2005) 99% of self-reported invasive breast cancer with medical records was confirmed, 98% of causes of death were ascertained by death certificates. Diet was assessed by FFQ (118 items). Analyses were controlled for potential confounders but there was lack of complete information on disease severity and treatment.
The LACE cohort consists of early stage breast cancer survivors who were enrolled on average 2 years after diagnosis. The results are only valid for breast cancer patients with survival higher than two years. Analyses were controlled for main potential confounders.

Table 4 Table of studies 12 months or more after diagnosis dietary pattern and all-cause mortality, mortality for breast cancer and for other causes

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status	Treatment info	Response rate	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast RR (95% CI)	Adjustments
Kroenke (2005)	Nurses' Health Study United States	Cancer diagnosis: 1982 - 1998, Follow-up until 2002	Cancer survivors of prospective cohort study of Nurses	2619 participants 30 - 55 years at baseline	Median 9 years	~ 24% Node positive	~82% ER+	~60% Tamoxifen ~33% Chemotherapy	Not available	FFQ (118 items) Diet measured at least 12 months after diagnosis	414 deaths, 242 of breast cancer, and 172 from other causes	Family, postal authorities, National Death Index	Prudent dietary pattern Q5 vs Q1 Total mortality 0.78 (0.54-1.12) Death from breast cancer 1.07 (0.66- 1.03) Death from other causes 0.54 (0.31 -0.95) p=0.03 Western dietary pattern Q5 vs Q1 Total mortality All women 1.53 (1.03-2.29) Node-negative cancer 1.04 (0.61-1.80) Node-positive cancer 2.95 (1.44-6.06) Death from breast cancer 1.01 (0.60-1.70) Death from other causes 2.31 (1.23-4.32)	Age , BMI, energy intake, smoking, physical activity, age at menarche, oral contraceptive use, birth index ,menopausal status and use of postmenopausal hormone therapy ,age at menopause , tamoxifen use, chemotherapy stage at diagnosis, time between dietary assessment and diagnosis
Kwan, 2009 USA	Life After Cancer Epidemiology Study (LACE)	Cancer diagnosis: 1997 - 2000 Follow-up until 2008	Recruitment through cancer registries 11 to 39 months after diagnosis;	1,901 participants 18- 79 years at baseline	Median 4.2 years	~ 35 % Node positive ~45% Tumor size >2 cm	~83% ER+	~18% None ~26 % Radiation only ~20% Chemotherapy only	Free of recurrence at baseline	FFQ (122 items) Diet measured 11-39 months after diagnosis	226 deaths, 128 of breast cancer, 17 other cancers, 29 cardiovascular, and 52 other causes	Electronic data sources, family, death certificates to confirm cause of death.	Prudent pattern Q5 vs Q1 Total mortality 0.57 (0.36 -0.90) p<0.02 Death from breast cancer 0.79 (0.43 - 1.43) Death from other causes 0.35 (0.17- 0.73) p=0.003 Western pattern Q5 vs Q1 Total mortality 1.53 (0.93 -2.54) =0.05 Death from breast cancer 1.20 (0.62 - 2.32) Death from other causes 2.15 (0.97 - 4.77) p=0.02	Age at diagnosis, total energy intake (kcal), race, body mass index at enrolment, total physical activity, smoking, menopausal status at diagnosis, weight change from before diagnosis to baseline, stage of cancer, hormone receptor status, and treatment

1.1 Indices of diet quality

Two studies investigated indices of diet quality. The Nurses' Health Study (Kim, 2011) investigated indices of diet quality on before and 12 months or more after diagnosis diet. The Health, Eating, Activity, and Lifestyle (HEAL) Study (George, 2011) investigated on diet after diagnosis.

The indices of diet quality investigated were the Alternate Healthy Eating Index (AHEI); Diet Quality Index–Revised (DQIR); Recommended Food Score (RFS); and Alternate Mediterranean Diet Score (Amed) in the Nurses' Health Study (Kim, 2011) and the Healthy Eating Index (HEI) in the HEAL study (George, 2011).

The AHEI and the HEI were designed to target food choices associated with reduced risk for chronic diseases: vegetables, fruits, nuts and soy, cereal fibre, ratio of white to red meat, trans fat, polyunsaturated: saturated fat ratio, and alcohol, and duration of multivitamin use.

The DQIR addressed diet diversity and moderation and was based on 10 components including grains, vegetables, fruits, total fat, saturated fat, cholesterol, iron, calcium, diet diversity, and added fat and sugar moderation.

The RFS includes recommended foods from five categories: fruits, vegetables, whole grains, low saturated fat proteins, and low-fat dairy products.

The aMed Diet Score was adapted from the original Mediterranean score and includes vegetables, legumes, fruits, nuts, whole-grain products, red and processed meat alcohol, and the monounsaturated: saturated fat ratio.

Before diagnosis indices of data quality and all-cause mortality, mortality for breast cancer and for other causes

In the Nurses' Health Study, before diagnosis diet quality based on a single dietary questionnaire was not associated with total mortality, breast cancer mortality, or non-breast-cancer mortality (data not shown in the paper). A number of 572 women deaths were ascertained; 302 women died from breast cancer and 270 women died from causes other than breast cancer. Of the 270 non-breast-cancer-related deaths, 139 deaths were from cardiovascular disease (51%), 33 deaths from respiratory disease, and 21 deaths were from primary lung cancer (Kim, 2011).

Table 5 Table of studies before diagnosis on indices of diet quality and all-cause mortality, mortality for breast cancer and for other causes

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status	Treatment info	Response rate	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast RR (95% CI)	Adjustments
Kim, 2011 USA	**Nurses' Health Study United States**	**Cancer diagnosis: 1978 - 1998, Follow-up until 2004**	**Cancer survivors of prospective cohort study of Nurses**	**2729 participants 30 - 55 years at baseline**	**Median 9 years**	Invasive Stage 1–3 ~ 24% Node positive	**~82% ER+**	**~60% Tamoxifen ~33% Chemotherapy**	**Not available**	**Diet measured at least 12 months after diagnosis FFQ (130 items)**	**572 deaths, 302 of breast cancer, and 270 from other causes**	**Family, postal authorities, National Death Index**	AHEI, DQIR, RFS and Amed not related to breast, other causes or overall mortality	**Time since diagnosis, age, alcohol- only for RFS- multivitamin use – except for AHEI),body mass index, weight change, oral contraceptive use smoking status, physical activity, stage, treatment, age at first birth and parity, menopausal status and postmenopausal hormone use.**

12 months or more after diagnosis Indices of diet quality and all-cause mortality, mortality for breast cancer and for other causes

None of the indices of diet quality investigated in the Nurses' Health Study was associated with all-cause mortality (414 deaths), breast cancer mortality (242 deaths) or non-breast-cancer-related mortality (172 deaths) with the exception of higher diet quality assessed by the RFS that was associated with a significant increased breast cancer mortality trend ($RR_{Q5\ vs\ Q1}$ 1.54; 95% CI 0.95-2.47; p_{trend} = 0.02). However, investigation of each component of RFS did not indicate any significant relationships with breast cancer mortality (data not shown the paper). A higher aMED score was associated with a lower risk of non-breast-cancer death in women with low physical activity; the RR comparing the highest to lowest tertile was 0.39 (95% CI 0.20–0.75; p_{trend} = 0.0004) (Kim, 2011).

In the HEAL study, better quality data as assessed by the HEI-2005 was related to improved survival (HR $_{Q4\ vs\ Q1}$ 0.40; 95% CI 0.17-0.94; 62 deaths) and deaths from breast cancer (HR $_{Q4\ vs\ Q1}$ 0.12; 95% CI 0.02-0.99; 24 deaths) (George, 2011).

Study quality

Only 670 patients were included in the HEAL study. The study has low power. Patients were recruited from different locations and the response time frame (last month vs. last year) for the FFQ differed by study location.

In the Nurses' Health Study (Kim, 2011) 99% of self-reported invasive breast cancer with medical records was confirmed, 98% of causes of death were ascertained by death certificates. Diet was assessed by FFQ (130 items). Analyses were controlled for potential confounders but there was lack of complete information on disease severity and treatment. The results on indices of diet quality are not consistent with the results on "a posteriori" dietary patterns in the same cohort (Kroenke, 2005) and this was attributed to the use of factor analysis, which is data driven and allows for inclusion of all possible dietary exposures within a population (Kim, 2011).

Table 6 Table of studies 12 months or more after diagnosis on indices of diet quality and all-cause mortality, mortality for breast cancer and for other causes

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status	Treatment info	Response rate	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast RR (95% CI) Q5 vs Q1	Adjustments
Kim, 2011 USA	Nurses' Health Study United States	Cancer diagnosis: 1978 - 1998, Follow-up until 2004	Cancer survivors of prospective cohort study of Nurses	2729 participants 30 - 55 years at baseline	Median 9 years	Invasive Stage 1–3 ~ 24% Node positive	~82% ER+	~60% Tamoxifen ~33% Chemotherapy	Not available	FFQ (118 items) Diet measured at least 12 months after diagnosis	414 deaths, 242 of breast cancer, and 172 from other causes	Family, postal authorities, National Death Index	Total mortality AHEI 0.85 (0.63-1.17) DQIR 0.78 (0.58-1.07) RFS 1.03 (0.74-1.42) aMed 0.87 (0.64-1.17)	Time since diagnosis, age, alcohol- only for RFS- multivitamin use – except for AHEI),body mass index, weight change, oral contraceptive use smoking status, physical activity, stage, treatment, age at first birth and parity, menopausal status and postmenopausal hormone use.
													Death from breast cancer AHEI 1.53 (0.98-2.39) P trend 0.08 DQIR 0.81 (0.53-1.24 RFS 1.54 (0.95- 2.47) P trend 0.02 aMed 1.15 (0.74- 1.77) Death from other causes AHEI 0.52 (0.32- 0.83) P trend 0.09 DQIR 0.85 (0.54- 1.34) RFS 0.86 (0.54- 1.37) aMed 0.80 (0.50-1.26)	
George, 2011 USA	HEAL	Cancer diagnosis: 1995 - 1999, Follow-up until 2006	Patients identified through cancer registries	670 women with first primary breast cancer	Mean 6 years after 30 months post-diagnosis	In situ to regional breast cancer ~70% localized	~20% ER+	~50% Tamoxifen ~24% only surgery ~30% surgey&radiation &chemotherapy	Not available	FFQ (122 items) Diet measured 30 months after diagnosis	62 deaths, 24 of breast cancer	State mortality files and National Death Index	HEI-2005 Q4 vs Q1 Total mortality 0.40 (0.17-0.94) Death from breast cancer 0.12 (0.02-0.99)	Energy intake, physical activity, race, stage, tamoxifen use, BMI

2 Fruit and vegetables

No meta-analyses could be conducted because there were not enough studies with the required information. The studies identified are described below. The purpose of the description is to complement the information shown in the section Fruits and in the section Vegetables.

Fruit and vegetables intake and total mortality

Three studies on fruit and vegetables and total mortality were identified. No meta-analysis could be conducted. Participants in two of the studies were cases of invasive breast cancer from previous case-control studies that reported on their fruit and vegetables intake one year before diagnosis (Fink, 2006; Dal Maso, 2008). The participants in the third study were women with early stage breast cancer in the control arm of a randomised trial of the effect of plant-based dietary patterns on additional breast cancer events and survival (WHEL study, Pierce, 2007a,b).

In one study (Dal Maso, 2008) women that reported to eat less than 4 servings of fruit and vegetables per day before breast cancer diagnosis experienced higher risk of all-cause mortality (HR 1.27; 95% CI 1.00–1.61; p_{trend}= 0.04) compared to those that consumed 6 or more servings/day. The results were consistent across strata of hormone receptor status. In the LIBCSP study (Fink, 2006), mortality was not significantly related to fruit and vegetables intake before breast cancer diagnosis.

In the follow-up of participants in the control arm of the WHEL trial (Pierce, 2007a,b), in an analysis combining fruit and vegetable intake, and physical activity level, breast cancer survivors consuming five or more daily servings of fruit and vegetables with high level of physical activity (equivalent to walking 30 minutes 6 days/week), experienced longer survival than women with lower intake of fruit and vegetables and lower levels of physical activity (HR 0.56; 95% CI 0.31- 0.98). In univariate analysis, the survival advantage was restricted to women with ER-positive, PR-negative (p = 0.04) and ER-positive, PR-positive groups (p = 0.01).

Fruit and vegetables intake and breast cancer mortality

One study on fruit and vegetables intake before breast cancer diagnosis and breast cancer mortality was identified (Dal Maso, 2008) and the association was close to statistical significance when comparing women who reported less than 4 servings compared with 6 or more servings per day servings of fruit and vegetables per day (HR 1.26; 95% CI 0.96-

1.64; p_{trend}=0.08). The relationship was more evident but not statistically significant in women with stage I–II tumors.

2.1 Vegetable intake

Only studies on before or 12 months or more after diagnosis vegetable intake in relation to all cause mortality and breast cancer related mortality were identified. No study with second cancers as outcome was identified.

Table 7 Summary results of meta-analysis on before diagnosis vegetable intake and total mortality*

Comparison	No. of studies	No. of events in studies	RR (95% CI)	I^2, $P_{heterogeneity}$
Highest vs. lowest	3	592	0.90 (0.63-1.30)	61.3% p = 0.08
Per 3 servings/week	4	618	0.98 (0.93-1.03)	40.2%, p = 0.17

*No studies on breast cancer mortality and second cancers were included in the meta-analyses. Only studies on vegetable intake before diagnosis could be included in meta-analyses.

Table 8 Table for subgroup analysis of before diagnosis vegetable intake and total mortality

Comparison	No. of studies	No. of events in studies	RR (95% CI)	I^2, $P_{heterogeneity}$
Per 3 servings/week				
Menopausal status				
Premenopausal	2	48	1.02 (0.96-1.08)	0%, p = 0.88
Postmenopausal	4	570	0.97 (0.93-1.02)	24.7%, p = 0.26

Vegetable intake and total mortality

Six studies on vegetables and total mortality were identified. Four studies were on vegetable intake before diagnosis and total mortality and a dose-response meta-analysis was conducted. Two studies were on vegetable intake 12 months or more after diagnosis and total mortality; no dose-reponse meta-analysis was conducted.

Vegetable intake before diagnosis and total mortality

Methods

The four studies identified were included in the dose-response meta-analysis. One study (Buck, 2011b) reported vegetable intake in grams per day, which was converted to servings per week using 80 g as conversion unit for one serving of vegetables.
In addition to the four studies, a follow-up of 1122 women with primary, incident, histologically confirmed breast cancer identified between 1996 and 2001 reported that there was no association between mortality and intakes of vegetables 12-24 months before diagnosis in both pre- and postmenopausal women, but no data were reported (McCann, 2010).

Main results and heterogeneity

The summary RR per 3 servings/week was 0.98 (95% CI 0.93-1.03; 4 studies). Moderate heterogeneity was observed (I^2 = 40.2%; p = 0.17). After stratification by menopausal status the RR for pre-menopausal women was 1.02 (95% CI = 0.96-1.08; 2 studies) and for post-menopausal women was 0.97 (95% CI 0.93-1.02; 4 studies). In the highest versus lowest forest plot the overall RR was 0.90 (95% CI 0.63-1.30; 3 studies). There was no evidence of a non-linear association between vegetable intake pre-diagnosis and total mortality, $p_{non\text{-}linearity}$ = 1.0.

Study quality

Three studies (Saxe, 1999; Fink, 2006, Buck, 2011b) included in situ and invasive breast cancers. The dietary assessment referred to the year prior to diagnosis for all the studies included. In one study (Fink, 2006) diet was assessed on average 3 months after diagnosis when 2/3 of the patients had not started chemotherapy treatment. In the study by Saxe, 1999, the assessment was during the first month after surgical treatment. The number of potential participants with complete follow-up was about 70% in two studies (Fink, 2006; Buck, 2011b). The follow-up time ranged from 5 years (Saxe, 1999) to 7 years (Fink, 2006). Two studies (Saxe, 1999; McEligot, 2006) reported less than 100 events. The number of events ranged from 175 (Fink, 2006) to 321 deaths (Buck, 2011b). Two studies (Saxe, 1999; Fink, 2006) analysed pre and postmenopausal women separately and the other studies included only postmenopausal women. All studies provided multivariable adjusted results. Two studies evaluated treatment for primary breast cancer as confounder but this variable did not modify the results (Fink, 2006; Buck, 2011b). Two studies (McEligot, 2006; Buck, 2011b) were adjusted for tumour stage and hormone receptor status and one study (Fink, 2006) stratified results according to hormone receptor status.

Figure 2 Highest versus lowest forest plot of vegetable intake before diagnosis and total mortality

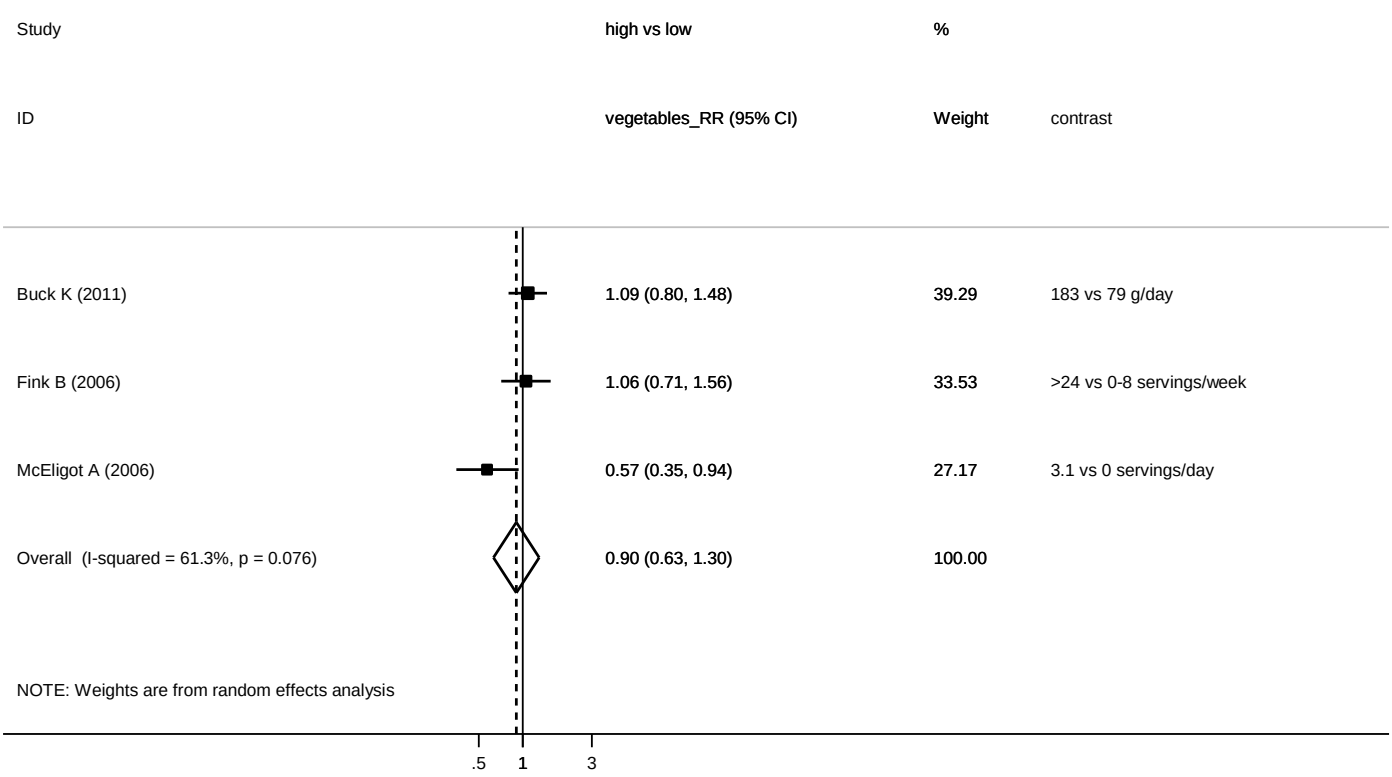


Figure 3 Linear dose-response meta-analysis of vegetable intake before diagnosis and total mortality

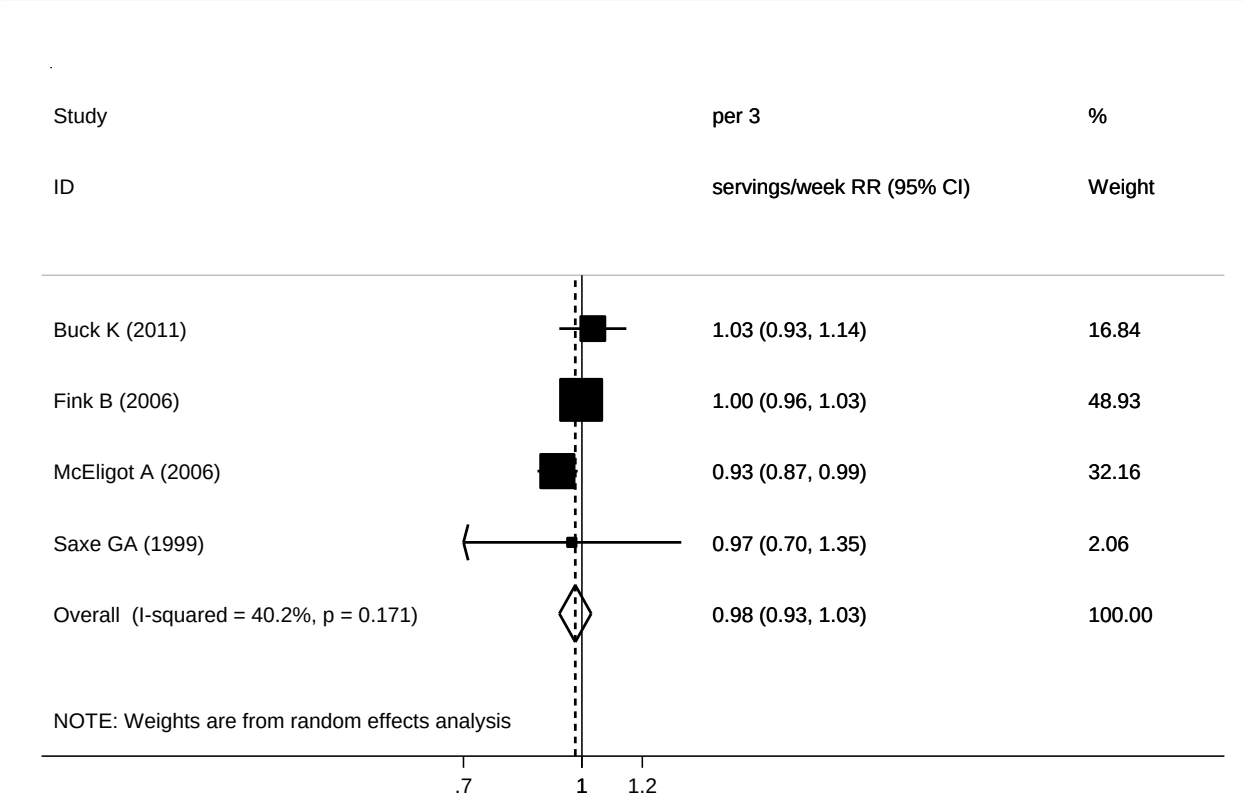


Figure 4 Individual dose-response graph of vegetable intake before diagnosis and total mortality

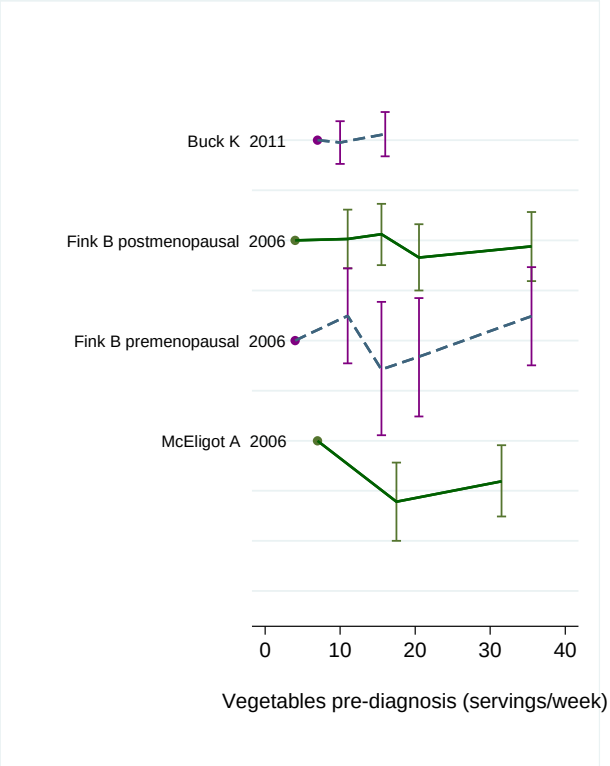


Figure 5 Linear dose-response meta-analysis of vegetable intake before diagnosis and total mortality by menopausal status

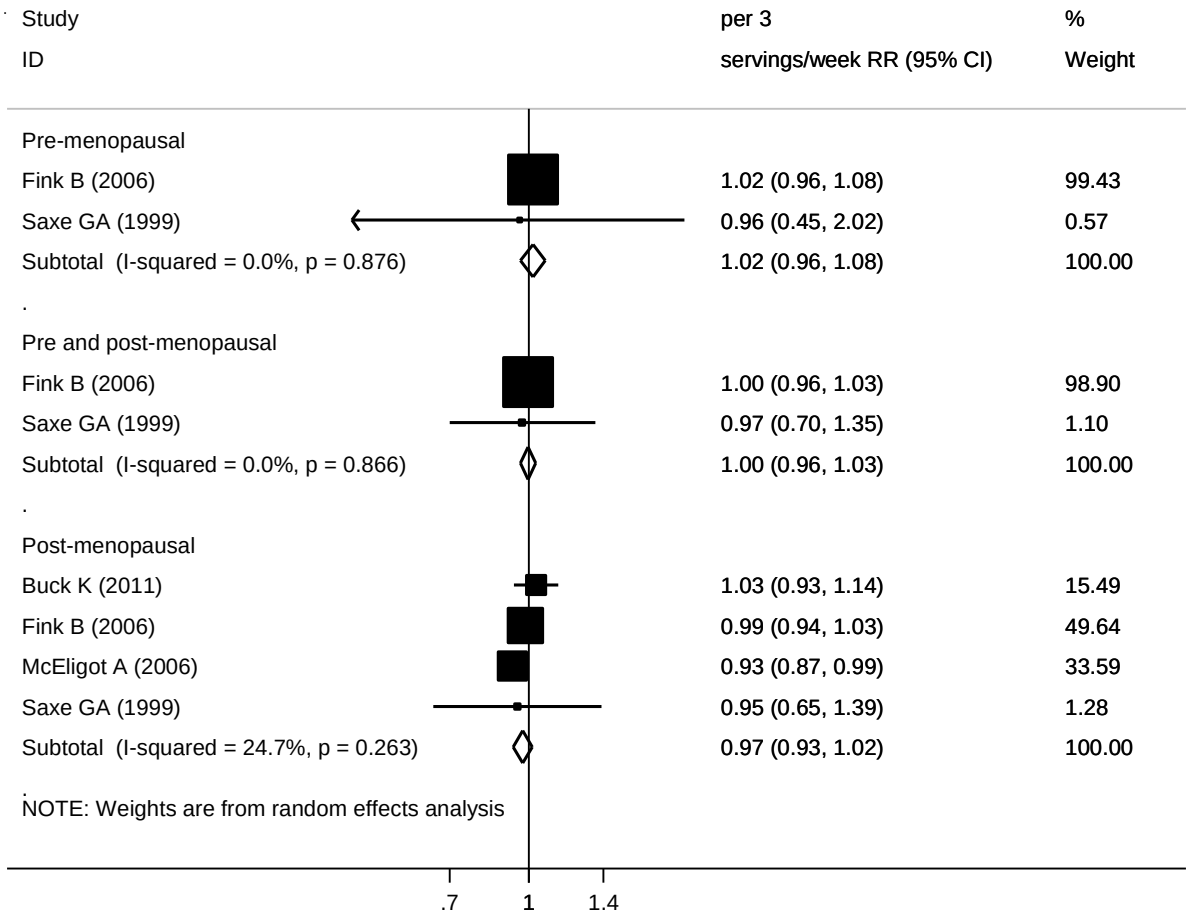


Table 9 Table of included studies on vegetable intake before diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments Remarks
Buck (2011)b	Hamburg and Rhein-Neckar-Karlsruhe, Follow-up Study Germany	Cancer diagnosis: 2002-2005, Study follow-up: Until 2009	Follow-up of cases of population-based case-control study	2653 participants 50 - 74 years Postmenopausal HRT use: 47.4% yes, 51.9% no/past, 0.7% missing	6.1 years	Primary invasive or in situ breast tumour any stage; Grades: 65.5% G1+G2, 24.9% G3+G4, 6% in situ, 3.3% neoadjuvant chemotherapy, 0.3% missing; Metastasis: 2.7% yes, 90.8% no, 6% in situ, 0.6% missing	58% ER+/PR+, 17.7% ER+/PR- or ER-/PR+, 14.6% ER-/PR-, 6% in situ, 3.3% neoadjuvant chemotherapy, 0.3% missing; 16.3% HER2-neu+, 64.9% HER2-neu-, 6% in situ, 3.3% neoadjuvant chemotherapy, 9.5% missing 28.9% +ve, 61.4% -ve, 6% in situ, 3.3% neoadjuvant chemotherapy, 0.5% missing	Surgery: 12.8% breast ablation, 32.1% breast conservation, 55% missing	Completed	Diet 1 year prior to diagnosis	2653 participants 321 deaths, 235 breast cancer mortality	Death certificate	183 vs. 79g/d	1.09 (0.80–1.48)	Tumor size, nodal status, metastasis, grade, estrogen and progesterone receptor status, breast cancer detection type, diabetes, HRT use at diagnosis, study centre, energy intake, age at diagnosis
Fink B (2006)	Long Island Breast Cancer Study Project United States	Cancer diagnosis:1996-1997; Study follow up: 2002-2004	Follow up of cases of a case-control study	1235 participants 25 - 98 years 419 premenopausal and 966 postmenopausal	7 years	Invasive breast cancer		98.5% radiation, 98.3% chemotherapy, 96.4% hormone therapy	868 patients 405 patients lost	Assessed in the interview 3 months after diagnosis; diet history in the previous 12 months prior to diagnosis	1235 participants 175 deaths, 125 breast cancer mortality, 22 other cancer mortality, 24 death from cardiovascular disease, 21 death from other causes	National Death Index	>24vs. 0-8 servings/week	Premenopausal 1.40 (0.71–2.76) Postmenopausal 0.92 (0.57–1.48)	Age and energy-adjusted
McEligot A (2006)	Orange County California Study United States	Cancer diagnosis: 1994-1995, Study follow-up: Until 2003 Recruited within 6 months of diagnosis	Prospective cohort of breast cancer survivors	516 participants 64.78 years (mean) Postmenopausal 92.3% non-Hispanic white HRT use: 36.2% estrogen only, 1.9% progesterone only, 35.1%estrogen and progesterone, 26.7% non-	80 months	Stages: 14.9% in situ, 59.3% localized, 24.2% regional, 1.55% metastatic			98% 2% lost	Self-reported at diagnosis for dietary habits 1 year prior to diagnosis, FFQ	516 participants 96 deaths, 41 breast cancer mortality, 13 deaths from cardiovascular disease, 31 other causes of deaths, 11 unknown causes of deaths	Cancer registry + National Death Index	3.1 vs. <2 servings/day	0.57 (0.35–0.94)	Tumor stage, age at diagnosis, BMI, parity, HRT, alcohol intake, multivitamins, energy intake

				users											
Saxe GA (1999)	Medical Center, Michigan University Follow-up Study United States	Study recruitment: 1989-1991, Recruited during first medical center visit for suspected or newly diagnosed	Prospective cohort of breast cancer survivors	149 participants 57.8 years (mean) 26 - 95 years White: 90.6%, black:7.2% and other: 2.2%, 34.2 34.2% premenopausal, 65.8% postmenopausal	5 Years (min)	Primary breast cancer, stages: 19.6% in situ, 34.5% I, 34.5% II, 8.8% III, 2.7% IV	73.4% ER+, 26.6% ER- 43% +ve, 57% -ve		0% lost	Interviewed close to time of diagnosis for diet a year prior to diagnosis, semi-quantitative FFQ	149 participants 26 deaths	Hospital records	Per 3 servings/week	0.97 (0.70- 1.35)	Tumor stage, energy intake Dose-response analysis only, only continuous results

Vegetable intake less than 12 months after diagnosis and total mortality

No study has reported data.

Vegetable intake 12 months or more after diagnosis and total mortality

The two studies identified (Beasley, 2011; Holmes, 1999) showed no association between vegetable intake 12 months or more after diagnosis and total mortality.

In the follow-up of cases with a history of invasive breast cancer diagnosed between 1987 and 1999 and participating in the CWLS, the hazard ratio comparing the highest (median 2.5 servings/day) to the lowest (medians 0.4 serving/day) quintile of vegetable intake post-diagnosis was 1.44 (95% CI 0.91-2.27; p_{trend} = 0.35) (Beasley, 2011). In participants in the NHS with breast carcinoma diagnosed between 1976–1990 the hazard ratio for all-cause mortality comparing women with 12 months or more after diagnosis vegetable intake of more than 4.2 servings/day to those with less than 2.1 serving/day was 0.81 (95% CI 0.59-1.11; p_{trend} = 0.35) (Holmes, 1999).

Vegetable intake and breast cancer mortality

Three studies on vegetable intake and breast cancer mortality were identified. One study was on before diagnosis vegetable intake (Buck, 2011b) and two studies were on vegetable intake post-diagnosis (Hebert, 1998; Beasley, 2011). None of the studies showed an association between vegetable intake and breast cancer mortality.

In the study on pre-diagnosis vegetable intake, the relative risk estimate for breast cancer mortality was 1.01 (95% CI 0.70-1.46) for the highest (183 g/day) compared to the lowest tertile (79 g/day) of intake (Buck, 2011b).

In regard to studies on 12 months or more after diagnosis vegetable intake, the hazard ratios were 0.47 (p = 0.09) for an increase of one serving/day (Hebert, 1998) and 0.96 (95% CI 0.38-2.45) for the highest (2.5 servings/day) compared to the lowest tertile (0 servings/day) of intake (Beasley, 2011).

2.2 Fruit intake

Table 10 Summary results of meta-analysis on before diagnosis fruit intake and total mortality*

Comparison	No. of studies	No. of events in studies	RR (95% CI)	I^2, $P_{heterogeneity}$
Highest vs. lowest	3	592	0.82 (0.66-1.02)	0%, p = 0.50
Per 7 servings/week	4	618	0.96 (0.90-1.02)	0%, p = 0.43

*No studies on breast cancer mortality and second cancers were included in the meta-analyses. Only studies on fruit intake before diagnosis could be included in meta-analyses.

Table 11 Table for subgroup analysis of before diagnosis fruit intake and total mortality

Comparison	No. of studies	No. of events in studies	RR (95% CI)	I^2, $P_{heterogeneity}$
Per 7 servings/week				
Menopausal status				
Premenopausal	2	48	0.83 (0.38-1.78)	46.2%, p = 0.18
Postmenopausal	4	570	0.96 (0.88-1.04)	22.4%, p = 0.28

Fruit intake and total mortality

Six studies on fruit intake and total mortality were identified. Four studies were on fruit intake before diagnosis and total mortality (Saxe, 1999; McEligot, 2006; Fink, 2006; Buck, 2011b) and two studies were on fruit intake 12 months or more after diagnosis and total mortality (Holmes, 1999; Beasley 2011).

Fruit intake before diagnosis and total mortality

Methods

The four studies identified were included in the dose-response meta-analysis. One study (Buck, 2011b) reported fruit intake in grams per day, which was converted to servings per week using as conversion unit one serving of fruit as 80 g of fruit.

In addition to the four studies, a follow-up of 1122 women with primary, incident, histologically confirmed breast cancer identified between 1996 and 2001 reported that there was no association between mortality and intakes of fruits 12-24 months before diagnosis in both pre- and postmenopausal women, but no data were reported (McCann, 2010).

Main results and heterogeneity

The summary RR per 7 servings/week was 0.96 (95% CI 0.90-1.02; 4 studies). No heterogeneity was observed (I^2 = 0%; p = 0.43). Only one study was on pre-menopausal women, the other three were on post-menopausal women. After stratification by menopausal status the RR for post-menopausal women was 0.96 (95% CI 0.88-1.04, 4 studies). In the highest versus lowest forest plot the overall RR was 0.82 (95% CI 0.66-1.02, 3 studies). There was no evidence of a non-linear association between fruit before diagnosis and total mortality, $p_{non\text{-}linearity}$ = 0.32.

Study quality

Two studies (Saxe, 1999; McEligot, 2006) reported less than 100 events. All other studies reported a higher number of events, ranging from 175 (Fink, 2006) to 321 (Buck, 2011b) deaths. The follow-up time ranged from 5 years (Saxe, 1999) to 7 years (Fink, 2006). Two studies (Saxe, 1999; Fink, 2006) analysed pre- and postmenopausal women separately and the other studies included only postmenopausal women. The dietary assessment was on the year prior to diagnosis for all the studies included. One study (Buck, 2011b) was from Europe and the other three were from the United States.

Figure 6 Highest versus lowest forest plot of fruit intake before diagnosis and total mortality

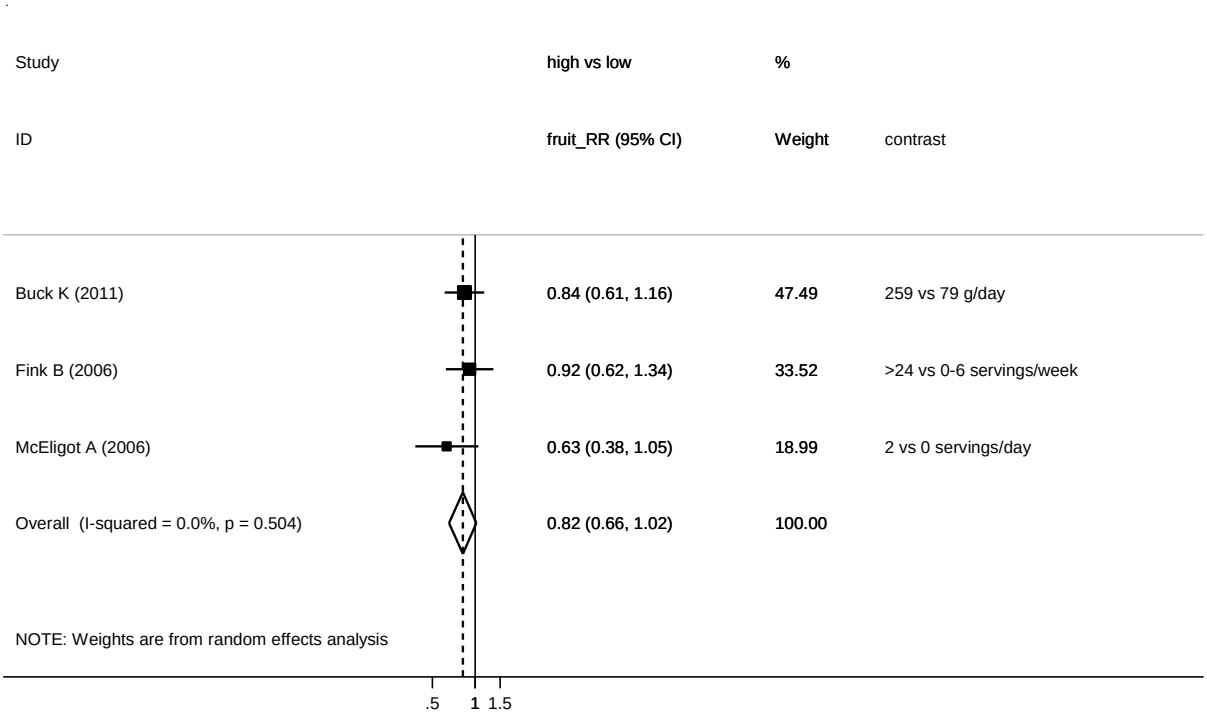


Figure 7 Linear dose-response meta-analysis of fruit intake before diagnosis and total mortality

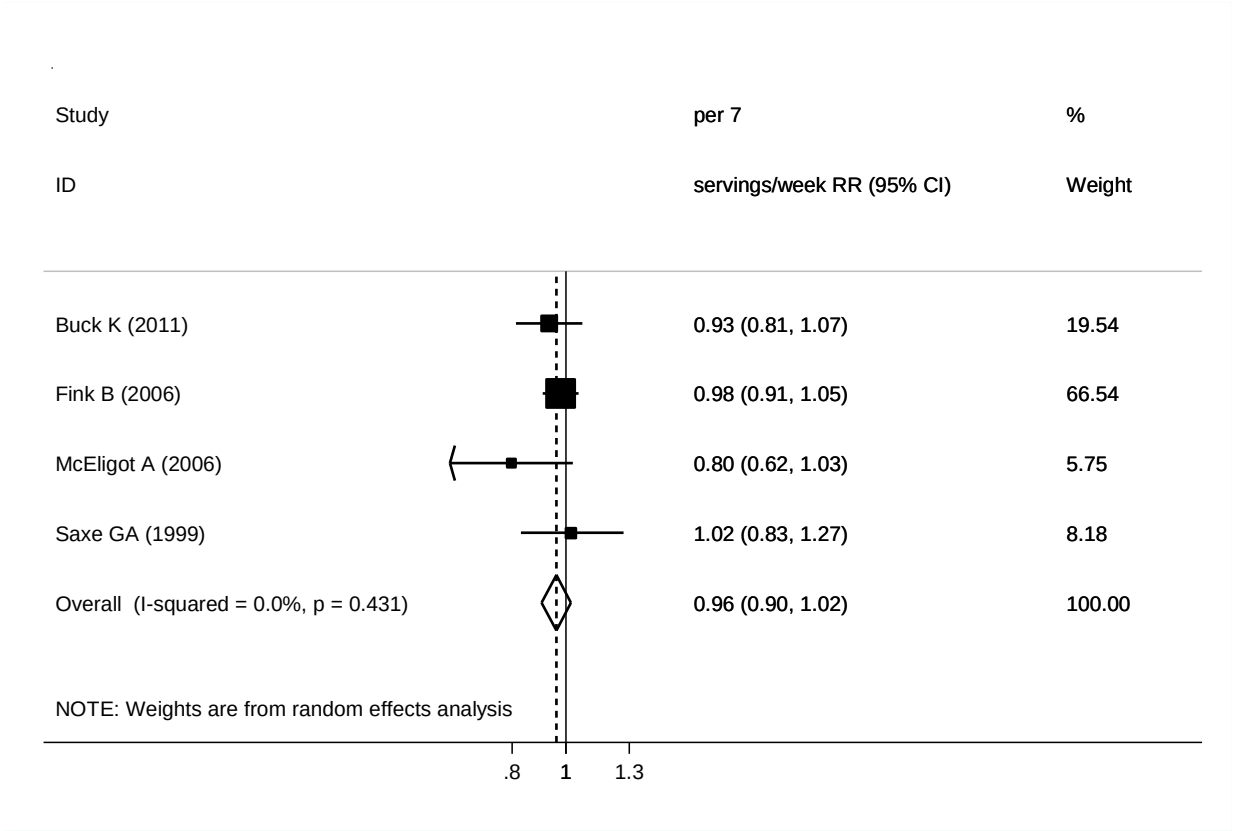


Figure 8 Individual dose-response graph of fruit intake before diagnosis and total mortality

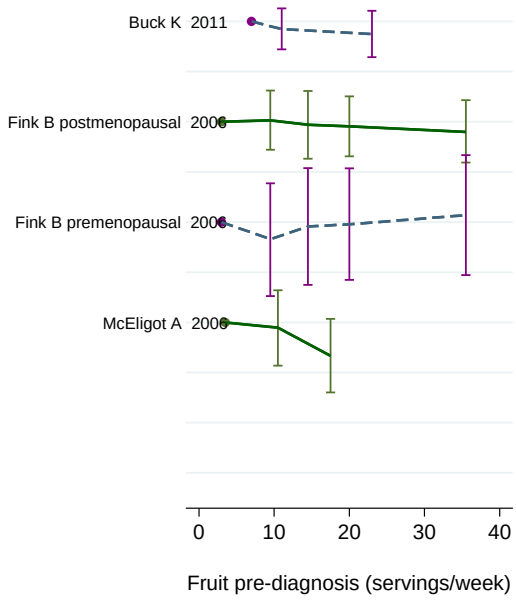


Figure 9 Linear dose-response meta-analysis of fruit intake before diagnosis and total mortality by menopausal status

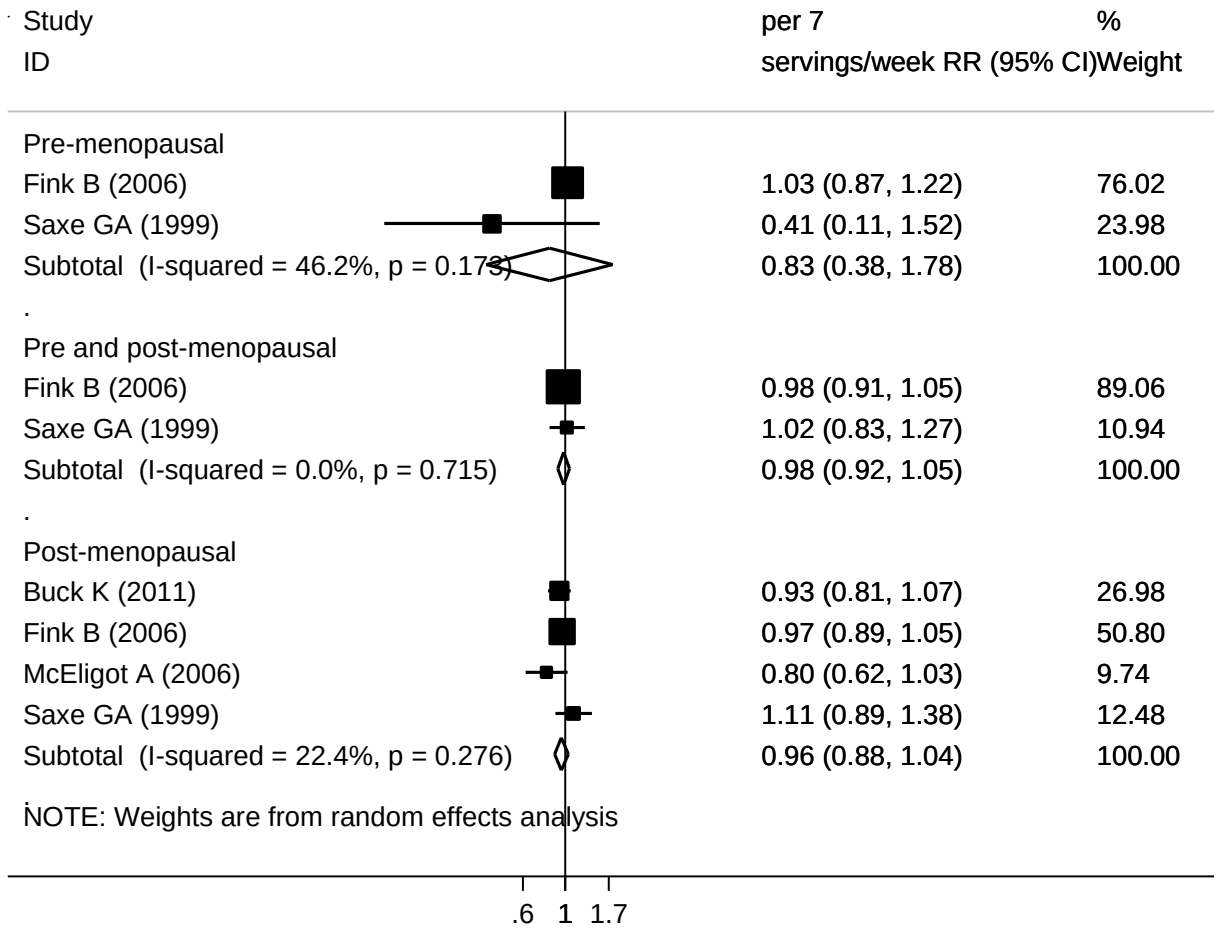


Table 12 Table of included studies on fruit intake before diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments Remarks
Buck (2011)b	Hamburg and Rhein-Neckar-Karlsruhe, Follow-up Study Germany	Cancer diagnosis: 2002-2005, Study follow-up: Until 2009	Follow-up of cases of population-based case-control study	2653 participants 50 - 74 years Postmenopausal HRT use: 47.4% yes, 51.9% no/past, 0.7% missing	6.1 years	Primary invasive or in situ breast tumour any stage; Grades: 65.5% G1+G2, 24.9% G3+G4, 6% in situ, 3.3% neoadjuvant chemotherapy, 0.3% missing; Metastasis: 2.7% yes, 90.8% no, 6% in situ, 0.6% missing	58% ER+/PR+, 17.7% ER+/PR- or ER-/PR+, 14.6% ER-/PR-, 6% in situ, 3.3% neoadjuvant chemotherapy, 0.3% missing; 16.3% HER2-neu+, 64.9% HER2-neu-, 6% in situ, 3.3% neoadjuvant chemotherapy, 9.5% missing 28.9% +ve, 61.4% -ve, 6% in situ, 3.3% neoadjuvant chemotherapy, 0.5% missing	Surgery: 12.8% breast ablation, 32.1% breast conservation, 55% missing	Completed	Diet 1 year prior to diagnosis	2653 participants 321 deaths, 235 breast cancer mortality	Death certificate	259 vs. 79g/d	0.84 (0.61 – 1.16)	Tumor size, nodal status, metastasis, grade, estrogen and progesterone receptor status, breast cancer detection type, diabetes , HRT use at diagnosis, study centre, energy intake, age at diagnosis
Fink B (2006)	Long Island Breast Cancer Study Project United States	Cancer diagnosis:1996-1997; Study follow up: 2002-2004	Follow up of cases of a case-control study	1235 participants 25 - 98 years 419 premenopausal and 966 postmenopausal	7 years	Invasive breast cancer		98.5% radiation, 98.3% chemotherapy, 96.4% hormone therapy	868 patients 405 patients lost	Assessed in the interview 3 months after diagnosis; diet history in the previous 12 months prior to diagnosis	1235 participants 175 deaths, 125 breast cancer mortality, 22 other cancer mortality, 24 death from cardiovascular disease, 21 death from other causes	National Death Index	>24 vs. 0-6 servings/week	Premenopausal 1.10 (0.48–2.52) Postmenopausal 0.87 (0.57–1.35)	Age and energy-adjusted
McEligot A (2006)	Orange County California Study United States	Cancer diagnosis: 1994-1995, Study follow-up: Until 2003 Recruited within 6 months of diagnosis	Prospective cohort of breast cancer survivors	516 participants 64.78 years (mean) Postmenopausal 92.3% non-Hispanic white HRT use: 36.2% estrogen only, 1.9% progesterone only, 35.1% estrogen and progesterone, 26.7% non-users	80 months	Stages: 14.9% in situ, 59.3% localized, 24.2% regional, 1.55% metastatic			98% 2% lost	At diagnosis; dietary habits during the 1 year prior to diagnosis FFQ	516 participants 96 deaths, 41 breast cancer mortality, 13 deaths from cardiovascular disease, 31 other causes of deaths, 11 unknown causes of deaths	Cancer registry + National Death Index	2 vs. <1.1 servings/day	0.63 (0.38–1.05)	Tumor stage, age at diagnosis, BMI, parity, HRT, alcohol intake, multivitamins, energy intake

Saxe GA (1999)	Medical Center, Michigan University Follow-up Study United States	Study recruitment: 1989-1991, Recruited during first medical center visit for suspected or newly diagnosed	Prospective cohort of breast cancer survivors	149 participants 57.8 years (mean) 26 - 95 years White: 90.6%, black:7.2% and other: 2.2%, 34.2% premenopausal, 65.8% postmenopausal	5 Years (min)	Primary breast cancer, stages: 19.6% in situ, 34.5% I, 34.5% II, 8.8% III, 2.7% IV	73.4% ER+, 26.6% ER- 43% +ve, 57% -ve		0% lost	Interviewed close to time of diagnosis for diet a year prior to diagnosis, semi-quantitative FFQ	149 participants 26 deaths	Hospital records	Per 14 servings/week	1.06 (0.69-1.63)	Tumor stage, energy intake Dose-response analysis only, only continuous results

Fruit intake less than 12 months after diagnosis and total mortality

No study has reported data.

Fruit intake 12 months or more after diagnosis and total mortality

Two studies on fruits 12 months or more after diagnosis and total mortality were identified (Beasley, 2011; Holmes, 1999). Both showed no significant association between fruit intake 12 months or more after diagnosis and total mortality.

In the follow-up of cases with a history of invasive breast cancer diagnosed between 1987 and 1999 and participating in the CWLS, the hazard ratio comparing the highest (median 2.5 servings/day) to the lowest (median 0.1 serving/day) quartile of 12 months or more after diagnosis intake of fruit was 1.38 (95% CI 0.88-2.17, p_{trend} = 0.67) (Beasley, 2011). In participants in the NHS with breast carcinoma diagnosed between 1976 and 1990 the hazard ratio for all-cause mortality for the highest vs. the lowest quartile of fruit intake was 1.07 (95% CI 0.77-1.49; p_{trend} = 0.40) (Holmes, 1999).

Fruit intake and breast cancer mortality

Three studies on fruit intake and breast cancer mortality were identified. Two studies were on fruit intake before diagnosis (Ingram 1994; Buck, 2011b) and one study was on fruit intake 12 months or more after diagnosis (Beasley, 2011). None of the studies showed a significant association between fruit and breast cancer mortality. In the small Australian study (103 subjects; 21 breast cancer deaths), higher before diagnosis fruit intake had a benefit on survival (p_{trend} = 0.01) (Ingram, 1994) but no association was observed in a more recent study (HR 0.86, 95% CI 0.59-1.25; p_{trend} = 0.82) for the highest vs. lowest intake tertile (Buck, 2011b). In the study on 12 months or more after diagnosis fruit intake, the HR for breast cancer death for the highest vs. the lowest quartile of intake was 1.39 (95% CI 0.64 – 2.99; p_{trend} = 0.16) (Beasly, 2011).

3 Alcohol intake

Table 13 Summary results of meta-analyses on alcohol intake and total mortality, breast cancer mortality and second primary breast cancer

	Total mortality			Breast cancer mortality			Second primary breast cancer		
	No. of studies	**No. of events in studies**	**RR (95% CI) I^2, $P_{heterogeneity}$**	**No. of studies**	**No. of events in studies**	**RR (95% CI) I^2, $P_{heterogeneity}$**	**No. of studies**	**No. of events in studies**	**RR (95% CI) I^2, $P_{heterogeneity}$**
Alcohol intake assessed before breast cancer diagnosis									
Highest vs. lowest meta-analysis	6	2650	0.93 (0.82-1.06) 9.7%, p = 0.35	5	1329	1.18 (0.81-1.72) 71.6%, p<0.01	-		-
Dose-response meta-analysis per 1 drink/week	7	2676	1.00 (0.99-1.00) 0%, p = 0.56	4	1296	1.0 (0.97-1.02) 73.5%, p = 0.01	-		-
Alcohol intake assessed 12 months or more after breast cancer diagnosis									
Highest vs. lowest meta-analysis	7	3827	0.89 (0.72-1.09) 63.4%, p = 0.01	3	403	1.22 (0.88-1.69) 26.2%, p = 0.26	5	2347	1.19 (0.96-1.47) 49%, p = 0.09
	per 10 g/day			per 10 g/day			per 1 drink/week		
Dose-response meta-analysis	6	3779	0.98 (0.93-1.03) 50.2%, p = 0.07	3	403	1.06 (0.79-1.42) 65.2%, p = 0.06	5	2347	1.01 (0.99-1.03) 44%, p = 0.13

Alcohol intake

Alcohol and total mortality

Eighteen studies on alcohol intake and total mortality were identified. Nine studies were on alcohol intake before diagnosis (Zhang, 1995; Saxe 1999; Goodwin, 2003; Reding, 2008; Dal Maso, 2008; Barnett, 2008; Hellman, 2010; Allemani, 2011; Harris, 2012a), two studies were on alcohol intake less than 12 months after diagnosis (Yu, 1997; Pierce, 2007a) and seven studies were on alcohol intake 12 months or more after diagnosis (Ewertz, 1991; Tominaga, 1998; Holmes, 1999; Barnett, 2008; Kwan, 2010; Flatt, 2010; Beasley, 2011). One study (Barnett, 2008) reported on alcohol intake before diagnosis and 12 months or more after diagnosis.

Alcohol intake before breast cancer diagnosis and total mortality

Methods

From the 9 studies identified, 7 were included in the dose-response meta-analysis. Two studies (Allemani, 2011; Goodwin 2003) were excluded. In one of the excluded studies (Allemani, 2011) 5-year relative survival was lower in European women who drank more than 13 g/day of alcohol (65%; 95% CI 47-78) than in non-drinkers (88%; 95% CI 75-95). The excess risk of death within 10 years was 4.32 (95% CI 1.80-10.36). The study was conducted in 264 European women diagnosed with breast cancer from 1987 through 2001 and participating in population cohort studies. The time between alcohol assessment and breast cancer diagnosis varied between 1 and 14 years (average 7.6 years). A study in Canada (Goodwin, 2003) found no association of alcohol intake one year before diagnosis and survival in a clinical cohort of 477 women diagnosed with operable breast cancer from 1989 through 1996 and followed-up for 6.1 years on average ($p_{trend} = 0.99$). Both studies adjusted for stage and tumour characteristics.

From the seven studies included in the meta-analysis, four reported alcohol intake as drinks per week, therefore the analysis was conducted using alcohol measured in drinks per week. Two studies study (Zhang, 1995; Harris 2012a) reported alcohol intake in grams per day. For these studies the alcohol intake was converted to drinks per week using as conversion unit one serving of alcohol as 10 g of ethanol.

Main results

The summary RR per 1 drink/week was 1.00 (95% CI 0.99-1.00, 7 studies). After excluding one study only on postmenopausal women (Zhang, 1995) the result remained the same. No heterogeneity was observed ($I^2 = 0\%$; $p = 0.56$). Egger's test suggested evidence of publication bias, $p = 0.07$. The overall RR when comparing the highest vs. the lowest category of alcohol intake was 0.93 (95% CI 0.82-1.06; 6 studies). There was no evidence of a non-linear association between alcohol intake before diagnosis and total mortality, $p_{non\text{-}linearity} = 1.0$.

Study quality

Two studies (Zhang, 1995; Saxe, 1999) reported less than 100 events. All the other studies reported a higher number of events, ranging from 323 (Hellman, 2010) to

860 (Harris, 2012a) deaths. The follow-up time ranged from 2.9 years (Zhang, 1995) to 12.6 years (Dal Maso, 2008). All the studies except one (Zhang, 1995), included pre and postmenopausal women. The alcohol assessment timeframe varies from alcohol intake at age 30 years, approximately 20 years before diagnosis, (Barnett, 2008) to alcohol intake in the year before diagnosis (Saxe, 1999). Four studies were from Europe (Dal Maso, 2008; Barnett, 2008; Hellman, 2010; Harris, 2012a) and three studies were from the United States (Zhang, 1995; Saxe, 1999; Reding 2008).

Only one study reported a benefit of alcohol intake on survival (Reding, 2008). This study was on women with breast cancer diagnosis before age 45 years. It was not possible to interview 15% of the women eligible for the original case-control studies on which this population-based cohort study was based. At 5 years, 43.5% of the noninterviewed cases and 14.5% of the interviewed cases were deceased.

Figure 10 Highest versus lowest forest plot of alcohol intake before breast cancer diagnosis and total mortality

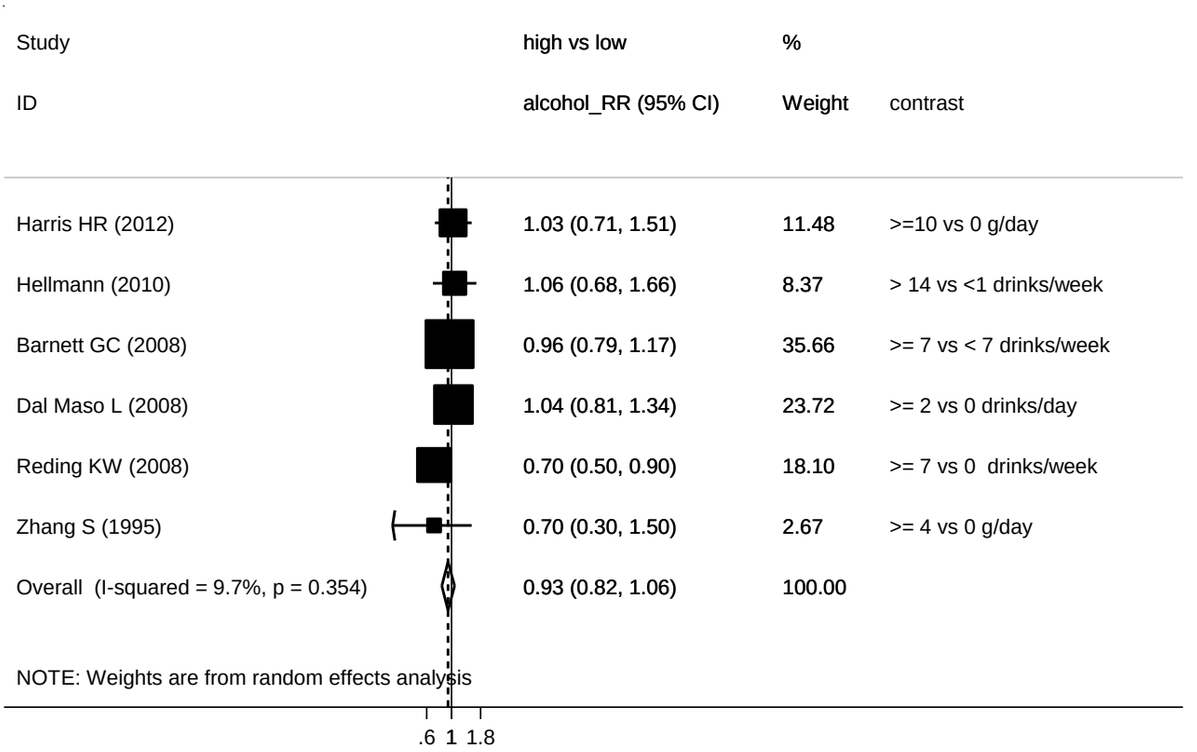


Figure 11 Linear dose-response meta-analysis of alcohol intake before breast cancer diagnosis and total mortality

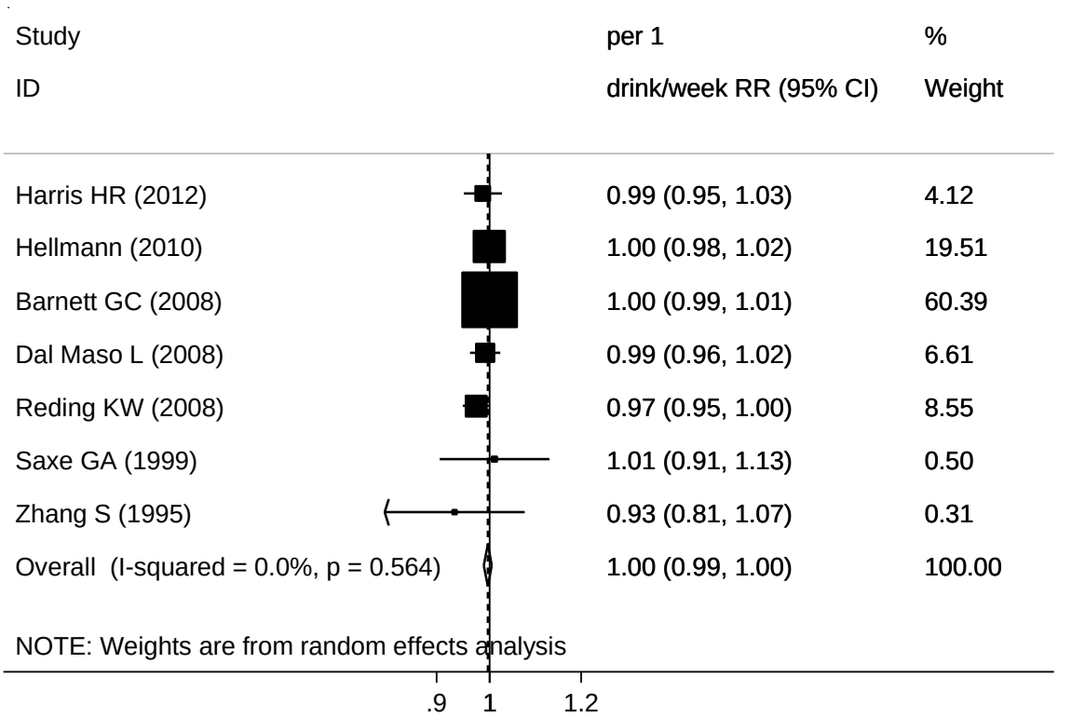
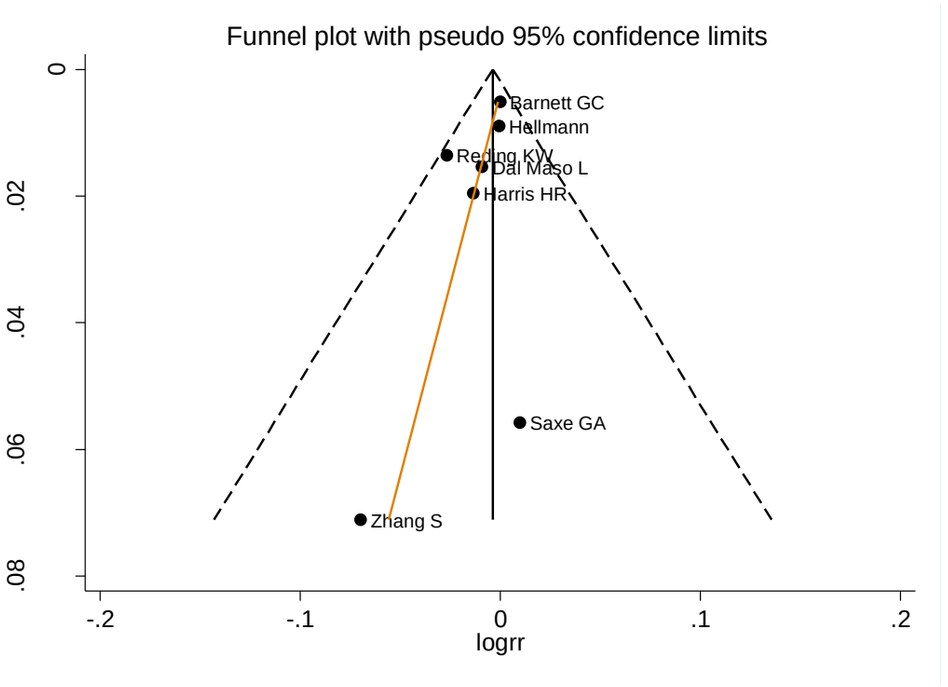


Figure 12 Funnel plot of studies of alcohol intake before breast cancer diagnosis and total mortality



Each dot represents the logarithm of relative risk estimate against standard error as a measure of study size. Solid line is the logarithm of summary risk estimate from the meta-analysis. Dashed lines are its 95% confidence interval. Egger's test p = 0.07

Figure 13 Individual dose-response graph of alcohol intake before breast cancer diagnosis and total mortality

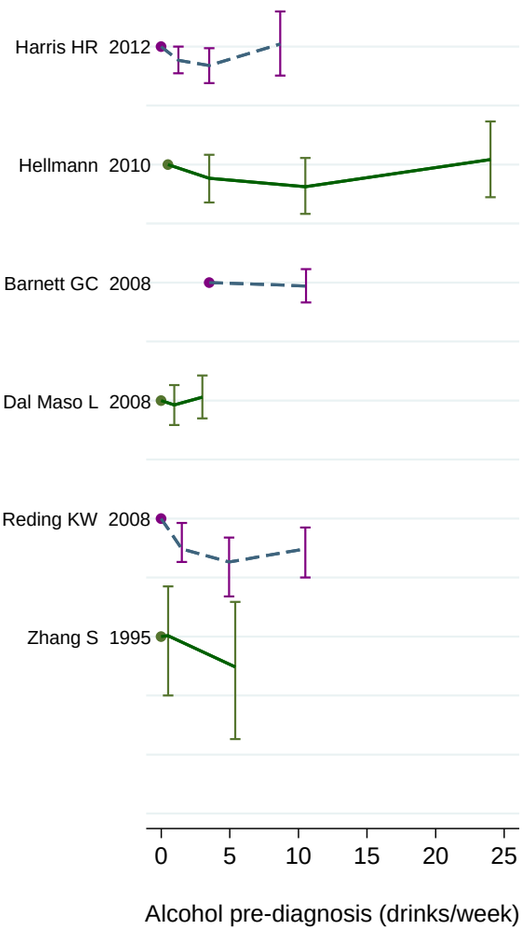


Table 14 Table of included studies on alcohol intake before breast cancer diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments / Remarks
Harris H (2012)a	Swedish Mammography Cohort Sweden	Cancer diagnosis:1987-1990; Study follow up: until 2008	Cancer survivors of a population-based prospective cohort study	3146 participants 65 years (mean) Mostly white Mammography cohort	25940 Person-years	Invasive breast cancer: any stages I-IV	62% ER+ve/PR+ve, 20% ER+ve/PRve, 5% ER-		Complete	At baseline; alcohol during the previous 6 months (1987) or year (1997), pre diagnosis and dietary change after diagnosis	3146 participants 860 deaths, 385 breast cancer mortality	Death certificate	>=10 vs. 0g/d	1.03 (0.71–1.51)	Age, energy intake, education, marital status, menopausal status, BMI, year of diagnosis, stage of disease, radiotherapy, chemotherapy, hormonal therapy
Hellmann (2010)	Copenhagen City Heart Study Denmark	Study recruitment:1976; Study follow up: until 2007	Cancer survivors of a population-based prospective cohort study	528 participants 66.9 years (mean) 33.1 - 95.4 years Mostly Caucasian 16.1% premenopausal, 83.9% postmenopausal HRT use: 71.2% unexposed, 28.8% exposed	7.8 years	Primary breast cancer, one sarcoma, 527 carcinomas; TNM; 56.2% local, 33.7 regional, 6.3 metastatic, 3.8% unknown		7.4% radiotherapy, 7.4% chemotherapy, 22.4% hormonal therapy	74% at the 1st, 70% at the 2nd , 61% at the 3rd and 50% at the 4th examination / 1% lost	Measured at study baseline	528 participants 323 deaths, 174 breast cancer mortality, 126 other causes of death including 43.6% death from cardiovascular disease and 25.6% other cancers	Cancer registry	>14 vs. <1 units/week	1.06 (0.68–1.66)	Age, smoking, physical activity , alcohol intake, hormonal therapy, tumor stage, parity, education, treatment
Barnett GC (2008)	Studies of Epidemiology and Risk Factors in Cancer Heredity Breast Cancer Study UK	Cancer diagnosis: 1991-2005	Cancer survivors of a population-based prospective cohort study	4560 participants 51.5 years (mean) 23 - 69 years Mostly white Among those with data: 55.2% pre-menopausal, 44.7% postmenopausal HRT use: 62 % never usage, 37.9% ever usage	6.82 years	Invasive breast cancer; 73% incident and 27% prevalent; among those with data: 49.7% stage I, 45.8% stage II, 3.3% stage III, 1.1% stage IV; 24.1% grade 1, 47.2% grade 2, 28.6% grade 3	18.7% ERve, 81.2% ER+ve		67%	Alcohol consumption at age 30y	4560 participants 544 deaths	Cancer registry + death certificate	>7 vs. <=7 units/week	0.96 (0.79 - 1.17)	Age at diagnosis, tumor stage, tumor grade, ER status
Dal Maso L (2008)	Six Italian Regions Follow-up Study Italy	Cancer diagnosis: 1991-1994; Study follow up: until 2005-2006 diagnosed no longer than 1 year before the interview	Follow-up of cases of a case-control study	1453 participants 55 years (mean) 23 - 74 years Among those with data, pre diagnosis data: 45.5 % peri/pre menopausal, 54.9% postmenopausal HRT use: 91.3% never, 8.6%	12.6 years	Invasive breast cancer; TNM; 32.7% Stage I, 44.1% stage II, 13.2% stage III-IV, 9.8% unknown	41.5% ER+ve/PR+ve, 3.5% ERve/PR+ve, / 45.6% no node+ve, 44.2% node+ve, 10.1%		2.70% lost	Before diagnosis (diagnosed no longer than 1 year before the interview)	1453 participants 503 deaths, 398 breast cancer mortality, 6.2% death from other cancers, 7.4% from cardiovascular disease	Cancer registry	>=2 vs. 0 drinks/d	1.04 (0.81–1.34)	Region, Age at diagnosis, year of diagnosis, TNM stage, receptor status

				ever											
Reding KW (2008)	Fred Hutchinson Cancer Research Center Follow-up study United States	Cancer diagnosis: 1983-1992, Study follow-up: Until 2002 Recruited at diagnosis	Follow-up of cases of case-control studies	1286 participants 45 years (mean) Multi-ethnic Premenopausal HRT use: 41.4% ever had, 58.6% had not among those with data	9 years	First primary invasive breast cancer; 57.94% local, 409% regional, 1.97% distant	59.3% ER+ve, 40.7% ERve, 60.5% PR+ve,	Chemotherapy: 68.9% yes, 31.1% no; Radiotherapy 53.8% yes, 46.2% no; Hormone therapy 35.3% yes, 64.7% no, among those with data	83.3%, 83.9% in original studies	5 years before diagnosis were recalled at interview	1286 participants 364 deaths, 335 breast cancer mortality, 22 other causes of deaths, 7 unknown causes of deaths	Medical records	>=7 vs. 0 drinks/week	0.7 (0.5-0.9)	Age, diagnosis year, and mammography
							41.1% +ve, 58.9% -ve, among those with data		93.1% contacted within 12 months of end of F/U, 6.9% loss						
Saxe GA (1999)	Medical Center, Michigan University Follow-up Study United States	Study recruitment: 1989-1991, Recruited during first medical center visit for suspected or newly diagnosed	Prospective cohort of breast cancer survivors	149 participants 57.8 years (mean) 26 - 95 years White: 90.6%, black:7.2% and other: 2.2%, 34.2% premenopausal, 65.8% postmenopausal	5 Years (min)	Primary breast cancer, stages: 19.6% in situ, 34.5% I, 34.5% II, 8.8% III, 2.7% IV	73.4% ER+, 26.6% ER-			Interviewed close to time of diagnosis for diet a year prior to diagnosis, semi-quantitative FFQ	149 participants 26 deaths	Hospital records	Per 2 drinks/week	1.02 (0.82-1.27)	Tumor stage, energy intake
							43% +ve, 57% -ve		0% lost						Dose-response analysis only, only continuous results
Zhang S (1995)	Iowa Women's Health Study United States	Study recruitment:1986; Study follow up: until 1991	Cancer survivors of population-based prospective cohort study	698 participants 55 - 69 years Mostly white Mostly white: 98%, Postmenopausal	2.9 years	Unilateral breast cancer; 10% in situ, 58% local, 28% regional, 3%distant, and 1% unknown; 55% tumour size <2cm, 33% size >= 2cm and 11% unknown	Among those with data: 85% ER+ve and 72% PR+ve		42.60%	Self reported questionnaire within 6 years before diagnosis semi-quantitative FFQ	698 participants 56 deaths, 40 breast cancer mortality (among the causes of death) and 2 death from coronary heart disease	Death Certificate + National Death Index	>=4 vs. 0 g/d	0.7 (0.3-1.5)	Age, smoking, education, tumor stage, ER status, tumor size
									< 1% migration rate						

Table 15 Table of excluded studies on alcohol intake before breast cancer diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments / Exclusion reason
Allemani C (2011)	ORDET (Hormones and Diet in the Etiology of Breast Cancer) & UROCARE (European Cancer Registry-based Study of Survival and Care of cancer patients	Cancer diagnosis: 1987-2001, Study follow-up: Until 2005	Prospective cohort of breast cancer survivors	264 participants 34 - 70 years	7.6 years	Tumor stages: 47.7% T1N0M0 , 9.8% T2-3N0M0, 42.4% T1-3N+M0/T4/M1				Possibly collected during baseline interview; alcohol intake over the 12 months prior to recruitment	43 deaths	Clinical records	>13 vs. 0g/d	Relative excess risk 4.32 (1.80-10.36)	BMI Reported relative excess risk and not relative risk
Goodwin P (2003)	University of Toronto Hospitals Follow-up Study Canada	Study recruitment: 1989-1996 At diagnosis	Prospective cohort of breast cancer survivors	477 participants 50.4 years (mean) 75 years 57.7% premenopausal , 3.6% perimenopausal, 38.8% postmenopausal	6.1 years	Tumor stages: 55.6% T1, 32.3% T2, 5.2%, 6.9% unknown; Grades: 13% 1, 40.7% 2, 33.1% 3, 13.2% unknown	62.5% ER+, 18.7% ER-, 13.4% unknown; 56.6% PR+, 22.9% PR-, 14.9% unknown	Mastectomy: 23.3% yes; Lumpectomy: 76.7% yes; Chemotherapy only: 28.3% yes; Chemotherapy plus tamoxifen 9.6%; Tamoxifen only: 29.6%; None: 32.5% yes		FFQ completed 9.3 ± 4.6 weeks after diagnosis, reporting intake over preceding 12 months	52 deaths	Medical records			BMI, age, tumor stage, nodal status, hormonal therapy, chemotherapy, energy intake There was not enough information

Alcohol intake less than 12 months after diagnosis and total mortality

Two studies were identified. One hospital cancer registry based study indicated that survival in breast cancer patients was not associated with alcohol intake (data not shown in the article, Yu, 1997). Another study (Allin, 2011) reported an RR of 0.79 (95% CI 0.53-1.19, > 168 vs. ≤ 168 g of alcohol per week).

Alcohol intake 12 months or more after primary breast cancer diagnosis and total mortality

Methods

Seven studies (eight publications) were identified from which six were included in the dose-response meta-analysis. In the Women's Healthy Eating and Living Study control group, subsequent mortality was lower in drinkers and higher in never drinkers compared to former drinkers (p_{trend}= 0.03). These results were obtained in univariate analyses and the data published was insufficient for its inclusion in the dose-response meta-analysis (Pierce, 2007a). Two publications on the Danish Breast Cancer Cooperative Group study were identified (Ewertz, 1991; Ewertz 1993). The first publication was used because data were complete and the study population was the same.

Four of the six included studies reported alcohol intake in grams therefore the analysis was conducted using alcohol measured in grams per day. One study (Beasley, 2011) reported alcohol intake as percentage of energy from alcohol, which was converted to grams of alcohol using the median quintile of energy intake reported in the paper. Another study (Barnett, 2008) reported alcohol intake as drinks per week that was converted to grams per day using the conversion unit reported in the study (8 g of pure alcohol per unit).

Main results

The summary RR per 10 g/day of ethanol was 0.98 (95% CI 0.93-1.03, 6 studies). Moderate heterogeneity was observed (I^2 = 50.2%, p = 0.07). Egger's test suggested no evidence of publication bias, p = 0.58. The RR ranged from 0.96 (95% CI 0.91-1.01) when excluding the Danish Breast Cancer Cooperative Group study (Ewertz, 1991) to 0.99 (95% CI 0.92-1.07) when excluding the Collaborative Women's Longevity Study (Beasley, 2011). It was not possible to conduct a meta-analysis stratified by menopausal status. After stratification by time after diagnosis the RR was 1.05 (95% CI 0.97-1.14; I^2 = 0%; p = 0.56) when alcohol intake was measured less than 2 years after diagnosis and 0.97 (95% CI 0.93-1.01; I^2 = 57.5%; p = 0.09) when the assessment referred to alcohol intake more than 2 years after diagnosis. In the highest versus lowest forest plot the overall RR was 0.89 (95% CI 0.72-1.09; 7 studies). The test for non-linearity was statistically significant ($p_{non\text{-}linearity}$ = 0.01) but the non-linearity is evident at the lowest intake levels. Non-linearity was suggested in categorical analyses in two studies (Holmes, 1999; Beasley, 2011).

Study quality

One study (Tominaga, 1998) reported less than 100 events. All other studies reported a higher number of events, ranging from 273 (Kwan, 2010) to 805 (Ewertz, 1991) deaths. The follow-up time ranged from 5.5 years (Beasley, 2011) to 13 years (Holmes, 1999). All the studies included pre and postmenopausal women. The alcohol assessment timeframe varies from 1 year after diagnosis (Ewertz, 1991) to 5 years after diagnosis (Beasley, 2011). Four studies were from the United States (Holmes, 1999; Flat, 2010; Kwan, 2010;

Beasley, 2011), two studies were from Europe (Ewertz, 1991; Barnett, 2008) and one study was from Asia (Tominaga, 1998).

Published pooled analysis

The After Breast Cancer Pooling Project (Kwan, 2012a) reported no association between alcohol consumption 12 months or more after diagnosis and total mortality, (HR 0.80; 95% CI 0.64-1.01; ≥ 24 g/day vs. < 0.36 g/day) or breast cancer mortality (HR 0.83; 95% CI 0.60-1.13; ≥ 24 g/day vs. < 0.36 g/day).

Figure 14 Highest versus lowest forest plot of alcohol intake 12 months or more after primary breast cancer treatment and total mortality

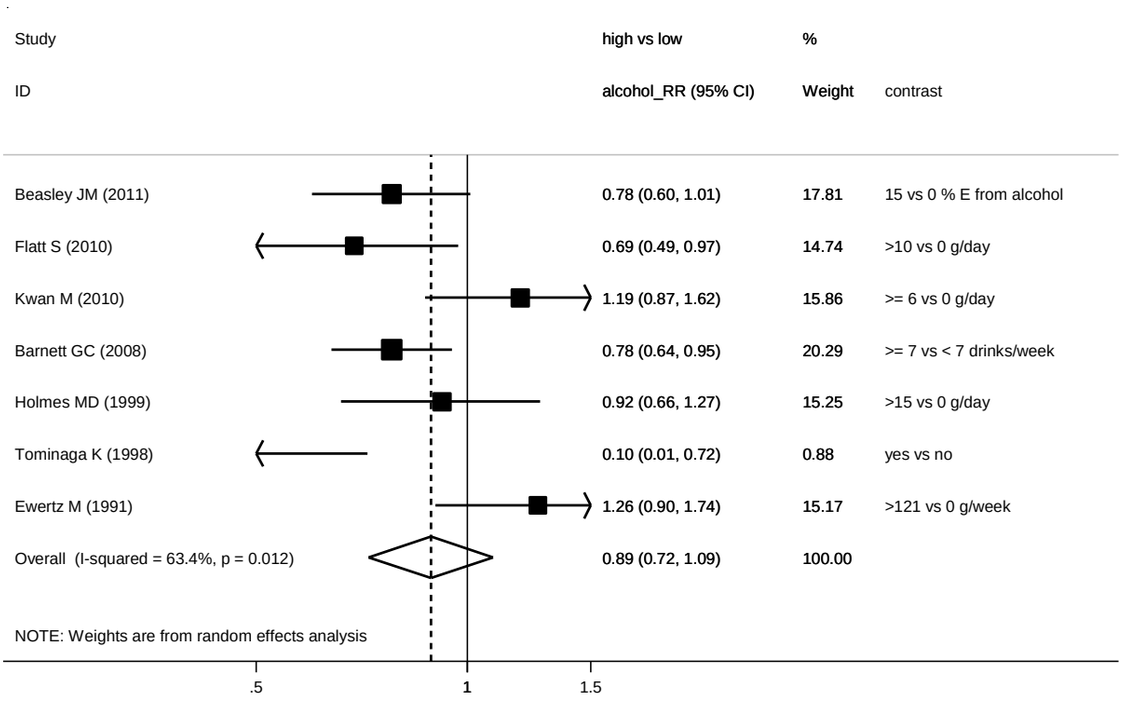


Figure 15 Linear dose-response meta-analysis of alcohol intake 12 months or more after primary breast cancer diagnosis and total mortality

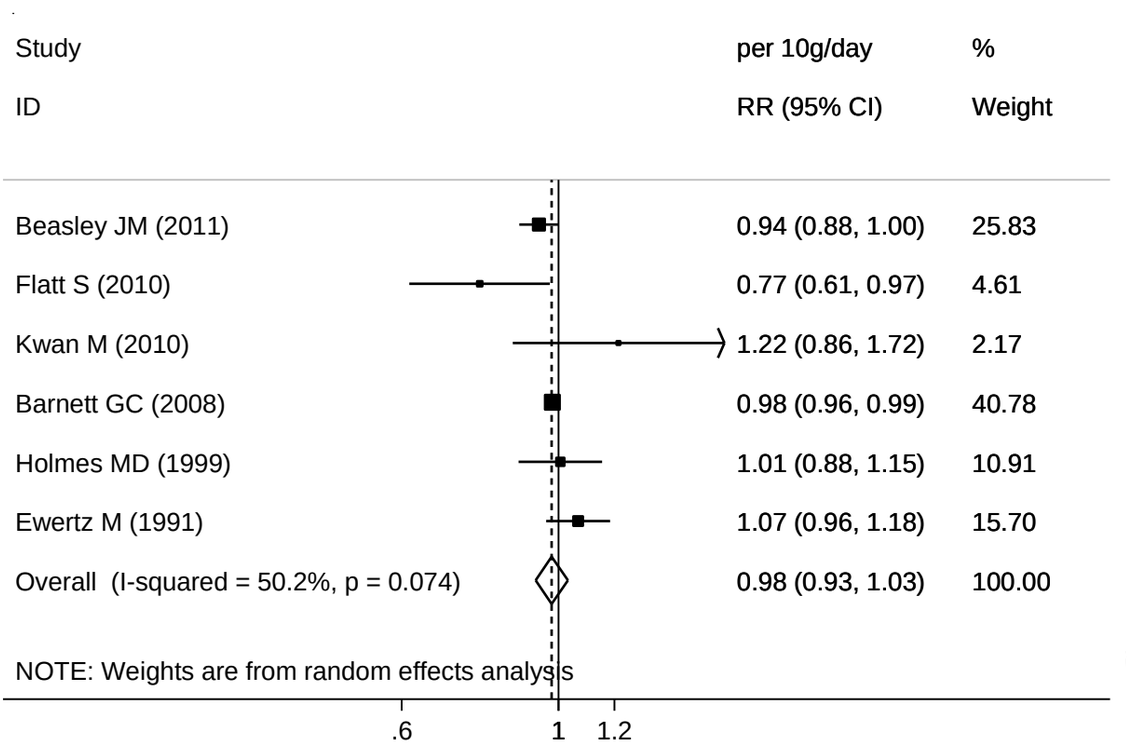
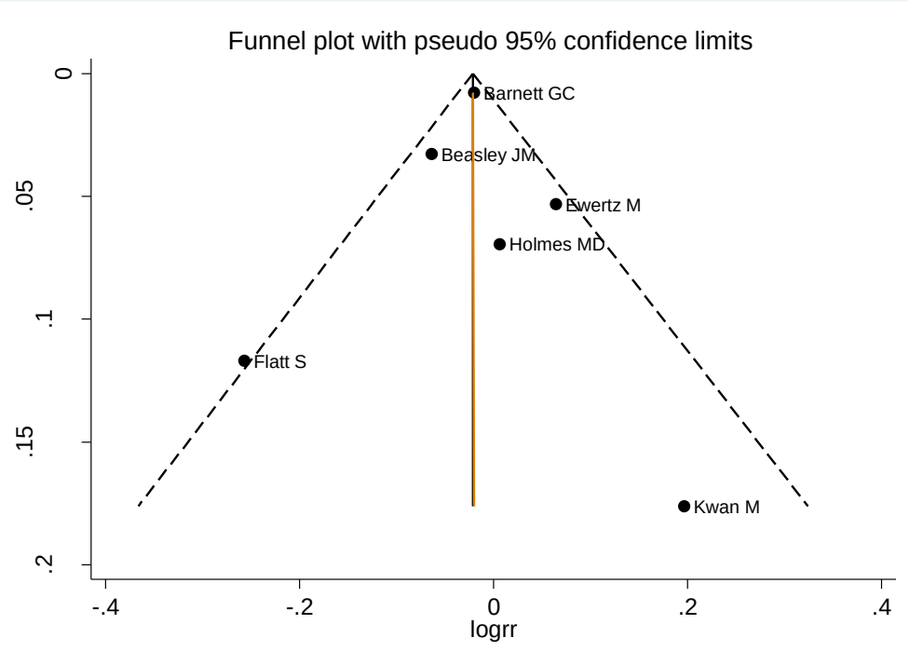


Figure 16 Funnel plot of studies of alcohol intake 12 months or more after primary breast cancer diagnosis and total mortality



Each dot represents the logarithm of relative risk estimate against standard error as a measure of study size. Solid line is the logarithm of summary risk estimate from the meta-analysis. Dashed lines are its 95% confidence interval.

Egger's test p = 0.58

Figure 17 Individual dose-response graph of alcohol intake 12 months or more after primary breast cancer diagnosis and total mortality

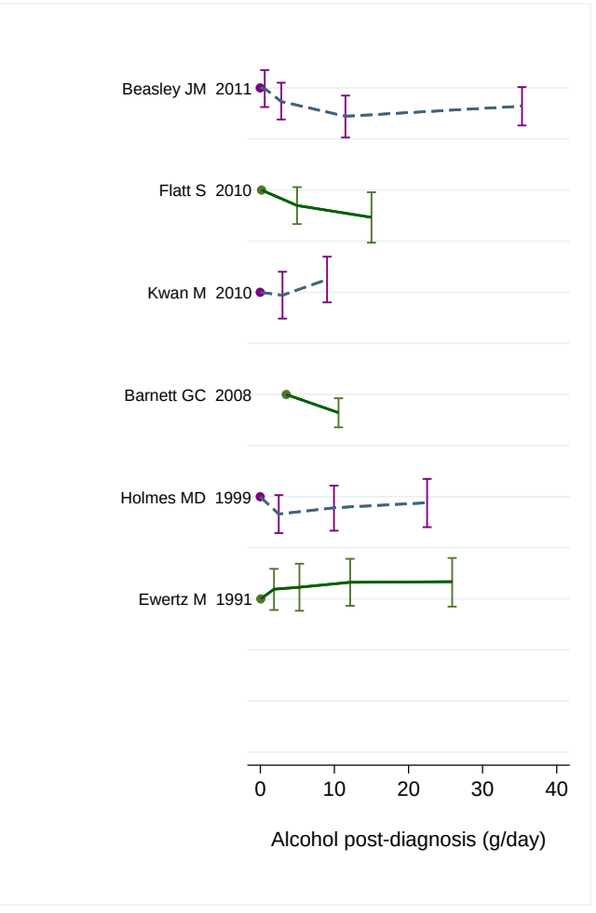
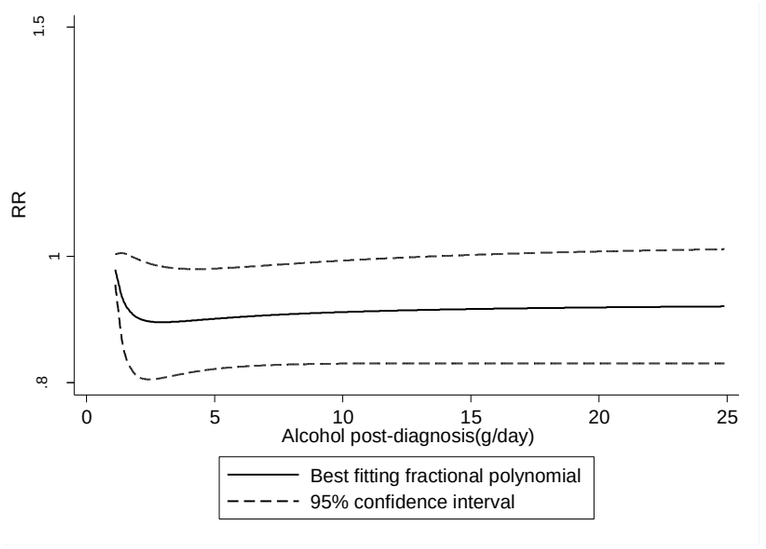
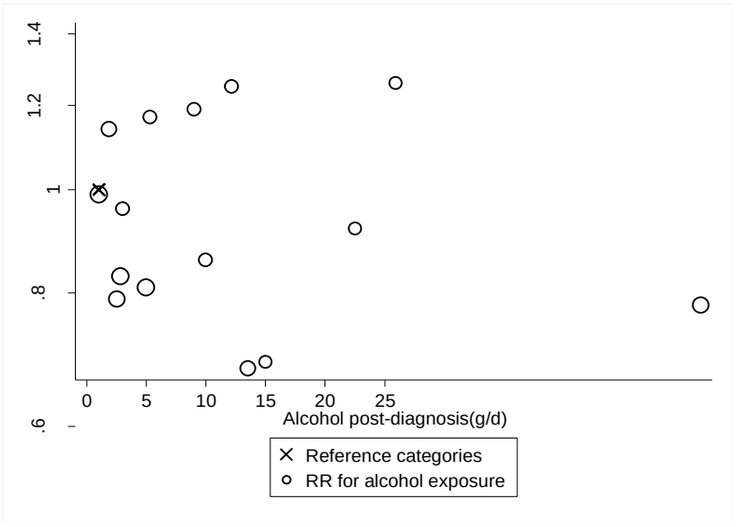


Figure 18 Non-linear dose-response meta-analysis of alcohol intake 12 months or more after primary breast cancer diagnosis and total mortality





$p_{non\text{-}linearity} = 0.01$

Table 16 Table with alcohol intake values and corresponding RRs (95% CIs) for non-linear analysis of alcohol intake 12 months or more after primary breast cancer diagnosis and total mortality

Alcohol (g/day)	RR (95%CI)
0	1
5	0.89 (0.82-0.98)
10	0.90 (0.82-0.99)
20	0.91 (0.82 1.00)

Table 17 Table of included studies on alcohol intake 12 months or more after primary breast cancer diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments / Remarks
Beasley JM (2011)	Collaborative Women's Longevity Study United States	Study recruitment: 1998-2001, Study follow-up: Until 2005 On average 5 years (range 1-16 years) post-diagnosis	Follow up of cases of population-based case-control studies	4441 participants 20 - 79 years Mostly white 22.8% premenopausal, 73.3% postmenopausal among those with data HRT use: 33.2% yes, 56.9% no	5.5 years	Primary invasive breast cancer; Stages: 72.8% local, 27.2% regional		Surgery: 97.9% yes; Radiotherapy: 49.8% yes; Hormonal therapy: 57.8% yes; Chemotherapy: 31.9% yes	42%	Assessed on average 5 years (range 1–16) after diagnosis, usual intake over the past year	4441 participants 525 deaths, 137 breast cancer mortality, 132 deaths from cardiovascular disease	Death certificate	15 vs. 0 % E ethanol	0.78 (0.60–11)	Age, residence, menopausal status, smoking, stage, alcohol intake, hormonal therapy, interval between diagnosis and baseline interview, BMI, physical activity , breast cancer treatment, energy intake
Flatt S (2010)	Women's Healthy Eating and Living Study United States	Cancer diagnosis: 1991-2000; Study recruitment:1995-2000, Follow up: until June 2006 Up to 4 years; 1698 patients <2y and 1390 patients 2-4 y	Prospective cohort of breast cancer survivors	3088 participants 52 years (mean) 18 - 70 years	7.3 years	Invasive breast cancer: 38.5% stage I (=1 cm), 45.5% stage II, 15.9% stage III; 15.7% grade 1, 40.1% grade2, 35.9% grade 3, 8.2% unspecified	Among those with data: 24.8% ER-ve, 75.1%		96%	Assessed on average of 2 y, and a maximum of 4 y after diagnosis (estimated the consumption over the previous 3 mo)	3088 participants 315 deaths (83% of which were BC–related, and only 8% of which were not from any cancer), 518 breast cancer events (69% of which were distal recurrences)	Medical records	>300 g/mo vs. <10g/mo	0.69 (0.49 - 0.97)	Tumor stage, tumor grade, years btw diagnosis and study entry, physical activity, parity, education, ethnicity, weight, smoking
Kwan M (2010)	LACE United States	Cancer diagnosis: 46% 1997-2000; Study recruitment: 2000- 2002 11 and 39 months post diagnosis	Prospective cohort of breast cancer survivors	2269 participants 18 - 70 years Among those with data: 21.3% premenopausal, 64.9% postmenopausal, 13.7% unknown	7.4 years	Invasive breast cancer; among those with data: 47.7% stage I, 32.6% stage IIA, 16.6% stage IIB, 36% stage IIIA	Among those with data:15.6% ER-ve/PR-ve, 1.86% ER-ve/PR+ve, 14.7% ER+ve/PR-ve, 67.7% ER+ve/PR+ve / 33.7% node+ve	Surgery: 50.1% conserving, 49.8% mastectomy; None treatment: 17.4%; Chemotherapy only: 19.5%; Radiation only: 25.9%; Both radian and chemotherapy: 37.1%; Tamoxifen use: 77.8%	46%	Half-reported on average 2 years after diagnosis at cohort entry; consumption of previous 12 months	2269 participants 273 deaths, 154 breast cancer mortality, 24 other cancers mortality, 32 cardiovascular causes, and 63 other causes, 268 second breast cancer	Medical record + death certificate	>= 6 vs. 0 g/day	1.19 (0.87-1.62)	Age at-diagnosis, BMI, folate intake, tumor stage, receptor status, tamoxifen use, treatment, nodal status
Barnett GC (2008)	Studies of Epidemiology and Risk Factors in Cancer Heredity Breast Cancer Study UK	Cancer diagnosis: 1991-2005	Cancer survivors of a population-based prospective cohort study	4560 participants 51.5 years (mean) 23 - 69 years Mostly white Among those with data: 55.2% pre-menopausal, 44.7% postmenopausal HRT use: 62 % never usage, 37.9% ever usage	6.82 years	Invasive breast cancer; 73% incident and 27% prevalent; among those with data: 49.7% stage I, 45.8% stage II, 3.3% stage III, 1.1% stage IV; 24.1% grade 1, 47.2% grade 2, 28.6% grade 3	18.7% ERve, 81.2% ER+ve		67%	Alcohol consumption at age 30y	4560 participants 544 deaths	Cancer registry + death certificate	>7 vs. <=7 units/week	0.96 (0.79 - 1.17)	Age at diagnosis, tumor stage, tumor grade, ER status

Holmes MD (1999)	Nurses' Health Study United States	Cancer diagnosis: 1976–1990, Study follow-up: Until 1994	Cancer survivors of population-based prospective cohort study	1982 participants 54 years (mean) 35.1% premenopausal, 64.9% postmenopausal, among those with data	157 months	Invasive breast carcinoma; Grade 1-3			95% 5% lost	On average 24 months (SD 18m) after diagnosis	1978 participants 378 deaths, 326 breast cancer mortality	Death certificate	>15 vs. 0 g/day	0.92 (0.66-1.27)	Age, diet interval, calendar year of diagnosis, body mass index, oral contraceptive use, menopausal status, postmenopausal hormone use, smoking, age at first birth and parity, number of metastatic lymph nodes, tumor size, energy intake
Tominaga K (1998)	Tochigi Cancer Center Hospital Japan	Breast surgery: 1986-1995, Study follow-up: Until 1995	Follow-up of patients of a hospital-based study	398 participants 35.7% had between 40-49y		TNM stages: 29.1% I, 52.3% II, 15.3% III, 3.2% IV		Mastectomy: 13% partial, 1% simple, 57% modified radical, 29% radical; Chemotherapy: 65% yes, 35% no; Hormone therapy: 44% yes, 56% no; Radiation therapy: 13% yes, 87% no	 2 patients lost	At diagnosis; drinking habits	398 participants 48 deaths	Hospital records	Yes vs. no	0.1 (0.01-0.72)	Age at-diagnosis, TNM stage, curability Highest vs lowest analysis only, only binary results (yes/no)
Ewertz M (1991)	Danish Breast Cancer Cooperative Group Denmark	Cancer diagnosis:1983-1984; Study follow up: until 1990	Cancer survivors of a population-based prospective cohort study	2445 participants <=70 years Among those with data, HRT use:66.1% never usage, 33.8% ever usage	7 years	Primary Invasive breast cancer; 44.8%Grade I, 42.3% Grade II, 12.8% Grade III breast cancer	 58.5% none node+ve, 28.6% 1-3 node+ve, 12.8% >4 node+ve		87%	Self-reported 1 year after diagnosis	805 total death, 1744 participants 533 deaths were included in the analysis	Cancer registry	121 vs. 0 g/w	1.26 (0.9 - 1.74)	Age, tumor size, nodal status, tumor grade, skin invasion, area of residence

Table 18 Table of excluded studies on alcohol intake 12 months or more after primary breast cancer diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments Exclusion reason
Ewertz M (1993)	Danish Breast Cancer Cooperative Group Denmark	Cancer diagnosis: 1983-1984; Study follow up: until 1990	Follow up of cases of a population based case-control study	2445 participants	7 years	Primary invasive breast cancer; 44.8% grade I, 42.3% grade II, 12.8% grade III	58.5% none node +ve, 28.6% 1-3 nodes +ve, 12.7% >= 4 nodes+ve	Adjuvant therapy	3 patients emigrated	From the recorded data one year after the diagnosis		Death record	Yes vs. no	1.3 (0.1-1.75)	The same as Ewertz, 1991, but no category range provided
Pierce J (2007)a	Women's Healthy Eating and Living Study United States	Cancer diagnosis:1991-2000; Study follow up: until 2005 Within 48 months of diagnosis (average, 24 months)	Randomised controlled trial of dietary intervention	1490 participants 50 years (mean)	6.7 years	Early stage breast cancer; AJCC; 40% Stage I (>=1cm), 45% Stage II, 15% stage III, 15.9% grade I, 39.8% grade II, 35.8% grade III, 8.3% unknown	63.1% ER+ve/PR+ve, 10.8% ER+ve/PR-ve, 5.1%ER-ve/PR+ve, 20.8% ER-ve/PR-ve	31.4% none-chemotherapy, 25.7% nonanthracycline, 42.8% anthracycline; 42% adjuvant tamoxifen, 58% no adjuvant tamoxifen		Self-reported at baseline, on average 2 yrs after diagnosis	135 total deaths, 118 breast cancer mortality, 10 death from other cancers, 7 death from non-cancer, 236 breast cancer events	Death certificate	>60 drinks/month vs. never	0.47 p-value=0.03	There was not enough information

Alcohol and breast cancer mortality

Ten studies on alcohol intake and breast cancer mortality were identified. Five studies were on alcohol intake before diagnosis, three studies were on alcohol intake less than 12 months after diagnosis and three studies on alcohol intake 12 months or more after diagnosis.

Alcohol before breast cancer diagnosis and breast cancer mortality

Methods

From the five studies identified, four were included in the dose-response meta-analysis. The analysis was conducted using alcohol measured in drinks per week. One study (McDonald, 2002) presented results for two exposure categories and was only included in the highest versus lowest analysis.

Main results

The excluded study was on 125 African American postmenopausal women diagnosed with invasive breast carcinoma between 1989 and 1994, and accrued to a hospital-based study and followed for survival through December 1998 (McDonald, 2002). Premorbid alcohol consumption of at least one drink per week was associated with 2.7-fold increase in risk of death (95% CI 1.3-5.8).

The summary RR per 1 drink/week was 1.00 (95% CI 0.97-1.02; 4 studies). High heterogeneity was observed (I^2 = 73.5%; p = 0.01). The RR ranged from 0.99 (95% CI 0.96-1.01) when excluding the study by Harris, 2012a to 1.00 (95% CI 0.99-1.01) when excluding the study by Reding, 2008. It was not possible to conduct a meta-analysis stratified by menopausal status. In the highest versus lowest forest plot the overall RR was 1.18 (95% CI 0.81-1.72; 5 studies). There was no evidence of non-linear association ($p_{non\text{-}linearity}$ = 1.0).

Study quality

All the studies, except one (McDonald, 2002) reported more than 100 events, ranging from 178 breast cancer deaths (Hellman, 2010) to 398 breast cancer deaths (Dal Maso, 2008). The follow-up time ranged from 64.8 months (McDonald, 2002) to 12.6 years (Dal Maso, 2008). All the studies, except one (McDonald, 2002), included pre- and postmenopausal women. The alcohol assessment timeframe varies from 1 year before diagnosis (Dal Maso, 2008) to 5 years before diagnosis (Reding, 2008). Two studies were from the United States (McDonald, 2002; Reding, 2008) and three studies were from Europe (Dal Maso, 2008; Hellman, 2010; Harris, 2012a).

Figure 19 Highest versus lowest forest plot of alcohol intake before breast cancer diagnosis and breast cancer mortality

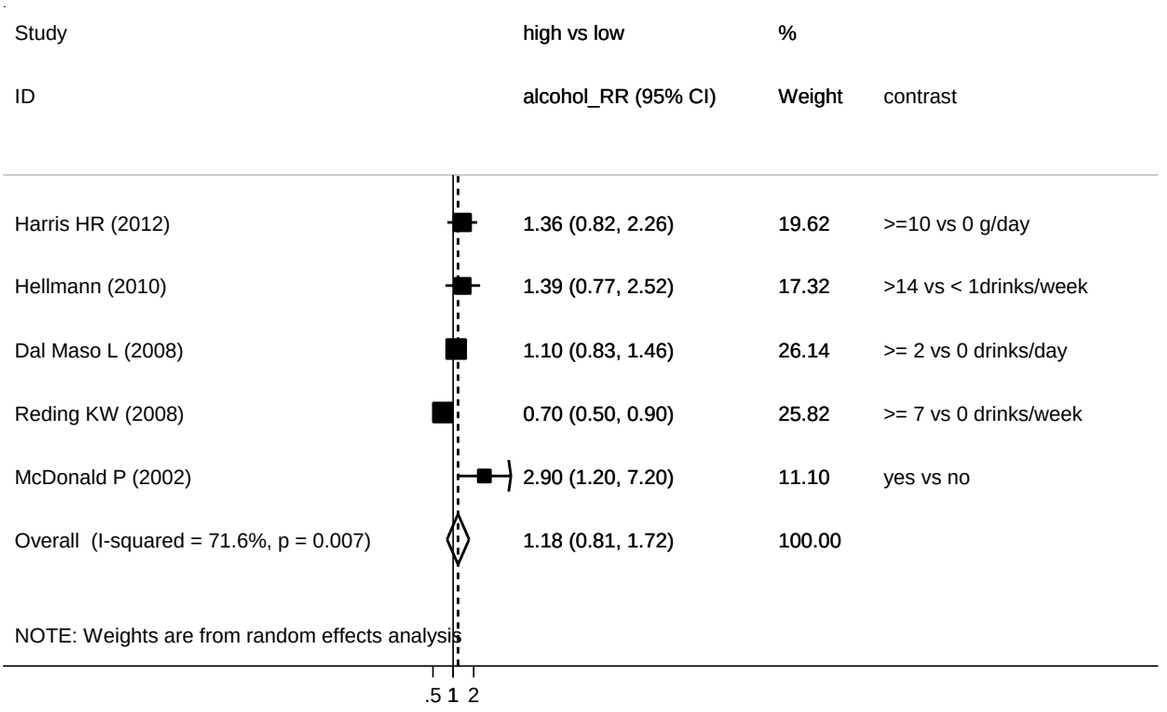


Figure 20 Linear dose-response meta-analysis of alcohol intake before breast cancer diagnosis and breast cancer mortality

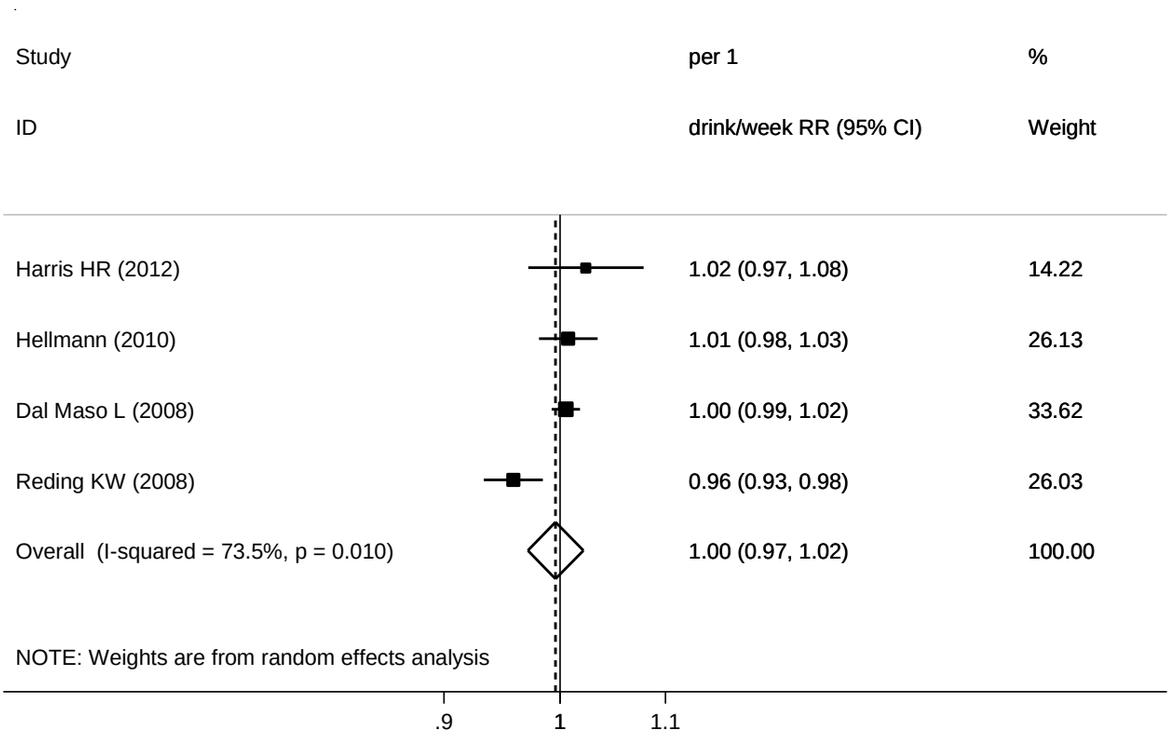


Figure 21 Individual dose-response graph of alcohol intake before breast cancer diagnosis and breast cancer mortality

Table 19 Table of included studies on alcohol intake before breast cancer diagnosis and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments / Remarks
Harris H (2012)a	Swedish Mammography Cohort Sweden	Cancer diagnosis:1987-1990; Study follow up: until 2008	Cancer survivors of a population-based prospective cohort study	3146 participants 65 years (mean) Mostly white Mammography cohort	25940 Person-years	Invasive breast cancer: any stages I-IV	62% ER+ve/PR+ve, 20% ER+ve/PRve, 5% ER-		Complete	At baseline; alcohol during the previous 6 months (1987) or year (1997), pre diagnosis and dietary change after diagnosis	3146 participants 860 deaths, 385 breast cancer mortality	Death certificate	>=10 vs. 0g/d	1.36 (0.82–2.26)	Age, energy intake, education, marital status, menopausal status, BMI, year of diagnosis, stage of disease, radiotherapy, chemotherapy, hormonal therapy
Hellmann (2010)	Copenhagen City Heart Study Denmark	Study recruitment:1976; Study follow up: until 2007	Cancer survivors of a population-based prospective cohort study	528 participants 66.9 years (mean) 33.1 - 95.4 years Mostly Caucasian 16.1% premenopausal, 83.9% postmenopausal HRT use: 71.2% unexposed, 28.8% exposed	7.8 years	Primary breast cancer, one sarcoma, 527 carcinomas; TNM; 56.2% local, 33.7 regional, 6.3 metastatic, 3.8% unknown		7.4% radiotherapy, 7.4% chemotherapy, 22.4% hormonal therapy	74% at the 1st, 70% at the 2nd , 61% at the 3rd and 50% at the 4th examination / 1% lost	Measured at study baseline	528 participants 323 deaths, 178 breast cancer mortality, 126 other causes of death including 43.6% death from cardiovascular disease and 25.6% other cancers	Cancer registry	>14 vs. <1 units/week	1.39 (0.77–2.52)	Age, smoking, physical activity , alcohol intake, hormonal therapy, tumor stage, parity, education, treatment
Dal Maso L (2008)	Six Italian Regions Follow-up Study Italy	Cancer diagnosis: 1991-1994; Study follow up: until 2005-2006 diagnosed no longer than 1 year before the interview	Follow-up of cases of a case-control study	1453 participants 55 years (mean) 23 - 74 years Among those with data, pre diagnosis data: 45.5 % peri/pre menopausal, 54.9% postmenopausal HRT use: 91.3% never, 8.6% ever	12.6 years	Invasive breast cancer; TNM; 32.7% Stage I, 44.1% stage II, 13.2% stage III-IV, 9.8% unknown	41.5% ER+ve/PR+ve, 3.5% ERve/PR+ve, / 45.6% no node+ve, 44.2% node+ve, 10.1%		2.70% lost	Before diagnosis (diagnosed no longer than 1 year before the interview)	1453 participants 503 deaths, 398 breast cancer mortality, 6.2% death from other cancers, 7.4% from cardiovascular disease	Cancer registry	>=2 vs. 0 drinks/d	1.10 (0.83–1.46)	Region, age at diagnosis, year of diagnosis, TNM stage, receptor status
Reding KW (2008)	Fred Hutchinson Cancer Research Center Follow-up study United States	Cancer diagnosis: 1983-1992, Study follow-up: Until 2002 Recruited at diagnosis	Follow-up of cases of case-control studies	1286 participants 45 years (mean) Multi-ethnic Premenopausal HRT use: 41.4% ever had, 58.6% had not among those with data	9 years	First primary invasive breast cancer; 57.94% local, 409% regional, 1.97% distant	59.3% ER+ve, 40.7% ERve, 60.5% PR+ve, / 41.1% +ve, 58.9% -ve, among those with data	Chemotherapy: 68.9% yes, 31.1% no; Radiotherapy 53.8% yes, 46.2% no; Hormone therapy 35.3% yes, 64.7% no, among those with data	83.3%, 83.9% in original studies / 93.1% contacted within 12 months of end of F/U, 6.9% loss	5 years before diagnosis were recalled at interview	1286 participants 364 deaths, 335 breast cancer mortality, 22 other causes of deaths, 7 unknown causes of deaths	Medical records	>=7 vs. 0 drinks/week	0.6 (0.5-0.9)	Age, diagnosis year, and mammography

McDonald P (2002)	Grampian University Hospitals Follow-up Study United States	Cancer diagnosis:1989-1994; Study follow up: until 1998	Prospective cohort of breast cancer survivors	125 participants 64.2 years (mean) All postmenopausal	64.8 months	Invasive breast cancer; 54.4% localized, 41.6% regional, 4% distant and diffuse; 11.2 % Intraductai In situ, 78.4% Infiltrating ductal, 10.4% others	43.2% ER+ve, 24.8% ER-ve, 32% unknown; 31.2% PR+ve, 36.8% PR-ve, 32% unknown	98.2% surgery, 45.6% chemotherapy, 44% radiotherapy	94.40%	Assessed before diagnosis; regular alcohol consumption in lifetime	125 participants 33 breast cancer mortality, 12 death from other causes	Death certificate	Yes vs. no	2.9 (1.2 - 7.2)	Tumor stage, radiotherapy, smoking, alcohol intake
							56% no +ve node, 16.8% 1-3 nodes +ve, 21.6% >= 4 nodes +ve		5.60% lost						Highest vs. lowest analysis only, only binary results (yes/no)

Alcohol less than 12 months after diagnosis and breast cancer mortality

Three studies were identified (Hebert, 1998; Borugian, 2004, Allin, 2011). One study (Hebert, 1998) reported an increased risk of mortality for breast cancer in relation to beer intake (RR 1.58; 95% CI 1.0-2.78; per drinks/day), the study by Borugian (2004) did not find any association with alcohol intake (RR 0.99; 95% CI 0.94-1.04; per percentage of energy from alcohol), and the study by Allin (2011) reported a RR of 0.96 (95% CI 0.59-1.55; > 168 vs. ≤ 168 g of alcohol per week). There was not enough information to conduct a meta-analysis.

Alcohol intake 12 months or more after primary breast cancer diagnosis and breast cancer mortality

Methods

Three studies were identified and included in the dose-response meta-analysis. From the three studies, two reported alcohol intake in grams per day therefore the analysis was conducted using this measure. One study (Beasley, 2011) reported alcohol intake as percentage of energy from alcohol that was converted to grams of alcohol using the median quintile of energy intake reported in the article.

Main results

The summary RR per 10 g/day was 1.06 (95% CI 0.79-1.42; 3 studies). High heterogeneity was observed (I^2 = 65.2%; p = 0.06). The RR ranged from 0.95 (95% CI 0.73-1.24) when excluding the LACE study (Kwan, 2010) to 1.20 (95% CI 0.82-1.77) when excluding the study by Rohan, 1993. It was not possible to conduct a meta-analysis stratified by menopausal status. In the highest versus lowest forest plot the overall RR was 1.22 (95% CI 0.88-1.69; 3 studies). There was no evidence of a non-linear association between alcohol less than 12 months after diagnosis and breast cancer mortality, $p_{non\text{-}linearity}$ = 1.0.

Study quality

All studies reported more than 100 events, ranging from 112 (Rohan, 1993) to 137 (Beasley, 2011) breast cancer deaths. The follow-up time ranged from 5.5 years (Beasley, 2011) to 7.4 years (Kwan, 2010). All the studies included pre- and postmenopausal women. The alcohol assessment timeframe varies from 5 months after diagnosis (Rohan, 1993) to 5 years after diagnosis (Beasley, 2011). Two studies were from the United States (Kwan, 2010; Beasley, 2011) and one study was from Australia (Rohan, 1993).

Figure 22 Highest versus lowest forest plot of alcohol intake 12 months or more after primary breast cancer diagnosis and breast cancer mortality

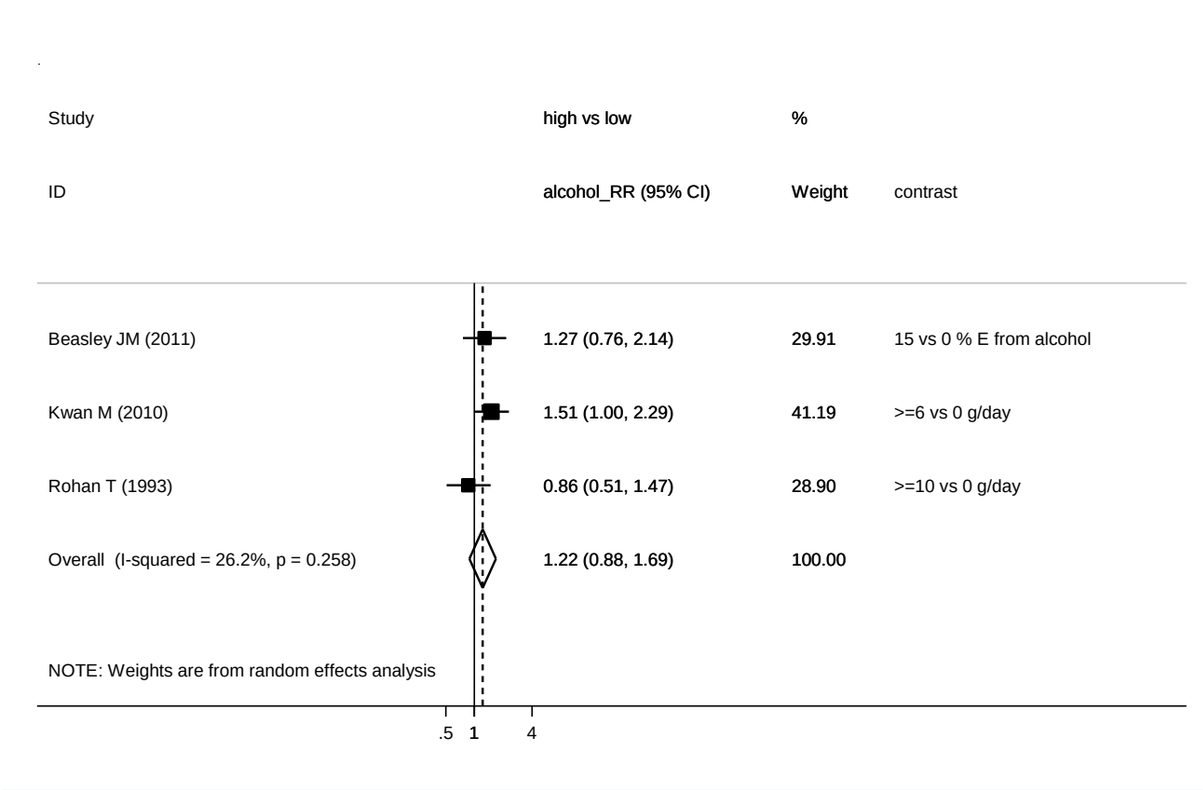


Figure 23 Linear dose-response meta-analysis of alcohol intake 12 months or more after primary breast cancer diagnosis and breast cancer mortality

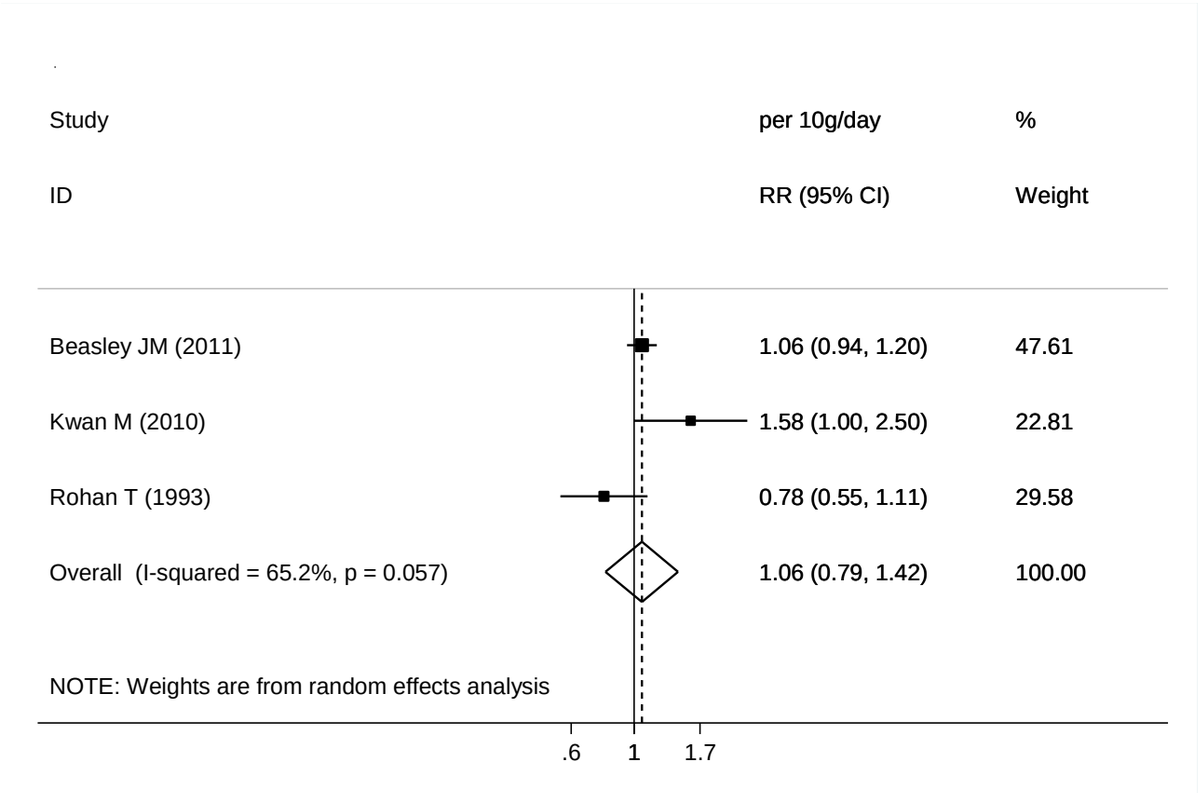


Figure 24 Individual dose-response graph of alcohol intake 12 months or more after primary breast cancer diagnosis and breast cancer mortality

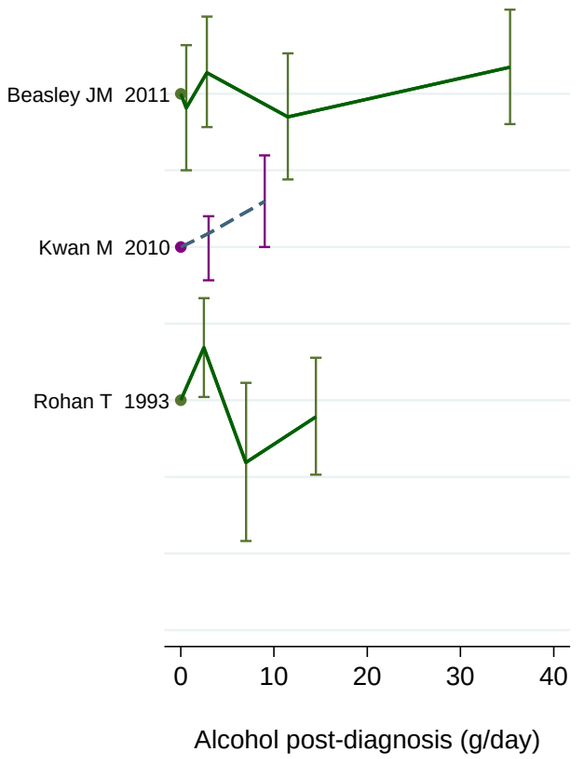


Table 20 Table of included studies on alcohol intake 12 months or more after primary breast cancer diagnosis and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Beasley JM (2011)	Collaborative Women's Longevity Study United States	Study recruitment: 1998-2001, Study follow-up: Until 2005	Follow up of cases of population-based case-control studies	4441 participants 20 - 79 years Mostly white 22.8% premenopausal, 73.3% postmenopausal among those with data HRT use: 33.2% yes, 56.9% no	5.5 years	Primary invasive breast cancer; Stages: 72.8% local, 27.2% regional		Surgery: 97.9% yes; Radiotherapy: 49.8% yes; Hormonal therapy: 57.8% yes; Chemotherapy: 31.9% yes	42%	Assessed on average 5 years (range 1–16) after diagnosis, usual intake over the past year	4441 participants 525 deaths, 137 breast cancer mortality, 132 deaths from cardiovascular disease	Death certificate	15 vs. 0 % E ethanol	0.78 (0.60–11)	Age, residence, menopausal status, smoking, stage, alcohol intake, hormonal therapy, interval between diagnosis and baseline interview, BMI, physical activity , breast cancer treatment, energy intake
Kwan M (2010)	LACE United States	Cancer diagnosis: 46% 1997-2000; Study recruitment: 2000-2002 11 and 39 months post diagnosis	Prospective cohort of breast cancer survivors	2269 participants 18 - 70 years Among those with data: 21.3% premenopausal, 64.9% postmenopausal, 13.7% unknown	7.4 years	Invasive breast cancer; among those with data: 47.7% stage I, 32.6% stage IIA, 16.6% stage IIB, 36% stage IIIA	Among those with data:15.6% ER-ve/PR-ve, 1.86% ER-ve/PR+ve, 14.7% ER+ve/PR-ve, 67.7% ER+ve/PR+ve 33.7% node+ve	Surgery: 50.1% conserving, 49.8% mastectomy; None treatment: 17.4%; Chemotherapy only: 19.5%; Radiation only: 25.9%; Both radian and chemotherapy: 37.1%; Tamoxifen use: 77.8%	46%	Half-reported on average 2 years after diagnosis at cohort entry; consumption of previous 12 months	2269 participants 273 deaths, 154 breast cancer mortality, 24 other cancers mortality, 32 cardiovascular causes, and 63 other causes, 268 second breast cancer	Medical record + death certificate	>= 6 vs. 0 g/day	1.19 (0.87-1.62)	Age at-diagnosis, BMI, folate intake, tumor stage, receptor status, tamoxifen use, treatment, nodal status
Rohan T (1993)	Diet and Breast Cancer in Australia Follow-up Study Australia	Cancer diagnosis: 1982-1984, Study follow-up: Until 1989	Follow-up of cases of population-based case-control study	412 participants 55.1 years (mean) 20 - 74 years 30.7% premenopausal, 5.4% perimenopausal, 64% postmenopausal, among those with data	5.5 years	Primary breast cancer, any stages			80.70% 39 patients lost	Interval between diagnosis and interview was 4.8months	412 participants 112 breast cancer mortality, 11 other causes of deaths	Cancer registry + death certificate	>= 10 vs. 0 g/d	0.86 (0.51 - 1.47	Energy intake, age of menarche, Quetelet Index

Alcohol and second primary breast cancer

Seven studies on alcohol intake and second primary breast cancer were identified. Two studies were on alcohol intake less than 12 months after diagnosis and second primary breast cancer (Li, 2003; Li, 2009); 5 studies were on alcohol intake 12 months or more after diagnosis and second primary breast cancer (Trentham-Dietz, 2007; Li, 2009; Knight, 2009; Kwan, 2010; Flatt, 2010). One study (Li, 2009) reported both alcohol intake less than 12 months after diagnosis and alcohol intake 12 months or more after diagnosis.

Alcohol before breast cancer diagnosis and second primary breast cancer

No study was identified.

Alcohol less than 12 months after diagnosis and second primary breast cancer

Alcohol intake was not related to contralateral breast cancer in a follow-up of 1285 with pre-menopausal women participating in two case-control studies conducted in the US and diagnosed with a first invasive breast carcinoma from 1983 to 1992 and followed through 2001 (Li, 2003). The relative risk for more than 3 drinks per week compared to less than 1 or none was 0.9 (95% CI 0.5-1.5).

Alcohol consumption was positively associated with the risk of second primary breast cancer in a case-control nested in a cohort of women diagnosed from 1990 to 2005, with a first primary invasive, stage I to IIIB, ER+ breast cancer at age 40 to 79 years. The relative risks for more than 7 drinks/week compared to none were 1.7 (95% CI 1.0- 2.9, $p < 0.05$) for alcohol intake less than 12 months after diagnosis of primary breast cancer and 1.9 (95% CI 1.1- 3.2) for alcohol consumption between first breast cancer diagnosis and reference date (Li, 2009).

Alcohol intake 12 months or more after breast cancer diagnosis and second primary breast cancer

Methods

The five studies identified were included in the dose-response meta-analysis. Three studies reported alcohol intake as number of drinks per week therefore the analysis was conducted using alcohol measured in drinks per week. Two studies (Flatt, 2010; Kwan, 2010) reported the alcohol intake in grams per day. For these studies the alcohol intake was converted to drinks per week using the conversion unit referred in the study, 10 and 13.7 g of ethanol as one serving of alcohol, respectively.

Main results

The summary RR per 1 drink/week was 1.01 (95% CI 0.99-1.03; 5 studies). Moderate heterogeneity was observed ($I^2 = 43.6\%$; $p = 0.13$). Egger's test showed no evidence of publication bias, $p = 0.18$, but visual inspection of the funnel plot suggests that small studies showing inverse and null associations are missing, and that the smallest studies have reported stronger positive associations than the other studies. However, the number of studies is very low and any interpretation of the forest plot should be taken cautiously. The RR ranged from 1.00 (95% CI 0.99-1.02) when excluding the LACE study (Kwan, 2010) to 1.01 (95% CI 0.99-1.04) when excluding the WHEL study (Flatt, 2010). It was not

possible to conduct a meta-analysis stratified by menopausal status. In the highest versus lowest forest plot the overall RR was 1.19 (95% CI 0.96-1.47; 5 studies). There was no evidence of a non-linear association between alcohol more than 12 months after diagnosis and primary second cancer, $p_{nonlinearity} = 1.0$.

One study (Trentham-Dietz, 2007) reported the risk of second primary cancers others than breast cancer. When comparing the intake of more than seven drinks/week with no recent alcohol consumption, the relative risk of a second primary colorectal cancer was 1.92 (95% CI 1.07-3.43), the relative risk of a second primary endometrial cancer was 0.84 (95% CI 0.42-1.69), and the risk of a second primary ovarian cancer was 0.55 (95% CI 0.18-1.72).

Study quality

Only one study (Trentham-Dietz, 2007) had less than 100 events. All other studies reported a higher number of events, ranging from 365 (Li, 2009) to 708 (Knight, 2009) second primary breast cancers. The follow-up time ranged from 7.1 years (Trentham-Dietz, 2007) to 17 years (Li, 2009). All the studies included pre and postmenopausal women. The alcohol assessment timeframe varies from 1 year after diagnosis (Trentham-Dietz, 2007) to 4 years after diagnosis (Flatt, 2010). Four studies were from the United States and one study was conducted both in the United States and Europe (Knight, 2009).

Figure 25 Highest versus lowest forest plot of alcohol intake 12 months or more after diagnosis and second primary breast cancer

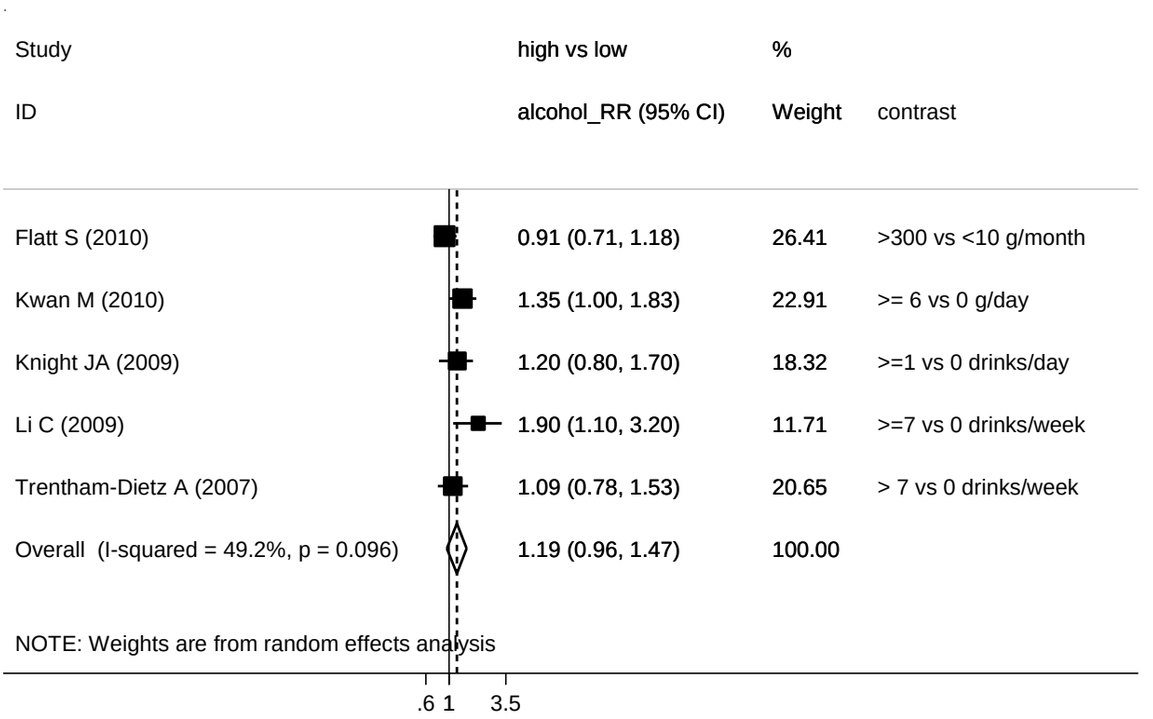


Figure 26 Linear dose-response meta-analysis of alcohol intake 12 months or more after diagnosis and second primary breast cancer

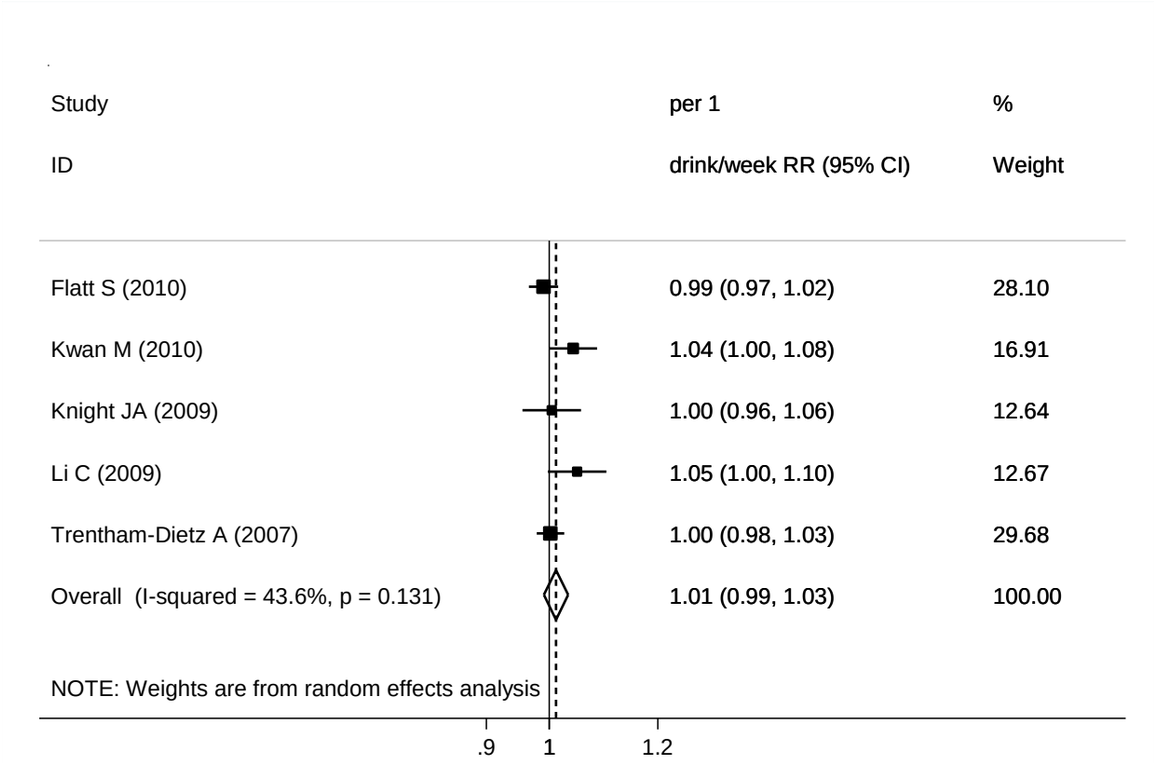
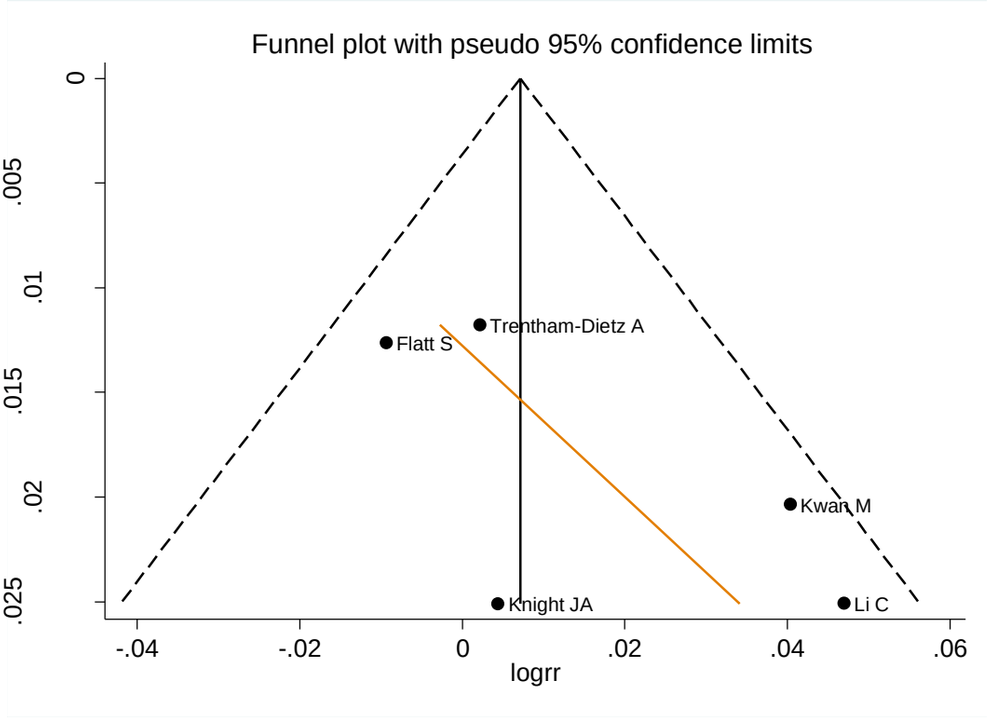


Figure 27 Funnel plot of studies of alcohol intake 12 months or more after diagnosis and second primary breast cancer



Each dot represents the logarithm of relative risk estimate against standard error as a measure of study size. Solid line is the logarithm of summary risk estimate from the meta-analysis. Dashed lines are its 95% confidence interval.

Egger's test p = 0.18

Figure 28 Individual dose-response graph of alcohol intake 12 months or more after diagnosis and second primary breast cancer

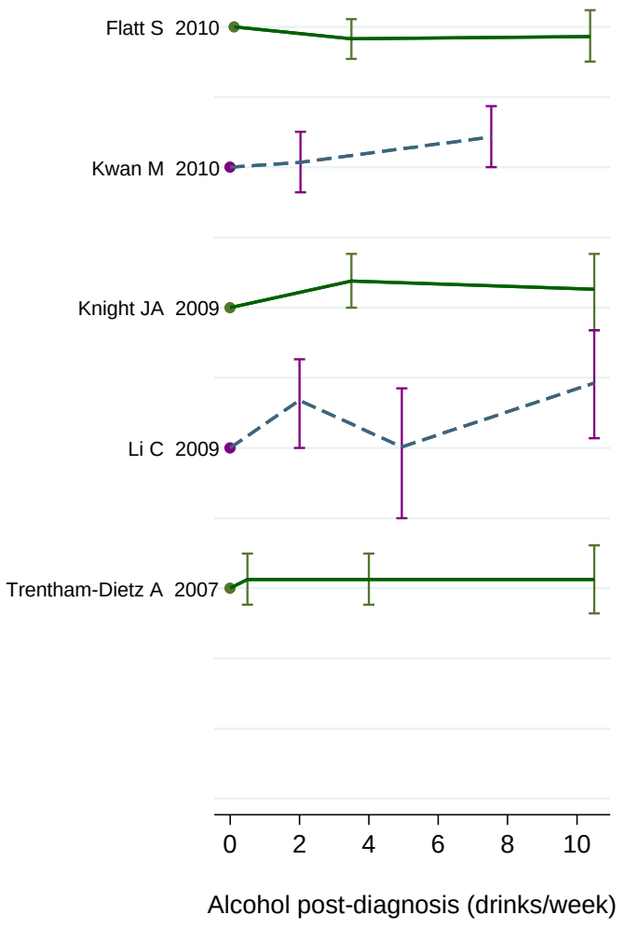


Table 21 Table of included studies on alcohol intake 12 months or more after diagnosis and second primary breast cancer

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Flatt S (2010)	Women's Healthy Eating and Living Study United States	Cancer diagnosis: 1991-2000; Study recruitment:1995-2000, Follow up: until June 2006 Up to 4 years; 1698 patients <2y and 1390 patients 2-4 y	Prospective cohort of breast cancer survivors	3088 participants 52 years (mean) 18 - 70 years	7.3 years	Invasive breast cancer: 38.5% stage I (=1 cm), 45.5% stage II, 15.9% stage III; 15.7% grade 1, 40.1% grade2, 35.9% grade 3, 8.2% unspecified	Among those with data: 24.8% ER-ve, 75.1%		96%	Assessed on average of 2 y, and a maximum of 4 y after diagnosis (estimated the consumption over the previous 3 mo)	3088 participants 315 deaths (83% of which were BC–related, and only 8% of which were not from any cancer), 518 breast cancer events (69% of which were distal recurrences)	Medical records	>300 g/mo vs. <10g/mo	0.69 (0.49 - 0.97)	Tumor stage, tumor grade, years btw diagnosis and study entry, physical activity, parity, education, ethnicity, weight, smoking
Kwan M (2010)	LACE United States	Cancer diagnosis: 46% 1997-2000; Study recruitment: 2000-2002 11 and 39 months post diagnosis	Prospective cohort of breast cancer survivors	2269 participants 18 - 70 years Among those with data: 21.3% premenopausal, 64.9% postmenopausal, 13.7% unknown	7.4 years	Invasive breast cancer; among those with data: 47.7% stage I, 32.6% stage IIA, 16.6% stage IIB, 36% stage IIIA	Among those with data:15.6% ER-ve/PR-ve, 1.86% ER-ve/PR+ve, 14.7% ER+ve/PR-ve, 67.7% ER+ve/PR+ve / 33.7% node+ve	Surgery: 50.1% conserving, 49.8% mastectomy; None treatment: 17.4%; Chemotherapy only: 19.5%; Radiation only: 25.9%; Both radian and chemotherapy: 37.1%; Tamoxifen use: 77.8%	46%	Half-reported on average 2 years after diagnosis at cohort entry; consumption of previous 12 months	2269 participants 273 deaths, 154 breast cancer mortality, 24 other cancers mortality, 32 cardiovascular causes, and 63 other causes, 268 second breast cancer	Medical record + death certificate	>= 6 vs. 0 g/day	1.19 (0.87-1.62)	Age at-diagnosis, BMI, folate intake, tumor stage, receptor status, tamoxifen use, treatment, nodal status
Knight JA (2009)	The Women's Environmental Cancer and Radiation Epidemiology Study USA and Denmark	Cancer diagnosis: 1985-2000	Population-based nested case-control study	2107 participants 55 years	Maximum 16y	Stages: 67.5% local, 32.5% regional; Histology: 10.5% lobular, 4% medullary, 85.5% ductal and other		Chemotherapy: 51.8% yes, 48.2% no; Radiotherapy: 70.2% yes, 29.8% no; Hormone therapy: 32.5% yes, 67.5% no among those with data	71% cases, 66% controls	After 1st diagnosis and before the 2nd cancer diagnosis	2107 participants 708 contralateral second primary breast cancers	Medical record + pathology report	>=1 vs. 0 drinks/day	1.2 (0.8 - 1.7)	Age
Li C (2009)	Seattle-Puget Sound Region Nested Case-Control Study United States	Cancer diagnosis: 1990-2005	Population-based nested case-control study	1091 participants 40 - 79 years HRT use: 19.6% current estrogen alone users, 17% current estrogen + progestin users, 10.2% former users, 47.1% never users, 6% missing	17 years	AJCC stages: 67.4% I, 32.6% II or III; Tumor size (cm): 33.4% <=1, 41.7% 1.1-2, 21.9% >2, 3% missing	23.8% +ve, 76.2% -ve	Chemotherapy: 26.1% yes, 73.9% no; Radiotherapy: 65.4% yes, 34.6% no, 0.1% missing; Adjuvant hormone therapy: 66.8% yes, 33.2% no	83%cases, 75%controls	Post-treatment; lifetime alcohol consumption	1091 participants 365 contralateral breast cancers	Cancer registry	>=7 vs. 0 drinks/week	1.9 (1.1 - 3.2)	Age, year of diagnosis, county, race, tumor stage, survival time, hormonal therapy, chemotherapy, BMI
Trentham-Dietz A (2007)	Wisconsin Follow-up Study of Women with Invasive	Cancer diagnosis: 1987-2000, Study follow-up: Until	Follow-up of cases of case-control studies	10953 participants 59.4 years (mean) 18 - 79 years	7.1 years	Stages: 63% local, 28.9% regional, 2.3% distant, 5.8%			83.30%	Self reported 1y after diagnosis	10953 participants 1188 second cancers: 488 second breast cancers, 132 colorectal cancers, 113 endometrial cancers,	Cancer registry	> 7 vs. 0 drinks/week	1.09 (0.78-1.53)	Age, year of diagnosis, tumor stage, family history, smoking, alcohol intake, parity, HRT, menopausal status, BMI

	Breast Cancer United States	2002 Recruited approximately 1 year after diagnosis				unknown					36 ovarian cancers				

4 Dietary constituents

4.1 Carbohydrate intake

Table 22 Summary results of meta-analysis on carbohydrates and total mortality, breast cancer mortality

	Total mortality			Breast cancer mortality		
Comparison	**No. of studies**	**No. of events in studies**	**RR (95% CI) I^2, $P_{heterogeneity}$**	**No. of studies**	**No. of events in studies**	**RR (95% CI) I^2, $P_{heterogeneity}$**
Carbohydrate intake before diagnosis						
Highest vs. lowest	2	152	0.67 (0.16-2.84) 92%, p<0.001			
Per 100 g/day	3	178	0.80 (0.33-1.94) 87.1%, p<0.001			
Carbohydrate intake 12 months or more after diagnosis						
Highest vs. lowest	3	1092	0.91 (0.74-1.12) 0%, p = 0.68	3	332	0.73 (0.51-1.04) 0%, p = 0.50
Per 100 g/day				3	332	0.87 (0.71-1.06) 0%,p = 0.45

*No studies on second cancers were included in the meta-analyses. Only studies on carbohydrate intake before and after diagnosis could be included in meta-analyses.

Carbohydrate intake and total mortality

Eight studies on carbohydrate and total mortality were identified. Four studies were on carbohydrate intake before diagnosis and total mortality (Zhang, 1995; Saxe, 1999; Goodwin, 2003 and McEligot, 2006) and three studies were on carbohydrate intake 12 months or more after diagnosis and total mortality (Holmes, 1999; Belle, 2011 and Beasley, 2011).

Carbohydrate intake before diagnosis and total mortality

Methods

From the 4 studies identified, 3 were included in the dose-response meta-analysis. One study (Goodwin, 2003) was excluded because it did not provide enough information for the analysis. This study found no association with carbohydrate intake (g/day) but suggested a U-shaped relationship with energy from carbohydrate. One study (Saxe, 1999) reported energy from carbohydrates, which was converted to grams of carbohydrates using the mean energy intake provided in the study. The two other studies reported carbohydrate intake in grams per day.

Main results and heterogeneity

The summary RR per 100 g/day was 0.80 (95% CI 0.33-1.94; 3 studies). High heterogeneity was observed (I^2 = 87.1%; p < 0.001). It was not possible to conduct a stratified analysis by menopausal status. In the highest versus lowest forest plot the overall RR was 0.67 (95% CI 0.16-2.84; 2 studies).

Study quality

The studies reported less than 100 events. The follow-up time ranged from 2.9 years (Zhang, 1995) to 6.6 years (McEligot, 2006). One study (Saxe, 2006) analysed pre and postmenopausal women separately and the other studies included only postmenopausal women. The dietary assessment ranged from 6 years (Zhang, 1995) to one year before diagnosis (Saxe, 1999; McEligot, 2006). The three studies were from the United States.

Figure 29 Highest versus lowest forest plot of carbohydrate intake before diagnosis and total mortality

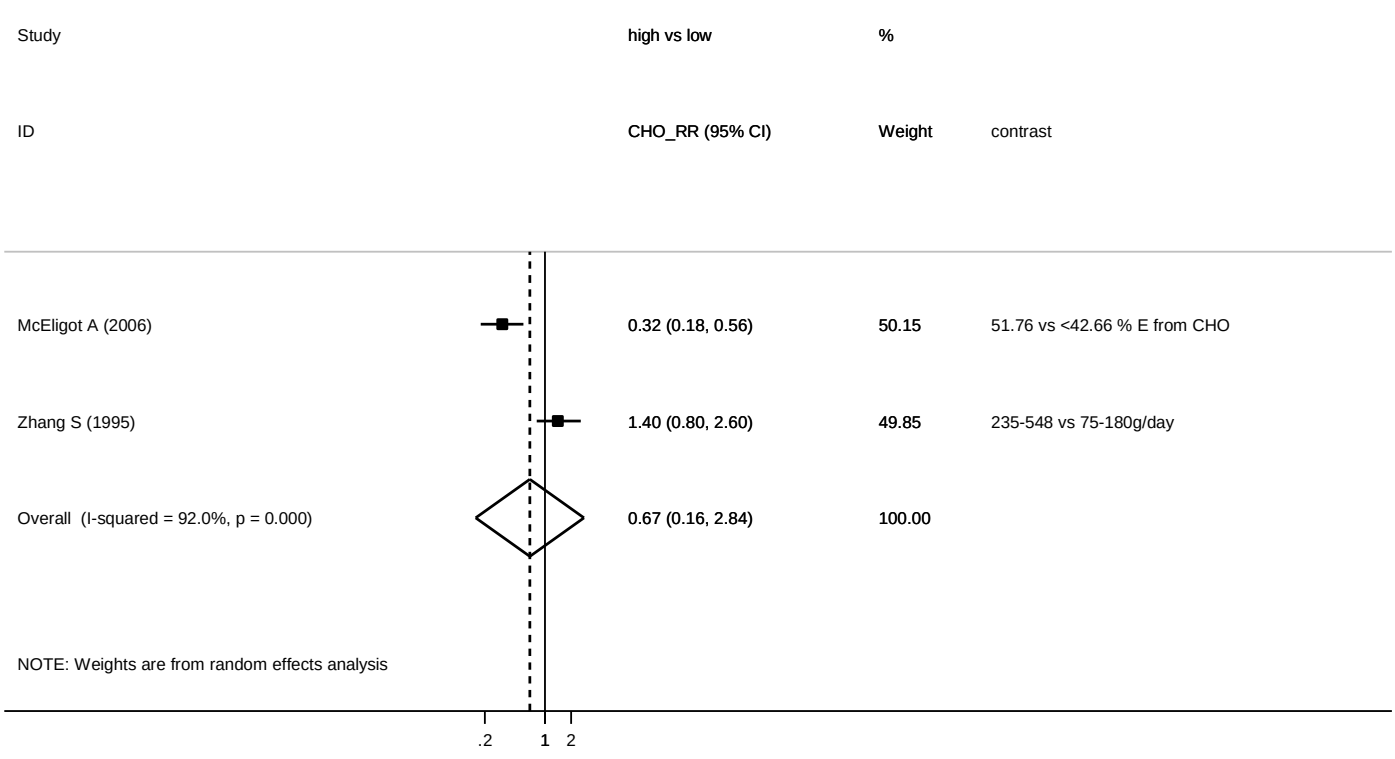


Figure 30 Linear dose-response meta-analysis of carbohydrate intake before diagnosis and total mortality

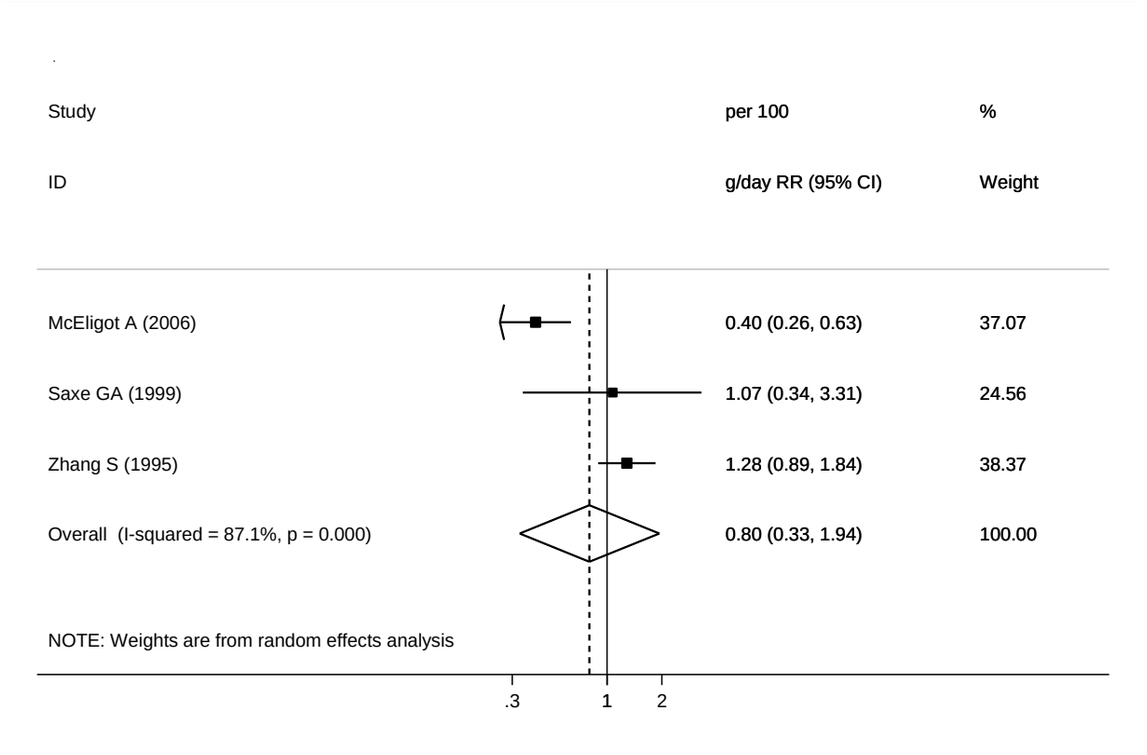


Figure 31 Individual dose-response graph of carbohydrate intake before diagnosis and total mortality

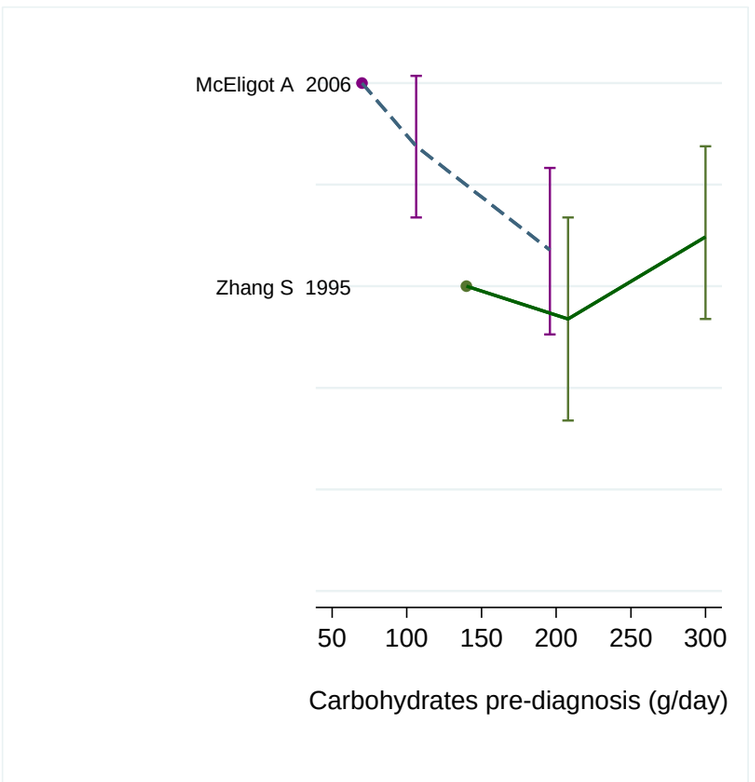


Table 23 Table of included studies on carbohydrate intake before diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments / Remarks
McEligot A (2006)	Orange County California Study United States	Cancer diagnosis: 1994-1995, Study follow-up: Until 2003 Recruited within 6 months of diagnosis	Prospective cohort of breast cancer survivors	516 participants 64.78 years (mean) Postmenopausal 92.3% non-Hispanic white HRT use: 36.2% estrogen only, 1.9% progesterone only, 35.1% estrogen and progesterone, 26.7% non-users	80 months	Stages: 14.9% in situ, 59.3% localized, 24.2% regional, 1.55% metastatic			98% / 2% lost	At diagnosis; dietary habits during the 1 year prior to diagnosis FFQ	516 participants 96 deaths, 41 breast cancer mortality, 13 deaths from cardiovascular disease, 31 other causes of deaths, 11 unknown causes of deaths	Cancer registry + National Death Index	51.76 vs. <42.66 g/d	0.32 (0.18-0.56)	Tumor stage, age at diagnosis, BMI, parity, HRT, alcohol intake, multivitamins, energy intake
Saxe GA (1999)	Medical Center, Michigan University Follow-up Study United States	Study recruitment: 1989-1991, Recruited during first medical center visit for suspected or newly diagnosed	Prospective cohort of breast cancer survivors	149 participants 57.8 years (mean) 26 - 95 years White: 90.6%, black:7.2% and other: 2.2%,34.2% premenopausal, 65.8% postmenopausal	5 Years (min)	Primary breast cancer, stages: 19.6% in situ, 34.5% I, 34.5% II, 8.8% III, 2.7% IV	73.4% ER+, 26.6% ER- / 43% +ve, 57% -ve		0% lost	Interviewed close to time of diagnosis for diet a year prior to diagnosis, semi-quantitative FFQ	149 participants 26 deaths	Hospital records	Per 10% of energy	1.03 0.64-1.65	Tumor stage, energy intake / Dose-response analysis only, only continuous results
Zhang S (1995)	Iowa Women's Health Study United States	Study recruitment:1986; Study follow up: until 1991	Cancer survivors of population-based prospective cohort study	698 participants 55 - 69 years Mostly white: 98%, Postmenopausal	2.9 years	Unilateral breast cancer; 10% in situ, 58% local, 28% regional, 3%distant, and 1% unknown; 55% tumour size <2cm, 33% size >= 2cm and 11% unknown	Among those with data: 85% ER+ve and 72% PR+ve		42.60% / < 1% migration rate	Self reported questionnaire within 6 years before diagnosis semi-quantitative FFQ	698 participants 56 deaths, 40 breast cancer mortality (among the causes of death) and 2 death from coronary heart disease	Death Certificates + National Death Index	548 vs. 235 g/d	1.4 (0.8-2.6)	Age, smoking, education, tumor stage, ER status, tumor size

Table 24 Table of excluded studies on carbohydrate intake before diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments Exclusion reason
Goodwin P (2003)	University of Toronto Hospitals Follow-up Study, Canada	Study recruitment: 1989-1996,	Prospective cohort of breast cancer survivors	477 participants 50.4 years (mean) <=75 years 57.7% premenopausal, 3.6% perimenopausal, 38.8% postmenopausal	6.1 years	Tumor stages: 55.6% T1, 32.3% T2, 5.2%, 6.9% unknown; Grades: 13% 1, 40.7% 2, 33.1% 3, 13.2% unknown	62.5% ER+, 18.7% ER-, 13.4% unknown; 56.6% PR+, 22.9% PR-, 14.9% unknown 30.6% +ve, 69.4% -ve	Mastectomy: 23.3% yes; Lumpectomy: 76.7% yes; Chemotherapy only: 28.3% yes; Chemotherapy plus tamoxifen 9.6%; Tamoxifen only: 29.6%; None: 32.5% yes	8 patients lost	FFQ comleted 9.3 ± 4.6 weeks after diagnosis, reporting intake over preceding 12 months	477 participants, 52 deaths, 2 non-breast cancer related deaths	Medical records		P for linear=0.99, P for non-linear=0.22	BMI,age,tumor stage,nodal status,hormonal therapy,chemotherapy, energy intake Study examined the association of dietary factors with breast cancer survival. HRs were provided from linear and non-linear models, but without 95% CIs or p-values

Carbohydrate intake less than 12 months after diagnosis and total mortality

No study has reported data.

Carbohydrate intake 12 months or more after diagnosis and total mortality

Three studies were identified (Beasley, 2011; Belle, 2011; Holmes, 1999). One study (Holmes, 1999) that reported no association between carbohydrates intakes and overall mortality did not provide the intake range therefore dose-response meta-analysis was not conducted. Only the high versus low analysis was possible, the overall RR was 0.91 (95% CI 0.74-1.12, 3 studies).

Figure 32 Highest versus lowest forest plot of carbohydrate intake 12 months or more after diagnosis and total mortality

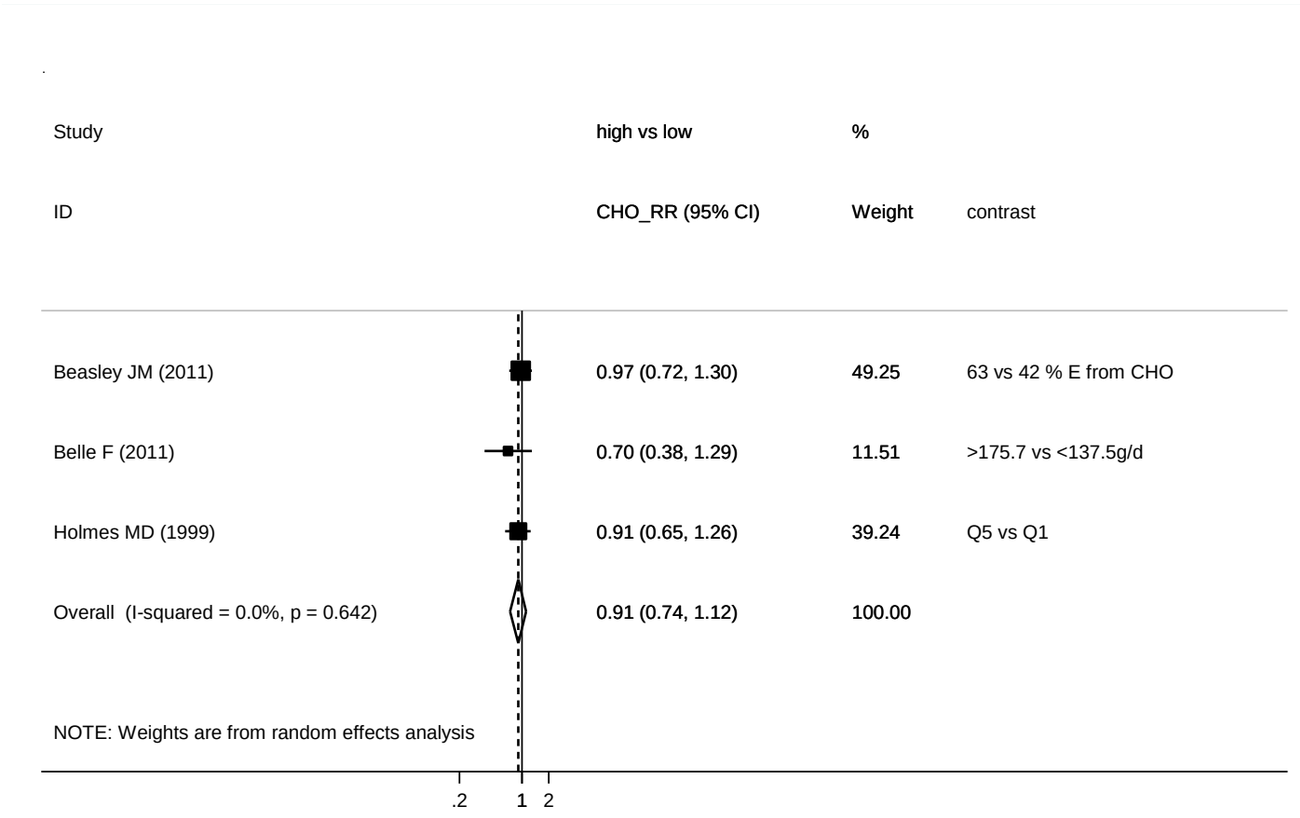


Table 25 Table of included studies on carbohydrate intake 12 months or more after diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Beasley JM (2011)	Collaborative Women's Longevity Study United States	Study recruitment: 1998-2001, Study follow-up: Until 2005 On average 5 years (range 1-16 years) post-diagnosis	Follow up of cases of population-based case-control studies	4441 participants 20 - 79 years Mostly white 22.8% premenopausal, 73.3% postmenopausal among those with data HRT use: 33.2% yes, 56.9% no	5.5 years	Primary invasive breast cancer; Stages: 72.8% local, 27.2% regional		Surgery: 97.9% yes; Radiotherapy: 49.8% yes; Hormonal therapy: 57.8% yes; Chemotherapy: 31.9% yes	42%	Assessed on average 5 years (range 1–16) after diagnosis, usual intake over the past year	4441 participants 525 deaths, 137 breast cancer mortality, 132 deaths from cardiovascular disease	Death certificate	63 vs. 42 %E from CHO	0.97 (0.72–1.30)	Factors at diagnosis (age, state of residence, menopausal status, smoking, breast cancer stage, alcohol, history of hormone replacement therapy), interval between diagnosis and diet assessment, and factors at follow-up (energy intake, breast cancer treatment, body mass index, and physical activity)
Belle F (2011)	Health Eating Activity and Lifestyle Study United States	Study recruitment: 1995-1998, Study follow-up: Until 2004	Prospective cohort of breast cancer survivors	688 participants 55.3 years (mean) 60.9% postmenopausal HRT use: 43.6% ever	6.7 years	Stage 0 to IIIA breast cancer			7.7% (92.3% completed)	On average 31.5 months after diagnosis about usual intake either from the previous month or previous year	688 participants 189 deaths, 83 breast cancer mortality, 106 other causes of deaths	SEER record	>175.7 vs. <137.5g/d	0.70 (0.38–1.29)	Total energy intake (kcal/d), physical activity (MET h/wk), tumor stage, treatment, and tamoxifen use
Holmes MD (1999)	Nurses' Health Study United States	Cancer diagnosis: 1976–1990, Study follow-up: Until 1994	Cancer survivors of population-based prospective cohort study	1982 participants 54 years (mean) 35.1% premenopausal, 64.9% postmenopausal, among those with data	157 months	Invasive breast carcinoma; Grade 1-3			95% / 5% lost	On average 24 months (SD 18m) after diagnosis	1982 participants 378 deaths, 326 breast cancer mortality	Death certificate	Q5 vs. Q1	0.91 0.65–1.26	Age, diet interval, calendar year of diagnosis, body mass index, oral contraceptive use, menopausal status, postmenopausal hormone use, smoking, age at first birth and parity, number of metastatic lymph nodes, tumor size, energy intake

Carbohydrate intake and breast cancer mortality

Five studies on carbohydrate intake and breast cancer mortality were identified. One study (Jain, 1997) assessed carbohydrate intake before diagnosis in cases from a population cohort study in Canada; one study (Borugian, 2004) was on carbohydrate intake less than 12 months after diagnosis in a clinical series follow-up and three studies (Belle, 2011; Beasley, 2011; Rohan, 1993) were on carbohydrate intake 12 months or more after diagnosis, one was a prospective cohort of cancer survivors and the other two were a follow-up of cases from case-control studies. None of the studies reported a significant association between carbohydrate intake or percentage of energy from carbohydrate and mortality for breast cancer.

Carbohydrate intake before diagnosis and breast cancer mortality

No significant association was reported in the only study identified (Jain, 1997).

Carbohydrate intake less than 12 months after diagnosis and breast cancer mortality

No significant association was reported in the only study identified (Borugian, 2004).

Carbohydrate intake 12 months or more after diagnosis and breast cancer mortality

Methods

Three studies were identified and included in the dose-response meta-analysis. One study (Beasley, 2011) reported carbohydrate as energy from carbohydrate, which was converted to grams of carbohydrate using the mean energy intake provided in the study. All the other studies reported carbohydrate intake in grams per day.

Main results and heterogeneity

The summary RR per 100 g/day was 0.87 (95% CI 0.71-1.06; 3 studies). No heterogeneity was observed ($I^2 = 0\%$, $p = 0.44$). It was not possible to conduct a stratified analysis by menopausal status. In the highest versus lowest forest plot the overall RR was 0.73 (95% CI 0.51-1.04; 3 studies). The non-linear association between carbohydrate intake 12 months or more after diagnosis and breast cancer mortality was not significant, $p_{non\text{-}linearity} = 0.69$ (only 3 studies).

Study quality

One study (Belle, 2011) reported less than 100 events. For the other studies the number of breast cancer deaths ranged from 112 (Rohan, 1993) to 137 (Beasley, 2011). The follow-up time ranged from 5.5 years (Rohan, 1993; Beasley, 2011) to 6.7 years (Beasley, 2011). All studies included pre and postmenopausal women combined. The dietary assessment timeframe ranged from 4.8 months (Rohan, 1993) to 5 years after diagnosis (Beasley, 2011). One study (Rohan, 1993) was from Australia and the other two studies (Beasley, 2011; Belle, 2011) were from the United States.

Figure 33 Highest versus lowest forest plot of carbohydrate intake 12 months or more after diagnosis and breast cancer mortality

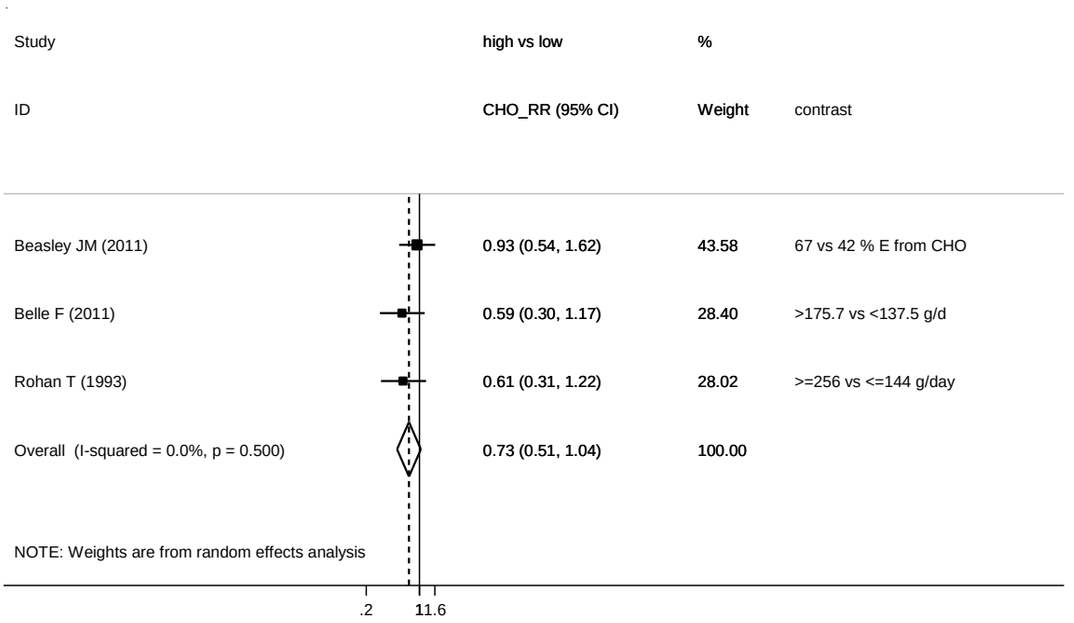


Figure 34 Linear dose-response meta-analysis of carbohydrate intake 12 months or more after diagnosis and breast cancer mortality

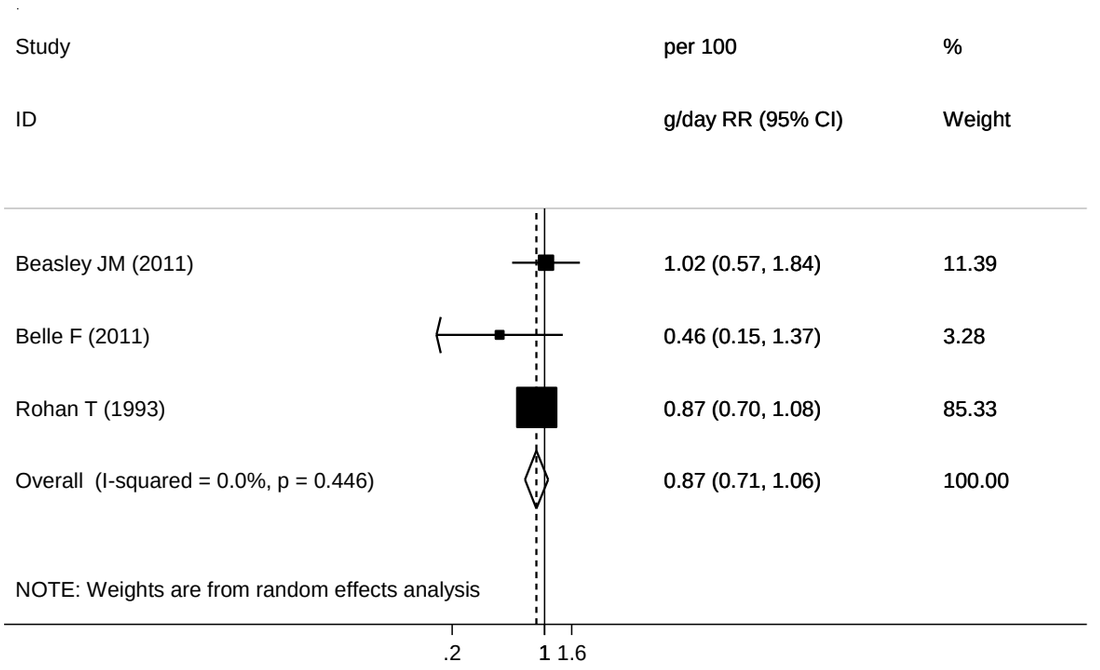


Figure 35 Individual dose-response graph of carbohydrate intake 12 months or more after diagnosis and breast cancer mortality

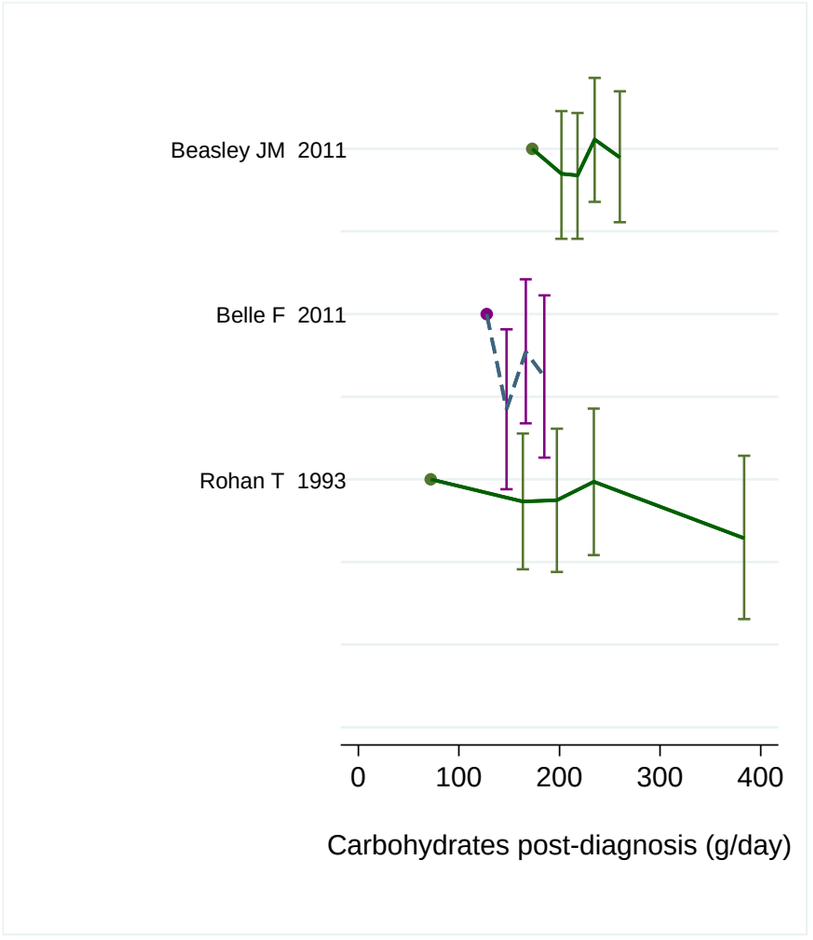


Table 26 Table of included studies on carbohydrate intake 12 months or more after diagnosis and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Beasley JM (2011)	Collaborative Women's Longevity Study United States	Study recruitment: 1998-2001, Study follow-up: Until 2005 On average 5 years (range 1-16 years) post-diagnosis	Follow up of cases of population-based case-control studies	4441 participants 20 - 79 years Mostly white 22.8% premenopausal, 73.3% postmenopausal among those with data HRT use: 33.2% yes, 56.9% no	5.5 years	Primary invasive breast cancer; Stages: 72.8% local, 27.2% regional		Surgery: 97.9% yes; Radiotherapy: 49.8% yes; Hormonal therapy: 57.8% yes; Chemotherapy: 31.9% yes	42%	Assessed on average 5 years (range 1–16) after diagnosis, usual intake over the past year	4441 participants 525 deaths, 137 breast cancer mortality, 132 deaths from cardiovascular disease	Death certificate	63 vs. 42% E CHO	0.93 (0.54–1.62)	Factors at diagnosis (age, state of residence, menopausal status, smoking, breast cancer stage, alcohol, history of hormone replacement therapy), interval between diagnosis and diet assessment, and factors at follow-up (energy intake, breast cancer treatment, body mass index, and physical activity)
Belle F (2011)	Health Eating Activity and Lifestyle Study United States	Study recruitment: 1995-1998, Study follow-up: Until 2004	Prospective cohort of breast cancer survivors	688 participants 55.3 years (mean) 60.9% postmenopausal HRT use: 43.6% ever	6.7 years	Stage 0 to IIIA breast cancer			7.7% (92.3% completed)	On average 31.5 months after diagnosis about usual intake either from the previous month or previous year	688 participants 189 deaths, 83 breast cancer mortality, 106 other causes of deaths	SEER record	>175.7 vs. <137.5g/d	0.59 (0.30–1.17)	Energy, fibre, folate intake, tumor stage, treatment, and tamoxifen use
Rohan T (1993)	Diet and Breast Cancer in Australia Follow-up Study Australia	Cancer diagnosis: 1982-1984, Study follow-up: Until 1989	Follow-up of cases of population-based case-control study	412 participants 55.1 years (mean) 20 - 74 years 30.7% premenopausal, 5.4% perimenopausal, 64% postmenopausal, among those with data	5.5 years	Primary breast cancer, any stages			80.70% 39 patients lost	Interval between diagnosis and interview was 4.8months	412 participants 112 breast cancer mortality, 11 other causes of deaths	Cancer registry + death certificate	>=256 vs. <=144g/d	0.61 (0.31-1.22)	Energy intake, age of menarche, Quetelet Index

4.2 Glycemic index, glycemic load, total mortality and breast cancer mortality

Only two studies were identified and no meta-analysis was conducted. The study results are shown here to complement the section on carbohydrate intake.

Two studies on glycemic load and total mortality were identified, one on diet before diagnosis and the other on diet 12 months or more after diagnosis, Dal Maso, 2008 and Belle, 2011, respectively. In the follow-up of cases from case-control studies, the relative risk for the highest vs. the lowest tertile of glycemic load was 0.96 (95% CI 0.77-1.19) for all-cause mortality and 0.94 (95% CI 0.73-1.20) for breast cancer mortality (Dal Masso, 2008). In the Health, Eating, Activity, and Lifestyle (HEAL) study the relative risk for the highest vs. the lowest tertile of glycemic index was 1.40 (95% CI 0.78-2.50) for all-cause mortality and 1.60 (95% CI 0.80-3.21) for breast cancer death, and for glycemic load the relative risks were 1.23 (95% CI 0.46-3.31) for overall mortality and 1.11 (95% CI 0.37-3.34) for breast cancer death (Belle, 2011).

4.3 Fibre intake

Table 27 Summary results of meta-analysis on fibre and total mortality and breast cancer mortality*

	Total mortality			Breast cancer mortality		
Comparison	**No. of studies**	**No. of events in studies**	**RR (95% CI) I^2, $P_{heterogeneity}$**	**No. of studies**	**No. of events in studies**	**RR (95% CI) I^2, $P_{heterogeneity}$**
Fibre intake before diagnosis						
Highest vs. lowest	2	417	0.50 (0.35-0.73) 0%, p = 0.83			
Per 10 g/day	3	443	0.68 (0.56-0.84) 0%, p = 0.41			
Fibre intake 12 months or more after diagnosis						
Highest vs. lowest	3	1092	0.76 (0.58-0.98) 0%, p = 0.99	3	332	0.82 (0.57-1.20) 0%, p = 0.95
Per 10 g/day	3	1092	0.88(0.78-0.99) 0%, p = 0.97	3	332	0.93 (0.80-1.07) 0%, p = 0.64

*No studies on second cancers were included in the meta-analyses. Only studies onfibre intake before and 12 months or more after diagnosis could be included in meta-analyses.

Table 28 Table for subgroup analysis of fibre intake before diagnosis and total mortality

Comparison	**No. of studies**	**No. of events in studies**	**RR (95% CI)**	**I^2, $P_{heterogeneity}$**
Per 10 g/day				
Menopausal status				
Premenopausal	1	5	0.42 (0.06-2.99)	-
Postmenopausal	3	297	0.69 (0.55-0.86)	5.7%, p = 0.34

Fibre intake and total mortality

Seven studies on fibre and total mortality were identified. Three studies were on fibre intake before diagnosis (Saxe, 1999; McEligot, 2006 and Buck, 2011b) and four studies were on fibre intake 12 months or more after diagnosis (Holmes, 1999; Pierce, 2007a; Belle, 2011 and Beasley, 2011).

Fibre intake before diagnosis and total mortality

Methods

The three studies identified were included in the dose-response meta-analysis. All the studies reported fibre intake in grams per day.

Main results and heterogeneity

The summary RR per 10 g/day was 0.68 (95% CI 0.56-0.84; 3 studies). No heterogeneity was observed (I^2 = 0%; p = 0.41). Two of the studies were on post-menopausal women only and the results were the same when the meta-analysis was restricted to women with post-menopausal breast cancer (RR 0.69; 95% CI 0.55-0.86). There were only 5 deaths with diagnosis of pre-menopausal breast cancer (Saxe, 1999). In one study, the inverse association of fibre intake with mortality was not modified by hormone receptor status (data not shown in the paper) (Buck, 2011b).

Study quality

Diet was assessed within a maximum period of one year after breast cancer diagnosis and referred to diet one year prior to diagnosis in all the studies. The study by Saxe et al, 1999 was a clinical series (n = 149) in pre- and post-menopausal women with a diagnosis of breast cancer during 1989 and 1990. Only 26 deaths were identified during five or more years of follow-up. A selection of potential confounders was done that included stage status but it is unclear what covariates were included in the final model. The study was conducted in USA. The study by McEligot et al (2006) was on 516 post-menopausal women with a diagnosis of in situ or invasive breast cancer during 1994-1995. Cases were identified within 6 months of diagnosis. There was almost complete follow-up (98%) until 2003. The number of deaths was 96 from which 43% died from breast cancer, 14% from cardiovascular diseases and the rest from other causes. The study results were adjusted for stage of disease, age at diagnosis, body mass index, parity, harmone replacement therapy use, alcohol use, multivitamin use, and energy intake.

The third was a study in Germany (Buck, 2011b) on 2653 postmenopausal women with diagnosis of in situ or invasive breast cancer between 2001 and 2005. Women participated in a case-control study and were followed for vital status until 2009. During a median follow-up time of 6.4 years, a total of 321 deaths occurred, of which 235 were due to breast cancer. Further causes of death included other cancers (n = 41), cardiovascular diseases (n = 22), and other causes (n = 23). Study results were adjusted for tumour size, nodal status, metastasis, grade, ER/PR status, breast cancer detection type, diabetes, menopausal hormone therapy use at diagnosis and other variables.

Figure 36 Highest versus lowest forest plot of fibre intake before diagnosis and total mortality

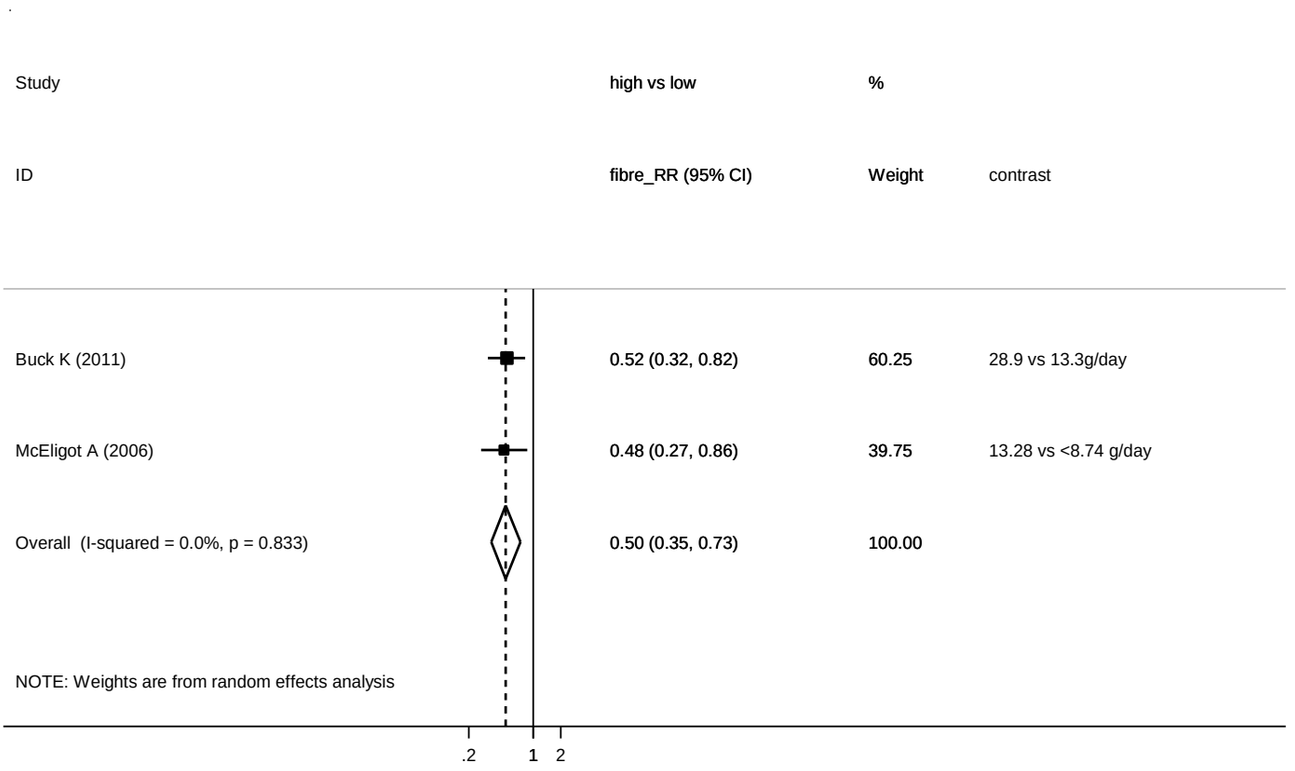


Figure 37 Linear dose-response meta-analysis of fibre intake before diagnosis and total mortality

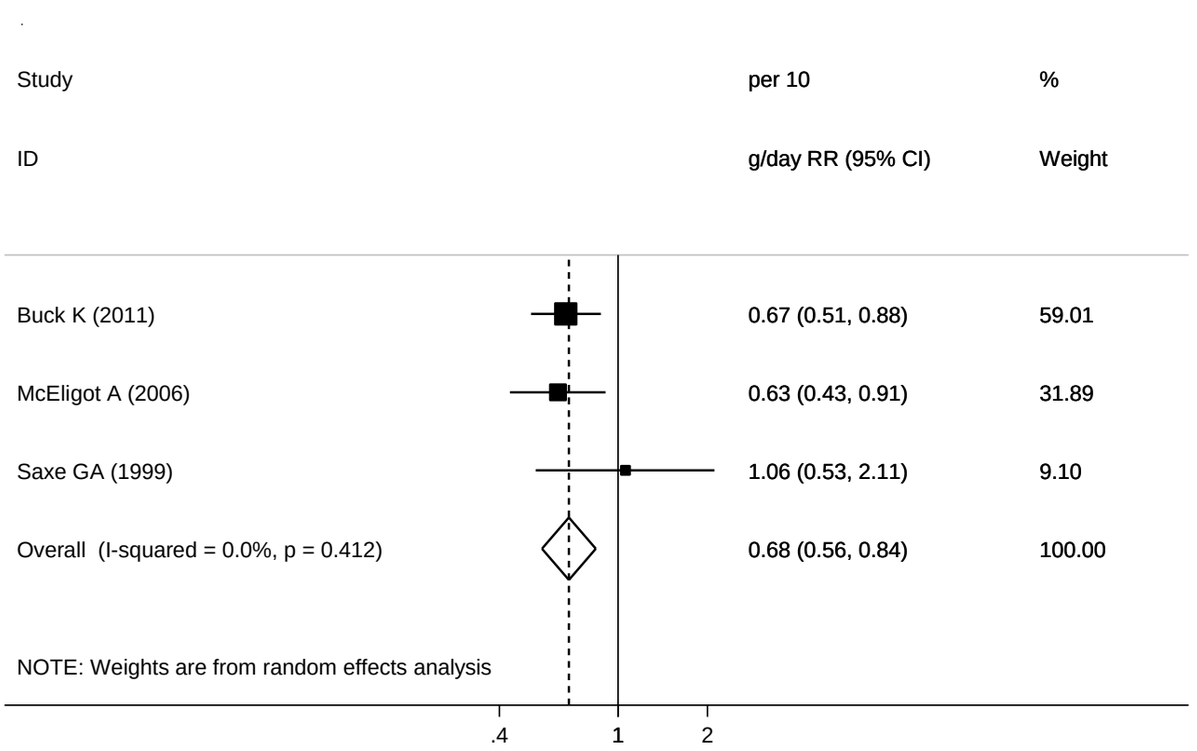


Figure 38 Individual dose-response graph of fibre intake before diagnosis and total mortality

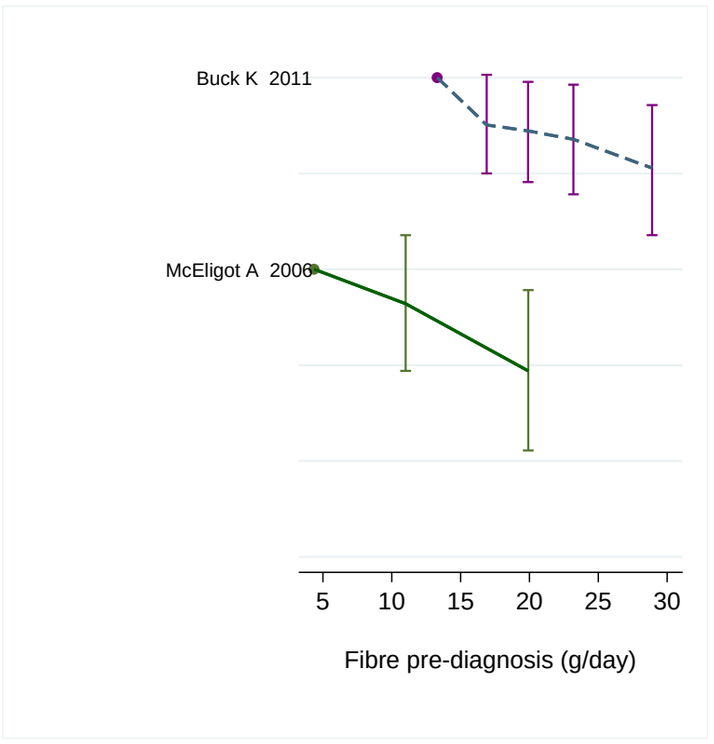


Figure 39 Linear dose-response meta-analysis of fibre intake before diagnosis and total mortality by menopausal status

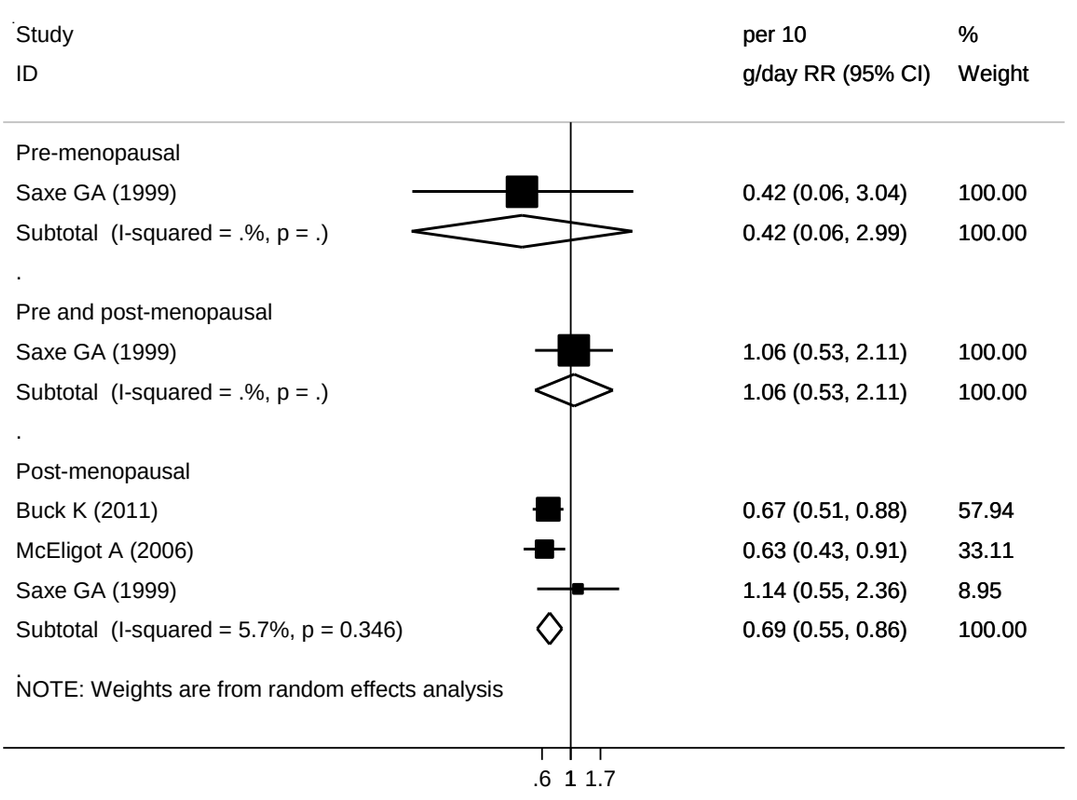


Table 29 Table of included studies on fibre intake before diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments Remarks
Buck K (2011)b	Hamburg and Rhein-Neckar-Karlsruhe, Follow-up Study Germany	Cancer diagnosis: 2002-2005, Study follow-up: Until 2009	Follow-up of cases of population-based case-control study	2653 participants 50 - 74 years Postmenopausal HRT use: 47.4% yes, 51.9% no/past, 0.7% missing	6.1 years	Primary invasive or in situ breast tumour any stage; Grades: 65.5% G1+G2, 24.9% G3+G4, 6% in situ, 3.3% neoadjuvant chemotherapy, 0.3% missing; Metastasis: 2.7% yes, 90.8% no, 6% in situ, 0.6% missing	58% ER+/PR+, 17.7% ER+/PR- or ER-/PR+, 14.6% ER-/PR-, 6% in situ, 3.3% neoadjuvant chemotherapy, 0.3% missing; 16.3% HER2-neu+, 64.9% HER2-neu-, 6% in situ, 3.3% neoadjuvant chemotherapy, 9.5% missing 28.9% +ve, 61.4% -ve, 6% in situ, 3.3% neoadjuvant chemotherapy, 0.5% missing	Surgery: 12.8% breast ablation, 32.1% breast conservation, 55% missing	Completed	diet 1 year prior to diagnosis	2653 participants 321 deaths, 235 breast cancer mortality	Death certificate	Per 28.9g/d	0.52 (0.32-0.82)	Tumor size, nodal status, metastasis, grade, estrogen and progesterone receptor status, breast cancer detection type, diabetes, HRT use at diagnosis, study centre, energy intake, age at diagnosis
McEligot A (2006)	Orange County California Study United States	Cancer diagnosis: 1994-1995, Study follow-up: Until 2003 Recruited within 6 months of diagnosis	Prospective cohort of breast cancer survivors	516 participants 64.78 years (mean)92.3% non-Hispanic white Postmenopausal HRT use: 36.2% estrogen only, 1.9% progesterone only, 35.1% estrogen and progesterone, 26.7% non-users	80 months	Stages: 14.9% in situ, 59.3% localized, 24.2% regional, 1.55% metastatic			98% 2% lost	At diagnosis; dietary habits during the 1 year prior to diagnosis FFQ	516 participants 96 deaths, 41 breast cancer mortality, 13 deaths from cardiovascular disease, 31 other causes of deaths, 11 unknown causes of deaths	Cancer registry + National Death Index	13.28 vs. <8.74 g/d	0.48 (0.27-0.86)	Tumor stage, age at diagnosis, BMI, parity, HRT, alcohol intake, multivitamins, energy intake
Saxe GA (1999)	Medical Center, Michigan University Follow-up Study United States	Study recruitment: 1989-1991, Recruited during first medical center visit for suspected or newly diagnosed	Prospective cohort of breast cancer survivors	149 participants 57.8 years (mean) 26 - 95 years White: 90.6%, black:7.2% and other: 2.2%,34.2% premenopausal, 65.8% postmenopausal	5 Years (min)	Primary breast cancer, stages: 19.6% in situ, 34.5% I, 34.5% II, 8.8% III, 2.7% IV	73.4% ER+, 26.6% ER- 43% +ve, 57% -ve		0% lost	Interviewed close to time of diagnosis for diet a year prior to diagnosis, semi-quantitative FFQ	149 participants 26 deaths	Hospital records	Per 10g/d	1.06 (0.53-2.11)	Tumor stage, energy intake Dose-response analysis only, only continuous results

Fibre intake less than 12 months after diagnosis and total mortality

No study has reported data.

Fibre intake 12 months or more after diagnosis and total mortality

Methods

From the 4 studies identified, 3 were included in the dose-response meta-analysis. All the studies reported fibre intake in grams per day. One study (Pierce, 2007a) was excluded because it did not provide confidence intervals. A sensitivity analysis was conducted estimating confidence interval from p values and including the study in the analysis.

Main results and heterogeneity

The summary RR per 10 g/day was 0.88 (95% CI 0.78-0.99; 3 studies). No heterogeneity was observed (I^2 = 0%; p = 0.97). When Pierce, 2007a was included the RR was 0.71 (95% CI 0.41-1.24; 4 studies; I^2 = 98%, p < 0.001). It was not possible to conduct a meta-analysis stratified by menopausal status. In the highest versus lowest forest plot the overall RR was 0.76 (95% CI 0.58-0.98; 3 studies). There was no evidence of a non-linear association between fibre intake 12 months or more after diagnosis and total mortality, $p_{non\text{-}linearity}$ = 0.52.

Study quality

All the studies reported more than 100 events, ranging from 106 (Belle, 2011) to 525 (Beasley, 2011) deaths. The follow-up time ranged from 5.5 years (Rohan, 1993; Beasley 2011) to 13 years (Holmes, 1999). All the studies combined pre and postmenopausal women. The dietary assessment ranged from 4.8 months (Rohan, 1993) to 5 years after diagnosis (Beasley, 2011). One study was from Australia (Rohan, 1993) and three studies were from the United States.

Figure 40 Highest versus lowest forest plot of fibre intake 12 months or more after diagnosis and total mortality

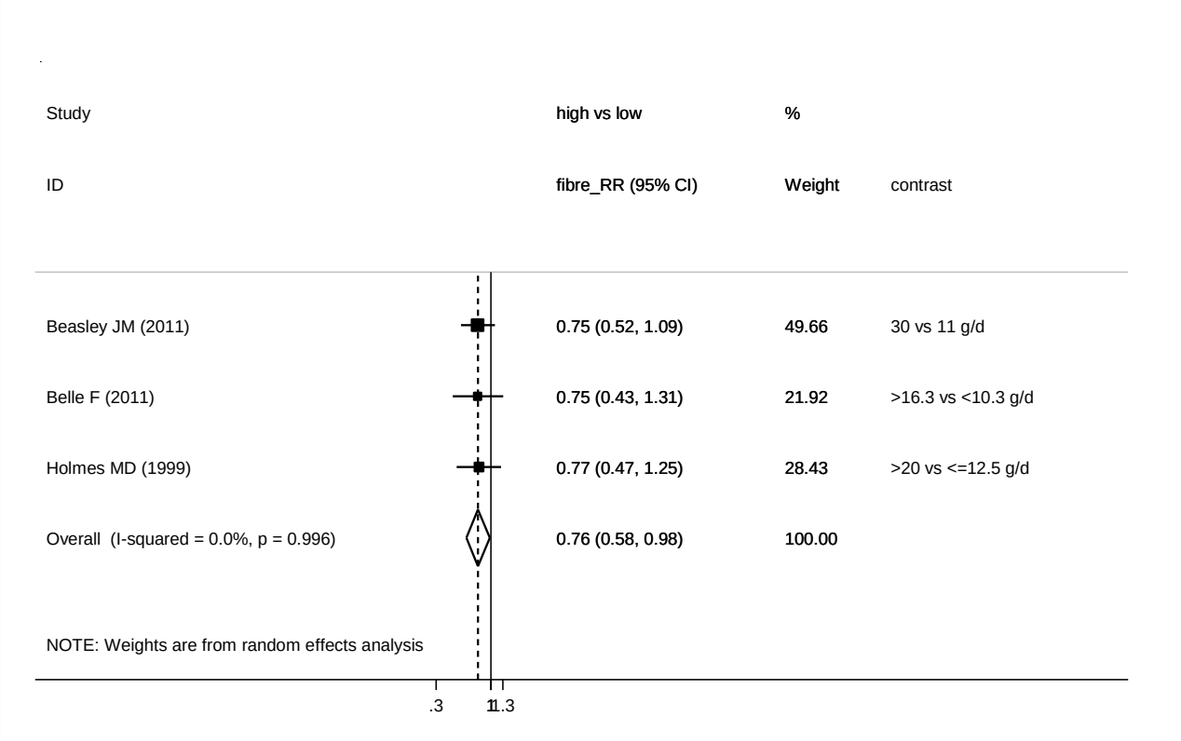


Figure 41 Linear dose-response meta-analysis of fibre intake 12 months or more after diagnosis and total mortality

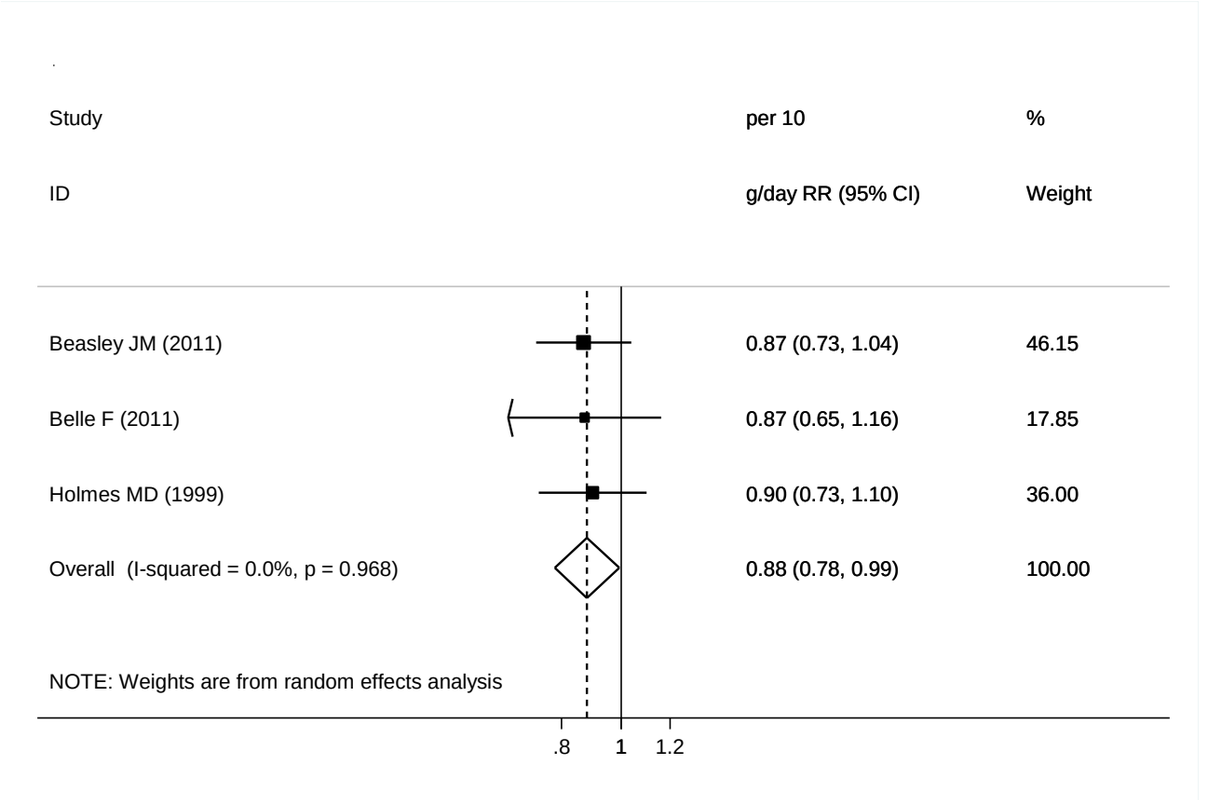


Figure 42 Individual dose-response graph of fibre intake 12 months or more after diagnosis and total mortality

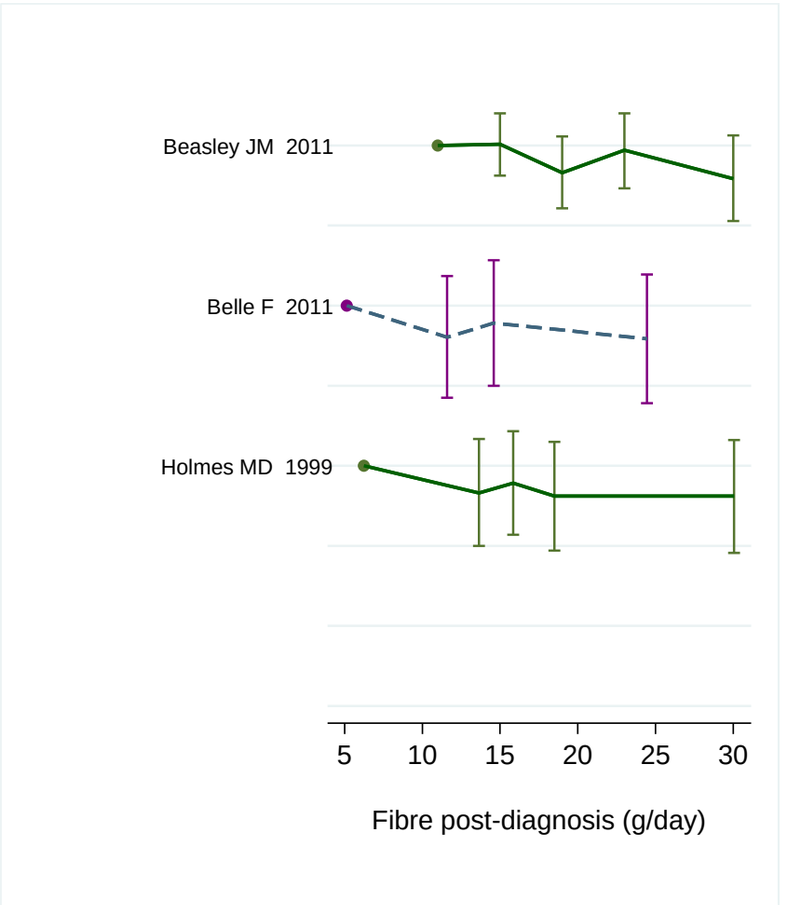


Table 30 Table of included studies on fibre intake 12 months or more after diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Beasley JM (2011)	Collaborative Women's Longevity Study United States	Study recruitment: 1998-2001, Study follow-up: Until 2005 On average 5 years (range 1-16 years) post-diagnosis	Follow up of cases of population-based case-control studies	4441 participants 20 - 79 years Mostly white 22.8% premenopausal, 73.3% postmenopausal among those with data HRT use: 33.2% yes, 56.9% no	5.5 years	Primary invasive breast cancer; Stages: 72.8% local, 27.2% regional		Surgery: 97.9% yes; Radiotherapy: 49.8% yes; Hormonal therapy: 57.8% yes; Chemotherapy: 31.9% yes	42%	Assessed on average 5 years (range 1–16) after diagnosis, usual intake over the past year	4441 participants 525 deaths, 137 breast cancer mortality, 132 deaths from cardiovascular disease	Death certificate	30 vs. 11 g/d	0.75 (0.52–19)	Factors at diagnosis (age, state of residence, menopausal status, smoking, breast cancer stage, alcohol, history of hormone replacement therapy), interval between diagnosis and diet assessment, and factors at follow-up (energy intake, breast cancer treatment, body mass index, and physical activity)
Belle F (2011)	Health Eating Activity and Lifestyle Study United States	Study recruitment: 1995-1998, Study follow-up: Until 2004	Prospective cohort of breast cancer survivors	688 participants 55.3 years (mean) 60.9% postmenopausal HRT use: 43.6% ever	6.7 years	Stage 0 to IIIA breast cancer			7.7% (92.3% completed)	On average 31.5 months after diagnosis about usual intake either from the previous month or previous year	688 participants 189 deaths, 83 breast cancer mortality, 106 other causes of deaths	SEER record	>16.3 vs. <10.3g/d	0.75 (0.43–1.31)	Total energy intake (kcal/d), physical activity (MET h/wk), tumor stage, treatment, and tamoxifen use
Holmes MD (1999)	Nurses' Health Study United States	Cancer diagnosis: 1976–1990, Study follow-up: Until 1994	Cancer survivors of population-based prospective cohort study	1982 participants 54 years (mean) 35.1% premenopausal, 64.9% postmenopausal, among those with data	157 months	Invasive breast carcinoma; Grade 1-3			95% / 5% lost	On average 24 months (SD 18m) after diagnosis	1982 participants 378 deaths, 326 breast cancer mortality	Death certificate	>20 vs. <=12.5 g/day	0.77 (0.47-1.25)	Age, diet interval, calendar year of diagnosis, body mass index, oral contraceptive use, menopausal status, postmenopausal hormone use, smoking, age at first birth and parity, number of metastatic lymph nodes, tumor size, energy intake

Table 31 Table of excluded studies on fibre intake 12 months or more after diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments / Exclusion reason
Pierce J (2007)a	Women's Healthy Eating and Living Study United States	Cancer diagnosis:1991-2000; Study follow up: until 2005 Within 48 months of diagnosis (average, 24 months)	Randomised controlled trial of dietary intervention	1490 participants 50 years (mean)	6.7 years	Early stage breast cancer; AJCC; 40% Stage I (>=1cm), 45% Stage II, 15% stage III, 15.9% grade I, 39.8% grade II, 35.8% grade III, 8.3% unknown	63.1% ER+ve/PR+ve, 10.8% ER+ve/PR-ve, 5.1%ER-ve/PR+ve, 20.8% ER-ve/PR-ve	31.4% none-chemotherapy, 25.7% nonanthracycline, 42.8% anthracycline; 42% adjuvant tamoxifen, 58% no adjuvant tamoxifen		Self-reported at baseline, on average 2 yrs after diagnosis	1490 participants 135 deaths, 118 breast cancer mortality, 10 death from other cancers, 7 death from non-cancer, 236 breast cancer events	Death certificate	23.5-59.7 vs. 5.1-15.6 g/d	0.61 p-value=0.12	There was not enough information

Fibre intake and breast cancer mortality

Six studies on fibre intake and breast cancer mortality were identified. Two studies were on fibre intake before diagnosis and breast cancer mortality (Jain, 1994a, Buck 2011b), one study (Borugian, 2004) was on fibre intake less than 12 months after diagnosis and breast cancer mortality and three studies on fibre intake 12 months or more after diagnosis and breast cancer mortality (Beasley, 2011; Belle, 2011; Rohan, 1993). All of the studies showed a non-significant association between fibre intake and breast cancer mortality.

Fibre intake before diagnosis and breast cancer mortality

Not enough information for meta-analysis. One study on Canadian women reported a HR per 5 g/day increase in fibre intake of 0.92 (95% CI 0.78-1.10; 76 deaths) (Jain, 1994a) and one study on postmenopausal breast cancer patients in Germany reported a HR for 28.9 vs. 13.3 g/day of 0.64 (95% CI 0.37- 1.11, p_{trend} = 0.01; 235 deaths) (Buck, 2011).

Fibre intake less than 12 months after diagnosis and breast cancer mortality

Only one study was identified. No association was observed, RR 0.7 (95% CI 0.4-1.3, p_{trend} = 0.34, Q4 vs. Q1) (Borugian, 2004).

Fibre intake 12 months or more after diagnosis and breast cancer mortality

Methods

Three studies were identified and included in the dose-response meta-analysis. All the studies reported fibre intake in grams per day.

One additional study reported on cereal fibre and was not summarised with the three studies on total fibre intake. In the Nurses' Health Study (Holmes, 2009) cereal fibre was not associated to breast cancer mortality (RR 1.00, 95% CI 0.71-1.40, highest vs. lowest quintile) (446 deaths) in participants with breast cancer. In analyses stratified by estrogen receptor status, the hazard ratios for the highest vs. the lowest quintile were 1.04 (95% CI 0.70-1.55) for ER+ (271 deaths) and 0.59 (95% CI 0.17-2.05) (73 deaths; $p_{interaction}$ = 0.05).

Main results and heterogeneity

The summary RR per 10 g/day was 0.93 (95% CI 0.80-1.07; 3 studies). No heterogeneity was observed (I^2 = 0%; p = 0.64). It was not possible to conduct a stratified analysis by menopausal status. In the highest versus lowest forest plot the overall RR was 0.82 (95% CI 0.57-1.20; 3 studies). There was no evidence of a non-linear association between fibre intake post-diagnosis and total mortality, $p_{non\text{-}linearity}$ = 0.85.

Study quality

One study (Belle, 2011) reported less than 100 events. For the other studies the number of breast cancer deaths ranged from 112 (Rohan, 1993) to 137 (Beasley, 2011). The follow-up time ranged from 5.5 years (Rohan, 1993; Beasley, 2011) to 6.7 years (Beasley, 2011). All studies included pre and postmenopausal women combined. The dietary assessment timeframe ranged from 4.8 months (Rohan, 1993) to 5 years after diagnosis (Beasley, 2011). One study (Rohan, 1993) was from Australia and the other two studies (Beasley, 2011; Belle, 2011) were from the United States.

Figure 43 Highest versus lowest forest plot of fibre intake 12 months or more after diagnosis and breast cancer mortality

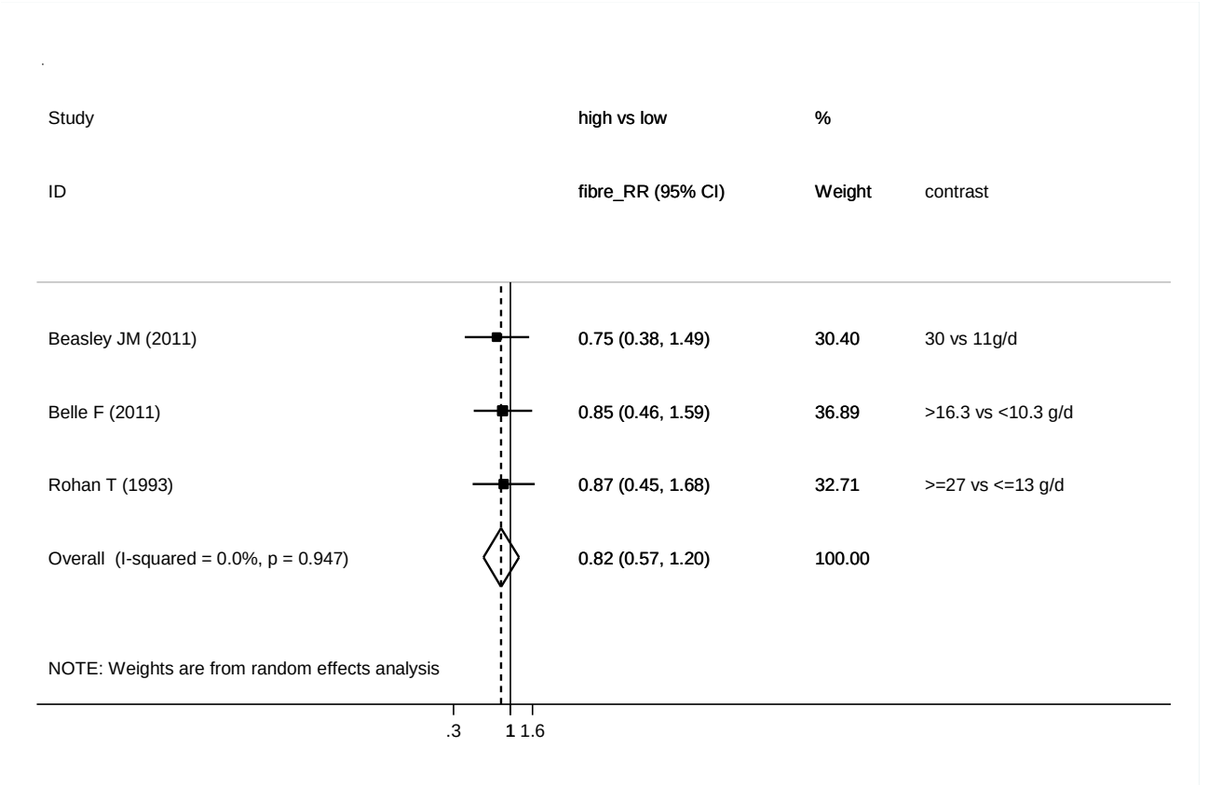


Figure 44 Linear dose-response meta-analysis of fibre intake 12 months or more after diagnosis and breast cancer mortality

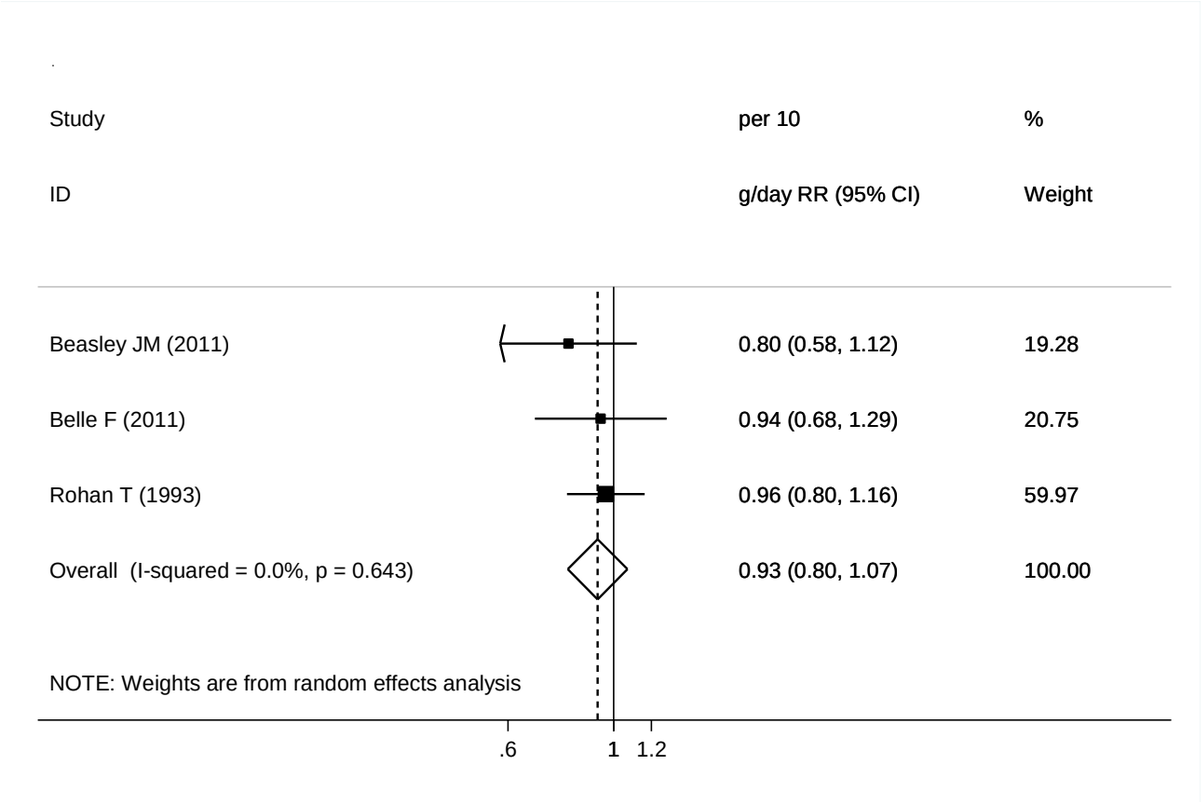


Figure 45 Individual dose-response graph of fibre intake 12 months or more after diagnosis and breast cancer mortality

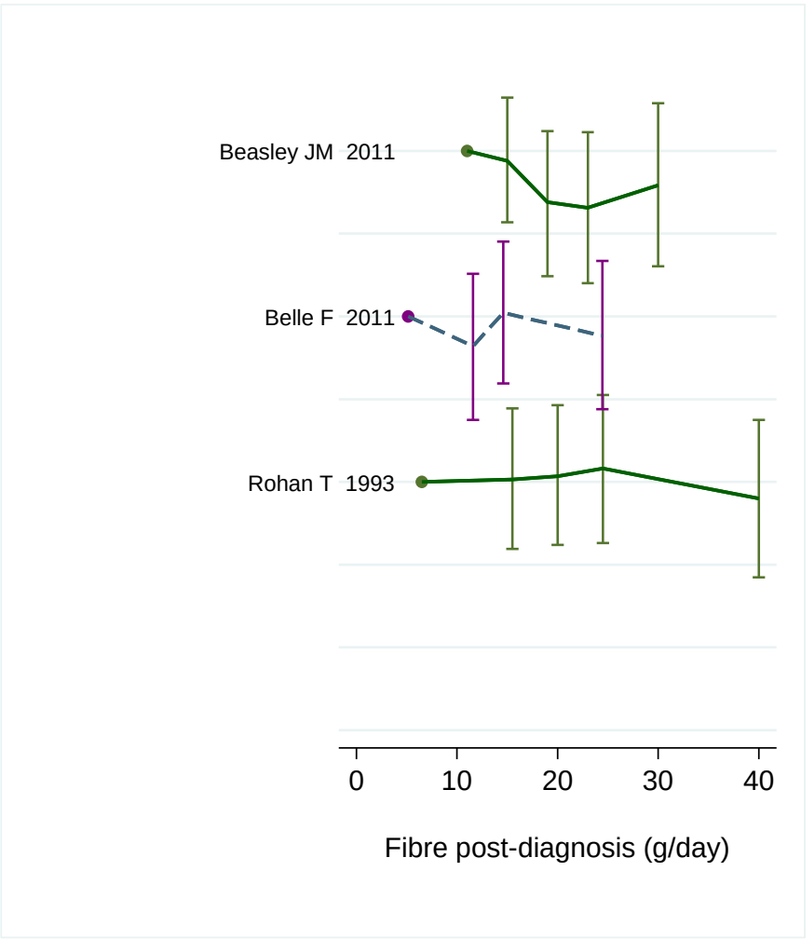


Table 32 Table of included studies on fibre intake 12 months or more after diagnosis and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Beasley JM (2011)	Collaborative Women's Longevity Study United States	Study recruitment: 1998-2001, Study follow-up: Until 2005 On average 5 years (range 1-16 years) post-diagnosis	Follow up of cases of population-based case-control studies	4441 participants 20 - 79 years Mostly white 22.8% premenopausal, 73.3% postmenopausal among those with data HRT use: 33.2% yes, 56.9% no	5.5 years	Primary invasive breast cancer; Stages: 72.8% local, 27.2% regional		Surgery: 97.9% yes; Radiotherapy: 49.8% yes; Hormonal therapy: 57.8% yes; Chemotherapy: 31.9% yes	42%	Assessed on average 5 years (range 1–16) after diagnosis, usual intake over the past year	4441 participants 525 deaths, 137 breast cancer mortality, 132 deaths from cardiovascular disease	Death certificate	30 vs. 11 g/d	0.75 (0.38–1.49)	Factors at diagnosis (age, state of residence, menopausal status, smoking, breast cancer stage, alcohol, history of hormone replacement therapy), interval between diagnosis and diet assessment, and factors at follow-up (energy intake, breast cancer treatment, body mass index, and physical activity)
Belle F (2011)	Health Eating Activity and Lifestyle Study United States	Study recruitment: 1995-1998, Study follow-up: Until 2004	Prospective cohort of breast cancer survivors	688 participants 55.3 years (mean) 60.9% postmenopausal HRT use: 43.6% ever	6.7 years	Stage 0 to IIIA breast cancer			7.7% (92.3% completed)	On average 31.5 months after diagnosis about usual intake either from the previous month or previous year	688 participants 189 deaths, 83 breast cancer mortality, 106 other causes of deaths	SEER record	>16.3 vs. <10.3g/d	0.85 (0.46–1.59)	Total energy intake (kcal/d), physical activity (MET h/wk), tumor stage, treatment, and tamoxifen use
Rohan T (1993)	Diet and Breast Cancer in Australia Follow-up Study Australia	Cancer diagnosis: 1982-1984, Study follow-up: Until 1989	Follow-up of cases of population-based case-control study	412 participants 55.1 years (mean) 20 - 74 years 30.7% premenopausal, 5.4% perimenopausal, 64% postmenopausal, among those with data	5.5 years	Primary breast cancer, any stages			80.70% / 39 patients lost	Interval between diagnosis and interview was 4.8months	412 participants 112 breast cancer mortality, 11 other causes of deaths	Cancer registry + death certificate	>=27 vs. <13g/d	0.87 (0.45-1.68)	Energy intake, age of menarche, Quetelet Index

4.4 Total fat intake

Table 33 Summary results of meta-analysis on total fat intake and total mortality and breast cancer mortality*

	Total mortality			Breast cancer mortality		
Comparison	**No. of studies**	**No. of events in studies**	**RR (95% CI) I^2, $P_{heterogeneity}$**	**No. of studies**	**No. of events in studies**	**RR (95% CI) I^2, $P_{heterogeneity}$**
Total fat intake before breast cancer diagnosis						
Highest vs. lowest	3	655	1.87 (0.76-4.57) 90.1%,p < 0.001	4	521	1.13 (0.71-1.77) 53.5%, p = 0.09
Per 10 g/day	4	178	1.19 (1.01-1.41) 82.0%, p=0.001			
Total fat intake 12 months or more after breast cancer diagnosis						
Highest vs. lowest	3	1436	1.08 (0.90-1.30) 24.4%, p = 0.27	4	648	1.19 (0.94-1.50) 0%, p = 0.41
Per 10 g/day	-	-	-	3	575	1.01 (0.95-1.08) 24.0%, p = 0.27

*No studies on second cancers were included in the meta-analyses. Only studies on fat intake before and 12 months or more after diagnosis could be included in meta-analyses.

Total fat intake and total mortality

Ten studies on total fat intake and total mortality were identified. Seven studies were on total fat intake before diagnosis (Gregorio, 1985; Zhang, 1995; Holmes, 1999; Saxe, 1999; Goodwin, 2003; McEligot, 2006; Dal Maso, 2008) and four studies were on total fat intake 12 months or more after diagnosis (Ewertz, 1991; Holmes, 1999; Beasley, 2011; Pierce, 2007a). Holmes et al. (1999) reported on both before and 12 months or more after diagnosis total fat intake.

Total fat intake before diagnosis and total mortality

Methods

From the seven studies identified, four studies could be included in the linear dose-response meta-analysis and three studies could be included in the highest versus lowest meta-analysis. Holmes et al. (1999) reported that fat intake before diagnosis was associated with a 70% increased risk of mortality comparing the highest versus the lowest quantile of intake, with a statistically significant trend (data not shown). Goodwin et al. (2003) observed no relationship between total fat intake and breast cancer survival. The format of data in Holmes et al. (1999) and Goodwin et al. (2003) was not sufficient to include in the highest versus lowest and dose-response meta-analyses. Dal Maso et al. (2008) did not quantified fat intake and was excluded from the dose-response meta-analysis. No significant relationship of fat intake with mortality was reported in this study. Gregorio et al. (1985) and Saxe et al. (1999) only reported dose-response results. One study (McEligot, 2006) reported intake in percentage energy from fat, which was converted to grams of fat using the mean energy intake provided in the study. All the other included studies reported fat intake in grams per day. Only three studies provided adequate data for the highest versus lowest forest plot.

Main results and heterogeneity

The summary RR per 10 g/day was 1.19 (95% CI 1.01-1.41; 4 studies). There is evidence of high heterogeneity (I^2 = 82.0%; p = 0.001) that was driven by the study of McEligot et al. (2006). The summary RR ranged from 1.05 (95% CI 1.01-1.10) when McEligot et al.

(2006) was omitted to 1.29 (95% CI 1.00-1.65) when Gregorio et al. (1985) was omitted in an influence analysis. For the highest compared to the lowest intake, the summary RR was 1.87 (95% CI 0.76-4.57; I^2 = 90.1%; p < 0.0001; 3 studies).

Study quality

Two studies had less than 60 deaths amongst breast cancer patients (Zhang, 1995; Saxe, 1999) and one study had only 96 deaths (McEligot, 2006). The diagnosis of breast cancer was before 1985 in one study (Gregorio, 1985), between 1976 and 1991 in three studies (Zhang, 1995; Holmes, 1999; Saxe, 1999) and between 1991 and 1994 in two studies (Dal Maso, 2008; McEligot, 2006). Three studies (Zhang, 1995; Saxe, 1999; McEligot, 2006) included *in situ* and invasive breast cancers and three studies (Gregorio, 1985; Holmes, 1999; Dal Maso, 2008) included only invasive cases. Diet was assessed before breast cancer diagnosis (Zhang, 1995) only in one study. In the other studies diet was assessed in the year after diagnosis with one year prior to diagnosis as referent period. All studies adjusted for stage at diagnosis or tumor size and node involvement. Only three studies adjusted for hormone status (Zhang, 1995; Saxe, 1999; Dal Maso, 2008). One study was restricted to post-menopausal breast cancer (McEligot, 2006). Other studies included pre- and post-menopausal women.

In the study of McEligot (2006) diet was assessed by a self-administered FFQ completed via mail. Women diagnosed with breast cancer were instructed to complete the questionnaire based on dietary habits during the year prior to diagnosis. A number of 516 women were included and after 80 months of follow-up, 96 deaths were identified.

Figure 46 Highest versus lowest forest plot of total fat intake before diagnosis and total mortality

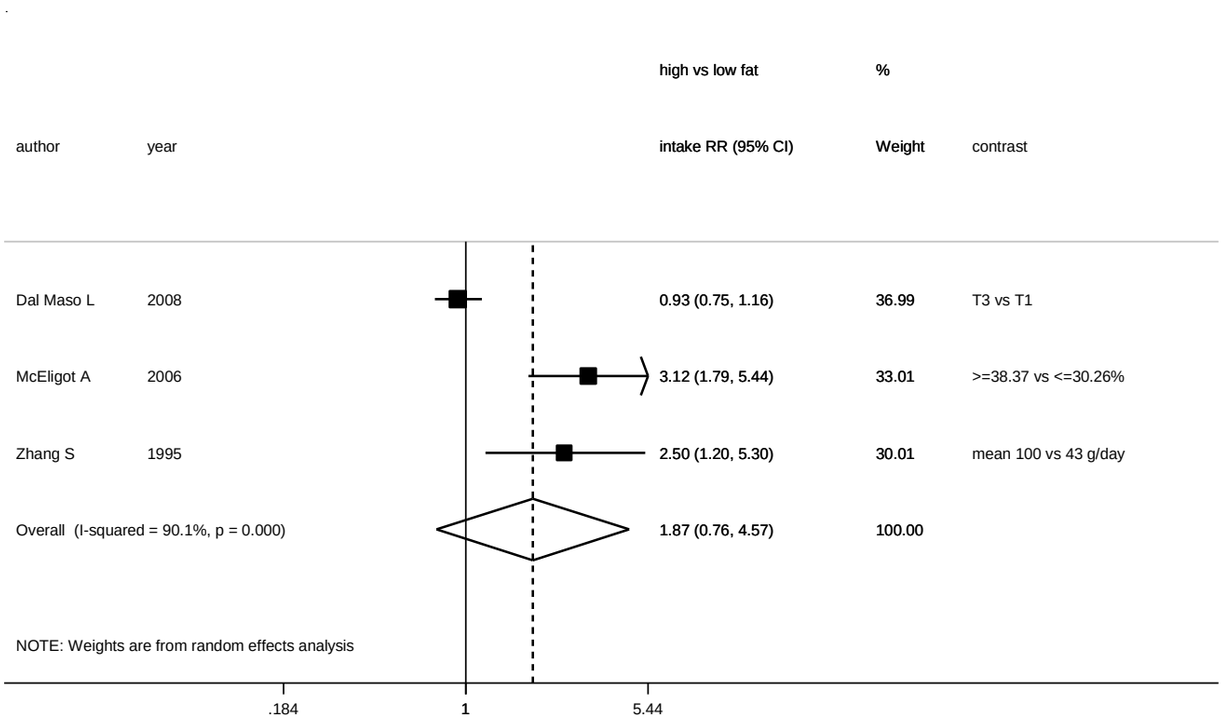


Figure 47 Linear dose-response meta-analysis of total fat intake before diagnosis and total mortality

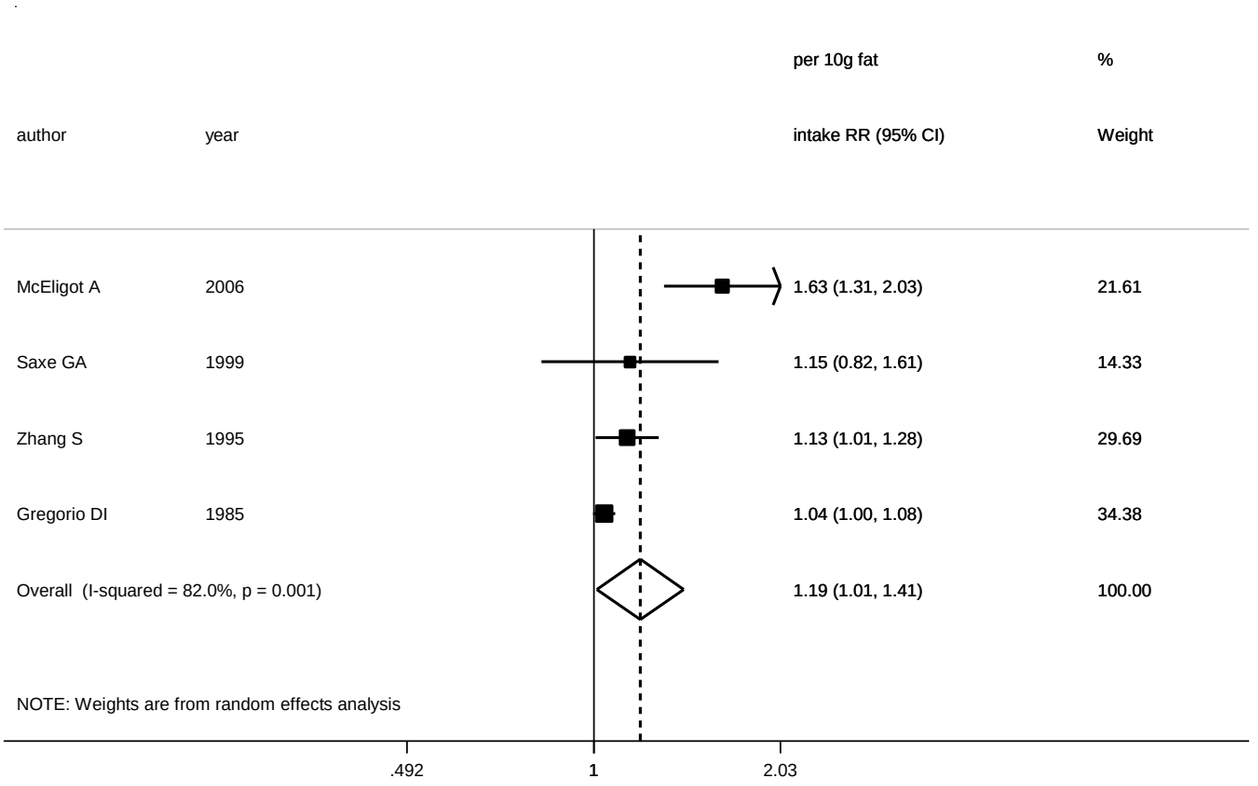


Figure 48 Individual dose-response graph of total fat intake before diagnosis and total mortality

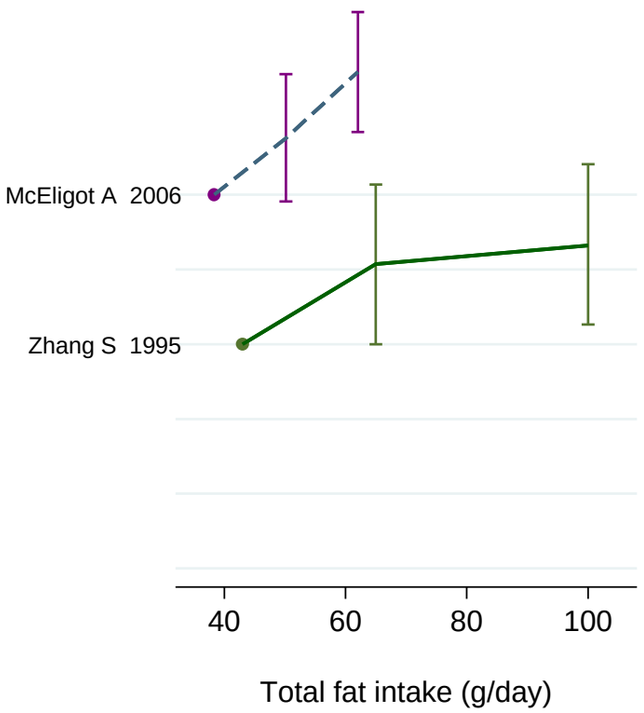


Table 34 Table of included studies on total fat intake before diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments / Remarks
Dal Maso L (2008)	Six Italian Regions Follow-up Study Italy	Cancer diagnosis: 1991-1994; Study follow up: until 2005-2006 diagnosed no longer than 1 year before the interview	Follow-up of cases of a case-control study	1453 participants 55 years (mean) 23 - 74 years Among those with data, pre diagnosis data: 45.5 % peri/pre menopausal, 54.9% postmenopausal HRT use: 91.3% never, 8.6% ever	12.6 years	Invasive breast cancer; TNM; 32.7% Stage I, 44.1% stage II, 13.2% stage III-IV, 9.8% unknown	41.5% ER+ve/PR+ve, 3.5% ERve/PR+ve, / 45.6% no node+ve, 44.2% node+ve, 10.1%		/ 2.70% lost	Self-reported at study baseline for diet before diagnosis	1453 participants 503 deaths, 398 breast cancer mortality, 6.2% death from other cancers, 7.4% from cardiovascular disease	Cancer registry	Highest vs. lowest	0.93 (0.75–1.16)	Region, age at diagnosis, year of diagnosis, TNM stage, receptor status, energy intake / Highest vs lowest meta-analysis only; missing exposure values
McEligot A (2006)	Orange County California Study United States	Cancer diagnosis: 1994-1995, Study follow-up: Until 2003 Recruited within 6 months of diagnosis	Prospective cohort of breast cancer survivors	516 participants 64.78 years (mean) All Postmenopausal; 92.3% non-Hispanic white HRT use: 36.2% estrogen only, 1.9% progesterone only, 35.1% estrogen and progesterone, 26.7% non-users	80 months	Stages: 14.9% in situ, 59.3% localized, 24.2% regional, 1.55% metastatic			98% / 2% lost	Self-reported at diagnosis for dietary habits 1 year prior to diagnosis, FFQ	516 participants 96 deaths, 41 breast cancer mortality, 13 deaths from cardiovascular disease, 31 other causes of deaths, 11 unknown causes of deaths	Cancer registry + National Death Index	>=38.37 vs. <=30.26 % energy from fat	3.12 (1.79–5.44)	Tumor stage, age at diagnosis, BMI, parity, HRT, alcohol intake, multivitamins, energy intake
Saxe GA (1999)	Medical Center, Michigan University Follow-up Study United States	Study recruitment: 1989-1991, Recruited during first medical center visit for suspected or newly diagnosed	Prospective cohort of breast cancer survivors	149 participants 57.8 years (mean) 26 - 95 years White: 90.6%, black:7.2% and other: 2.2%, 34.2% premenopausal, 65.8% postmenopausal	5 Years (min)	Primary breast cancer, stages: 19.6% in situ, 34.5% I, 34.5% II, 8.8% III, 2.7% IV	73.4% ER+, 26.6% ER- / 43% +ve, 57% -ve		/ 0% lost	Interviewed close to time of diagnosis for diet a year prior to diagnosis, semi-quantitative FFQ	149 participants 26 deaths	Hospital records	Per 30g/day increase	1.51 (0.55-4.14)	Energy intake / Dose-response analysis only; only continuous results
Zhang S (1995)	Iowa Women's Health Study United States	Study recruitment:1986; Study follow up: until 1991	Cancer survivors of population-based prospective cohort study	698 participants 55 - 69 years Mostly white: 98%, Postmenopausal	2.9 years	Unilateral breast cancer; 10% in situ, 58% local, 28% regional, 3%distant, and 1% unknown; 55% tumour size <2cm, 33% size >= 2cm and 11% unknown	Among those with data: 85% ER+ve and 72% PR+ve		42.60% / < 1% migration rate	Self reported within 6 years before diagnosis, semi-quantitative FFQ	698 participants 56 deaths, 40 breast cancer mortality (among the causes of death) and 2 death from coronary heart disease	Death certificates, National death index	100 vs. 43g/d	2.5 (1.2-5.3)	Age, smoking, education, tumor stage, ER status, tumor size
Gregorio DI (1985)	Roswell Park Memorial Institute	Cancer diagnosis: 1957-1965; Study	Prospective cohort of breast cancer survivors	854 participants white Any age Distrubution by		Among those with data: 29.8% local,				Assessed at diagnosis by interview for fat consumption prior			Per 1000g/month increase	1.14, p-value>0.05	Age, tumor stage, obesity, treatment delay

	Review Study United States	follow up: until 1983	(historical prospective cohort)	menopausal status not reported		45.6% regional and 24.5% distant			83 patients lost	to diagnosis and onset of symptoms, 33-item FFQ					Dose-response analysis only; only continuous results

Table 35 Table of excluded studies on total fat intake before diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments Exclusion reason
Holmes MD (1999)	Nurses' Health Study United States	Cancer diagnosis: 1976–1990, Study follow-up: Until 1994	Cancer survivors of population-based prospective cohort study	1982 participants 54 years (mean) 35.1% premenopausal, 64.9% postmenopausal, among those with data	157 months	Invasive breast carcinoma; Grade 1-3			95% 5% lost	Most recent prediagnosis diet questionnaire participants had completed	1978 participants 378 deaths, 326 breast cancer mortality	Death certificate	Q5 vs. Q1	1.7, P for trend<0.05	Age, diet interval, calendar year of diagnosis, body mass index, oral contraceptive use, menopausal status, postmenopausal hormone use, smoking, age at first birth and parity, number of metastatic lymph nodes, tumor size, energy intake Insufficient data – Q5 vs. Q1 only, missing 95% CI
Goodwin P (2003)	University of Toronto Hospitals Follow-up Study, Canada	Study recruitment: 1989-1996,	Prospective cohort of breast cancer survivors	477 participants 50.4 years (mean) <=75 years 57.7% premenopausal, 3.6% perimenopausal, 38.8% postmenopausal	6.1 years	Tumor stages: 55.6% T1, 32.3% T2, 5.2%, 6.9% unknown; Grades: 13% 1, 40.7% 2, 33.1% 3, 13.2% unknown	62.5% ER+, 18.7% ER-, 13.4% unknown; 56.6% PR+, 22.9% PR-, 14.9% unknown 30.6% +ve, 69.4% -ve	Mastectomy: 23.3% yes; Lumpectomy: 76.7% yes; Chemotherapy only: 28.3% yes; Chemotherapy plus tamoxifen 9.6%; Tamoxifen only: 29.6%; None: 32.5% yes	8 patients lost	FFQ comleted 9.3 ± 4.6 weeks after diagnosis, reporting intake over preceding 12 months	477 participants, 52 deaths, 2 non-breast cancer related deaths	Medical records		P for linear=0.90, P for non-linear=0.10	BMI,age,tumor stage,nodal status,hormonal therapy,chemotherapy, energy intake Study examined the association of dietary factors with breast cancer survival. HRs were provided from linear and non-linear models, but without 95% CIs or p-values

Total fat intake less than 12 months after diagnosis and total mortality

No study has reported data.

Total fat intake 12 months or more after diagnosis and total mortality

Methods

Four studies were identified (Ewertz, 1991; Holmes, 1999; Beasley, 2001; Pierce, 2007a). Dose-response meta-analysis was not conducted as only two studies provided enough data. Pierce et al. (2007a) reported a HR of 1.39 for the highest compared to the lowest quartile of energy from fat in total mortality. Since a 95% CI or p-value was missing, such result could not be included in the highest versus lowest and dose-response meta-analyses. Ewertz et al. (1991) did not provide details on the fat intake. Three studies could be included in the highest versus lowest meta-analysis (Ewertz, 1991; Holmes, 1999; Beasley, 2001). Beasley et al. (2011) reported intake in percentage energy from fat, which was converted to grams of fat using the mean energy intakes provided in the study. All the other studies reported fat intake in grams per day.

Main results and heterogeneity

For the highest compared to the lowest intake, the summary RR was 1.08 (95% CI 0.90-1.30; 3 studies), with low heterogeneity between studies (I^2 = 24.4%; p = 0.27).

Study quality

All studies were population-based cohorts or clinical series. Diet was assessed 1 to 4 years after diagnosis in all studies except in Beasley et al, 2001 in which the time between diagnosis and diet assessment ranged from 1 to 16 years. All studies adjusted for stage at diagnosis. None of the other studies adjusted for treatment or HR status. All studies included pre- and post-menopausal women

Figure 49 Highest versus lowest forest plot of total fat intake 12 months or more after diagnosis and total mortality

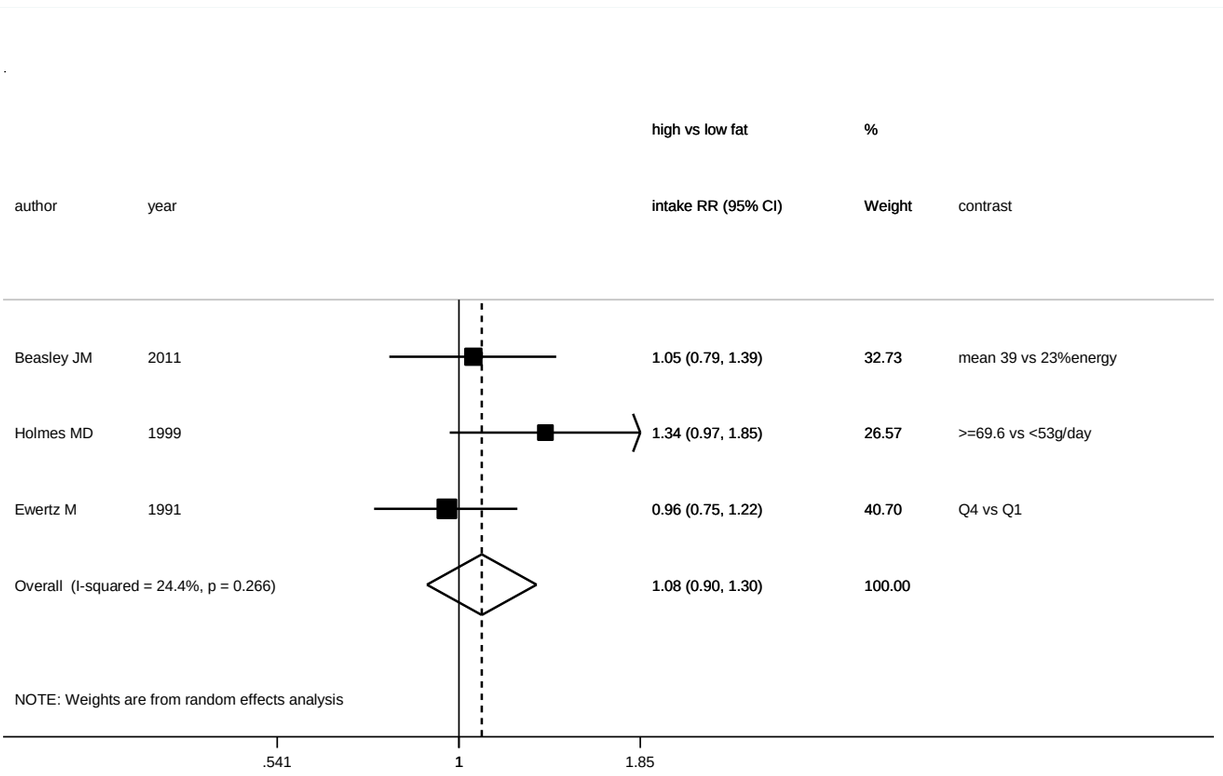


Table 36 Table of included studies on total fat intake 12 months or more after diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Beasley JM (2011)	Collaborative Women's Longevity Study United States	Study recruitment: 1998-2001, Study follow-up: Until 2005 On average 5 years (range 1-16 years) post-diagnosis	Follow up of cases of population-based case-control studies	4441 participants 20 - 79 years Mostly white 22.8% premenopausal, 73.3% postmenopausal among those with data HRT use: 33.2% yes, 56.9% no	5.5 years	Primary invasive breast cancer; Stages: 72.8% local, 27.2% regional		Surgery: 97.9% yes; Radiotherapy: 49.8% yes; Hormonal therapy: 57.8% yes; Chemotherapy: 31.9% yes	42%	Assessed on average 5 years (range 1–16) after diagnosis, usual intake over the past year	4441 participants 525 deaths, 137 breast cancer mortality, 132 deaths from cardiovascular disease	Death certificate	39 vs. 23 % energy from fat	1.05 (0.79–1.39)	Age, residence, menopausal status, smoking, stage, alcohol intake, hormonal therapy, interval between diagnosis and baseline interview, BMI, physical activity , breast cancer treatment, energy intake
Holmes MD (1999)	Nurses' Health Study United States	Cancer diagnosis: 1976–1990, Study follow-up: Until 1994	Cancer survivors of population-based prospective cohort study	1982 participants 54 years (mean) 35.1% premenopausal, 64.9% postmenopausal, among those with data	157 months	Invasive breast carcinoma; Grade 1-3			95% / 5% lost	On average 24 months (SD 18m) after diagnosis	1978 participants 378 deaths, 326 breast cancer mortality	Death certificate	>=69.6 vs. <53 g/day	1.34 (0.97-1.85)	Age, diet interval, calendar year of diagnosis, body mass index, oral contraceptive use, menopausal status, postmenopausal hormone use, smoking, age at first birth and parity, number of metastatic lymph nodes, tumor size, energy intake
Ewertz M (1991)	Danish Breast Cancer Cooperative Group Denmark	Cancer diagnosis:1983-1984; Study follow up: until 1990	Follow up of cases of population-based case-control study	2445 participants <=70 years Among those with data, HRT use: 66.1% never usage, 33.8% ever usage	7 Years (max)	Primary Invasive breast cancer; 44.8%Grade I, 42.3% Grade II, 12.8% Grade III breast cancer	58.5% none node+ve, 28.6% 1-3 node+ve, 12.8% >4 node+ve		87%	Self-reported 1 year after diagnosis	805 deaths, 1744 participants 533 deaths were included in the analysis	Cancer registry	Q4 vs. Q1	0.96 (0.75 - 1.22)	Age, tumor size, nodal status, tumor grade, skin invasion, area of residence

Table 37 Table of excluded studies on total fat intake 12 months or more after diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments / Exclusion reason
Pierce J (2007)a	Womens Healthy Eating and Living Study United States	Cancer diagnosis:1991-2000; Study follow up: until 2005 Recruited within 48 months of diagnosis (on average 24 months)	Randomised controlled trial of dietary intervention	1490 participants 50 years (mean) <= 70.0 years	6.7 years	Early stage breast cancer; AJCC; 40% Stage I (>=1cm), 45% Stage II, 15% stage III, 15.9% grade I, 39.8% grade II, 35.8% grade III, 8.3% unknown	63.1% ER+ve/PR+ve, 10.8% ER+ve/PR-ve, 5.1%ER-ve/PR+ve, 20.8% ER-ve/PR-ve	31.4% none-chemotherapy, 25.7% nonanthracycline, 42.8% anthracycline; 42% adjuvant tamoxifen, 58% no adjuvant tamoxifen	7 patients lost	Self-reported at baseline, on average 2 yrs after diagnosis	1490 participants 135 deaths,118 breast cancer mortality, 10 death from other cancers, 7 death from non-cancer	Death certificate	33.42-58.86% vs. 9.04-23.87% energy from fat	1.39, p for categoric=0 .59, p for trend=0.10	Insufficient data – missing 95% CI

Total fat intake and breast cancer mortality

Nine studies from 10 publications on total fat intake and breast cancer mortality were identified. Four studies from five publications were on total fat intake before diagnosis (Nomura, 1991; Dal Maso, 2008; Jain, 1997; Kyogoku, 1992; Jain, 1994a), one study was on total fat intake less than 12 months after diagnosis (Borugian, 2004), and four studies were on total fat intake 12 months or more after diagnosis (Beasley, 2011; Holmes, 1999; Rohan, 1993; Newman, 1986).

Total fat intake before diagnosis and breast cancer mortality

Methods

Only one (Jain, 1994a) of the four studies identified (five publications) (Nomura, 1991; Dal Maso, 2008; Jain, 1997; Kyogoku, 1992; Jain, 1994a) had sufficient data to be included in a linear dose-response meta-analysis. Hence a dose-response meta-analysis was not conducted. All four studies could be included in the highest versus lowest meta-analysis.

Main results and heterogeneity

The summary RR for the highest compared to the lowest intake was 1.13 (95% CI 0.71-1.77; 4 studies), with moderate to high heterogeneity between studies (I^2 = 53.5%; p = 0.09).

Study quality

All studies except one were population-based cohorts or clinical series except one study that was a follow-up of women participating in a breast cancer screening trial (Jain, 1997) and this was the only study in which pre-diagnosis diet was assessed before diagnosis. All studies had less than 120 breast cancer deaths with the exception of the study by Dal Maso et al (2008). The latest study adjusted for breast cancer stage, treatment, HR status and other potential confounders. All studies included pre- and post-menopausal women.

Figure 50 Highest versus lowest forest plot of total fat intake before diagnosis and breast cancer mortality

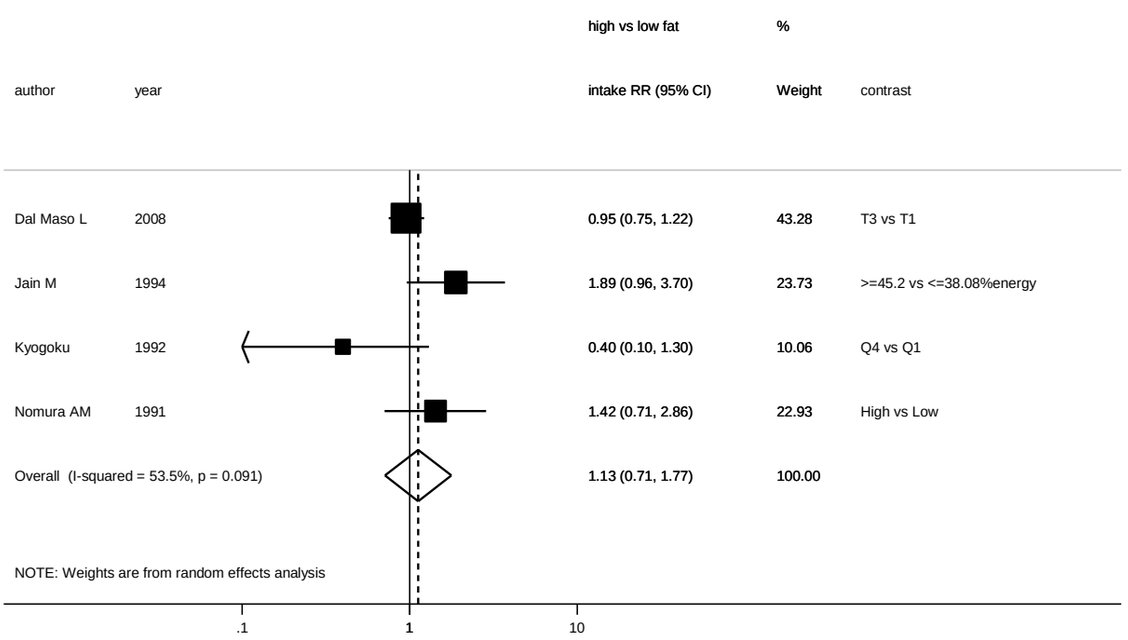


Table 38 Table of included studies on total fat intake before diagnosis and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Dal Maso L (2008)	Six Italian Regions Follow-up Study Italy	Cancer diagnosis: 1991-1994; Study follow up: until 2005-2006 diagnosed no longer than 1 year before the interview	Follow-up of cases of a case-control study	1453 participants 55 years (mean) 23 - 74 years Among those with data, pre diagnosis data: 45.5 % peri/pre menopausal, 54.9% postmenopausal HRT use: 91.3% never, 8.6% ever	12.6 years	Invasive breast cancer; TNM; 32.7% Stage I, 44.1% stage II, 13.2% stage III-IV, 9.8% unknown	41.5% ER+ve/PR+ve, 3.5% ERve/PR+ve, 45.6% no node+ve, 44.2% node+ve, 10.1%		2.70% lost	Self-reported at study baseline for diet before diagnosis	1453 participants 503 deaths, 398 breast cancer mortality, 6.2% death from other cancers, 7.4% from cardiovascular disease	Cancer registry	Highest vs. lowest	0.93 (0.75–1.22)	Region, age at diagnosis, year of diagnosis, TNM stage, receptor status, energy intake
Jain M (1994)a	National Breast Screening Study Canada	Cancer diagnosis: 1982-1992	Randomised controlled trial of mammography screening trial; ancillary analysis	678 participants 52.7 years (mean) Mostly white 37.3% premenopausal 62.7% postmenopausal, 55.6% allocated to mammography group	7.7 years	Tumor size (cm): 50.6% 0.1-1.5, 49.4% >1.5 among those with data	75.7% ER+, 24.3% ER-; 69.3% PR+, 30.7% PR- 70.5% 0, 17.8% 1-3, 11.7% >3 among those with data			Self-administered diet history questionnaire for diet in the previous months	678 participants 83 deaths, 76 breast cancer mortality, 7 other causes of deaths	Death certificate	Per 20g/day increase >=45.2 vs. <=38.08% energy from fat	1.21 (0.91-1.61) 1.89 (0.96-3.70)	Age at diagnosis, smoking, weight, energy intake
Kyogoku (1992)	Fukuoka Hospitals, Japan Follow-up Study Japan	Study recruitment: 98.60% 1975-1978, Study follow-up: Until 1987	Follow-up of cases of case-control study	212 participants		Stages I, II and III		All had surgery	98.60% 9 patients	Interviewed 1-3 months after the operation for diet over a typical week before the onset of the disease	212 participants 47 breast cancer mortality	Death certificate	Q4 vs. Q1	0.40 (0.10-1.30)	Tumor stage, BMI, age of menarche, age at first birth, radiotherapy, chemotherapy, hormonal therapy, surgery type, protein intake, age at surgery
Nomura AM (1991)	Hawaiian Caucasian, Japanese Follow-up Study United States	Cancer diagnosis:1975-1980; Study follow up: until 1987	Follow up of cases of a case-control study	343 participants 45 - 74 years Japanese; Caucasian	12.5 years (max)	Japanese: 12% in situ, 63% localized, 24%regional, 1% distant; Caucasian: 5% in situ, 56% localized, 36% regional, 3% distant			82.70% 10% of the Caucasian cases and 3% of the Japanese cases lost	Interviewed after diagnosis in mean of 2.2 months; diet history of usual consumption in a week (after diagnosis)	343 participants	Cancer registry	Caucasian High vs. low Japanese High vs. low	3.17 (1.17-8.55) 0.66 (0.25-1.76)	Tumor stage, menopausal status, hormonal therapy,obesity

Table 39 Table of excluded studies on total fat intake before diagnosis and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments / Exclusion reason
Jain M (1997)	National Breast Screening Study Canada	Cancer diagnosis: 1982-1985, Study follow-up: Until 1992 Recruited between1980-1985 and diagnosed after July 1982	Randomised controlled trial of mammography screening trial; ancillary analysis	676 participants 49.9 years (mean) 40 - 59 years 90% Caucasian 57% postmenopausal (at enrollment) 48.4% cases detected through mammography	7.7 years	Invasive breast cancer; any stage				Pre-diagnosis; diet history completed at enrollment	83 deaths, 76 breast cancer mortality, 7 other causes of deaths	Death certificate	With ER status With PR status With nodal status With tumour size Per 20g/d increase	1.26 (0.90-1.78) 1.26 (0.87-1.81) 1.22 (0.90-1.67) 1.22 (0.89-1.69)	Age at diagnosis, weight, smoking, energy intake, when appropriate ER status, PR status, nodal status, tumour size Superseded by Jain 1994a

Total fat intake less than 12 months after diagnosis and breast cancer mortality

Only one study reported data. Borugian et al. (2004) reported a RR of 1.8 (95% CI 0.9-4.8; p_{trend}=0.35) for ≥ 76 g compared to ≤ 43 g of fat intake/day.

Total fat intake 12 months or more after diagnosis and breast cancer mortality

Methods

Four studies were identified, of which three studies (Holmes, 1999; Rohan, 1993; Beasley, 2011) could be included in the dose-response meta-analysis. The remaining study (Newman, 1986) reported results by two fat intake categories and was included in the highest versus lowest meta-analysis only. One study (Beasley, 2011) reported intake in percentage energy from fat, which was converted to grams of fat using the mean energy intakes provided in the study. All the other studies reported fat intake in grams per day.

Main results and heterogeneity

The summary RR per 10 g/day was 1.01 (95% CI 0.95-1.08; I^2 = 24.0%; p = 0.27, 3 studies), that ranged from 1.00 (95% CI 0.94-1.06) when Holmes et al. (1999) was omitted to 1.06 (95% CI 0.98-1.15) when Beasley et al. (2011) was omitted in an influence analysis. For the highest compared to the lowest intake, the summary RR was 1.19 (95% CI 0.94-1.50, I^2 = 0%; p = 0.41; 4 studies).

Study quality

All studies were follow-up studies of cases from case-control studies except one study based on a population cohort (Holmes, 1999). Diet was assessed less than two years after diagnosis in two studies (Newman, 1986; Holmes, 1999). In one study the time between diagnosis and diet assessment ranged from 1 to 16 years (Beasley, 2011). Breast cancer cases were diagnosed before 1991 in all studies and before 1985 in two of the studies (Newman, 1986; Rohan, 1993). Three studies identified between 73 and 137 breast cancer deaths except Holmes et al (1999) in which 326 breast cancer deaths were identified. All studies included pre- and post-menopausal women.

Figure 51 Highest versus lowest forest plot of total fat intake 12 months or more after diagnosis and breast cancer mortality

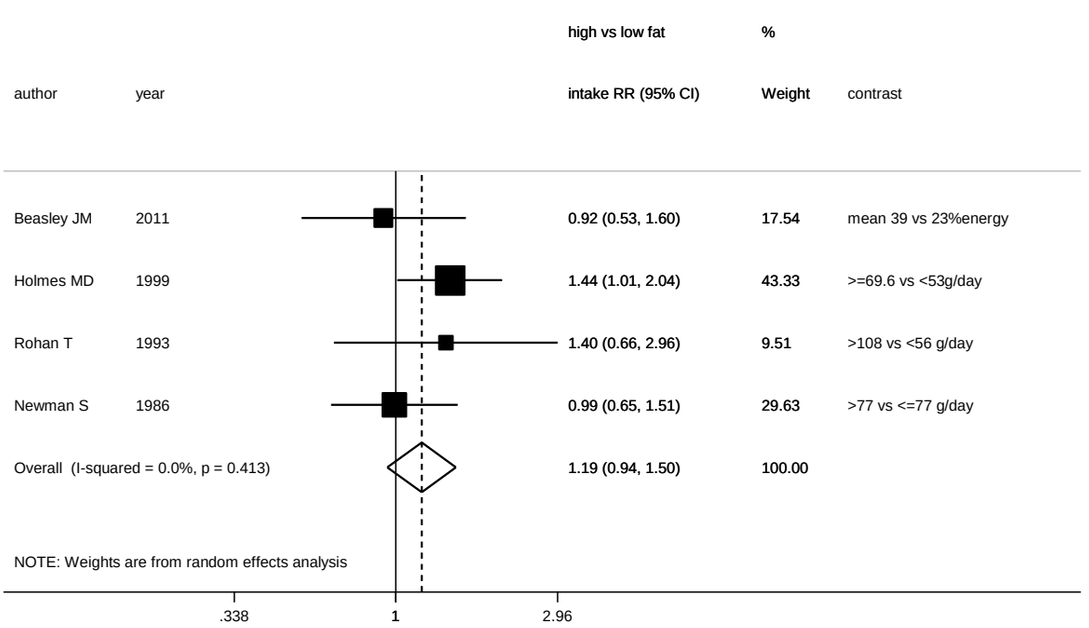


Figure 52 Linear dose-response meta-analysis of total fat intake 12 months or more after diagnosis and breast cancer mortality

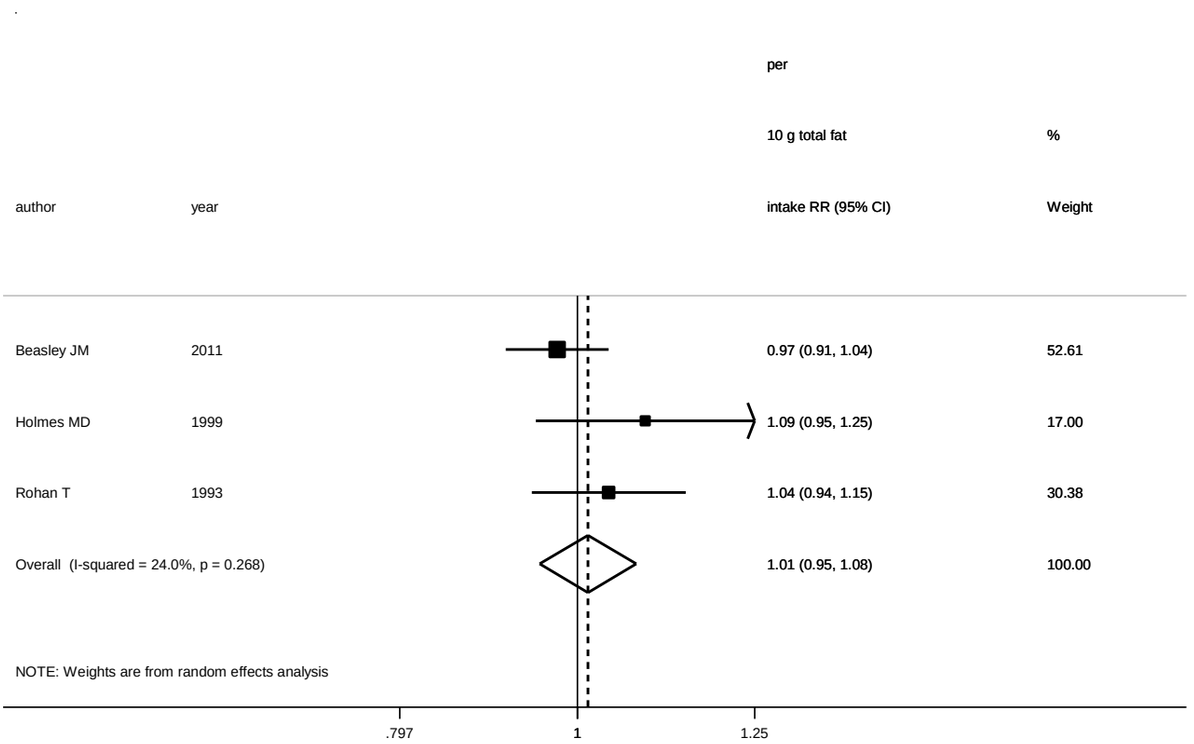


Figure 53 Individual dose-response graph of total fat intake 12 months or more after diagnosis and breast cancer mortality

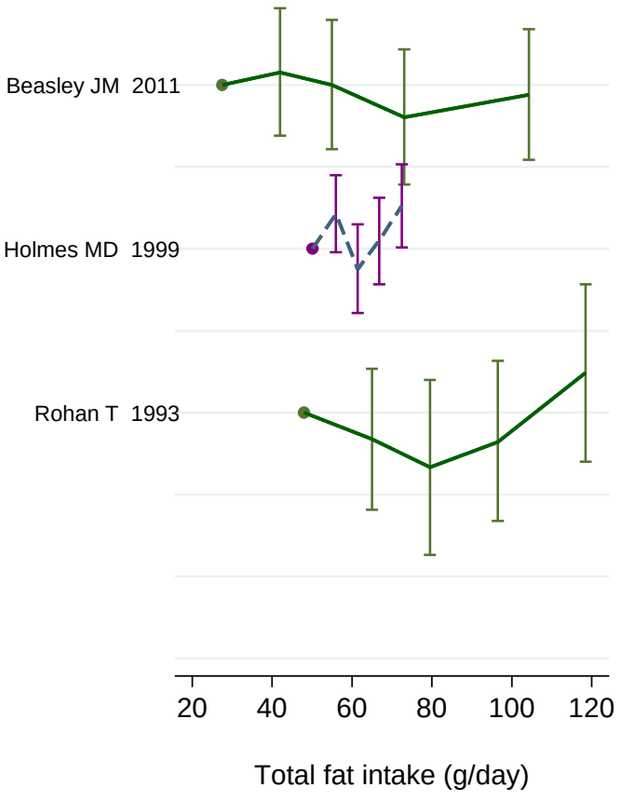


Table 40 Table of included studies on total fat intake 12 months or more after diagnosis and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments / Remarks
Beasley JM (2011)	Collaborative Women's Longevity Study United States	Study recruitment: 1998-2001, Study follow-up: Until 2005 On average 5 years (range 1-16 years) post-diagnosis	Follow up of cases of population-based case-control studies	4441 participants 20 - 79 years Mostly white 22.8% premenopausal, 73.3% postmenopausal among those with data HRT use: 33.2% yes, 56.9% no	5.5 years	Primary invasive breast cancer; Stages: 72.8% local, 27.2% regional		Surgery: 97.9% yes; Radiotherapy: 49.8% yes; Hormonal therapy: 57.8% yes; Chemotherapy: 31.9% yes	42%	Assessed on average 5 years (range 1–16) after diagnosis, usual intake over the past year	4441 participants 525 deaths, 137 breast cancer mortality, 132 deaths from cardiovascular disease	Death certificate	39 vs. 23 % energy from fat	0.92 (0.53-1.60)	Age, residence, menopausal status, smoking, stage, alcohol intake, hormonal therapy, interval between diagnosis and baseline interview, BMI, physical activity , breast cancer treatment, energy intake
Holmes MD (1999)	Nurses' Health Study United States	Cancer diagnosis: 1976–1990, Study follow-up: Until 1994	Cancer survivors of population-based prospective cohort study	1982 participants 54 years (mean) 35.1% premenopausal, 64.9% postmenopausal, among those with data	157 months	Invasive breast carcinoma; Grade 1-3			95% / 5% lost	On average 24 months (SD 18m) after diagnosis	1978 participants 378 deaths, 326 breast cancer mortality	Death certificate	>=69.6 vs. <53 g/day	1.44 (1.01-2.04)	Age, diet interval, calendar year of diagnosis, body mass index, oral contraceptive use, menopausal status, postmenopausal hormone use, smoking, age at first birth and parity, number of metastatic lymph nodes, tumor size, energy intake
Rohan T (1993)	Diet and Breast Cancer in Australia Follow-up Study Australia	Cancer diagnosis: 1982-1984, Study follow-up: Until 1989	Follow-up of cases of population-based case-control study	412 participants 55.1 years (mean) 20 - 74 years 30.7% premenopausal, 5.4% perimenopausal, 64% postmenopausal, among those with data	5.5 years	Primary breast cancer, any stages			80.70% / 39 patients lost	Interval between diagnosis and interview was 4.8months, FFQ	412 participants 112 breast cancer mortality, 11 other causes of deaths	Cancer registry + death certificate	>108 vs. <56g/d	1.40 (0.66-2.96)	Energy intake, age of menarche, Quetelet Index
Newman S (1986)	Study of Diet and Health Canada	Cancer diagnosis: 1973-1975, Study follow-up: Until 1980	Follow-up of cases of multicenter case-control study	300 participants 35 - 74 years	7 Years (max)					3 to 5 months post-surgery; typical diet during the 24 hours preceding the interview	300 participants 87 deaths, 73 breast cancer mortality	Death certificate	>77 vs. <=77g/d	0.99, p-value=0.963	Weight / Highest vs. lowest analysis only; two fat intake categories only

4.5 Saturated fat intake

Table 41 Summary results of meta-analysis on before diagnosis saturated fat intake and total mortality*

Comparison	No. of studies	No. of events in studies	RR (95% CI)	I^2, $P_{heterogeneity}$
Per 10 g/day	3	178	1.66 (1.26-2.19)	31.8%, p = 0.23

*No studies on breast cancer mortality and second cancers were included in the meta-analyses. Only studies on saturated fat intake before diagnosis could be included in the dose-response meta-analysis.

Saturated fat intake and total mortality

A total of six studies on total mortality were identified, four of which (Zhang, 1995; Saxe, 1999; Goodwin, 2003; McEligot, 2006) examined before diagnosis saturated fat intake, no study examined less than 12 months after diagnosis intake, and two studies (Holmes, 1999; Beasley, 2011) examined 12 months or more after diagnosis intake.

Saturated fat intake before diagnosis and total mortality

Methods

Three of the four studies identified could be included in the linear dose-response meta-analysis. Data from Goodwin et al. (2003) was not sufficient to include in the dose-reponse meta-analyses. No relationship between saturated fat intake and breast cancer survival was observed in this study. Saxe et al. (1999) only reported a dose-response result. Highest versus lowest meta-analysis was not conducted as only two studies were available. The study by McEligot et al. (2006) reported intake in percentage energy from fat, which was converted to grams of fat using the mean energy intake provided in the study. All the other studies reported fat intake in grams per day.

Main results and heterogeneity

The summary RR per 10 g/day was 1.66 (95% CI 1.26-2.19; 3 studies). There is evidence of low to moderate heterogeneity between studies (I^2 = 31.8%; p = 0.23). In an influence analysis, the summary RR ranged from 1.41 (95% CI 1.04-1.91) when McEligot et al. (2006) was omitted to 1.76 (95% CI 1.13-2.75) when Zhang et al. (1995) was omitted.

Study quality

Two studies were based on clinical series of breast cancer patients and one study was on cases identified in a population-based cohort study (Zhang, 1995). In the latter study diet was assessed before breast cancer diagnosis. The number of deaths in each study were 26 (Saxe, 1999), 56 (Zhang, 1995) and 96 (McEligot, 2006), respectively. Two studies were on postmenopausal women (Zhang, 1995; McEligot, 2006). Only one study adjusted for breast cancer stage less than 12 months after diagnosis (McEligot, 2006).

Figure 54 Linear dose-response meta-analysis of saturated fat intake before diagnosis and total mortality

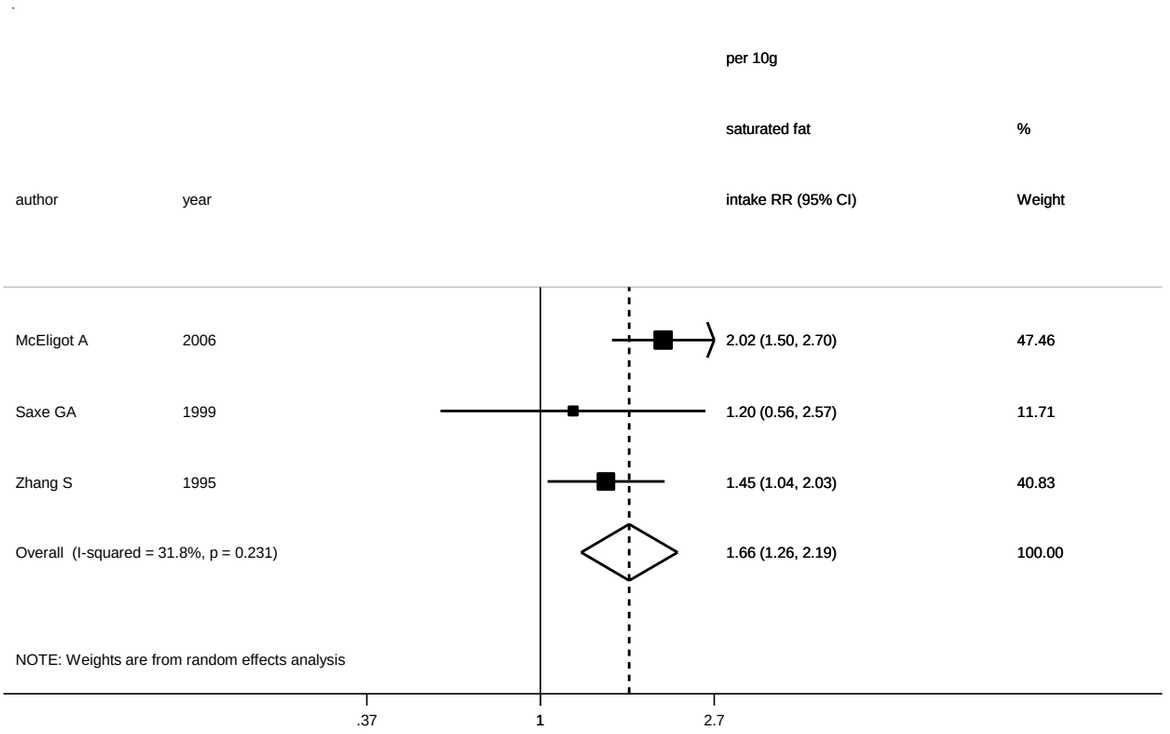


Figure 55 Individual dose-response graph of saturated fat intake before diagnosis and total mortality

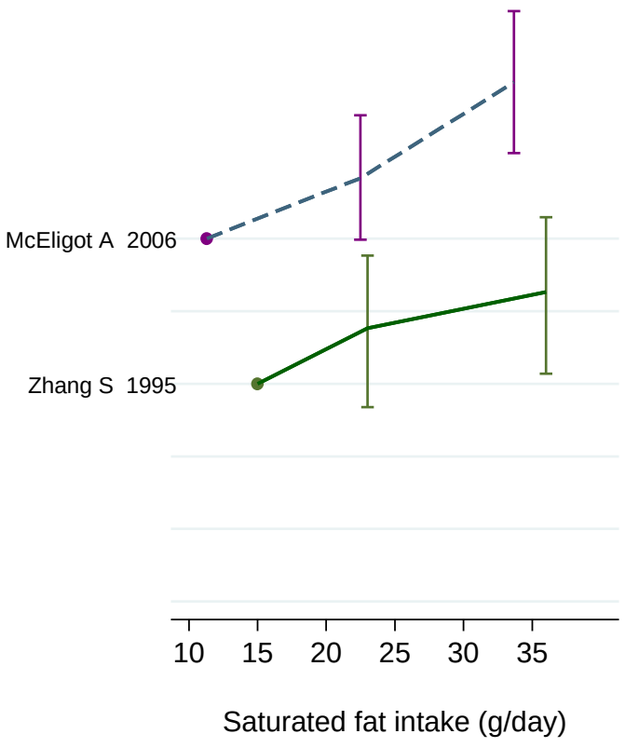


Table 42 Table of included studies on saturated intake before diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
McEligot A (2006)	Orange County California Study United States	Cancer diagnosis: 1994-1995, Study follow-up: Until 2003 Recruited within 6 months of diagnosis	Prospective cohort of breast cancer survivors	516 participants 64.78 years (mean) Postmenopausal 92.3% non-Hispanic white HRT use: 36.2% estrogen only, 1.9% progesterone only, 35.1% estrogen and progesterone, 26.7% non-users	80 months	Stages: 14.9% in situ, 59.3% localized, 24.2% regional, 1.55% metastatic			98% / 2% lost	Self-reported at diagnosis for dietary habits 1 year prior to diagnosis, FFQ	516 participants 96 deaths, 41 breast cancer mortality, 13 deaths from cardiovascular disease, 31 other causes of deaths, 11 unknown causes of deaths	Cancer registry + National Death Index	>=19.21 vs. <=11.55 % energy from fat	4.45 (2.26–8.78)	Tumor stage, age at diagnosis, BMI, parity, HRT, alcohol intake, multivitamins, energy intake
Saxe GA (1999)	Medical Center, Michigan University Follow-up Study United States	Study recruitment: 1989-1991, Recruited during first medical center visit for suspected or newly diagnosed	Prospective cohort of breast cancer survivors	149 participants 57.8 years (mean) 26 - 95 years White: 90.6%, black:7.2% and other: 2.2%, 34.2% premenopausal, 65.8% postmenopausal	5 years (min)	Primary breast cancer, stages: 19.6% in situ, 34.5% I, 34.5% II, 8.8% III, 2.7% IV	73.4% ER+, 26.6% ER- / 43% +ve, 57% -ve		0% lost	Interviewed close to time of diagnosis for diet a year prior to diagnosis, semi-quantitative FFQ	149 participants 26 deaths	Hospital records	Per 20g/day increase	1.45 (0.32-6.62)	Energy intake
Zhang S (1995)	Iowa Women's Health Study United States	Study recruitment:1986; Study follow up: until 1991	Cancer survivors of population-based prospective cohort study	698 participants 55 - 69 years Mostly white: 98%, Postmenopausal	2.9 years	Unilateral breast cancer; 10% in situ, 58% local, 28% regional, 3%distant, and 1% unknown; 55% tumour size <2cm, 33% size >= 2cm and 11% unknown	Among those with data: 85% ER+ve and 72% PR+ve		42.60% / < 1% migration rate	Self reported within 6 years before diagnosis, semi-quantitative FFQ	698 participants 56 deaths, 40 breast cancer mortality (among the causes of death) and 2 death from coronary heart disease	Death certificates, National death index	36vs. 15g/d	2.40 (1.10-4.90)	Age, smoking, education, tumor stage, ER status, tumor size

Table 43 Table of excluded studies on saturated intake before diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments Exclusion reason
Goodwin P (2003)	University of Toronto Hospitals Follow-up Study, Canada	Study recruitment: 1989-1996,	Prospective cohort of breast cancer survivors	477 participants 50.4 years (mean) <=75 years 57.7% premenopausal, 3.6% perimenopausal, 38.8% postmenopausal	6.1 years	Tumor stages: 55.6% T1, 32.3% T2, 5.2%, 6.9% unknown; Grades: 13% 1, 40.7% 2, 33.1% 3, 13.2% unknown	62.5% ER+, 18.7% ER-, 13.4% unknown; 56.6% PR+, 22.9% PR-, 14.9% unknown 30.6% +ve, 69.4% -ve	Mastectomy: 23.3% yes; Lumpectomy: 76.7% yes; Chemotherapy only: 28.3% yes; Chemotherapy plus tamoxifen 9.6%; Tamoxifen only: 29.6%; None: 32.5% yes	8 patients lost	FFQ comleted 9.3 ± 4.6 weeks after diagnosis, reporting intake over preceding 12 months	477 participants, 52 deaths, 2 non-breast cancer related deaths	Medical records		P for linear=0.24, P for non-linear=0.10	BMI,age,tumor stage,nodal status,hormonal therapy,chemotherapy, energy intake Study examined the association of dietary factors with breast cancer survival. HRs were provided from linear and non-linear models, but without 95% CIs or p-values

Saturated fat intake less than 12 months after diagnosis and total mortality

No study has reported data.

Saturated fat intake 12 months or more after diagnosis and total mortality

Only two studies reported data. Holmes et al. (1999) observed a statistically non-signficant increased risk (RR for Q5 vs. Q1 saturated fat intake 1.23; 95% CI 0.89-1.69), while Beasley et al. (2011) reported a significant increased risk of 1.40 (95% CI 1.06-1.87) for the comparison of 13% to 7% energy intake from saturated fat.

Saturated fat intake and breast cancer mortality

Four studies from five publications on breast cancer mortality were identified. Two publications on the same study (Jain, 1994a; Jain, 1997) were on before diagnosis, one study (Borugian, 2004) was on less than 12 months after diagnosis, and two studies (Rohan, 1993; Beasley, 2011) were on 12 months or more after diagnosis saturated intake respectively.

Saturated fat intake before diagnosis and breast cancer mortality

Two publications on the same study (Jain, 1994a; Jain, 1997) reported data. A HR of 1.23 (95% CI 0.97-1.55) for each 10 g/day intake increment was reported in a follow-up of breast cancer patients identified in a cohort study based on an intervention study on screening for breast cancer (Jain, 1994a). Similar results were observed when specific tumour characteristic was adjusted for in the models (Jain, 1997).

Saturated fat intake less than 12 months after diagnosis and breast cancer mortality

Only one study reported data. Borugian et al. (2004) observed a statistically significant increased risk (RR for Q4 vs. Q1 saturated fat intake 2.5; 95% CI 1.2-5.3; $p_{trend} = 0.07$).

Saturated fat intake 12 months or more after diagnosis and breast cancer mortality

Only two studies reported data. For the highest compared to the lowest saturated fat intake, Rohan et al. (1993) observed a statistically non-signficant increased risk (HR for ≥ 45 vs. < 20 g/day 1.65 (95% CI 0.73-3.75). Beasley et al. (2011) reported similar results on percentage energy intake from saturated fat (HR for 13% vs. 7% 1.55; 95% CI 0.88-2.75).

4.6 Protein intake

Table 44 Summary results of meta-analysis on before diagnosis protein intake and total mortality*

Comparison	No. of studies	No. of events in studies	RR (95% CI)	I^2, $P_{heterogeneity}$
Highest vs. lowest	4	738	0.94 (0.77-1.15)	24.7%, p = 0.26
Per 20 g/day	4	261	0.91 (0.74-1.12)	43.1%, p = 0.15

*No studies on breast cancer mortality or second cancers were included in the meta-analyses. Only studies on protein intake before diagnosis could be included in meta-analyses.

Protein intake and total mortality

Seven studies on protein intake and total mortality were identified. Five studies (Jain, 1994a; Zhang, 1995; Saxe, 1999; McEligot, 2006; Dal Maso, 2008) were on protein intake before diagnosis and total mortality and two studies (Holmes, 1999; Beasley, 2011) were on protein intake 12 months or more after diagnosis and total mortality.

Protein intake before diagnosis and total mortality

Methods

From the 5 studies identified, 4 were included in the dose-response meta-analysis. Two studies (Saxe, 1999; McEligot, 2006) reported protein as percentage of energy from protein, which was converted to grams of protein using the mean energy intake provided in the study. All the other studies reported protein intake in grams per day. One study (Dal Maso 2008) could not be included in the dose response meta-analysis because it did not provide the quintile range from protein intake. It did not report a significant association of protein intake with mortality in breast cancer survivors.

Main results and heterogeneity

The summary RR per 20 g/day increase was 0.91 (95% CI 0.74-1.12; 4 studies). Moderate heterogeneity was observed (I^2 = 43.1%; p = 0.153). In the highest versus lowest forest plot the overall RR was 0.94 (95% CI 0.77-1.15; 4 studies).

Study quality

All the studies except one (Dal Maso, 2008) reported less than 100 events, ranging from 26 (Saxe, 1999) to 503 (Dal Maso, 2008) deaths. The follow-up time ranged from 5 years (Saxe, 1999) to 12.6 years (Dal Maso, 2008). One study was based on a trial to evaluate breast cancer screening (Jain, 1994a) and another was based on a population cohort (Zhang, 1995). Diet was assessed before diagnosis in the latter. The remaining studies are built upon case-control studies, clinical series or cancer registries. Two studies included only post-menopausal women (Zhang, 1995; McEligot 2006) and the remaining combined pre and post-menopausal women. The dietary assessment was 1 year before diagnosis for all the studies. Three studies were from the United States (Zhang, 1995; Saxe, 1999; McEligot, 2006), one study was from Canada (Jain, 1994a) and the other one was from Europe (Dal Maso, 2008).

Figure 56 Highest versus lowest forest plot of protein intake before diagnosis and total mortality

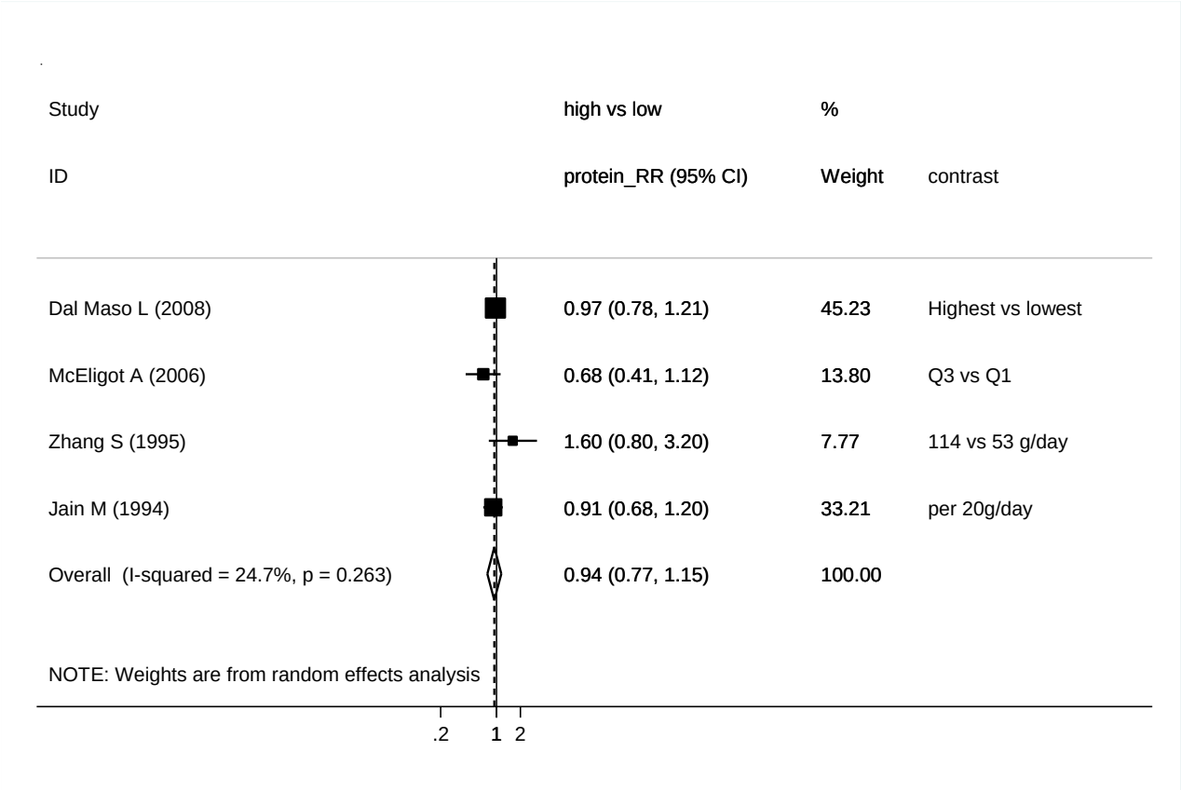


Figure 57 Linear dose-response meta-analysis of protein intake before diagnosis and total mortality

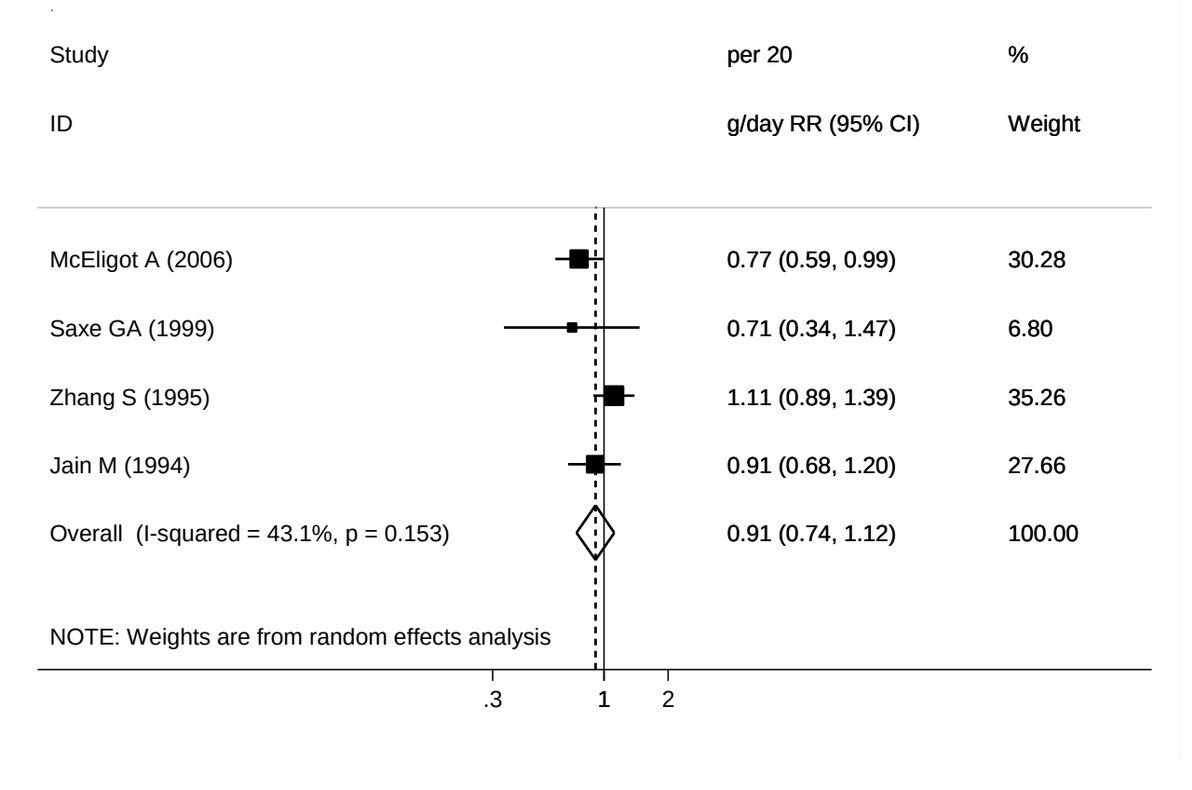


Table 45 Table of included studies on protein intake before diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments Remarks
Dal Maso L (2008)	Six Italian Regions Follow-up Study Italy	Cancer diagnosis: 1991-1994; Study follow up: until 2005-2006 diagnosed no longer than 1 year before the interview	Follow-up of cases of a case-control study	1453 participants 55 years (mean) 23 - 74 years Among those with data, pre diagnosis data: 45.5 % peri/pre menopausal, 54.9% postmenopausal HRT use: 91.3% never, 8.6% ever	12.6 years	Invasive breast cancer; TNM; 32.7% Stage I, 44.1% stage II, 13.2% stage III-IV, 9.8% unknown	41.5% ER+ve/PR+ve, 3.5% ERve/PR+ve, 45.6% no node+ve, 44.2% node+ve, 10.1%		 2.70% lost	Before diagnosis (diagnosed no longer than 1 year before the interview)	1453 participants 503 deaths, 398 breast cancer mortality, 6.2% death from other cancers, 7.4% from cardiovascular disease	Cancer registry	Highest vs. lowest	0.97 (0.78–1.21)	Region, age at diagnosis, year of diagnosis, TNM stage, Receptor status Highest vs. lowest analysis only, missing quintile range from protein intake
McEligot A (2006)	Orange County California Study United States	Cancer diagnosis: 1994-1995, Study follow-up: Until 2003 Recruited within 6 months of diagnosis	Prospective cohort of breast cancer survivors	516 participants 64.78 years (mean) Postmenopausal 92.3% non-Hispanic white HRT use: 36.2% estrogen only, 1.9% progesterone only, 35.1% estrogen and progesterone, 26.7% non-users	80 months	Stages: 14.9% in situ, 59.3% localized, 24.2% regional, 1.55% metastatic			98% 2% lost	At diagnosis; dietary habits during the 1 year prior to diagnosis FFQ	516 participants 96 deaths, 41 breast cancer mortality, 13 deaths from cardiovascular disease, 31 other causes of deaths, 11 unknown causes of deaths	Cancer registry + National Death Index	17.61 vs. <15.03 % E from protein	0.68 (0.41-1.12)	Tumor stage, age at diagnosis, BMI, parity, HRT, alcohol intake, multivitamins, energy intake
Saxe GA (1999)	Medical Center, Michigan University Follow-up Study United States	Study recruitment: 1989-1991, Recruited during first medical center visit for suspected or newly diagnosed	Prospective cohort of breast cancer survivors	149 participants 57.8 years (mean) 26 - 95 years White: 90.6%, black:7.2% and other: 2.2%,34.2% premenopausal, 65.8% postmenopausal	5 Years (min)	Primary breast cancer, stages: 19.6% in situ, 34.5% I, 34.5% II, 8.8% III, 2.7% IV	73.4% ER+, 26.6% ER- 43% +ve, 57% -ve		 0% lost	Interviewed close to time of diagnosis for diet a year prior to diagnosis, semi-quantitative FFQ	149 participants 26 deaths	Hospital records	Per 5% of energy	0.71 (0.34-1.47)	Tumor stage, energy intake Dose-response analysis only, only continuous results
Zhang S (1995)	Iowa Women's Health Study United States	Study recruitment:1986; Study follow up: until 1991	Cancer survivors of population-based prospective cohort study	698 participants 55 - 69 years Mostly white: 98%, Postmenopausal	2.9 years	Unilateral breast cancer; 10% in situ, 58% local, 28% regional, 3%distant, and 1% unknown; 55% tumour size <2cm, 33% size >= 2cm and 11% unknown	Among those with data: 85% ER+ve and 72% PR+ve		42.60% < 1% migration rate	Self reported questionnaire within 6 years before diagnosis semi-quantitative FFQ	698 participants 56 deaths, 40 breast cancer mortality (among the causes of death) and 2 death from coronary heart disease	Death certificates, National death index	90-309 vs. 20-68g/d	1.6 (0.8-3.2)	Age, smoking, education, tumor stage, ER status, tumor size
Jain M (1994)a	National Breast Screening Study Canada	Cancer diagnosis: 1982-1992	Randomised controlled trial of mammography screening trial; ancillary analysis	678 participants 52.7 years (mean) Mostly white 62.7% postmenopausal, 37.3% other 55.6% allocated to mammography, 44.4% no	7.7 years	Tumor size (cm): 50.6% 0.1-1.5, 49.4% >1.5 among those with data	75.7% ER+, 24.3% ER-; 69.3% PR+, 30.7% PR- 70.5% 0, 17.8% 1-3, 11.7% >3 among those with			Self-administered diet history questionnaire for diet in the previous months	678 participants 83 deaths, 76 breast cancer mortality, 7 other causes of deaths	Death certificate	Per 20g/d	0.91 (0.68-1.20)	Age at diagnosis, smoking, weight, energy intake

Protein intake less than 12 months after diagnosis and total mortality

No study reported data.

Protein intake 12 months or more after diagnosis and total mortality

One study (Holmes, 1999) reported a significant association between protein intake 12 months or more after diagnosis and total mortality (RR 0.65; 95% CI 0.47-0.88; > 81.5 vs. ≤ 60.9 g/day). The other study (Beasley, 2011) reported a non-significant association between protein intake 12 months or more after diagnosis and total mortality (RR 0.98; 95% CI 0.73-1.31; 21 vs. 13% of energy from protein). No meta-analysis was conducted.

Protein intake and breast cancer mortality

Four studies on protein and breast cancer mortality were identified. One study (Dal Maso, 2008) was on protein intake before diagnosis, one study (Borugian, 2004) was on protein intake less than 12 months after diagnosis and two studies (Rohan, 1993; Beasley, 2011) were on protein intake 12 months or more after diagnosis. Therefore it was not possible to conduct a meta-analysis on protein intake and breast cancer mortality.

Before diagnosis protein intake was not related to breast cancer mortality in a follow-up study of breast cancer cases from case-control studies (HR for T3 vs. T1 0.98; 95% CI 0.77-1.25; 398 events) (Dal Maso, 2008).

Breast cancer mortality was significantly inversely related with protein intake less than 12 months after diagnosis (HR for Q4 vs. Q1 0.4; 95% CI 0.2-0.8) and with percentage of energy from protein (HR for each 1% increase 0.87; 95% CI 0.82-0.93) in a cohort of breast cancer patients with diagnosis during 1991 and 1992. The primary outcome of interest was breast cancer mortality and 112 events were identified after 10 years of follow-up. The association was similar for pre- and post-menopausal cases (Borugian, 2004).

Energy from protein 12 months or more after breast cancer diagnosis was not related to mortality from breast cancer (112 events) (Rohan, 1993) in a follow-up of cases diagnosed in 1982-1984. No association was observed in a study of patients diagnosed in 1988-1991 in which 137 events were identified after 7 years of follow-up (Beasley, 2011).

Animal protein intake and breast cancer mortality

One study on animal protein and breast cancer mortality reported non-significant results (Kyogoku, 1992).

Soy protein intake and total mortality

Three studies on soy protein and total mortality. One study on soy protein intake before diagnosis (Boyapati, 2005) and two on soy protein intake 12 months or more after diagnosis (Shu, 2009; Zhang, 2012). These 2 studies reported a protective effect against total mortality for soy protein intakes above 13 g/day, RR 0.71 (95% CI 0.54-0.92; > 15.31 vs. ≤ 5.31 g/day) (Shu, 2009) and RR 0.71 (95% CI 0.52-0.98; >1 3.03 vs. < 2.12 g/day) (Zhang, 2012). For one study (Shu, 2009) this effect (> 15.31 vs. ≤ 5.31 g/day) was no longer significant after stratification by receptor status, RR 0.78 (95% CI 0.54-1.14) for ER+ and RR 0.67 (95% CI 0.45-1.00) for ER- or tamoxifen use status RR 0.65 (95% CI 0.33-1.29) for no tamoxifen use and RR 0.61 (95% CI 0.34-1.08) for tamoxifen use. For the other study (Zhang, 2012) the effect was only significant in ER+ cases (RR 0.66; 95% CI 0.44-0.93; > 13.03 vs. < 2.12 g/day), not in ER-cases (RR 0.77; 95% CI 0.53-1.00; > 13.03 vs. < 2.12 g/day).

4.7 Folate

Table 46 Summary results of meta-analysis on before diagnosis folate intake and total mortality

Comparison	No. of studies	No. of events in studies	RR (95% CI)	I^2, $P_{heterogeneity}$
Dietary folate intake before breast cancer diagnosis				
Highest vs. lowest	4	1226	0.70 (0.51-0.95)	50.2%, p = 0.11
Per 100 µg/day	4	1226	0.88 (0.78-0.98)	66.4%, p = 0.03
Total folate intake before breast cancer diagnosis				
Highest vs. lowest	3	374	0.97 (0.73-1.28)	0%, p = 0.94
Per 100 µg/day	3	374	1.00 (0.97-1.03)	0%, p = 0.92

*No studies on breast cancer mortality or second cancers were included in the meta-analyses. Only studies on folate intake before diagnosis could be included in meta-analyses.

Dietary folate and total mortality

Only folate intake from foods was investigated in the identified studies. Five studies on dietary folate and total mortality were identified. Four studies (Sellers, 2002; McEligot, 2006; Xu, 2008; Harris, 2012b) were on dietary folate before diagnosis and total mortality and one study (Holmes, 1999) was on dietary folate less than 12 months after diagnosis and total mortality.

Dietary folate before diagnosis and total mortality

Methods

The four studies identified were included in the dose-response meta-analysis. All studies reported dietary folate intake in µg per day, which was the unit used in the analysis.

Main results and heterogeneity

The summary RR per 100 µg/day was 0.88 (95% CI 0.78-0.98; 4 studies). High heterogeneity was observed (I^2 = 66.4%; p = 0.03), which by visual analysis can be explained by one study (McEligot, 2006). Two studies were on post-menopausal women, the other two were on pre and post-menopausal women. It was not possible to conduct a meta-analysis stratified by menopausal status. In the highest versus lowest forest plot the overall RR was 0.70 (95% CI 0.51-0.95; 4 studies). There was no evidence of a non-linear association between dietary folate before diagnosis and total mortality, $p_{non\text{-}linearity}$ = 0.21.

Study quality

One study included only breast cancer cases with chemotherapy as first course treatment (Sellers, 2002). One study included breast cancer cases identified in a cohort built upon the Swedish Mammography Study. In two studies (Sellers, 2002, Harris, 2012b) diet was assessed before cancer diagnosis and in the two others, less than 6 months after diagnosis on average. Two studies (Sellers, 2002; McEligot, 2006) reported less than 100 events. The two other studies reported 198 (Xu, 2008) and 852 (Harris, 2012b) deaths respectively. The follow-up time ranged from 5.6 years (Xu, 2008) to 14 years (Sellers, 2002). Two studies (Sellers, 2002; McEligot, 2006) included only postmenopausal women and the other two studies included pre and post-menopausal women combined. One study was from Europe (Harris, 2012b) and the other three were from the United States.

Figure 58 Highest versus lowest forest plot of dietary folate before diagnosis and total mortality

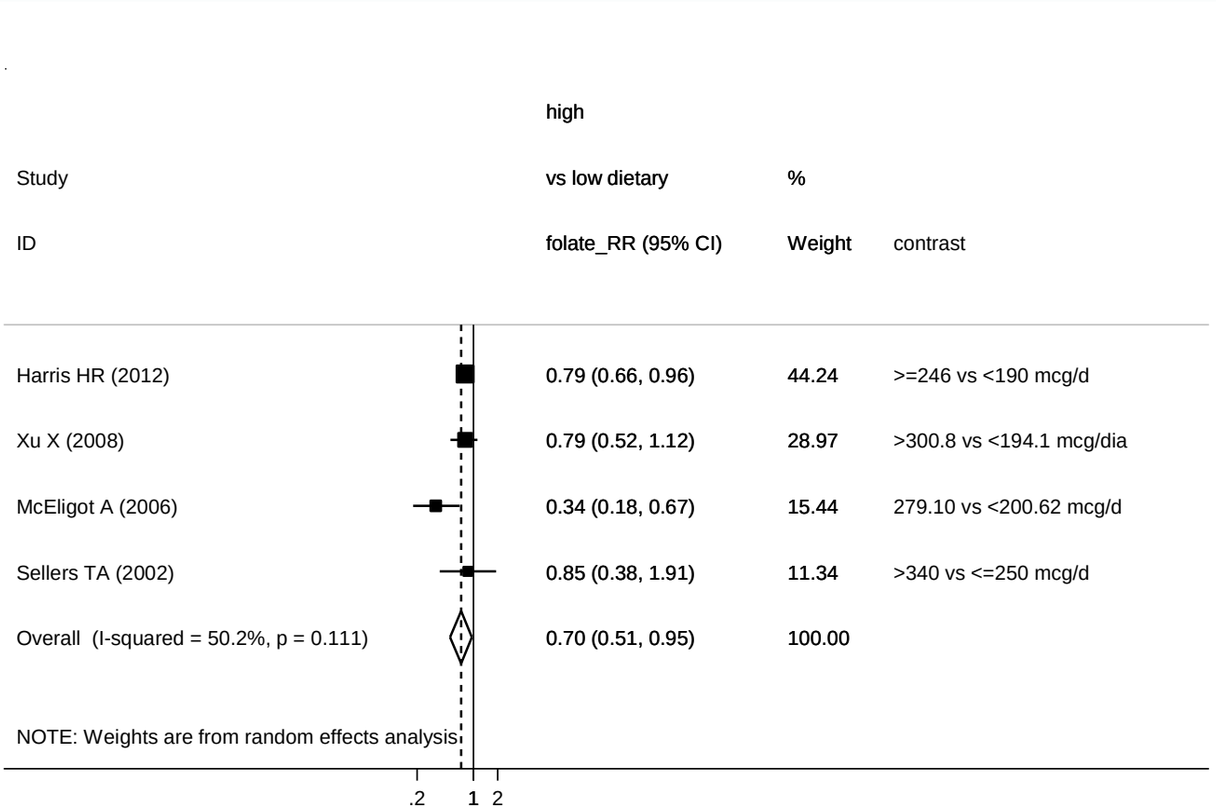


Figure 59 Linear dose-response meta-analysis of dietary folate before diagnosis and total mortality

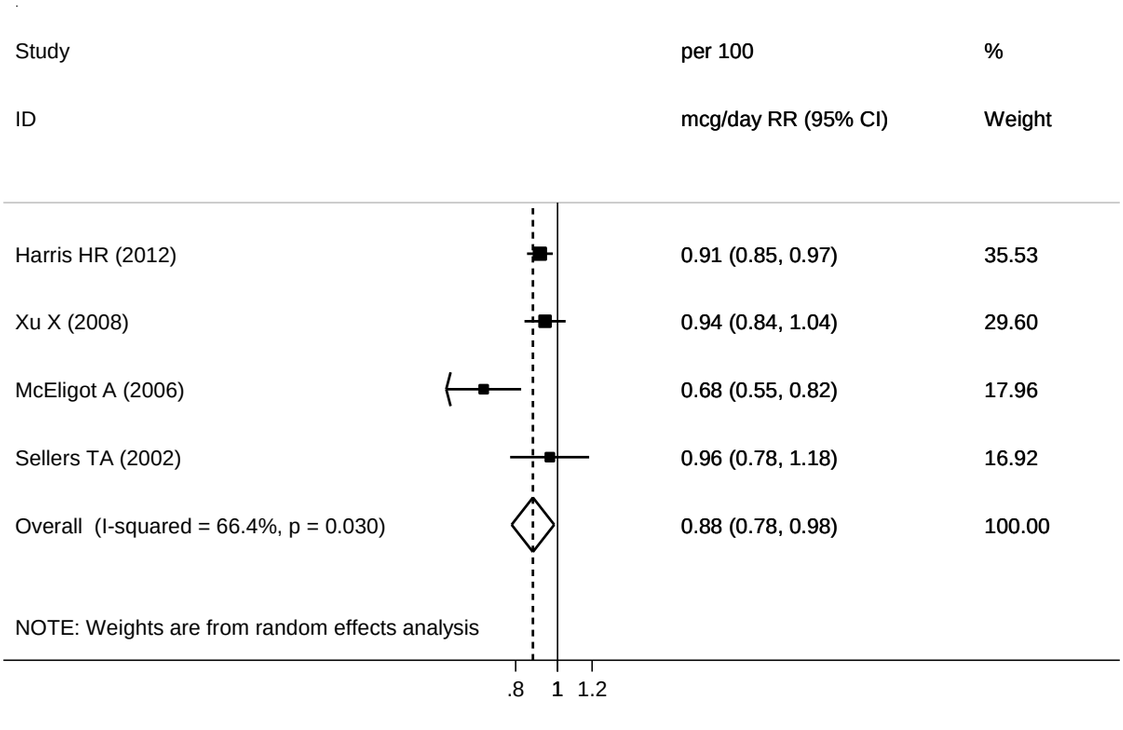


Figure 60 Individual dose-response graph of dietary folate before diagnosis and total mortality

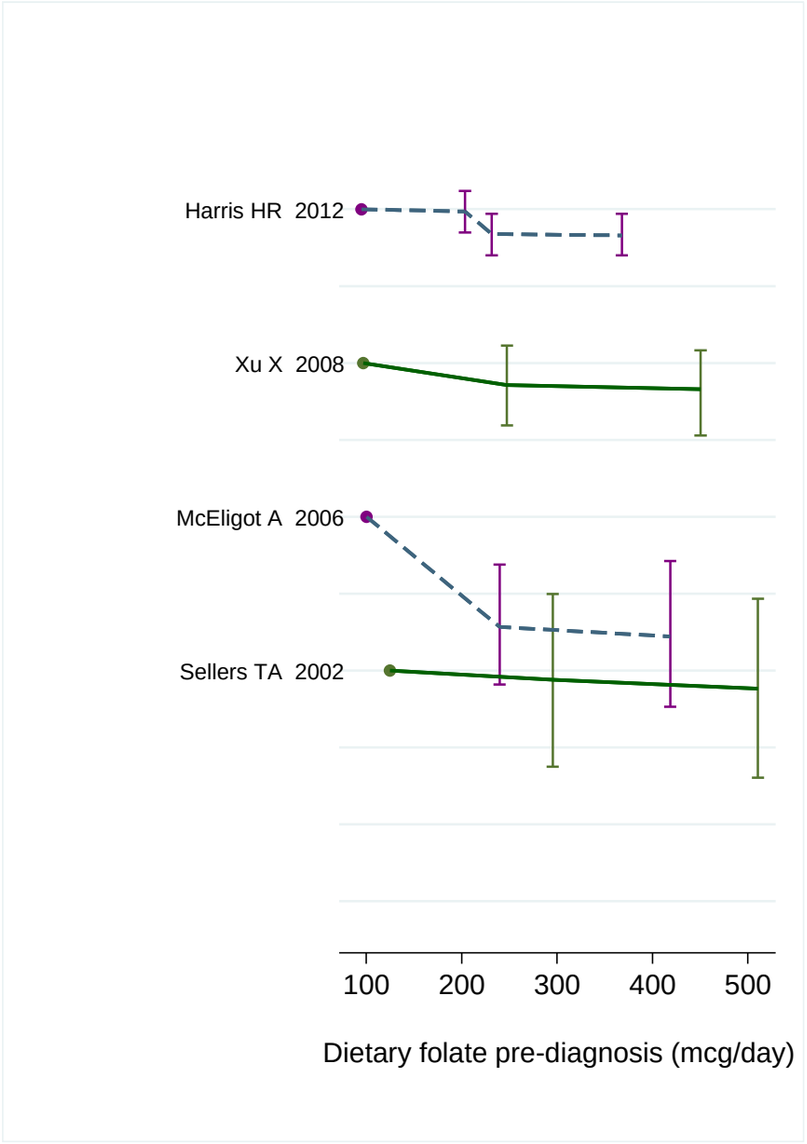


Table 47 Table of included studies on dietary folate before diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Harris H (2012)b	Swedish Mammography Cohort Sweden	Cancer diagnosis:1987-1990; Study follow up: until 2008	Cancer survivors of a population-based prospective cohort study	3116 participants 65 years (mean) Mostly white All detected by mammography	7.3 years	Incident invasive breast cancer; Any stages I-III			Nearly complete follow-up of all cases	At baseline; Consumption during the previous 6 months (1987) or year (1997), pre diagnosis and dietary change after diagnosis	3116 participants 852 deaths, 381 breast cancer mortality	Death certificate	>=246 vs. <190g/d	0.79 (0.66–0.96)	Age, energy intake, education, Marital status, menopausal status, BMI, alcohol intake, year of diagnosis, stage of disease, grade, radiotherapy, chemotherapy, hormonal therapy
Xu X (2008)	Long Island Breast Cancer Study United States	Cancer diagnosis: 1996-1997; Study follow up: 2002-2004 Newly diagnosed patients recruited	Follow up of cases of a population-based case-control study	1508 participants 31.3% premenopausal, 66.7% postmenopausal	5.6 years	Primary breast cancer including invasive and In situ; 15.6% carcinoma in situ and 84.4% invasive tumour	58.9% ER+ve/PR+ve, 14.4% ER+ve/PR-ve, 5.3%ER-ve/PR+ve, 21.4% ER-ve/PR-ve	41.4% chemotherapy		Self-reported at baseline (3 months after diagnosis); Dietary intake in the year before the diagnosis	1508 participants 198 deaths (by year 2002), 124 breast cancer mortality	National Death Index	>300.8 vs. <194.1	0.79 (0.52-1.12)	Age, energy intake
McEligot A (2006)	Orange County California Study United States	Cancer diagnosis: 1994-1995, Study follow-up: Until 2003 Recruited within 6 months of diagnosis	Prospective cohort of breast cancer survivors	516 participants 64.78 years (mean) Postmenopausal 92.3% non-Hispanic white HRT use: 36.2% estrogen only, 1.9% progesterone only, 35.1% estrogen and progesterone, 26.7% non-users	80 months	Stages: 14.9% in situ, 59.3% localized, 24.2% regional, 1.55% metastatic			98% / 2% lost	At diagnosis; dietary habits during the 1 year prior to diagnosis FFQ	516 participants 96 deaths, 41 breast cancer mortality, 13 deaths from cardiovascular disease, 31 other causes of deaths, 11 unknown causes of deaths	Cancer registry + National Death Index	279.10 vs. <200.62 mcg/d	0.34 (0.18–0.67)	Stage of disease, age at diagnosis, body mass index, parity, hormone replacement therapy use, alcohol use, multivitamin use, and energy intake
Sellers TA (2002)	Iowa Women's Health Study United States	Cancer diagnosis: 1986-1994; Study follow up: until 1999	Prospective cohort of breast cancer survivors	177 participants 55 - 69 years All postmenopausal	14 years	Primary breast cancer: 27.7% localized, 62.1% regional and 10.2% metastases		All had chemotherapy as part of their first course of treatment		Self-reported at baseline prior to diagnosis	177 participants 80 deaths, 72 death from cancer including 67 breast cancer mortality, 8 non cancer causes of deaths	Cancer registry + National Death Index	>340 vs. <=250 mcg/d	0.85 (0.38-1.91)	

Dietary folate less than 12 months after diagnosis and total mortality

No study was identified.

Dietary folate 12 months or more after diagnosis and total mortality

One study was identified. The relative risk for the highest vs. the lowest quintile of dietary folate was 0.82 (95% CI 0.59-1.14) in NHS participants with invasive breast carcinoma diagnosed between 1976-1990 (Holmes, 1999).

Dietary folate and breast cancer mortality

Two studies on dietary folate and breast cancer mortality were identified. Both were on before diagnosis dietary folate. In the Swedish Mammography Cohort there was a significant inverse trend between dietary folate intake and breast cancer mortality (HR > 246 vs. <190 µg/day = 0.78; 95% CI 0.58-1.03; p_{trend} = 0.03) (Harris, 2012b). The inverse association was strongest among women with ER-negative tumors (HR 0.42; 95% CI 0.22-0.79; p_{trend} = 0.01) comparing the highest to lowest quartile but no significant heterogeneity was observed. Dietary folate was not related to breast cancer mortality in the other study (RR 0.81; 95% CI 0.47-1.39; > 300.8 vs. <1 94.1 µg/day) (Xu, 2008)

Total folate and total mortality

Total folate was defined by the included studies as folate from food and supplements. Five studies on total folate and total mortality were identified. Three studies (Sellers, 2002; McEligot, 2006; Xu, 2008) were on total folate before diagnosis and total mortality, and two studies (Holmes, 1999; Saquib, 2011) were on total folate 12 months or more after diagnosis and total mortality.

Total folate before diagnosis and total mortality

Methods

The three studies identified were included in the dose-response meta-analysis. All studies reported dietary folate intake in mcg per day, which was the unit used in the analysis.

Main results and heterogeneity

The summary RR per 100 mcg/day was 1.00 (95% CI 0.97-1.03, 3 studies). No heterogeneity was observed (I^2 = 0%; p = 0.92). Two studies were on post-menopausal women, the other study was on pre and post-menopausal women. In the highest versus lowest forest plot the overall RR was 0.97 (95% CI 0.73-1.28; 3 studies). There was no evidence of a non-linear association between folate intake before diagnosis and total mortality, $p_{non\text{-}linearity}$ = 0.

The same studies also reported on dietary folate. The results were similar in two studies, but one study (McEligot, 2006) reported a significant inverse association for dietary folate and no association with total folate (diet and supplements). Overall in this study, nutrients from the diet only rather than from diet plus supplements were associated with survival.

Study quality

Two studies (Sellers, 2002; McEligot, 2006) reported less than 100 events and one study (Xu, 2008) reported 198 deaths. The follow-up time ranged from 5.6 years (Xu, 2008) to 14 years (Sellers, 2002). All studies ended after the year 2000. Two studies (Sellers, 2002; McEligot, 2006) included only postmenopausal women and the other study included pre and post-menopausal women combined. The three studies were from the United States.

Figure 61 Highest versus lowest forest plot of total folate before diagnosis and total mortality

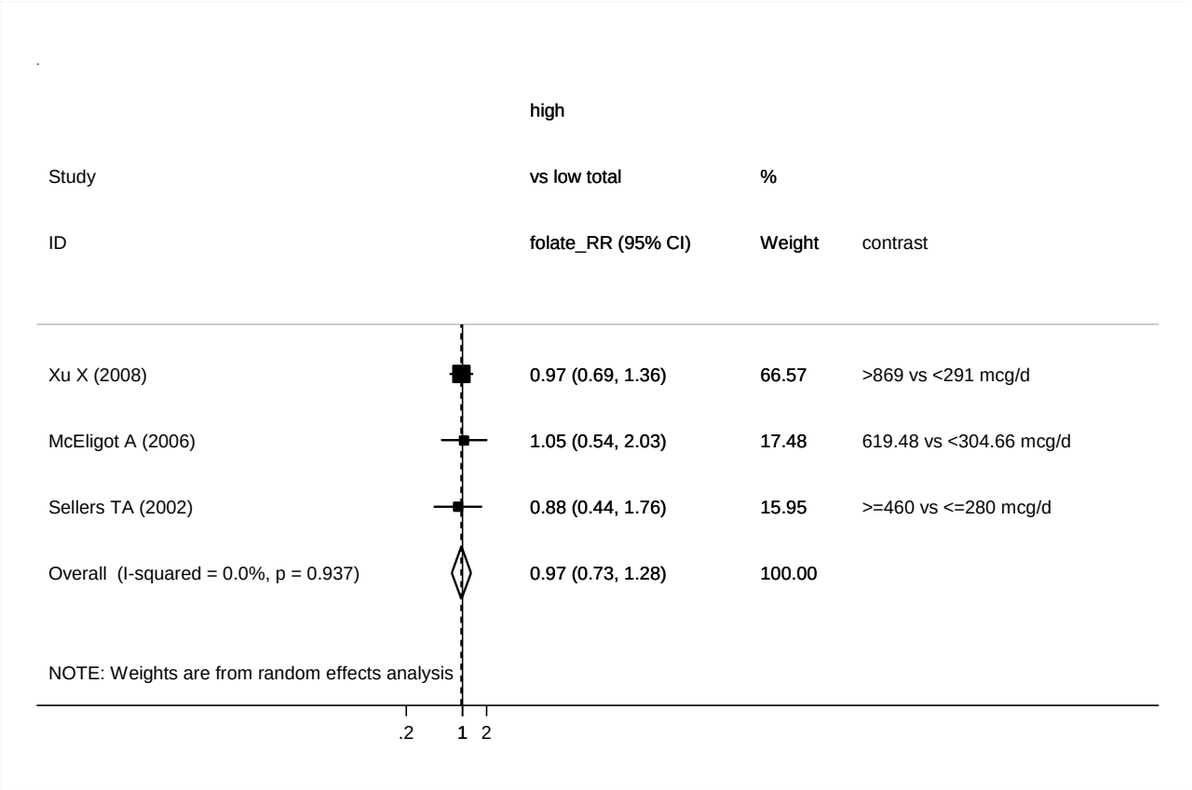


Figure 62 Linear dose-response meta-analysis of total folate before diagnosis and total mortality

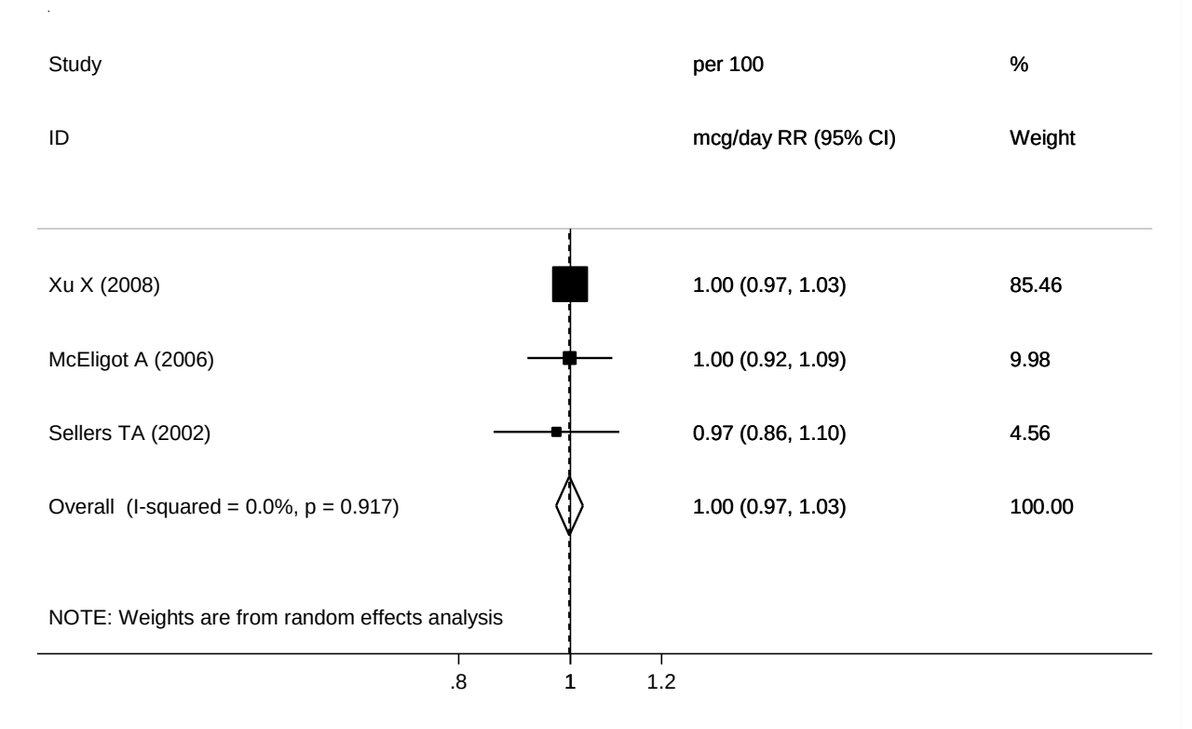


Figure 63 Individual dose-response graph of total folate before diagnosis and total mortality

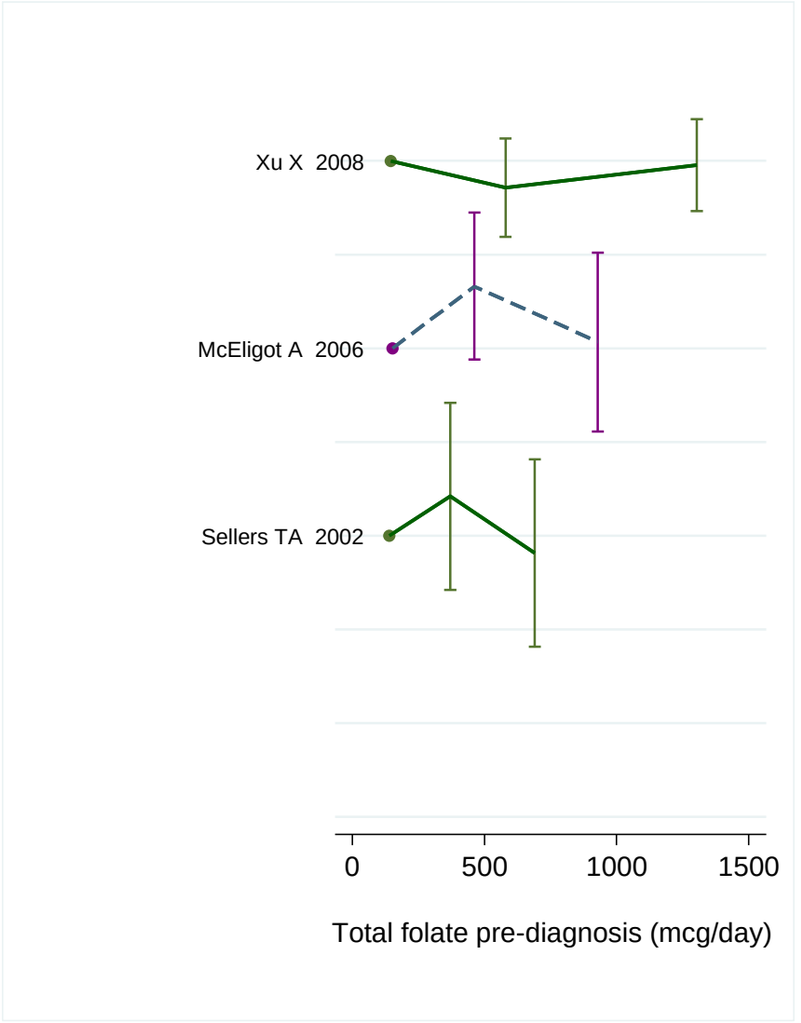


Table 48 Table of included studies on total folate before diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Xu X (2008)	Long Island Breast Cancer Study United States	Cancer diagnosis: 1996-1997; Study follow up: 2002-2004 Newly diagnosed patients recruited	Follow up of cases of a population-based case-control study	1508 participants 31.3% premenopausal, 66.7% postmenopausal	5.6 years	Primary breast cancer including invasive and In situ; 15.6% carcinoma in situ and 84.4% invasive tumour	58.9% ER+ve/PR+ve, 14.4% ER+ve/PR-ve, 5.3%ER-ve/PR+ve, 21.4% ER-ve/PR-ve	41.4% chemotherapy		Self-reported at baseline (3 months after diagnosis) for dietary intake 1y before diagnosis and for supplement/ multivitamin use 10-15y before interview	1508 participants 198 deaths (by year 2002), 124 breast cancer mortality	National Death Index	>869 vs. <291	0.97 (0.69-1.36)	Age, energy intake
McEligot A (2006)	Orange County California Study United States	Cancer diagnosis: 1994-1995, Study follow-up: Until 2003 Recruited within 6 months of diagnosis	Prospective cohort of breast cancer survivors	516 participants 64.78 years (mean) Postmenopausal 92.3% non-Hispanic white HRT use: 36.2% estrogen only, 1.9% progesterone only, 35.1% estrogen and progesterone, 26.7% non-users	80 months	Stages: 14.9% in situ, 59.3% localized, 24.2% regional, 1.55% metastatic			98% / 2% lost	At diagnosis; dietary habits during the 1 year prior to diagnosis FFQ	516 participants 96 deaths, 41 breast cancer mortality, 13 deaths from cardiovascular disease, 31 other causes of deaths, 11 unknown causes of deaths	Cancer registry + National Death Index	619.48 vs. <304.66 mcg/d	1.05 (0.54–2.03)	Stage of disease, age at diagnosis, body mass index, parity, hormone replacement therapy use, alcohol use, multivitamin use, and energy intake
Sellers TA (2002)	Iowa Women's Health Study United States	Cancer diagnosis: 1986-1994; Study follow up: until 1999	Prospective cohort of breast cancer survivors	177 participants 55 - 69 years All postmenopausal	14 years	Primary breast cancer: 27.7% localized, 62.1% regional and 10.2% metastases		All had chemotherapy as part of their first course of treatment		Self-reported at baseline prior to diagnosis	177 participants 80 deaths, 72 death from cancer including 67 breast cancer mortality, 8 non cancer causes of deaths	Cancer registry + National Death Index	>=460 vs. <=280 mcg/d	0.88 (0.44-1.76)	

Total folate less than 12 months after diagnosis and total mortality

No study was identified.

Total folate 12 months or more after diagnosis and total mortality

None of the two identified studies reported an association of all-cause mortality and total folate intake 12 months or more after diagnosis (Holmes, 1999; Saquib, 2011). The relative risk estimates were 0.88 (95% CI 0.64-1.23), for the highest versus lowest quartile in the Nurses' Health Study (Holmes, 1999). In a study based on the the Women's Healthy Eating and Living (WHEL) study the relative risk for the comparison of women with intake below recommended levels and those with adequate micronutrient intake was 1.10 (95% CI 0.88- 1.36) (Saquib, 2011).

Total folate and breast cancer mortality

One study (Xu, 2008) on total folate before diagnosis and breast cancer mortality was identified and no significant association was reported (HR High vs. Low 1.24; 95% CI 0.81-1.90).

4.8 Dietary supplement use

Dietary supplement use and total mortality

Five observational studies on dietary supplements and all-cause mortality or breast cancer related mortality were identified. Because of the differences in type of dietary supplement assessed, no summary estimates are presented in this review. The study results are described in text and shown in tables.

Dietary supplement use before diagnosis and total mortality

Two studies were identified. In the Nurses' Health Study, multivitamin use prior to breast cancer diagnosis was not associated with reduced mortality in 1982 women with breast cancer diagnosed in 1976–1990 (Holmes, 1999) (data not shown). The mean duration of follow-up was 157 months. Of the 378 patients who died, 326 (86%) died from breast carcinoma.

Combined pre- and post-diagnosis multivitamin use was investigated in the LACE cohort (Kwan, 2011). The results are included in the section on supplement use 12 months or more after diagnosis.

Detailed results are shown in the table of reviewed studies on before diagnosis dietary supplement use and total mortality.

Dietary supplement use less than 12 months after and cancer mortality

One study was identified. The association of vitamin supplement use with total mortality was investigated in the Shanghai Breast Cancer Survival Study (SBCSS), a population-based prospective cohort study of 4,877 women aged 20 to 75 years (Nechuta, 2010). The patients had been diagnosed with invasive breast cancer between March 2002 and April 2006.

Use of multivitamins and antioxidants was collected by interview for the time period from diagnosis to approximately 6 months after diagnosis; 36.4% of breast cancer survivors used any type of supplement after diagnosis. Women who reported supplement use tended to have higher education, income, exercise regularly and were more likely to have a lower BMI as well as to report not smoking. During a mean follow-up of 4.1 years, 444 deaths occurred (389 from breast cancer, 55 from other causes). Women who used antioxidants for three or more months had reduced mortality risk (HR 0.60 (95% CI 0.44–0.82) compared to nonusers. The inverse association was present only in women who did not receive radiotherapy (HR 0.65; 95% CI 0.47-0.92) and was not present in women who received radiotherapy (HR 1.00; 95% CI 0.73-1.37).

No other significant associations were observed. Detailed results are shown in the table of reviewed studies on dietary supplement use during treatment and total mortality.

Table 49 Table of reviewed studies on dietary supplement use before diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Holmes, 1999	Nurses' Health Study United States	Cancer diagnosis: 1976–1990, Study follow-up: Until 1994	Follow-up of breast cancer incident cases in population-based prospective cohort study	1982 breast cancer cases 54 years (mean) 35.1% premenopausal, 64.9% postmenopausal	157 months	Invasive breast carcinoma; Grade 1-3	Not available	**Not available**	95%	Prior to diagnosis	1978 participants 378 deaths, 326 breast cancer mortality	Death certificate	Multivitamin use prior to diagnosis was not associated with reduced mortality		Age, diet interval, calendar year of diagnosis, body mass index, oral contraceptive use, menopausal status, postmenopausal hormone use, smoking, age at first birth and parity, number of metastatic lymph nodes, tumour size, energy intake

Table 50 Table of reviewed studies on dietary supplement use less than 12 months after and total mortality

a. Study characteristics

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events	Outcome confirmation
Nechuta, 2010	Shanghai Breast Cancer Survival Study (SBCSS)	Enrolled between 2002 and 2006 within approximately 6 months of diagnosis	Prospective cohort of breast cancer survivors	4,877 **women aged** 20 to 75 years 48.9% premenopausal, 51.1% postmenopausal HRT use: 6.8% yes, 93.2% among those with data	4.1 years of follow-up (range: 0.5–6.2 years)	TNM: I : 34.5% II:59.9% III-IV: 10%	ER^+PR^+ 50% ER^-PR^- 27.7%	Chemotherapy: 92.2% Radiotherapy: 32.8% Tamoxifen:51.7%	80%	Data from the time period when most women received their cancer treatments (6 months interview) Approximately 36.4% of breast cancer survivors ever used any type of vitamin supplement after diagnosis	444 deaths (389 from breast cancer, 55 from other causes)	Shanghai Vital Statistics Registry database

Table 51 Table of reviewed studies on dietary supplement use less than 12 months after diagnosis and total mortality

b. Study results

Author, Year, Study	RR (95% CI)					
Nechuta, 2010, SBCSS	Type of supplement					
Group	Contrast	Any vitamin	Any antioxidant	Multivitamins	Vitamin E (excluding multivitamin users)	Vitamin C (excludes multivitamin users)
All (n=4877)	Post-diagnosis use vs never post-diagnosis	0.88 (0.72–1.08)	0.82 (0.65–1.02)	0.82 (0.57–1.17)	0.71 (0.46–1.11)	0.81 (0.61–1.07)
All (n=4877)	Never post-diagnosis ≤3 months >3 months	1 1.09 (0.81–1.45) 0.79 (0.62–1.00)	1 1.13 (0.85–1.50) 0.60 (0.44–0.82)	1 1.01(0.63–1.64) 0.69 (0.42–1.11)	1 0.97 (0.55–1.70) 0.52 (0.27–1.01)	1 1.08 (0.77–1.52) 0.56 (0.37–0.87)
Women who received chemotherapy (n=4497)	Post-diagnosis use vs never post-diagnosis	0.89 (0.72–1.09)	0.82 (0.64–1.04)			
	Used during chemotherapy vs never post-diagnosis	0.91 (0.72–1.14)	0.81 (0.62–1.05)			
	Did not use during chemotherapy vs never post-diagnosis	0.79 (0.52–1.22)	0.85 (0.55–1.31)			

Women who received radiotherapy (n=1597)	Post-diagnosis use vs never post-diagnosis	1.03 (0.77–1.38)	1.00 (0.73–1.37)			
	Used during radiotherapy vs never post-diagnosis	0.94 (0.67–1.32)	0.92 (0.63–1.33)			
	Did not use during radiotherapy vs never post-diagnosis	1.21 (0.80–1.84)	1.14 (0.72–1.80)			
Women who did not receive radiotherapy (n=3280)	Post-diagnosis use vs never post-diagnosis	0.75 (0.56–1.00)	0.65 (0.47–0.92)			

c. Study results of reviewed studies on dietary supplement use less than 12 months after diagnosis and total mortality (cont.)

Author, Year, Study	RR (95% CI)					
Nechuta, 2010, SBCSS	Type of supplement					
Group	Contrast	Any vitamin	Any antioxidant	Multivitamins	Vitamin E (excluding multivitamin users)	Vitamin C (excludes multivitamin users)
By tumour characteristics						
ER^+PR^+ (n = 2439)	Post-diagnosis use vs never post-diagnosis	0.98 (0.69–1.38)	0.91 (0.61–1.34)			
ER^-/PR^- (n= 1350)	Post-diagnosis use vs never post-diagnosis	0.84 (0.61–1.16)	0.77 (0.54–1.11)			
Stage I or II (n= 4162)	Post-diagnosis use vs never post-diagnosis	0.86 (0.67–1.10)	0.79 (0.59–1.05)			
Stage III or IV (n= 492)	Post-diagnosis use vs never post-diagnosis	0.87 (0.60–1.27)	0.84 (0.56–1.25)			
Used tamoxifen (n= 2523)	Post-diagnosis use vs never post-diagnosis	0.90 (0.66–1.22)	0.89 (0.64–1.25)			
Did not use tamoxifen (n=2354)	Post-diagnosis use vs never post-diagnosis	0.89 (0.68–1.18)	0.78 (0.57–1.06)			

Dietary supplement use 12 months or more after diagnosis and total mortality

Two studies (three publications) investigated dietary supplement use 12 months or more after breast cancer diagnosis and all-cause mortality. No association with multivitamin use was observed in the Nurses' Health Study (Holmes, 1999). The LACE study provided evidence of an increased risk of death in women using carotenoids and a decreased risk in relation to Vitamin E use (Greenlee, 2011).

In the Nurses' Health Study (Holmes, 1999), multivitamin use 12 months or more after breast cancer diagnosis was not associated with reduced mortality. The multivariate relative risk was 1.07 (95% CI 0.80-1.43). The study included 1982 women with breast cancer diagnosed in 1976–1990. The mean duration of follow-up was 157 months; 378 patients died from which 326 (86%) died from breast carcinoma. Multivitamin use was assessed 24 months after diagnosis on average.

In the LACE study (Greenlee, 2011), use of multivitamins, vitamin C alone, vitamin E alone, carotenoids combination, beta-carotene, lycopene, selenium and zinc was explored in relation to mortality. Vitamin E use was inversely related to risk of death (HR for frequent use compared to never use: 0.75; 95% CI 0.59-0.96; $p_{trend} = 0.02$). Use of carotenoids combination was positively associated to risk of death (HR 1.63; 95% CI 1.05-2.50; $p_{trend} = 0.04$). Multivitamins and other supplements analysed were not related to mortality. When the analyses were restricted to antioxidant users (81% of women), the association with vitamin E use was of borderline statistical significance (HR 0.76; 95% CI 0.58-1.00; $p_{trend} = 0.05$) and the association with frequent use of combination carotenoids was strengthened (HR 1.75; 95% CI 1.13-2.71; $p_{trend} = 0.01$). The positive association with carotenoids was strengthened in analyses restricted to women who received chemotherapy and radiation therapy. Conversely, the inverse association with vitamin E was stronger among women who received radiation therapy and hormone therapy.

Another publication of the LACE cohort (Kwan, 2011) showed that multivitamin use after diagnosis was not associated with mortality. However, in stratified analyses, women who consistently used multivitamins, ate more fruits/vegetables ($p_{trend} = 0.008$) and were more physically active ($p_{trend} = 0.034$) had better overall survival than women with "less healthy" lifestyle. The hazard ratios for persistent multivitamin use compared to no use were 0.28 (95% CI 0.11-0.72; $p_{trend}= 0.0078$) in women consuming more than 5.5 servings/day of fruits and vegetables and 0.39 (95% CI 0.16-0.95; $p_{trend} = 0.030$) in women with more than 67 METs-hour of physical activity. Detailed results of stratified analyses are showed in the tables.

Table 52 Table of reviewed studies on dietary supplement use 12 months or more after diagnosis and total mortality

a. Main characteristics and study results

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Holmes, 1999	Nurses' Health Study United States	Cancer diagnosis: 1976–1990, Study follow-up: Until 1994	Follow-up of breast cancer incident cases in population-based prospective cohort study	1982 breast cancer cases 54 years (mean) 35.1% premenopausal, 64.9% postmenopausal	157 months	Invasive breast carcinoma; Grade 1-3	Not available	**Not available**	95%	On average 24 months (SD 18m) after diagnosis	1978 participants 378 deaths, 326 breast cancer mortality	Death certificate	Multivitamin use vs no use	1.07 (0.80 –1.43)	Age, diet interval, calendar year of diagnosis, body mass index, oral contraceptive use, menopausal status, postmenopausal hormone use, smoking, age at first birth and parity, number of metastatic lymph nodes, tumour size, energy intake
Greenlee, 2011	LACE	Early stage, primary breast cancer diagnosed from 1997 to 2000	Cohort of breast cancer patients	2264 women who enrolled, on average, 2 years post-diagnosis	10 years	80.3% stage I or IIA	Not available	57.2% had chemotherapy, 63% radiation therapy, and 80.4% hormone therapy		Antioxidant use in the 2-year period after diagnosis. Mailed questionnaire	393 deaths, including 214 breast cancer deaths	Active follow-up Confirmation through death certificate	Multivitamins No use Occasional Frequent	1 0.83 (0.56-1.22) 0.84 (0.65-1.08)	Age at diagnosis, race/ethnicity, education, stage positive lymph nodes, hormone receptor status, treatment BMI, 1 year before diagnosis, smoking, alcohol, physical activity, fruits and vegetables, comorbidity score at enrolment. Mutual adjustment for the other antioxidants
													Vitamin C alone No use Occasional Frequent	1 0.78 (0.51-1.18) 0.78 (0.61-1.01) Ptrend 0.05	
													Vitamin E alone No use Occasional Frequent	1 0.88 (0.58-1.32) 0.75 (0.59-0.96) Ptrend 0.02	
													Carotenoids No use Occasional Frequent	1 0.95 (0.41-2.19) 1.63 (1.06-2.50) Ptrend 0.04	
													Beta-carotene No use Occasional Frequent	1 1.65 (0.61-4.46) 1.18 (0.71-1.97)	
													Lycopene No use Occasional Frequent	1 2.82 (0.39-20.67) 1.38 (0.41-4.61)	
													Selenium No use Occasional Frequent	1 1.72 (0.80-3.70) 0.80 (0.45-1.41)	
													Zinc No use Occasional Frequent	1 1.11 (0.58-2.12) 0.75 (0.46-1.21)	

a. Reviewed studies on dietary supplement use 12 months or more after diagnosis and total mortality (cont.)

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Kwan, 2011	LACE	Early stage, primary breast cancer diagnosed from 1997 to 2000 .	Cohort of breast cancer patients	2236 women who enrolled, on average, 2 years post-diagnosis	10 years	80.3% stage I or IIA	Not available	57.2% had chemotherapy, 63% radiation therapy, and 80.4% hormone therapy		Antioxidant use in the 2-year period after diagnosis. Mailed questionnaire	396 deaths, including 212 breast cancer deaths	Active follow-up Confirmation through death certificate	Type of multivitamin None Without minerals With minerals	 1 0.87 (0.50- 1.51) 0.93(0.71- 1.22)	Age at diagnosis, race/ethnicity, education, stage positive lymph nodes, hormone receptor status, treatment BMI, 1 year before diagnosis, smoking, alcohol, physical activity, fruits and vegetables, comorbidity score at enrolment. Mutual adjustment for the other antioxidants
													Frequency of use Never Occasional Frequently	 1 0.89 (0.59- 1.33) 0.92 (0.70- 1.20)	
													Combined pre and post diagnosis use Never New use Persistent use	 1 0.96 (0.66-1.39) 0.79 (0.56-1.12)	

b. Table with results of stratified and subgroup analyses in the LACE study

Author, Year, Study		GROUP				
Greenlee, 2011, LACE						
		Analyses restricted to 1829 antioxidant users (245 deaths)		Analyses restricted to 1051 antioxidant users who received chemotherapy	Analyses restricted to 1158 antioxidant users who received radiation therapy	Analyses restricted to 1476 antioxidant users who received hormonal therapy
Supplement	Contrast	RR (95% CI)	Contrast	RR (95% CI) No. of events	RR (95% CI) No. of events	RR (95% CI) No. of events
Multivitamins	No use Occasional Frequent	1 0.95 (059-1.55) 0.98 (0.67-1.42)				
Vitamin C alone	No use Occasional Frequent	1 0.80 (0.52-1.23) 0.82 (0.62-1.08)	Use vs. non use	0.73 (0.49-1.08) 289 deaths	0.69 (0.48-0.99) 45 deaths	0.83 (0.61-1.13) 71 deaths

Table with results of stratified and subgroup analyses in the LACE study (cont.).

Author, Year, Study		GROUP				
Greenlee, 2011, LACE						
		Analyses restricted to 1829 antioxidant users (245 deaths)		Analyses restricted to 1051 antioxidant users who received chemotherapy	Analyses restricted to 1158 antioxidant users who received radiation therapy	Analyses restricted to 1476 antioxidant users who received hormonal therapy
Vitamin E alone	No use Occasional Frequent	1 0.86 (0.56-1.33) 0.76 (0.58-1.00) Ptrend=0.01	Use vs. non use	0.85 (0.58-1.25) 378 deaths	0.69 (0.47-1.00) 69 deaths	0.68 (0.50-0.92) Ptrend=0.01 88 deaths
Combination carotenoids	No use Occasional Frequent	1 1.04 (0.45-2.42) 1.75 (1.13-2.71) Ptrend=0.01	Use vs. non use	2.09 (1.21-3.61) Ptrend=0.01 51 deaths	2.14 (1.20-3.82) Ptrend=0.01 14 deaths	1.66 (1.00-2.73) Ptrend=0.05 18 deaths
Beta-carotene alone	No use Occasional Frequent	1 1.80 (0.66-4.91) 1.18 (0.69-2.00)				
Lycopene alone	No use Occasional Frequent	1 3.24 (0.44-24.02) 1.44 (0.43-4.87)				
Selenium alone	No use Occasional Frequent	1 1.78 (0.82-3.85) 0.82 (0.46-1.45)				
Zinc alone	No use Occasional Frequent	1 1.25 (0.65-2.41) 0.80 (0.50-1.31)				

Table with results of stratified and subgroup analyses in the LACE study (cont.).

Author, Year, Study		GROUP				
Kwan, 2011, LACE						
Supplement	Contrast	Restricted to women without chemotherapy and radiation therapy	Restricted to women only with chemotherapy only	Restricted to women only with radiation therapy only	Restricted to women with radiation therapy and chemotherapy	
Combined pre and post diagnosis use of antioxidants	Never New use Persistent use	1 0.89 (0.37-2.15) 1.69 (0.77-3.68)	1 1.71 (0.62-4.76) 0.86 (0.34-2.21)	1 0.86 (0.41-1.79) 0.54 (0.26-1.10) p_{trend} = 0.083	1 0.66 (0.35-1.25) 0.59 (0.32-1.07) p_{trend} = 0.095	P interaction with chemotherapy and radiation therapy=0.030. No interaction with hormone therapy
		Restricted to women in the bottom quartile of fruit and vegetable consumption (< 2.4 serving/d)	Restricted to women in the top quartile of fruit and vegetable consumption (> 5.5 serving/d)	Restricted to women with METs-h < 30 (physical activity)	Restricted to women with METs-h > 67 (physical activity)	
	Never New use Persistent use	1 1.10 (0.55- 2.20) 0.82 (0.43- 1.58)	1 0.48 (0.21- 1.07) 0.28 (0.11- 0.72) p_{trend} = 0.0078	1 1.11 (0.60- 2.06) 0.73 (0.40- 1.32)	1 0.93 (0.42-2.09) 0.39 (0.16- 0.95) p_{trend} = 0.030	

Dietary supplement use and breast cancer mortality

Three observational studies (four publications) on dietary supplements and mortality or breast cancer mortality were identified. Because of the differences in type of dietary supplement assessed, no summary estimates are presented in this review. The main results are described in the text and shown in tables.

Dietary supplement use before diagnosis and breast cancer mortality

Two studies were identified. In the Nurses' Health Study, multivitamin use prior to breast cancer diagnosis was not associated with reduced mortality in 1982 women with breast cancer diagnosis in 1976–1990 (Holmes, 1999). The mean duration of follow-up was 157 months. Of the 378 patients who died, 326 (86%) died from breast carcinoma.

Combined pre- and post-diagnosis multivitamin use was investigated in the LACE cohort (Kwan, 2011). The results are included in the section on 12 months or more after diagnosis supplement use.

Dietary supplement use 12 months or more after diagnosis and breast cancer mortality

One study (LACE) reported the relationship of dietary supplements and breast cancer related mortality (Greenlee, 2011; Kwan, 2011). Use of multivitamins, vitamin C alone, vitamin E alone, beta-carotene, lycopene, selenium and zinc were not associated with breast cancer related mortality. Use of carotenoids combination was positively associated to risk of breast cancer related death in frequent users compared to non-users (HR 1.93; 95% CI 1.14-3.28; $p_{trend} = 0.03$) (Greenlee, 2011). When the analyses were restricted to antioxidant users (81% of women), the association with frequent use of combination carotenoids was strengthened (HR 2.07; 95% CI 1.21-3.56; $p_{trend} = 0.02$) and it was stronger in analyses restricted to women who received radiation therapy, chemotherapy or hormone therapy. Another publication of the LACE cohort (Kwan, 2011) showed that multivitamin use after diagnosis was not associated with breast cancer related mortality. Although in stratified analyses this study showed better survival in patients who consistently used multivitamins before and 12 months or more after diagnosis, and ate more

fruits/vegetables and were more physically active, the same analyses did not show any significant association with breast related cancer mortality.

Table 53 Table of reviewed studies on dietary supplement use before diagnosis and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome Confirmation	Contrast	RR (95% CI)	Adjustments
Holmes, 1999	Nurses' Health Study United States	Cancer diagnosis: 1976–1990, Study follow-up: Until 1994	Follow-up of breast cancer incident cases in population-based prospective cohort study	1982 breast cancer cases 54 years (mean) 35.1% premenopausal, 64.9% postmenopausal	157 months	Invasive breast carcinoma; Grade 1-3	Not available	**Not available**	95%	On average 24 months (SD 18m) after diagnosis	1978 participants 378 deaths, 326 breast cancer mortality	Death certificate	Multivitamin use vs. no use	1.07 (0.80–1.43)	Age, diet interval, calendar year of diagnosis, body mass index, oral contraceptive use, menopausal status, postmenopausal hormone use, smoking, age at first birth and parity, number of metastatic lymph nodes, tumour size, energy intake

Table 54 Table of reviewed studies on dietary supplement use 12 months or more after diagnosis and breast cancer mortality

a. Main characteristics and study results

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status	Treatment info	Response rate	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome Confirmation	Contrast	RR (95% CI)	Adjustments
Greenlee, 2011	LACE	Early stage, primary breast cancer diagnosed from 1997 to 2000	Cohort of breast cancer patients	2264 women who enrolled, on average, 2 years post-diagnosis	10 years	80.3% stage I or IIA	Not available	57.2% had chemotherapy, 63% radiation therapy, and 80.4% hormone therapy		Antioxidant use in the 2-year period after diagnosis. Mailed questionnaire	393 deaths, including 214 breast cancer deaths	Active follow-up Confirmation through death certificate	Multivitamins No use Occasional Frequent	 1 0.75 (0.45-1.25) 0.79 (0.56-1.12)	Age at diagnosis, race/ethnicity, education, stage positive lymph nodes, hormone receptor status, treatment BMI, 1 year before diagnosis, smoking, alcohol, physical activity, fruits and vegetables, comorbidity score at enrolment. Mutual adjustment for the other antioxidants
													Vitamin C alone No use Occasional Frequent	 1 0.84 (0.49-1.43) 0.82 (0.58-1.16)	
													Vitamin E alone No use Occasional Frequent	 1 1.08 (0.64-1.81) 0.85(0.61-1.18)	
													Carotenoids No use Occasional Frequent	 1 0.77 (0.24-2.48) 1.93 (1.14-3.28) Ptrend: 0.03	
													Beta-carotene No use Occasional Frequent	 1 1.56 (0.38-6.4) 1.33 (0.69-2.55)	
													Lycopene No use Occasional Frequent	 1 4.84 (0.64-36.4) 2.09 (0.59-7.43)	
													Selenium No use Occasional Frequent	 1 1.33 (0.48-3.67) 0.9 (0.45-1.79)	
													Zinc No use Occasional Frequent	 1 0.83 (0.31-2.27) 0.82 (0.44-1.53)	
Kwan, 2011	LACE	Early stage, primary breast cancer diagnosed from 1997 to 2000 .	Cohort of breast cancer patients	2236 women who enrolled, on average, 2 years post-diagnosis	10 years	80.3% stage I or IIA	Not available	57.2% had chemotherapy, 63% radiation therapy, and 80.4% hormone therapy		Antioxidant use in the 2-year period after diagnosis. Mailed questionnaire	396 deaths, including 212 breast cancer deaths	Active follow-up Confirmation through death certificate	Type of multivitamin None Without minerals With minerals	 1 0.82 (0.39- 1.73) 0.87 (0.60- 1.27)	Age at diagnosis, race/ethnicity, education, stage positive lymph nodes, hormone receptor status, treatment BMI, 1 year before diagnosis, smoking, alcohol, physical activity, fruits and vegetables, comorbidity score at
													Frequency of use Never Occasional Frequently	 1 0.82 (0.47- 1.40) 0.88 (0.61- 1.28)	

													Combined pre and post diagnosis use Never New use Persistent use	 1 0.99 (0.62- 1.58) 0.70 (0.44- 1.11)	enrolment. Mutual adjustment for the other antioxidants

b. Table with results of stratified and subgroup analyses in the LACE study

Author, Year, Study		GROUP				
Greenlee, 2011, LACE						
		Analyses restricted to 1829 antioxidant users (245 deaths)		Analyses restricted to 1051 antioxidant users who received chemotherapy	Analyses restricted to 1158 antioxidant users who received radiation therapy	Analyses restricted to 1476 antioxidant users who received hormonal therapy
Supplement	Contrast	RR (95% CI)	Contrast	RR (95% CI) No. of events	RR (95% CI) No. of events	RR (95% CI) No. of events
Multivitamins	No use Occasional Frequent	1 0.78 (0.41-1.47) 0.81 (0.49-1.33)				
Vitamin C alone	No use Occasional Frequent	1 0.88 (0.51-1.52 0.87 (0.60-1.26)	Use vs. non use	0.74 (0.47-1.18) 30 breast cancer deaths	0.68 (0.42-1.09) 28 breast cancer deaths	0.94 (0.61-1.43) 38 breast cancer deaths
Vitamin E alone	No use Occasional Frequent	1 1.13 (0.65-1.95) 0.91 (0.63-1.32)	Use vs. non use	0.86 (0.55-1.34) 40 breast cancer deaths	0.86 (0.55-1.36) 40 breast cancer deaths	0.84 (0.55-1.29) 48 breast cancer deaths
Combination carotenoids	No use Occasional Frequent	1 0.77 (0.24-2.52) 2.07 (1.21-3.56) $p_{trend} = 0.02$	Use vs. non use	2.54 (1.37-4.70) 13 breast cancer deaths	2.54 (1.28-5.05) 10 breast cancer deaths	2.14 (1.16-3.97) 12 breast cancer deaths

Beta-carotene alone	No use Occasional Frequent	1 1.70 (0.42-6.98) 1.44 (0.74-2.78)				
Lycopene alone	No use Occasional Frequent	1 5.03 (0.66-38.31) 2.16 (0.60-7.77)				
Selenium alone	No use Occasional Frequent	1 1.43 (0.52-3.97) 0.87 (0.43-1.74)				
Zinc alone	No use Occasional Frequent	1 0.83 (0.30-2.29) 0.86 (0.46-1.61)				

b. Table with results of stratified and subgroup analyses in the LACE study (cont.)

Author, Year, Study		GROUP				
Kwan, 2011, LACE						
Supplement	Contrast	Restricted to women without chemotherapy and radiation therapy	Restricted to women only with chemotherapy only	Restricted to women only with radiation therapy only	Restricted to women with radiation therapy and chemotherapy	
Combined pre and post diagnosis use of antioxidants	Never New use Persistent use	1 0.54 (0.08-3.54) 3.13 (0.77-12.74)	1 3.17 (0.85-11.85) 1.10 (0.30-4.00)	1 0.56 (0.19-1.66) 0.25 (0.09-0.68)	1 0.69 (0.33-1.45) 0.56 (0.28-1.15)	
		Restricted to women in the bottom quartile of fruit and vegetable consumption (< 2.4 serving/d)	Restricted to women in the top quartile of fruit and vegetable consumption (>5.5 serving/d)	Restricted to women with METs-h < 30 (physical activity)	Restricted to women with METs-h > 67 (physical activity)	
	Never New use Persistent use	1 1.34 (0.59-3.06) 0.76 (0.34-1.70)	1 1.04 (0.28-3.81) 0.48 (0.11-2.03)	1 0.98 (0.42-2.31) 0.57 (0.24-1.39)	1 1.03 (0.36-2.89) 0.45 (0.15-1.40)	

4.9 Complementary and alternative medicine (CAM)

Three studies had been identified.

The study by Cui et al, 2006, investigated the associations of ginseng use before cancer diagnosis with survival in a cohort of breast cancer patients recruited to the Shanghai Breast Cancer Study between August 1996 and March 1998, and followed through December 2002. In-person interviews were completed for 1,459 women (91.1%) at 66 days post-diagnosis (on average). Approximately 27% of these women were regular ginseng users before cancer diagnosis. The proportion of tamoxifen users was higher ($p = 0.02$) in the group using ginseng (69.1%) than in non-ginseng users (61.1%). Ginseng users were older than non-ginseng users ($p < 0.01$).
Compared with patients who never used ginseng, regular users had a significantly reduced risk of death; adjusted hazard ratios associated with ginseng use were 0.71 (95% confidence interval: 0.52, 0.98) for total mortality. The analyses were adjusted for age at diagnosis, marital status, education, income, tumour-node metastasis, estrogen and progesterone receptor status, surgery, chemotherapy, radiotherapy, and tamoxifen use. Body adiposity and lifestyle factors were not included in the models.

Herbal remedy use and mortality was investigated in 371 non-Hispanic/Hispanic white women who had survived more than 10 years after breast cancer diagnosis (Ma, 2011). The follow-up started in 1999-2000. Fifty-nine percent of the surviving patients were herbal remedy users. The patients were followed for mortality from the interview through 2007. Herbal remedy use was not significantly related to all-cause mortality or breast cancer mortality.

In a Swedish prospective cohort of 855 primary breast cancer patients, complementary alternative therapies (any kind) or multivitamins/minerals supplements were not related to breast cancer free survival (Hietala, 2011).

4.10 Isoflavone intake

Table 55 Summary results of meta-analysis on before and and 12 months or more after diagnosis isoflavone intake and total mortality*

Comparison	No. of studies	No. of events in studies	RR (95% CI)	I^2, $P_{heterogeneity}$
Isoflavone intake before breast cancer diagnosis				
Highest vs. lowest	3	624	0.87 (0.65-1.17)	59.4%, p = 0.06
Isoflavone intake 12 months or more after breast cancer diagnosis				
Highest vs. lowest	3	794	0.70 (0.56-0.88)	8.1%, p = 0.34
Per 10 mg/day	3	794	0.91(0.83-1.00)	67.7%, p = 0.05

*No studies on breast cancer mortality or second cancers were included in the meta-analyses.

Isoflavones intake and total mortality

Six studies on isoflavones intake and total mortality were identified. Three studies were on isoflavones intake before diagnosis (Fink, 2007; Boyapati, 2005; Kang, 2010) and total mortality and 3 studies were on isoflavones intake 12 months or more after diagnosis and total mortality (Shu, 2009; Caan, 2011; Zhang, 2012).

Isoflavones intake before diagnosis and total mortality

Methods

It was not possible to conduct a dose-response meta-analysis because one study (Boyapati, 2005) out of three did not provide the intake range for each quintile. The results were instead summarised in the highest versus lowest forest plot below.

Main results and heterogeneity

No association was observed in the highest versus lowest forest plot; the overall RR was 0.87 (95% CI 0.65-1.17; 3 studies). Moderate to high heterogeneity was observed (I^2 = 59.4%; p = 0.06).

Figure 64 Highest versus lowest forest plot of isoflavones intake before diagnosis and total mortality

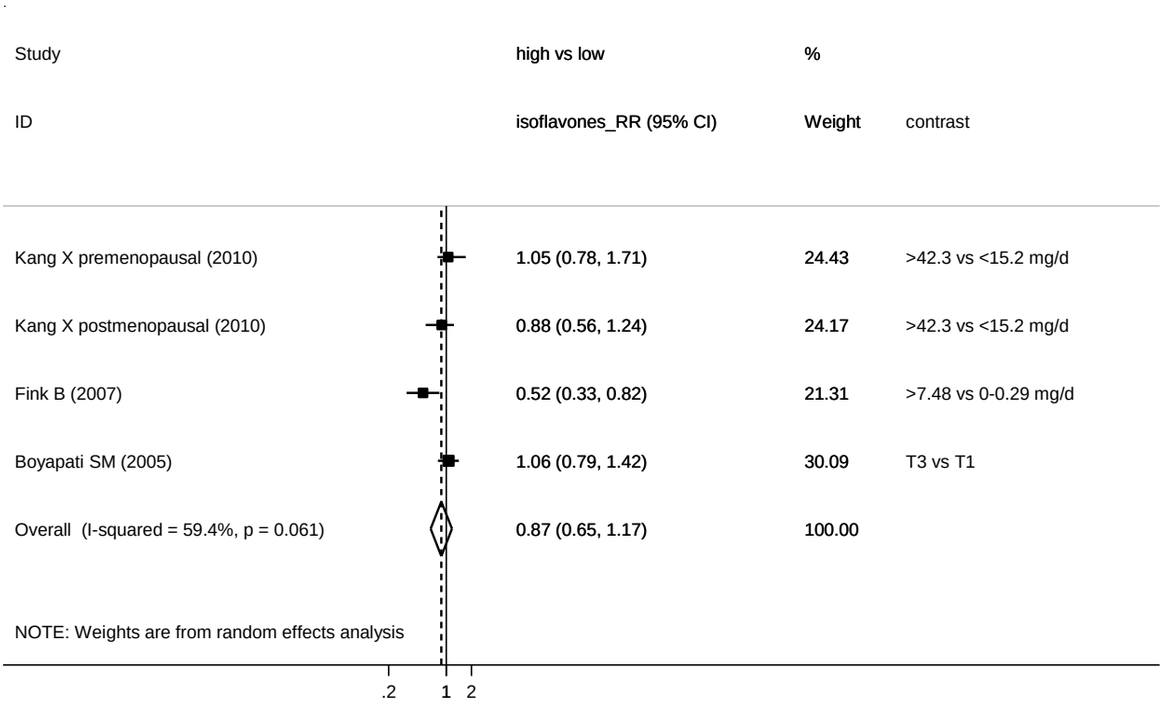


Table 56 Table of included studies on isoflavone intake before diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Kang X (2010)	Harbin Breast Cancer Survivors Follow-up Study China	Study recruitment: 2002-2003; Study follow up: until 2008	Prospective cohort of cancer survivors (cases identified from records of a hospital)	524 participants 29 - 72 years 47.3% premenopausal, 52.7% postmenopausal	5.1 years	TNM; 12.2% stage I, 65.8% stage II, 21.9% stage III	56.3% ER+ve/PR+ve, 29% ER+ve/PR-ve, 14.7% ER-ve/PR+ve	Chemotherapy: 85.1% yes, 14.9% no; Radiotherapy: 10.5% yes, 89.5% no; Endocrine therapy: 83.6% tamoxifen, 16.4% anastrozole		Self-reported after diagnosis at study baseline; consumption in the previous five years and its comparison with current	524 participants 154 deaths, 132 breast cancer mortality, 2 death from other cancers, 12 death from cardiovascular disease, 8 other causes of death	Medical records + death registry	Premenopausal >42.3 vs. 15.2mg/d Postmenopausal >42.3 vs. 15.2mg/d	1.05 (0.78-1.71) 0.88 (0.56-1.24)	Age at diagnosis, tumor stage, receptor status, chemotherapy, radiotherapy
Fink B (2007)	Long Island Breast Cancer Study Project United States	Cancer diagnosis:1976-1997; Study follow up: until 2004 (2002-2004) 96 days after diagnosis	Follow up of cases of a population-based case-control study	1210 participants 25 - 98 years All postmenopausal Mammography: 94.5% yes, 5.5% no	6 years	Invasive breast cancer; 78.2% tumour size 0-1.9 cm, 19.9% 2-5cm, 1.9% >5cm, 737 patients with missing data	44.1% ER+ve /PR+ve, 10.7% ER+ve /PR-ve, 3.9% ER-ve/ PR+ve, 16% ER-ve /PR-ve; 305 patients missing data			Self-reported shortly (mean 96 days) after diagnosis; dietary intake in the previous 12 months, prior diagnosis	1210 participants 173 deaths, 113 breast cancer mortality	National Death Index	>7.48 vs. 0-0.29 mg/d	0.52 (0.33-0.82)	Age, energy intake
Boyapati SM (2005)	Shanghai Breast Cancer Study China	Cancer diagnosis: 1996-1998 , Study follow-up: Until 2003 Median time interval between diagnosis and interview was 66 days	Follow-up of cases of population-based case-control study	1459 participants 25 - 64 years 951 premenopausal, 457 postmenopausal	5.2 years	TNM stages: 867 III, 114 III–IV, 74 unknown	52.8% ER+/PR+, 10.8% ER+/PR-, 10.5% ER-/PR+, 25.9% ER-/PR-	Surgery: 1048 yes, 1 no, 6 unknown; Chemotherapy: 985 yes, 58 no, 12 unknown; Radiotherapy: 403 yes, 500 no, 152 unknown	91.10% 11.60% lost	Usual diet over the past 5 years prior to diagnosis	1459 participants Approximately 297 deaths	Death registry	Q3 vs. Q1	1.06 (0.79-1.42)	Age, tumor stage, radiotherapy, hormone receptor status, energy intake

Isoflavones intake before diagnosis and total mortality

No study has reported data.

Isoflavones 12 months or more after diagnosis and total mortality

Methods

The 3 studies identified (Shu, 2009; Caan, 2011; Zhang, 2012) were included in the dose-response meta-analysis. All studies reported dietary isoflavones intake in mg per day, which was the unit used in the analysis.

Main results and heterogeneity

The summary RR per 10 mg/day was 0.91 (95% CI 0.83-1.00; 3 studies). High heterogeneity was observed (I^2 = 67.7%; p = 0.05). In the highest versus lowest forest plot the overall RR was 0.70 (95% CI 0.56-0.88; 3 studies).

The three studies explored potential effect modification by ER receptor status and two studies by tamoxifen use. However, there was no enough data in the papers to conduct dose-response meta-analysis. In the Shanghai Breast Cancer Survival Study (Shu, 2009) an inverse but no significant association of isoflavones intake and total mortality was observed in women with estrogen receptor positive or negative breast cancer (RR for highest vs. lowest quartile were 0.85; 95% CI 0.58-1.24 and 0.78; 95% CI 0.3-1.16 respectively) and was observed in both users and nonusers of tamoxifen. No interaction of estrogen or progesterone status was observed in the WHEL study (ER+ or PR+/ ER- PR- $p_{interaction}$ = 0.31) or by tamoxifen use ($p_{interaction}$ = 0.45) (Caan, 2011). In a study in Chinese women (619 women, 79 deaths) (Zhang, 2012) in which a protective effect of soy isoflavones was observed, this was more evident in women with ER+ tumours (RR > 28.83 vs < 7.53 mg 0.78 (95% CI 0.47-0.98)) than in women with ER+ (RR > 28.83 vs < 7.53 mg = 0.59 (95% CI 0.40-0.93). The association was significant for levels of soy isoflavones above 16 mg/day.

Study quality

One study from China (Zhang, 2012) was small (79 events). The other two studies reported a higher number of events, ranging from 271 (WHEL) (Caan, 2011) to 444 (SBCSS) (Shu, 2009) deaths. The WHEL study classified high number of participants in the lowest categories of intake. The follow-up time ranged from 3.6 years (Zhang, 2012) to 7.3 years (Caan, 2011). All studies ended after the year 2000. The three studies included pre and post-menopausal women combined. The dietary assessment timeframe was available for 2 of the 3 studies. The SBCSS (Shu, 2009) assessed the isoflavones intake at 6, 18, 36 and 60 months after diagnosis and the WHEL study (Caan, 2011) assessed the intake 2 years post diagnosis. Two studies were from Asia (Shu, 2009; Zhang, 2012) and one study from the United States (Caan, 2011). The highest category of intake were 26.7 g/day as median in the American study (Caan, 2011), and > 28.3 g/day (Zhang, 2012) and > 62.68 g/day (Shu, 2009) in the Asian studies.

Published pooled analysis

In a pooled analysis from cohort studies of US and Chinese women, the Shanghai Breast Cancer Survival Study (SBCSS), the Life After Cancer Epidemiology (LACE) Study, and the Women's Healthy Eating & Living (WHEL) Study (Nechuta, 2012), intake of ≥ 10 mg isoflavones/d was inversely but not significantly associated to all-cause mortality (HR 0.87; 95% CI 0.70-1.10). There was no significant interaction for menopausal status and tamoxifen use. The HR > 10 vs. < 4 mg were 0.91 (95% CI 0.69-1.20) for estrogen receptor positive and 0.81 (95% CI 0.54-1.23) for estrogen receptor negative tumours ($p_{interaction}$ < 0.01).

Figure 65 Highest versus lowest forest plot of isoflavone inake 12 months or more after diagnosis and total mortality

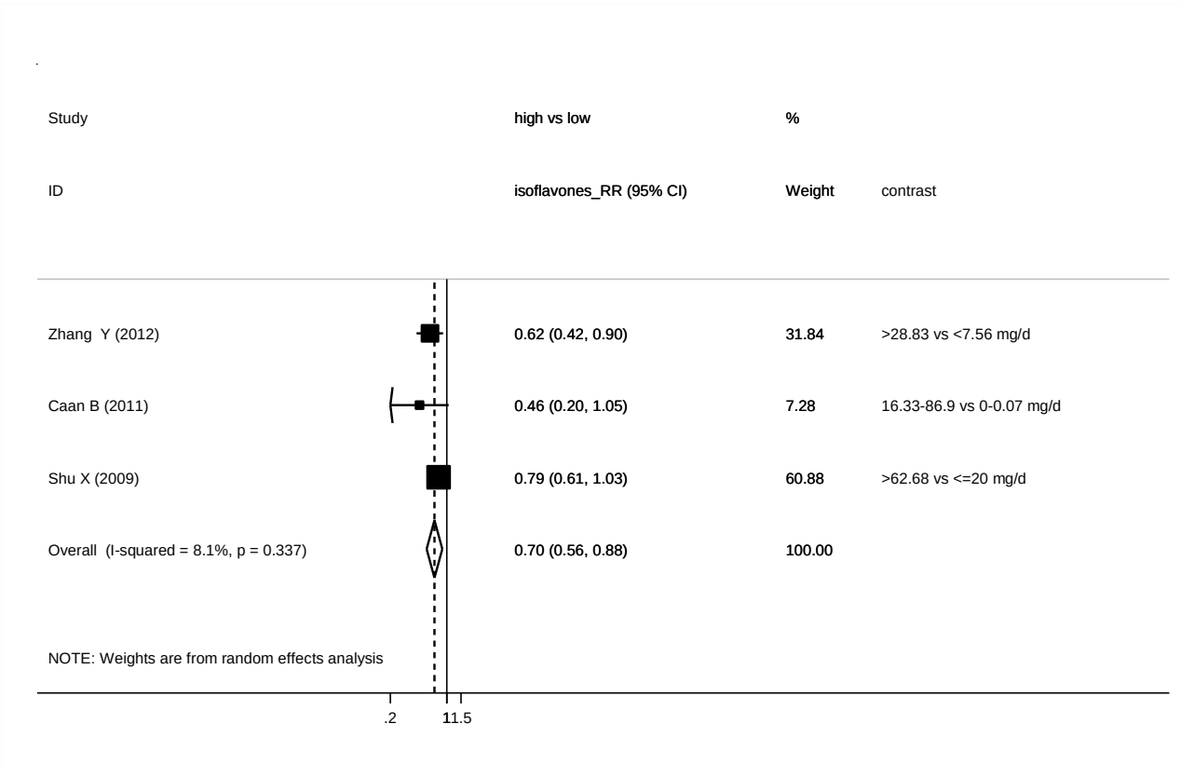


Figure 66 Linear dose-response meta-analysis of isoflavone intake 12 months or more after diagnosis and total mortality

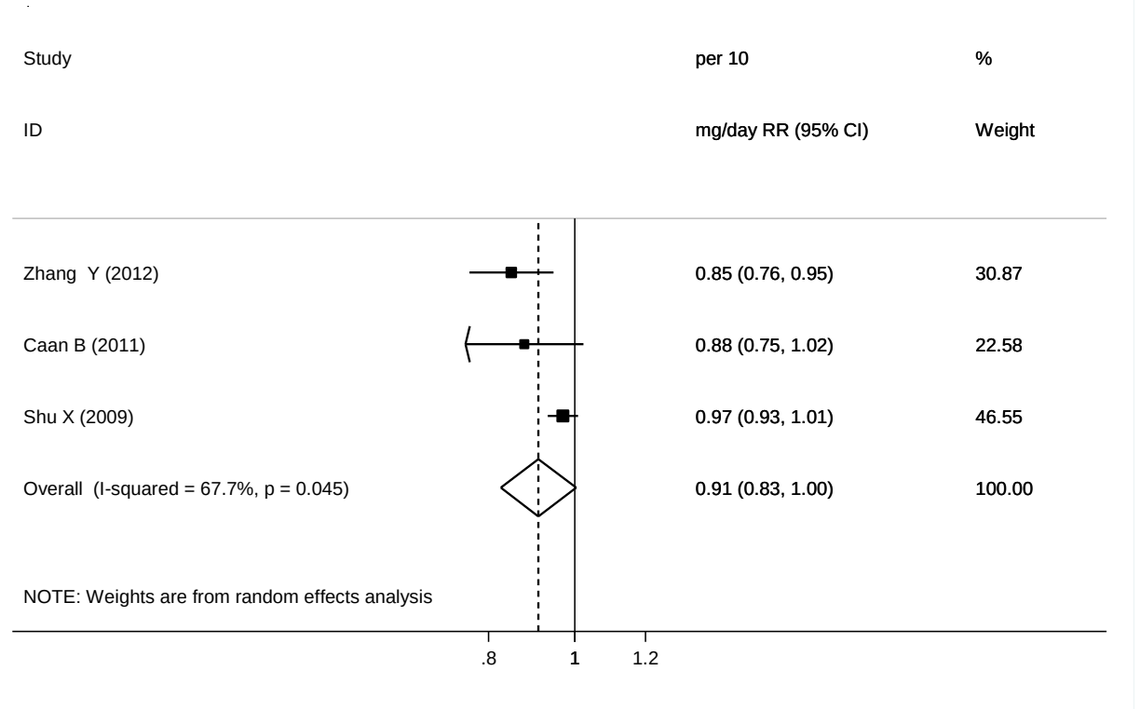


Figure 67 Individual dose-response graph of isoflavone intake 12 months or more after diagnosis and total mortality

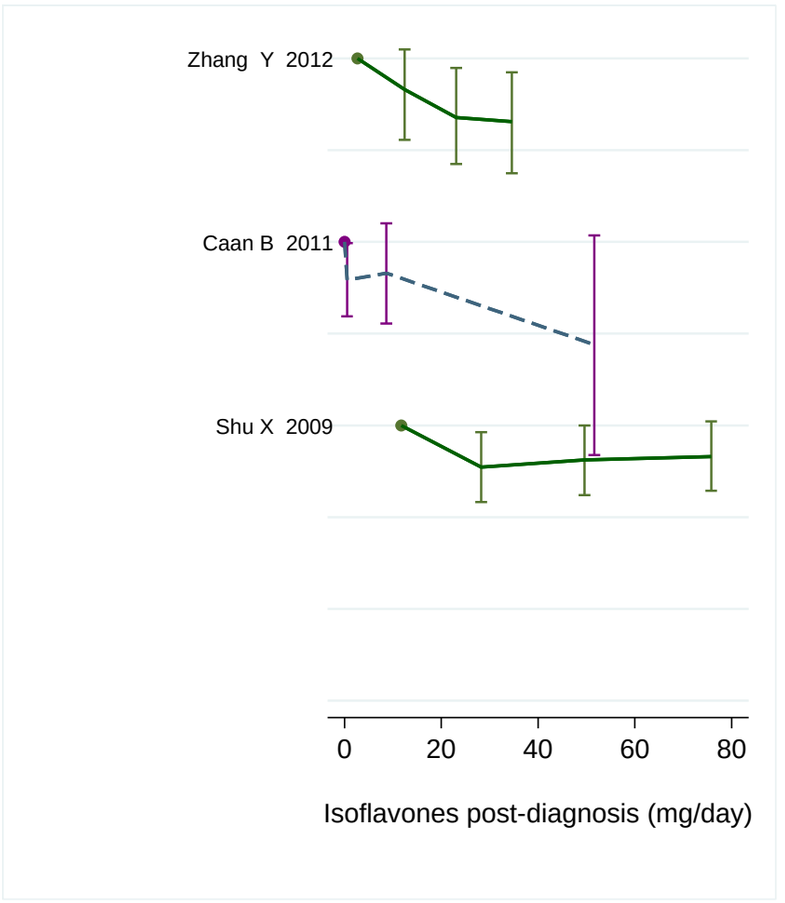


Table 57 Table of included studies on isoflavones intake 12 months or more after diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Zhang Y 2012	Affiliated Hospital of Inner Mongolia Medical College Study China	Study recruitment:2004-2006; Study follow-up: Until 2011	Follow-up of patients of a hospital-based study	616 participants 45.7 years (mean) 47.1% post- or perimenopausal, 52.9% premenopausal	52.1 months	81.3% stage I-II, 18.7% stageIII-IV	61.4% ER+ve, 38.6% ER-ve	Chemotherapy:86.7 %yes, 13.3%no; radiotherapy:64.9% yes, 35.1%no;hormone therapy:7.6%yes, 92.4%yes;tamoxifen use:56.8%yes, 43.2%no	94.9% 9 patients lost	Post-diagnosis	616 participants 79 deaths	Hospital records	>28.83 vs. <7.56 mg/d	0.62 (0.42-0.90)	Age, education level, smoking, drinking, family history of cancer, menopause status, tamoxifen use, TNM stage, ER status, chemotherapy and radiotherapy
Caan B (2011)	Women's Healthy Eating and Living Study United States	Cancer diagnosis: 1991-2000, post-diagnosis	Randomised controlled trial of dietary intervention trial; ancillary analysis	3088 participants 18 - 70 years 11.2% premenopausal, 88.8% peri- or postmenopausal	7.3 years	AJCC stages: 38.9% I, 45.8% II, 15.3% III	79.7% ER+ or PR+, 20.3% ER-/PR-, among those with data	Tamoxifen: 60.8% current, 32.7% never, 6.4% past user, among those with data		2 months to 4 years post-diagnosis	3088 participants 271 deaths	Death certificate	16.33 -86.9 vs. 0-0.07mg/d	0.46 (0.20-15)	Stage, menopausal status, chemotherapy, radiation therapy, age, education, hot flashes, race, tamoxifen use
Shu X (2009)	Shanghai Breast Cancer Survival Study China	Cancer diagnosis: 2002-2006, Study follow-up: Until 2008 6.5 months post-diagnosis	Prospective cohort of breast cancer survivors	5042 participants 20 - 75 years 48.9% premenopausal, 51.1% postmenopausal HRT use: 6.8% yes, 93.2% among those with data	3.9 years	TNM stages: 85.8% 0-II, 9.8% III-IV, 4.4% Unknown	63.2% ER+, 35.2% ER-, 1.6% missing; 57.5% PR+, 40.6% PR-, 1.9% missing	Radical mastectomy: 92.6% yes, 7.4% no; Radiotherapy: 32.1% yes, 67.9% no; Chemotherapy: 91.2% yes, 8.8% no; Tamoxifen: 52.1% yes, 47.9% no among those with data	80% 88.2 % is completed after 36 months interview, interview after 60 months is still ongoing	6.5 months post-diagnosis; diet over the preceding 6 months for the baseline survey, the preceding 12 months for the 18-month survey, and the preceding 18 months for the 36-month survey	5042 participants 444 deaths and 534 recurrences or breast cancer-related deaths	Vital statistics registry	>62.88 vs. <=20mg/d	0.79 (0.61-13)	Age at diagnosis, TNM stage, chemotherapy, radiotherapy, surgery type, BMI, menopausal status, receptor status, tamoxifen use, education, income, cruciferous vegetable, meat intake, supplements use, tea consumption, physical activity

Isoflavones intake and breast cancer mortality

One study on isoflavones and breast cancer mortality was identified. This study reported breast cancer mortliaty and recurrences combined into a single outcome. The RR for breast cancer mortality and recurrence together was 0.77 (95% CI 0.60-0.98; 62.68 mg/day vs. ≤ 20 mg/day) (Shu, 2009).

Published pooled analysis

In a pooled analysis from cohort studies of US and Chinese women, the Shanghai Breast Cancer Survival Study (SBCSS), the Life After Cancer Epidemiology (LACE) Study, and the Women's Healthy Eating & Living (WHEL) Study (Nechuta, 2012), intake of ≥ 10 mg isoflavones/day was inversely but not significantly associated to breast cancer mortality (HR 0.83; 95% CI 0.64-1.07). There was no significant interaction for menopausal status, tamoxifen use and estrogen receptor status.

Isoflavones intake and second primary breast cancer

One study on isoflavones and second primary breast cancer was identified. The RR for a second primary breast cancer was 0.78 (95% CI 0.46-1.31; 16.33-86.9 mg/day vs. 0-0.07 mg/day) (Caan, 2011).

5 Physical activity

Table 58 Summary results of meta-analysis on physical activity and total mortality and breast cancer mortality*

	Total mortality			Breast cancer mortality		
Comparison	**No. of studies**	**No. of events in studies**	**RR (95% CI) I^2, $P_{heterogeneity}$**	**No. of studies**	**No. of events in studies**	**RR (95% CI) I^2, $P_{heterogeneity}$**
Total physical activity before breast cancer diagnosis						
Highest vs. lowest	2	505	0.83 (0.62-1.12) 22.7%, p = 0.25	2	338	0.80 (0.59-1.10) 0%, p = 0.88
Recreational physical activity before breast cancer diagnosis						
Highest vs. lowest	8	2892	0.74 (0.67-0.83) 5%, p=0.39	7	1750	0.76 (0.61-0.95) 48.7%, p = 0.06
Total physical activity 12 months or more after breast cancer diagnosis						
Highest vs. lowest	3	514	0.63 (0.41-0.97) 44.1%, p = 0.16	2	217	0.81(0.48-1.36) 0%, p = 0.63
Per 10 MET-h/week	3	514	0.90 (0.79-1.03) 78.7%, p = 0.009	-	-	-
Recreational activity 12 months or more after breast cancer diagnosis						
Highest vs. lowest	5	2337	0.61 (0.50-0.74) 45.8%, p = 0.12	2	392	0.71 (0.45-1.12) 33%, p = 0.22
Per 10 MET-h/week	5	2337	0.81 (0.73-0.90) 63.8%, p = 0.03	-	-	-

* No studies on second primary cancers were included in the meta-analyses.

Table 59 Table for subgroup analysis of recreational physical activity 12 months or more after diagnosis and total mortality

Comparison	No. of studies	No. of events in studies	RR (95% CI)	I^2, $P_{heterogeneity}$
Per 10 MET-hour/week				
Menopausal status				
Premenopausal	2	225	0.76 (0.49-1.19)	42.3%, p = 0.18
Postmenopausal	4	902	0.74 (0.59-0.93)	73.6%, p = 0.01

Physical activity and total mortality

Fifteen studies on physical activity and total mortality were identified. Nine studies were on physical activity before diagnosis and total mortality (Abrahamson, 2006a; Dal Maso, 2008; Irwin, 2008; West-Wright, 2009, Friedenreich, 2009; Hellman, 2010; Emaus, 2010; Cleveland, 2011; Irwin, 2011) and 8 studies were on physical activity 12 months or more after diagnosis and total mortality (Holmes, 2005; Irwin, 2008; Holick, 2008; Sternfeld, 2009; Irwin, 2011; Chen, 2011; Bertram 2011; Buck, 2011a). Two studies (Irwin, 2008; Irwin, 2011) reported both on physical activity before and 12 months or more after diagnosis.

From the nine studies on physical activity before diagnosis, two were on total physical activity, eight were on recreational physical activity, one study (Friedenreich, 2009) reported on both total physical activity and recreational physical activity.

From the eight studies on physical activity 12 months or more after diagnosis, three studies were on total physical activity and five were on recreational physical activity.

Total physical activity was defined as the physical activities in different types of activities, e.g. occupational, recreational and household activities; or recreational and household activities; or non ocupational activity when it includes walking time, stair climbing and city block walking, since these activities are not considered as recreational activity but part of the daily routine activities.

Recreational physical activity was defined as physical activity in leisure time.

Vigorous physical activity was any type of vigorous activity in recreational and non-recreational activities.

Physical activity before diagnosis and total mortality

Total physical activity before diagnosis and total mortality

The wide variability in the measurement methods of physical activity-related exposures between the two studies identified made it difficult to pool the results together. Therefore the dose response meta-analysis was not possible to conduct. In the highest versus lowest forest plot the overall RR was 0.83 (95% CI 0.62-1.12; 2 studies).

Recreational physical activity before diagnosis and total mortality

The wide variability in the measurement methods of physical activity-related exposures between the eight studies identified made it difficult to pool the results together and dose response meta-analysis was not conducted. In the highest versus lowest forest plot the overall RR was 0.74 (95% CI 0.67-0.83; 8 studies).

Three studies reported the stratified results by BMI status. One study (Emaus, 2010) reported a significant association between moderate level of physical activity and total mortality for women with BMI < 25 kg/m^2 (HR 0.59; 95% CI 0.36-0.98), but not for women with BMI ≥ 25 kg/m^2 (HR 1.07; 95% CI 0.60-1.90; $p_{interaction}$ = 0.34). Abrahamson, (2006a) reported a significant association of recreational physical activity and total mortality for women with a BMI ≥ 25 kg/m^2 (HR 0.70; 95% CI 0.49-0.99; high vs. low physical activity level) but not for women with a BMI < 25 kg/m^2 (HR 1.08; 95% CI 0.77-1.52; high vs. low physical activity level; $p_{interaction}$ = 0.05). In the third study (Cleveland, 2011), recreational physical activity was significantly inversely associated to total mortality for women with BMI < 25 kg/m^2 (HR 0.44; 95% CI 0.27-0.70) and women with BMI ≥ 25 kg/m^2 (HR 0.66; 95% CI 0.46-0.96; $p_{interaction}$ = 0.08).

Figure 68 Highest versus lowest forest plot of physical activity before diagnosis and total mortality

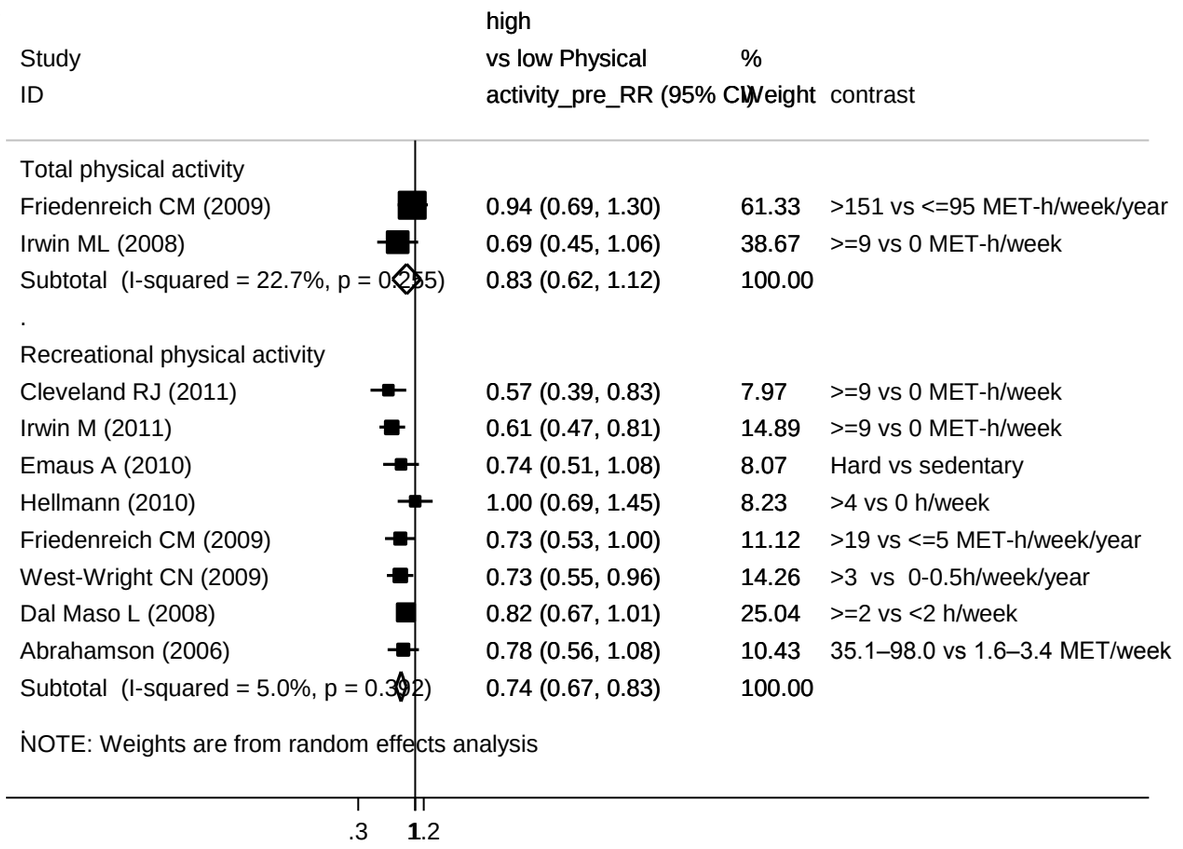


Table 60 Table of included studies on total physical activity before diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Friedenreich CM (2009)	Alberta Cancer Registry Follow-up Study Canada	Cancer diagnosis: 1995-1997; Study follow up: until 2008	Prospective cohort study of breast cancer survivors	1225 participants 56 years (mean) 62.4% postmenopausal HRT use: 34% 47.3% with comorbidities	8.3 years	Incident in situ and invasive breast cancer; 9% stage 0, 42.3% stage I, 39.8% stage II, 8.8% stage III+, 0.2% missing	68.2% ER+ve, 62.7% PR+ve	35.6% chemotherapy, 38.6% hormonal therapy, 54.7% radiotherapy		Self reported at baseline; lifetime PA	1225 participants 341 deaths, 223 breast cancer mortality	SEERS	>151 vs. <=95 MET-h/week/year	0.94 (0.69-1.30)	Age, tumor stage, treatment (chemotherapy, hormone therapy and radiation therapy), SBR grade, BMI and other comorbidity conditions
Irwin ML (2008)	Health Eating Activity and Lifestyle Study United States	Cancer diagnosis:1995-1998; Study follow up: until 2004	Prospective cohort study of breast cancer survivors	933 participants 18 - 64 years Multi-ethnic	6 years	Primary breast cancer				Assessed the year before & 2 years after diagnosis (during baseline interview (approximately 6 months after diagnosis)	933 participants 164 deaths, 115 breast cancer mortality, 56 breast cancer recurrence, 40 new breast cancer primaries	Cancer register	>=9 vs. 0 MET-h/week	0.69 (0.45-1.06)	Age, race, disease stage, initial treatment, and tamoxifen use

Table 61 Table of included studies on recreational physical activity before diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Irwin M (2011)	Women's Heath Initiave United States	Study recruitment: 1993-1998, Study follow-up: Until 2005	Cancer survivors of population-based prospective cohort study or clinical trials	4643 participants 50 - 79 years Postmenopausal	7 years	Stages I-IIIA		Chemotherapy: 25% yes among stage I, 78% yes among stageII/III patients		On average 4.1 years from pre-diagnosis physical activity assessment to cancer diagnosis. On average 1.8 years from diagnosis to post-diagnosis physical activity assessment	4643 participants 350 deaths, 194 breast cancer mortality	Death certificate	>=9 vs. 0 MET-h/week	0.61(0.47-0.81)	Age, ethnicity, WHI study arm, previous hormone therapy use, BMI, diabetes, alcohol, smoke, total calories, percentage calories from fat, and servings of fruit and vegetable
Cleveland RJ (2011)	Long Island Breast Cancer Study Project United States	Cancer diagnosis: 1996-1997, Study follow-up: Until Soon after diagnosis	Follow-up of cases of population-based case-control study	1508 participants 58.9 years (mean)	66.7 months	First primary in situ or invasive breast cancer					1508 participants 196 deaths, 128 breast cancer mortality	Death certificate	>=9 vs. 0 MET-h/week	0.57 (0.39-0.83)	Age at diagnosis, body mass index and menopausal status
Hellmann (2010)	Copenhagen City Heart Study Denmark	Study recruitment:1976; Study follow up: until 2007	Cancer survivors of a population-based prospective cohort study	528 participants 66.9 years (mean) 33.1 - 95.4 years 16.1% premenopausal, 83.9% postmenopausal HRT use: 71.2% unexposed, 28.8% exposed	7.8 years	Primary breast cancer, one sarcoma, 527 carcinomas; TNM; 56.2% local, 33.7 regional, 6.3 metastatic, 3.8% unknown		7.4% radiotherapy, 7.4% chemotherapy, 22.4% hormonal therapy	74% at the 1st, 70% at the 2nd , 61% at the 3rd and 50% at the 4th examination / 1% lost	Measured at study baseline	528 participants 323 deaths, 174 breast cancer mortality, 126 other causes of death including 43.6% death from cardiovascular disease and 25.6% other cancers	Cancer registry	>4 vs. 0h/w	1.0 (0.69-1.45)	Alcohol, smoking, physical activity, body mass index, hormone replacement therapy, age, disease stage, menopausal status, parity, education, and adjuvant treatment
Emaus A (2010)	Norwegian Health Surveys Follow-up Study, three counties Norway	Cancer diagnosis: 1975–2005;	Cancer survivors of a population-based prospective cohort study	1364 participants 57.5 years (mean) 27 - 79 years 61% postmenopausal HRT use: 30 patients, only measured in 3rd survey. Participants of a health screening cohort. Comorbidities: 8 diabetic patients	8.2 years	Invasive breast cancer; TNM; 49% Stage 1, 41% Stage 2, 4.5% stage 3, 5.3% stage 4			91% in the 1st, 91% in the 2nd and 88% in the 3rd survey / Complete follow up	Measured during health screening, prior to diagnosis (usual level of physical activity during leisure time in the year preceding each survey)	1364 participants 429 deaths, 355 breast cancer mortality, 27 death from other cancers, 23 death from cardiovascular disease, and 24 from other causes	Death record	Hard vs. sedentary	0.74 (0.51-18)	Age at diagnosis, pre-diagnostic observation time, tumor stage, region of residence, year at diagnosis before and after 1995 and BMI
Friedenreich CM (2009)	Alberta Cancer Registry Follow-up Study Canada	Cancer diagnosis: 1995-1997; Study follow up: until 2008	Prospective cohort study of breast cancer survivors	1225 participants 56 years (mean) 62.4% postmenopausal HRT use: 34% 47.3% with	8.3 years	Incident in situ and invasive breast cancer; 9% stage 0, 42.3% stage I, 39.8% stage II, 8.8% stage III+,	68.2% ER+ve, 62.7% PR+ve	35.6% chemotherapy, 38.6% hormonal therapy, 54.7% radiotherapy		Self reported at baseline; lifetime PA	1225 participants 341 deaths, 223 breast cancer mortality	SEERS	>151 vs. <=95 MET-h/week/year	0.94 (0.69-1.30)	Age, tumor stage, treatment (chemotherapy, hormone therapy and radiation therapy), SBR grade, BMI

				comorbidities		0.2% missing									and other comorbidity conditions
West-Wright CN (2009)	California Teachers Study United States	Study recruitment: 1995; Cancer diagnosis: 1995-2004; Study follow up: until 2005	Cancer survivors of a population-based prospective cohort study	3539 participants 58.9 years (mean) 26 - 94 years Mostly white: 89.7% Comorbidities: 111 diabetes, 106 cardiovascular disease; 24.5 %	9 Years (max)	Incident first primary invasive breast cancer; 68.9% localized, 28.4% regional, 1.86 metastatic, 0.8 % missing	72% ER+ve, 12.7% ERve, 15.3% unknown			Self-reported at baseline; PA within the 3 years prior to cohort entry, prior to diagnosis	3539 participants 460 deaths, 221 breast cancer mortality, 69 death from other causes including 24 death from other cancers, 68 cardiovascular disease deaths; 38 cerebrovascular disease deaths; 28 cardiopulmonary or pulmonary disease deaths; 4 diabetes death	Death certificate	>3 vs. 0-0.5 h/week/y	0.73 (0.55-0.96)	Age, for race, BMI, total caloric intake, number of comorbid conditions and estrogen receptor status
Dal Maso L (2008)	Six Italian Regions Follow-up Study Italy	Cancer diagnosis: 1991-1994; Study follow up: until 2005-2006 diagnosed no longer than 1 year before the interview	Follow-up of cases of a case-control study	1453 participants 55 years (mean) 23 - 74 years Among those with data, pre diagnosis data: 45.5 % peri/pre menopausal, 54.9% postmenopausal HRT use: 91.3% never, 8.6% ever	12.6 years	Invasive breast cancer; TNM; 32.7% Stage I, 44.1% stage II, 13.2% stage III-IV, 9.8% unknown	41.5% ER+ve/PR+ve, 3.5% ERve/ PR+ve, 45.6% no node+ve, 44.2% node+ve, 10.1%		2.70% lost	Self-reported (questionnaire) at study baseline	1453 participants 503 deaths, 398 breast cancer mortality, 6.2% death from other cancers, 7.4% from cardiovascular disease	Cancer registry	>=2 vs. <2h/week	0.82 (0.67-11)	Region, age at diagnosis, year of diagnosis, TNM stage, receptor status
Abrahamson (2006) a	Atlanta, Seattle, New Jersey Follow-up Study United States	Cancer diagnosis:1990-1992; Study follow up: until 2000	Follow-up of cases of a population-based case-control study	1264 participants 42 years (mean) 20 - 54 years 78% premenopausal	8.5 years	Invasive breast cancer; AJCC; any stage; 57% local, 43% regional/distant	62% ER+VE, 59% PR+ve		86% <2%lost	Measured 4.2 months after diagnosis; PA at age 12 to 13 years, age 20 years, and the year before diagnosis	1264 participants 290 deaths	Cancer registry	35.1-98 vs. 1.6-3.4 MET/week	0.78 (0.56-18)	Age at diagnosis, ethnicity, tumor stage, menopausal status, receptor status, education, WHR, BMI, household income

Physical activity less than 12 months after diagnosis and total mortality

No study has reported data.

Physical activity 12 months or more after diagnosis and total mortality

Total physical activity 12 months after or more after diagnosis and total mortality

Methods

The three studies identified were included in the dose response meta-analysis. All the studies reported physical activity in MET-h/week. The dose response meta-analysis was conducted using as cut-off 10 MET-h/week.

Main results and heterogeneity

The summary RR per 10 MET-h/week was 0.90 (95% CI 0.79-1.03; 3 studies). High heterogeneity was observed (I^2 = 78.7%; p = 0.009). All studies included before and more than 12 months after menopausal women combined. In the highest versus lowest forest plot the overall RR was 0.63 (95% CI 0.41-0.97; 3 studies).

Two studies (Irwin, 2008; Sternfeld, 2009) stratified the analysis by BMI and receptor status. In the LACE study (Sternfeld, 2009) a significant positive association was found for BMI < 25 kg/m^2 (RR 0.38; 95% CI 0.17-0.85, > 6 vs. < 1 h/week of moderate activity). In the HEAL study (Irwin, 2008) a significant positive association was found for BMI ≥ 25 kg/m^2 (RR 0.31; 95% CI 0.13-0.74, > 0 vs. 0 MET-h/week of physical activity, $p_{interaction}$ = 0.40). After stratification by receptor status, the LACE study (Sternfeld, 2009) found non-significant associations between moderate physical activity and total mortality for both ER/PR negative and ER/PR positive women. The HEAL study (Irwin, 2008) found a significant protective effect of physical activity post-diagnosis on total mortality in ER positive women (RR 0.20; 95% CI 0.09-0.46; >0 vs. 0 MET-h/week of physical activity, $p_{interaction}$ = 0.27).

Study quality

All the studies reported more than 100 events, ranging from 163 (Bertram, 2011) to 187 (Sternfeld, 2009) deaths. The follow-up time ranged from 6 years (Irwin, 2008) to 7.2 years (Bertram, 2011). All studies included pre and postmenopausal women mixed. The physical activity assessment timeframe ranged from 6 months after diagnosis to (Sternfeld, 2009) to 2 years post-diagnosis (Irwin, 2008). All studies were from the United States.

Recreational physical activity 12 months or more after diagnosis and total mortality

Methods

The 5 studies identified were included in the dose response meta-analysis. All the studies reported physical activity in MET-h/week. The dose response meta-analysis was conducted using as cut-off 10 MET-h/week.

Main results and heterogeneity

The summary RR per 10 MET-h/week was 0.81 (95% CI 0.73-0.90; 5 studies). High heterogeneity was observed (I^2 = 63.8%, p = 0.03). Egger's test suggested no evidence of publication bias, p = 0.52. The asymmetry of the funnel plot appears to be caused by the strong inverse association reported by the smallest study (Irwin, 2008) but any interpretation of the funnel plot should be cautious due to the low number of studies. In the highest versus lowest forest plot the overall RR was 0.61 (95% CI 0.50-0.74; 5 studies).

One study (Chen 2011) stratified the results by menopausal status. It reported a significant decreased risk of dying for postmenopausal women who did physical activity 12 months

or more after diagnosis, RR was 0.55 (95% CI 0.40-0.77, ≥ 8.3 vs. 0 MET-h/week). One study included pre and post-menopausal women combined (Holick, 2008) and two studies (Irwin, 2011; Buck, 2011a) were on post-menopausal women. After stratification by menopausal status, the RR per 10 MET-h/week for pre-menopausal women was 0.76 (95% CI 0.49-1.19; 2 studies) and for post-menopausal women was 0.74 (95% CI 0.59-0.93; 4 studies).

Both the CWLS (Holick, 2008) and the WHI study (Irwin, 2011) stratified the analysis by BMI status and receptor status. In the WHI study, significant positive associations were found for BMI < 25 kg/m^2 (RR 0.49; 95% CI 0.27-0.91, 0 vs. >0 MET-h/week), for BMI 25-29.9 kg/m^2 (RR 0.43; 95% CI 0.24-0.76, 0 vs. > 0 MET-h/week), for ER-positive cancers (RR 0.50; 95% CI 0.34-0.74, 0 vs. >0 MET-h/week) and for HER2-negative cancers (RR 0.37; 95% CI 0.19-0.75, 0 vs. >0 MET-h/week). There was no association between recreational activity and total mortality for BMI > 30 kg/m^2, ER-negative or HER2-postive cancers.

Study quality

All the studies reported more than 100 events, ranging from 412 (Holick, 2008) to 463 (Holmes, 2005) deaths. The follow-up time ranged from 4.3 years (Chen, 2011) to 8 years (Holmes 2005). Two studies (Buck, 2011a; Irwin, 2011) were on post-menopausal women and the other 3 studies combined pre- and post-menopausal women. The physical activity assessment timeframe ranged from at least one year after diagnosis to (Holick, 2008) to 6 years post-diagnosis (Irwin, 2011). Three studies were from the United States (Holick, 2008; Irwin, 2011; Holmes, 2005), one from Europe (Buck, 2011a) and one from Asia (Chen, 2011).

Published pooled analysis

These results are consistent with the results from the After Cancer Pooling Project (Beasley, 2012) which found that engaging in at least 10 MET-hours/week of PA was associated with a 27% reduction in all-cause mortality (n = 1468 events; HR 0.73, 95% CI, 0.66-0.82) and a 25% reduction in breast cancer mortality (n = 971 events; HR 0.75, 95% CI 0.65-0.85) compared to women who did not meet the PA Guidelines (< 10 MET-hours/week).

Figure 69 Highest versus lowest forest plot of physical activity 12 months or more after diagnosis and total mortality

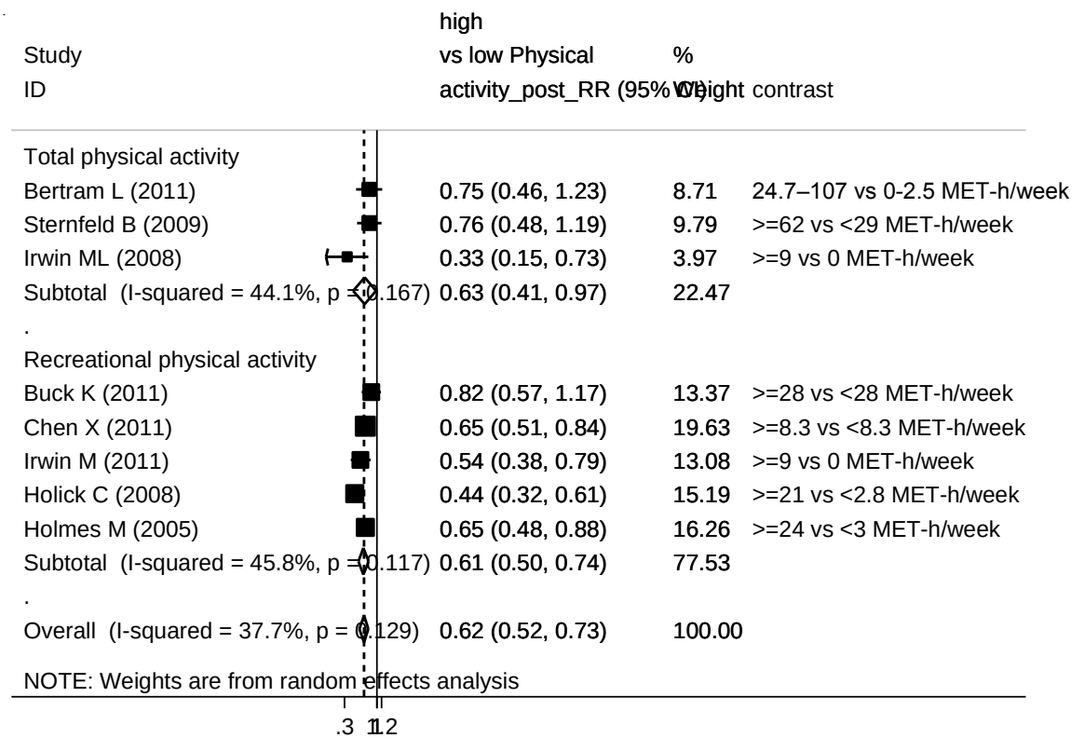


Figure 70 Dose-response meta-analysis of total physical activity 12 months or more after diagnosis and total mortality

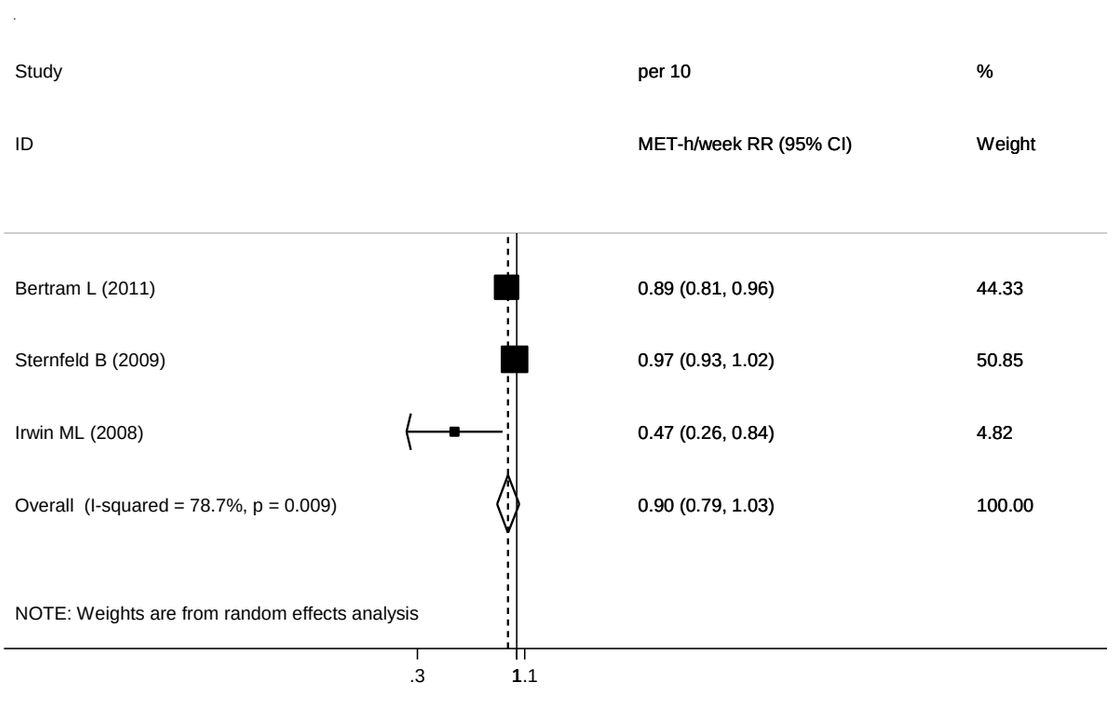


Figure 71 Individual dose-response graph of total physical activity 12 months or more after diagnosis and total mortality

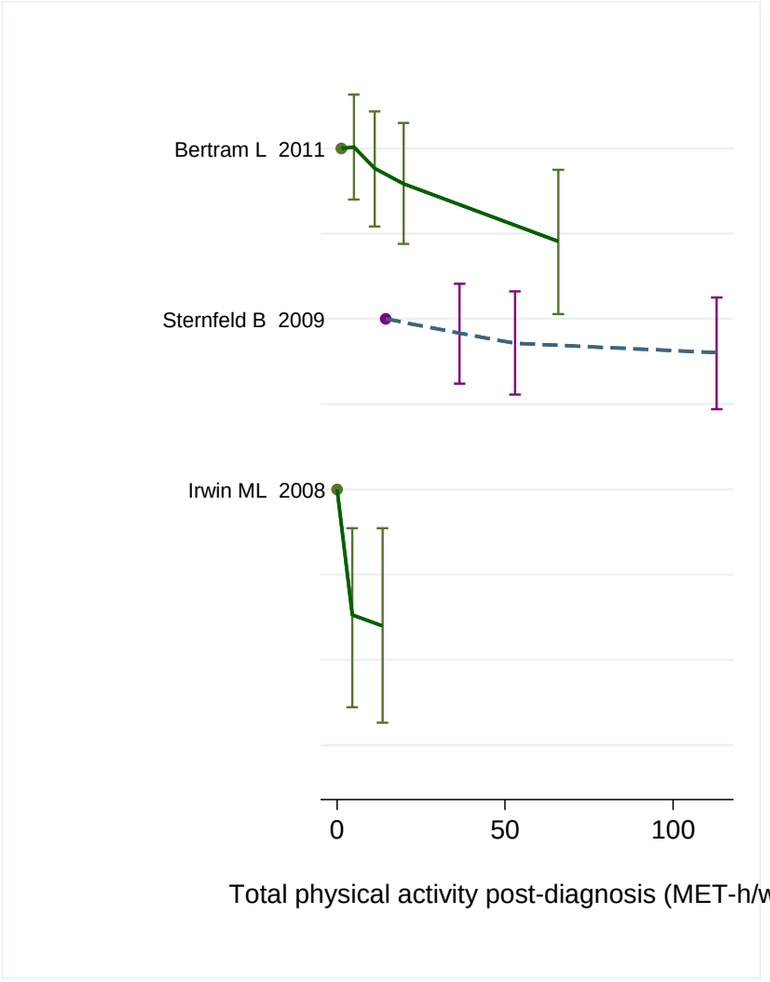


Table 62 Table of included studies on total physical activity 12 months or more after diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Bertram L (2011)	Women's Healthy Eating and Living Study United States	Study recruitment:1995-2000, Follow up: until June 2006	Randomised controlled trial of dietary intervention	2361 participants 80.7 % postmenopausal, 9.8% premenopausal, 9.4%peri menopausal	7.1 years	Invasive breast cancer: 40.5% stage I, 32.8% stage IIA, 12.4% stageIIB, 11.3% stage IIIA, 3% stage IIIC	/ 87.7% 0-3 node+ve, 12.3% >3 node+ve	68.2% chemotherapy, 61.6% radiation	/ 1 patient	Assessed at baseline and at various follow-up points after diagnosis	2361 participants 163 death from all causes, 295 additional breast cancer events	Medical record + death certificate	24.7-107 vs. 0-2.5 MET-h/week	0.75 (0.46-1.23)	Age at randomization, race, fruit and vegetable consumption, BMI at randomization, menopausal status, tumor type, tumor grade, tumor stage, anti-estrogen use, clinical site, time from diagnosis to randomization, hot flashes, and study group
Sternfeld B (2009)	LACE United States	Cancer diagnosis:1997-2000; Diagnosed within 39 months of enrolment in the original study	Prospective cohort study of breast cancer survivors	1970 participants 18 - 79 years Among those with data: 21 % premenopausal, 65.3% postmenopausal, 13.7% unknown	87 months	Early-stage breast cancer; AJCC; among those with data: 47.6% stage I, 33.4% stage IIa, 16% stage IIb, 2.9% stage IIIa	Among those with data: 68.2% ER+/ PR+, 14.2% ER+/ PR-, 1.8% ER-/ PR+, 15.8% ER-/ PR- / Among those with data: 64.2% node-ve, 35.8% node+ve (25.5 % 1-3 nodes+ve, 10.3% >= 3 nodes +ve)	Among those with data: Surgery: 50.4% conserving, 49.6% mastectomy; Chemotherapy: 56.3% yes, 43.7% no; Radiation therapy: 62.9 % yes, 37.1% no	/ 15 patients lost	Self-reported at baseline; PA after diagnosis (6 month prior to enrolment)	1970 participants 187 deaths, 102 breast cancer mortality	Death certificate	>=62 vs. <29 MET-h/week	0.76 (0.48-1.19)	Age, number of positive nodes, stage, weight at 18 y, education level and smoking status
Irwin ML (2008)	Health Eating Activity and Lifestyle Study United States	Cancer diagnosis:1995-1998; Study follow up: until 2004	Prospective cohort study of breast cancer survivors	933 participants 18 - 64 years Multi-ethnic	6 years	Primary breast cancer				Assessed the year before & 2 years after diagnosis (during baseline interview (approximately 6 months after diagnosis)	933 participants 164 deaths, 115 breast cancer mortality, 56 breast cancer recurrence, 40 new breast cancer primaries	Cancer register	>=9 vs. 0 MET-h/week	0.33 (0.15-0.73)	Age, race, disease stage, initial treatment, and tamoxifen use

Figure 72 Dose-response meta-analysis of recreational physical activity 12 months or more after diagnosis and total mortality

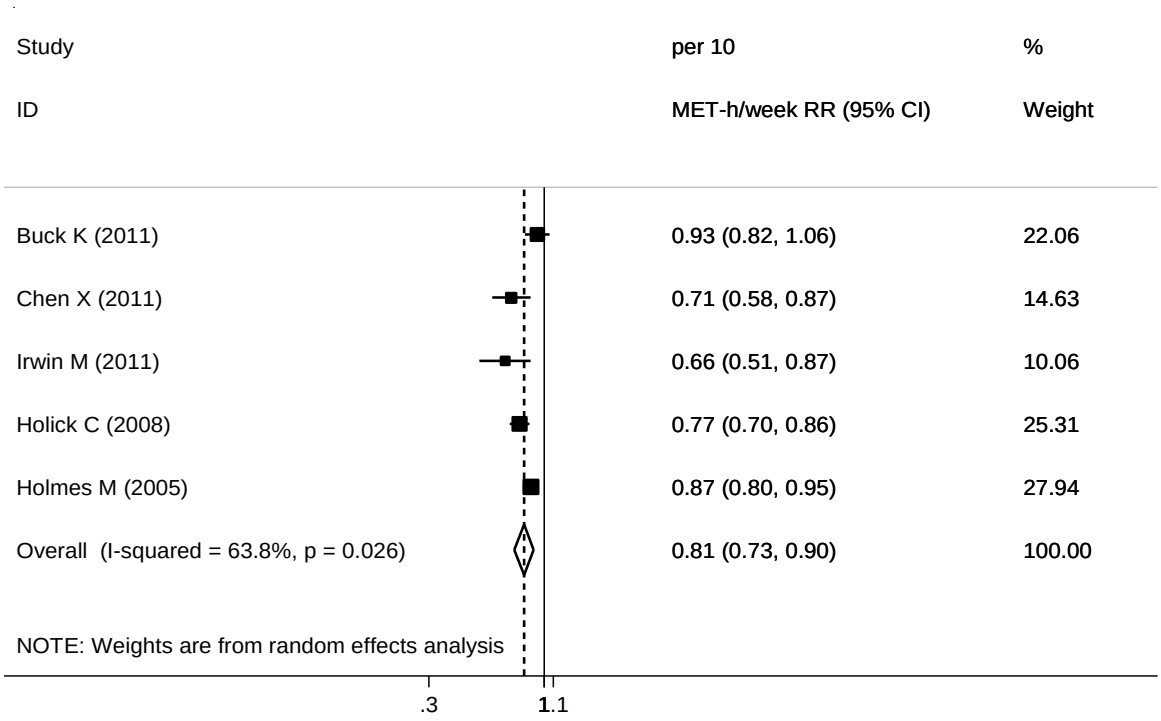
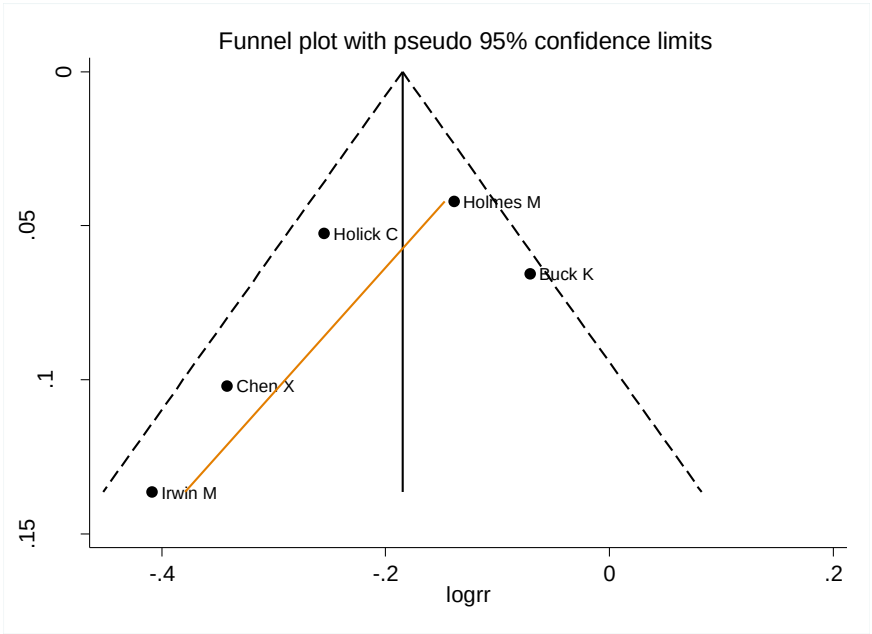


Figure 73 Funnel plot of studies of recreational physical activity 12 months or more after diagnosis and total mortality



Each dot represents the logarithm of relative risk estimate against standard error as a measure of study size. Solid line is the logarithm of summary risk estimate from the meta-analysis. Dashed lines are its 95% confidence interval. Funnel plot displayed when there are at least five studies. The asymmetry of the funnel plot appears to be due to the strong inverse association reported by the smallest study (Irwin, 2008). Egger's test p = 0.52

Figure 74 Individual dose-response graph of recreational physical activity 12 months or more after diagnosis and total mortality

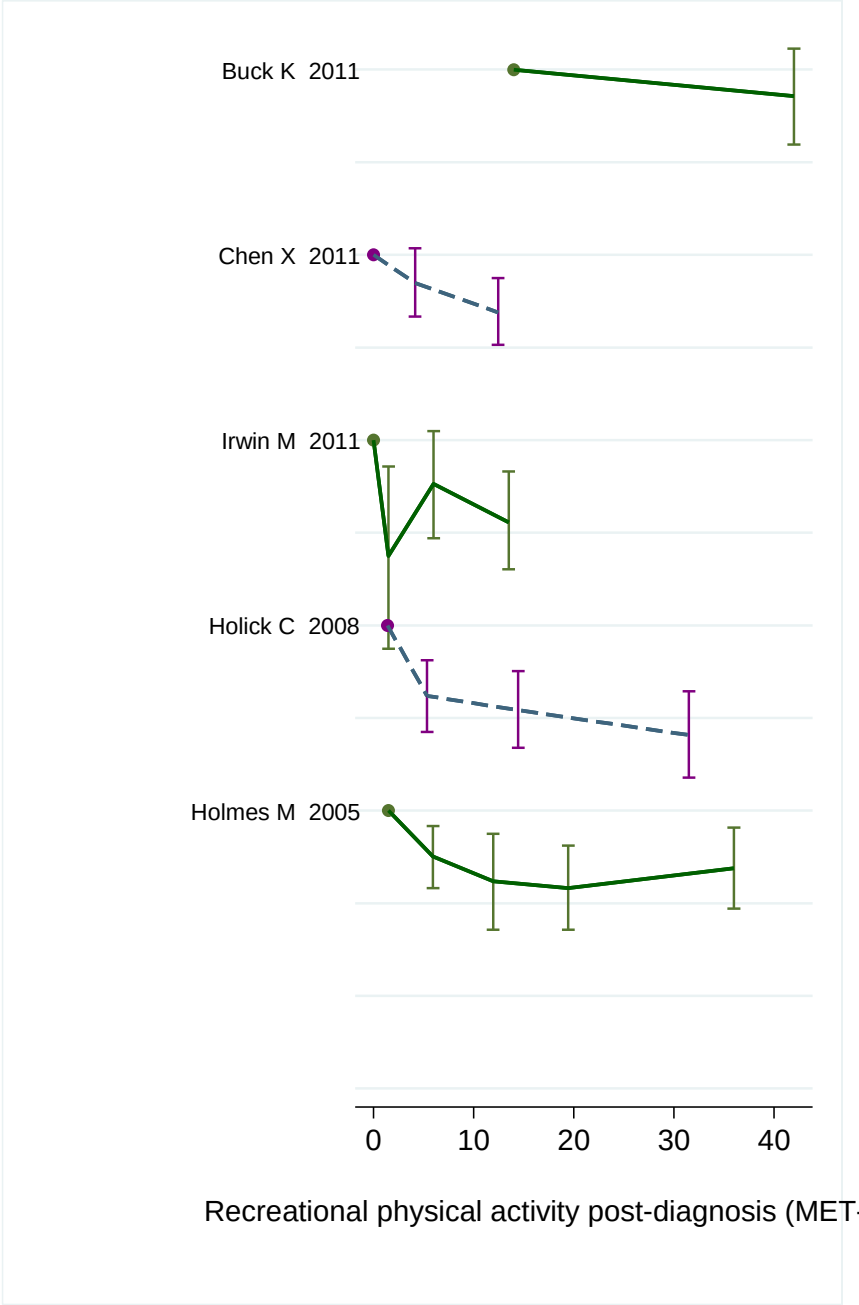


Figure 75 Dose-response meta-analysis of recreational physical activity 12 months or more after diagnosis and total mortality by menopausal status

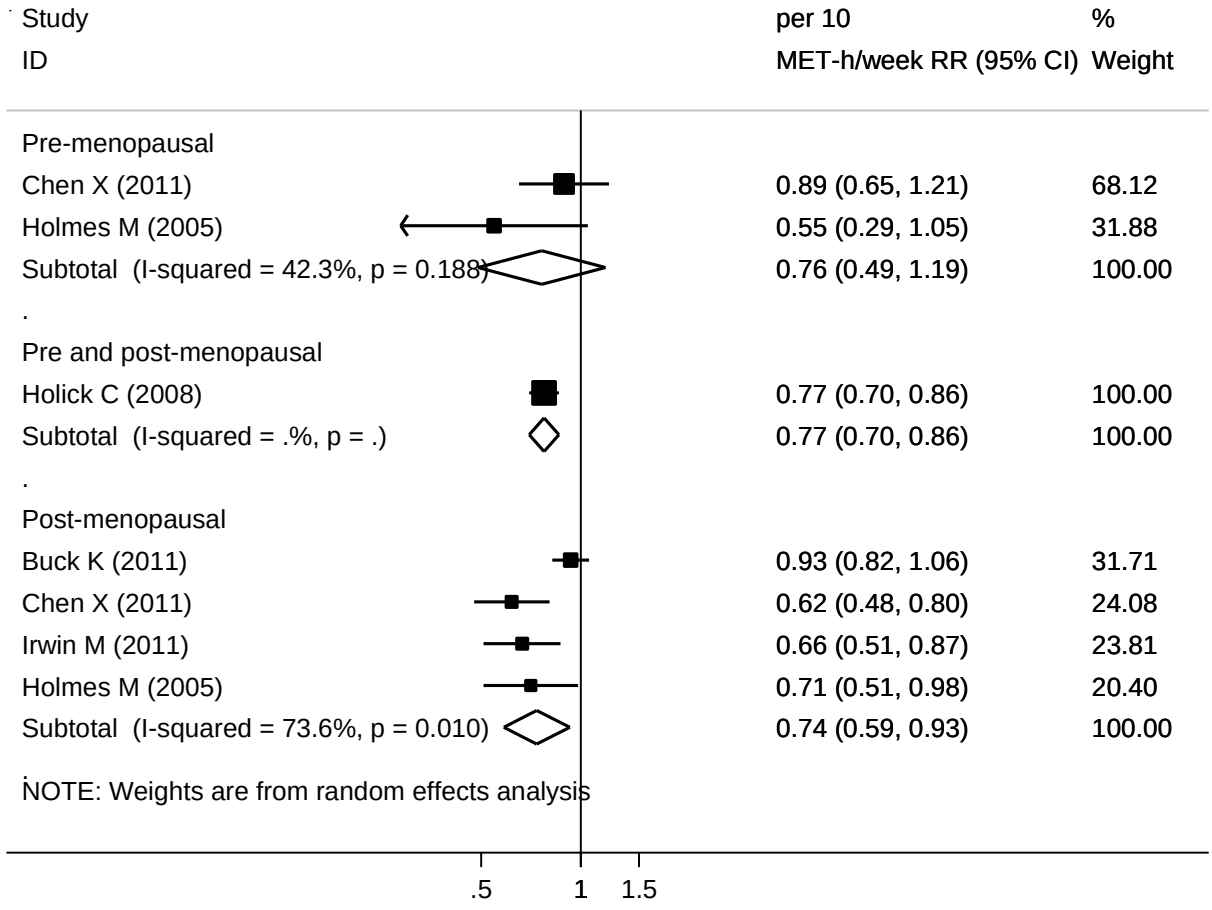


Table 63 Table of included studies on recreational physical activity 12 months or more after diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Chen X (2011)	Shangai Breast Cancer Study China	Study recruitment: 2002-2006 6 months after diagnosis	Prospective cohort of breast cancer survivors	4826 participants 53.5 years (mean) 20 - 75 years 48.6% premenopausal, 51.4% postmenopausal	4.3 years	TNM stages: 37.2% 0-I, 33.1% IIA, 16.6% IIB, 8.7% III-IV, 4.4% unknown	51.2% ER+/PR+, 26.9% ER-/PR-, 20.2% ER/PR mixed, 1.8% ER/PR unknown	Surgery: 94.3% mastectomy, 2.7% conservation surgery, 2.7% unknown type, 0.3% no surgery; Chemotherapy: 91% yes, 9% no; Tamoxifen use: 66.3% yes, 33.7% no; Radiotherapy: 31.2% yes, 68.8% no; Immunotherapy: 14.9% yes, 84.8% no, 0.2% unknown	80%	PA assessed approximately 6, 18, and 36 months post-diagnosis	4826 participants 436 deaths and 450 recurrences or breast cancer-related deaths	Cancer registry	>=8.3 vs. <8.3 MET-h/week	0.65 (0.51-0.84)	Date of birth, BMI at baseline, waist-to-hip ratio at baseline, menopausal status, income, education, QOL, cruciferous vegetable intake, soy protein intake, tea consumption, chemotherapy, radiotherapy, tamoxifen use, TNM status, and ER/PR status
Irwin M (2011)	Women's Heath Initiave United States	Study recruitment: 1993-1998, Study follow-up: Until 2005	Cancer survivors of population-based prospective cohort study or clinical trials	4643 participants 50 - 79 years Postmenopausal	7 years	Stages I-IIIA		Chemotherapy: 25% yes among stage I, 78% yes among stageII/III patients		On average 4.1 years from pre-diagnosis physical activity assessment to cancer diagnosis. On average 1.8 years from diagnosis to post-diagnosis physical activity assessment	4643 participants 350 deaths, 194 breast cancer mortality	Death certificate	>=9 vs. 0 MET-h/week	0.54(0.38-0.79)	Age, ethnicity, WHI study arm, previous hormone therapy use, BMI, diabetes, alcohol, smoke, total calories, percentage calories from fat, and servings of fruit and vegetables
Buck K (2011)a	Hamburg and Rhein-Neckar-Karlsruhe, Germany Follow-up Study Germany	Cancer diagnosis: 2002-2005, Study follow-up: Until 2009	Follow-up of cases of population-based case-control study	1140 participants 50 - 74 years Postmenopausal HRT use:39.8% current, 59.2% past/ever Diabetes: 10.5% yes, 89.4% no; Cardiovascular disease: 51.2% yes, 48.8% no	6.1 years	5.9% In situ, Grades: 63.7% 1-2, 24.1% 3, 17.7% HER2+, 66.3% HER2-, 3.9% metastasis, 6% unknown	54% ER+/PR+, 17.8% ER+/PR- or ER-/PR+, 16.2% ER-/PR- 29.8% +ve, 58.1% -ve	Surgery: 2.6% ablation, 26.4% ablation + axilla, 11.4% breast conserving surgery, 58.5% breast conserving surgery + axilla; Chemotherapy: 39% adjuvant, 6% neoadjuvant, 54.1% no; Radiotherapy: 76% yes, 23.9% no; Tamoxifen use: 59.8% yes, 30.4% no		Self-reported at baseline; PA at age 50y	1140 participants 162 deaths, 124 breast cancer mortality, 15 deaths from cardiovascular disease, 23 other causes of deaths	Death certificate	>=28 vs. <28 MET-h/week	0.82 (0.57-1.17)	Age at diagnosis, tumor size, nodal status, tumor grade, ER status, detection type, diabetes, HRT, BMI, physical activity

Holick C (2008)	Colloborative Women's Longevity Study United States	Cancer diagnosis: 1988-2001; Study follow up: until 2004 Within 2 years of diagnosis	Prospective cohort of breast cancer survivors	4482 participants 58.5 years (mean) 20 - 79 years 72.7% postmenopausal	5.5 years	Invasive breast cancer: 72.6% local, 27.4% regional				Self-reported after diagnosis; post diagnosis PA	4482 participants 412 deaths, 109 breast cancer mortality	National Death Index	>=21 vs. <2.8MET-h/week	0.44 (0.32-0.61)	Age at diagnosis, stage of disease at diagnosis, state of residence at diagnosis, and interval between diagnosis and physical activity assessment, post-diagnosis BMI, post-diagnosis menopausal status, post-diagnosis hormone therapy use, total energy intake year before enrollment in the CWLS, education level at diagnosis, family history of breast cancer at diagnosis, and initial treatment modality
Holmes M (2005)	Nurses' Health Study United States	Cancer diagnosis:1984 and 1998; Study follow up: until June 2002 Recruitment in 1976, Diagnosis in 1984-1998	Cancer survivors of population-based prospective cohort study	2987 participants 30 - 55 years Among those with data: 531 premenopausal and 2242 postmenopausal 986 postmenopausal HRT use:986 postmenopausal women only	96 months	Invasive breast cancer; stage I, II and III		991 patients had chemotherapy		Measured first at 2 years after diagnosis (1986) and reassessed in 1988, 1992, 1994, 1996, 1998, and 2000	2987 participants 463 deaths, 280 breast cancer mortality	Family+ National Death Index	>=24 vs. <3 MET-h/week	0.65 (0.48-0.88)	Age, time from diagnosis to exposure assessment, smoking, BMI, menopausal status, hormonal therapy, age at first birth, parity, oral contraceptive, energy intake, tumor stage, tamoxifen use, chemotherapy

Physical activity and breast cancer mortality

Twelve studies on physical activity and breast cancer mortality were identified. Eight studies were on physical activity before diagnosis and breast cancer mortality (Enger, 2004b; Dal Maso, 2008; Irwin, 2008; West-Wright, 2009, Friedenreich, 2009; Hellman, 2010; Emaus, 2010; Cleveland, 2011), one study on physical activity less than 12 months after diagnosis and breast cancer mortality (Borugian, 2004) and 4 studies were on physical activity 12 months or more after diagnosis and breast cancer mortality (Holmes, 2005; Irwin, 2008; Sternfeld, 2009; Rohan, 1995). One study published twice (Holmes, 2005; Holmes, 2009). The publication from 2009 did not provide enough information therefore the one from 2005 was included in the analysis. One study (Irwin 2008) reported both on physical activity before and 12 months or more after diagnosis.

From the 8 studies on physical activity before diagnosis, two were on total physical activity and seven were on recreational physical activity, one study reported on both total physical activity and recreational physical activity (Friedenreich, 2009).

From the 4 studies on physical activity 12 months or more after diagnosis, 2 studies were on total physical activity and 2 were on recreational physical activity.

Physical activity before diagnosis and breast cancer mortality

Total physical activity before diagnosis and breast cancer mortality

The wide variability in the measurement methods of physical activity-related exposures between the two studies identified made it difficult to pool the results together. Therefore the dose response meta-analysis was not possible to conduct. In the highest versus lowest forest plot the overall RR was 0.80 (95% CI 0.59-1.10; 2 studies).

Recreational physical activity before diagnosis and breast cancer mortality

The wide variability in the measurement methods of physical activity-related exposures between the seven studies identified made it difficult to pool the results together. Therefore the dose response meta-analysis was not possible to conduct. In the highest versus lowest forest plot the overall RR was 0.76 (95% CI 0.61-0.95; 7 studies).

Two studies stratified the analysis by BMI status. West-Wright, 2009 reported a significant protective effect of physical activity on breast cancer mortality for women with BMI ≥ 25 kg/m^2 (HR 0.41; 95% CI 0.23-0.74; >3 h/wk/y vs. >0.5 h/wk/y) but not for women with a BMI < 25 kg/m^2 (HR 1.15; 95% CI 0.58 -2.29; >3 h/wk/y vs. >0.5 h/wk/y). Cleveland, 2011 reported no decreasing trend in breast cancer mortality for those with increasing levels of recreational physical activity in either normal weight or overweight/obese women.

Figure 76 Highest versus lowest forest plot of physical activity before diagnosis and breast cancer mortality

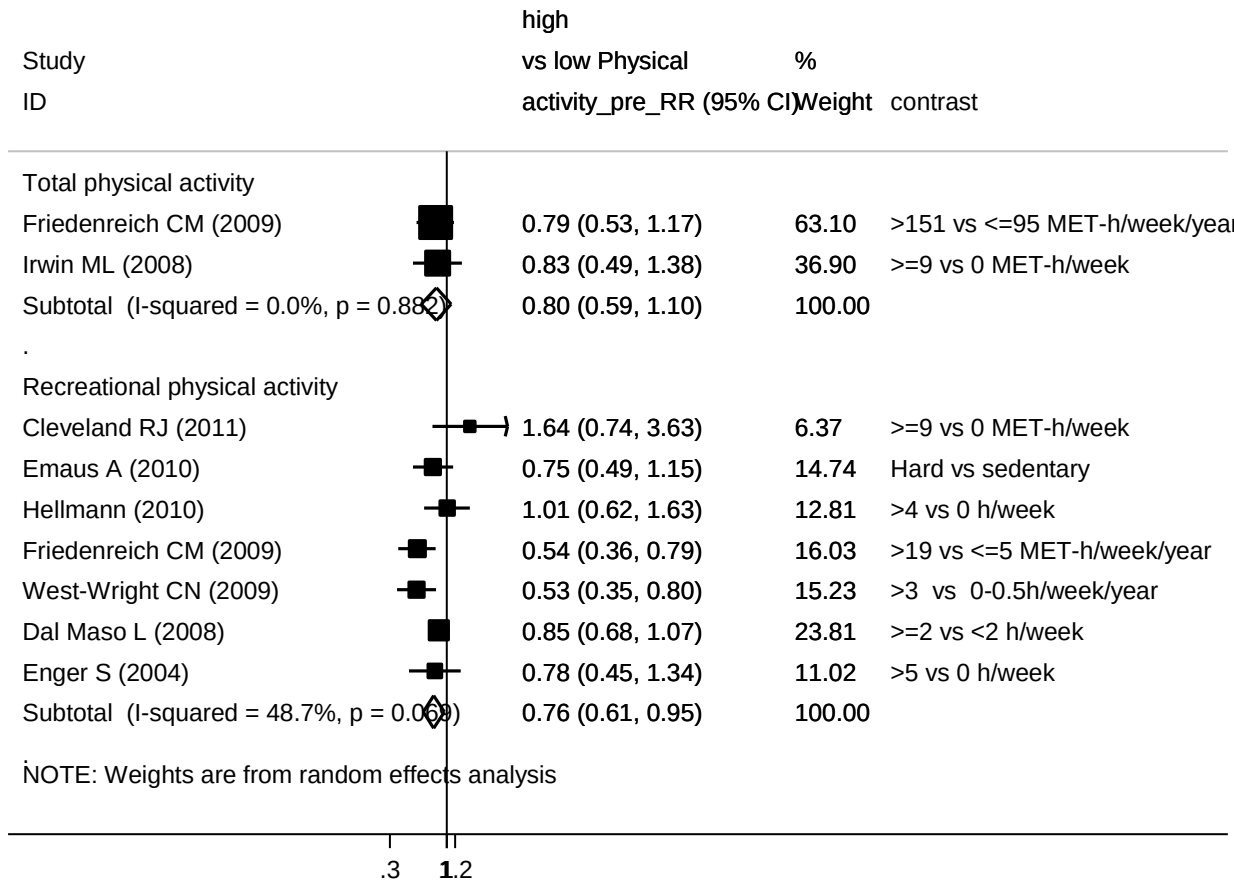


Table 64 Table of included studies on total physical activity before diagnosis breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Friedenreich CM (2009)	Alberta Cancer Registry Follow-up Study Canada	Cancer diagnosis: 1995-1997; Study follow up: until 2008	Prospective cohort study of breast cancer survivors	1225 participants 56 years (mean) 62.4% postmenopausal HRT use: 34% 47.3% with comorbidities	8.3 years	Incident in situ and invasive breast cancer; 9% stage 0, 42.3% stage I, 39.8% stage II, 8.8% stage III+, 0.2% missing	68.2% ER+ve, 62.7% PR+ve	35.6% chemotherapy, 38.6% hormonal therapy, 54.7% radiotherapy		Self reported at baseline; lifetime PA	1225 participants 341 deaths, 223 breast cancer mortality	SEERS	>151 vs. <=95 MET-h/week/year	0.79 (0.53-1.17)	Age, tumor stage, treatment (chemotherapy, hormone therapy and radiation therapy), SBR grade, BMI and other comorbidity conditions
Irwin ML (2008)	Health Eating Activity and Lifestyle Study United States	Cancer diagnosis:1995-1998; Study follow up: until 2004	Prospective cohort study of breast cancer survivors	933 participants 18 - 64 years Multi-ethnic ~59% post-menopausal	6 years	Primary breast cancer				Assessed the year before & 2 years after diagnosis (during baseline interview (approximately 6 months after diagnosis)	933 participants 164 deaths, 115 breast cancer mortality, 56 breast cancer recurrence, 40 new breast cancer primaries	Cancer register	>=9 vs. 0 MET-h/week	0.83 (0.49-1.38)	Age, race, disease stage, initial treatment, and tamoxifen use

Table 65 Table of included studies on recreational physical activity before diagnosis breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Cleveland RJ (2011)	Long Island Breast Cancer Study Project United States	Cancer diagnosis: 1996-1997, Study follow-up: Until Soon after diagnosis	Follow-up of cases of population-based case-control study	1508 participants 58.9 years (mean) ~68% post-menopausal	66.7 months	First primary in situ or invasive breast cancer					1508 participants 196 deaths, 128 breast cancer mortality	Death certificate	>=9 vs. 0 MET-h/week	1.64 (0.74-3.63)	Age at diagnosis, body mass index and menopausal status
Emaus A (2010)	Norwegian Health Surveys Follow-up Study, three counties Norway	Cancer diagnosis: 1975–2005;	Cancer survivors of a population-based prospective cohort study	1364 participants 57.5 years (mean) 27 - 79 years 61% postmenopausal HRT use: 30 patients, only measured in 3rd survey. Participants of a health screening cohort. Comorbidities: 8 diabetic patients	8.2 years	Invasive breast cancer; TNM; 49% Stage 1, 41% Stage 2, 4.5% stage 3, 5.3% stage 4			91% in the 1st, 91% in the 2nd and 88% in the 3rd survey / Complete follow up	Measured during health screening, prior to diagnosis (usual level of physical activity during leisure time in the year preceding each survey)	1364 participants 429 deaths, 355 breast cancer mortality, 27 death from other cancers, 23 death from cardiovascular disease, and 24 from other causes	Death record	Hard vs. sedentary	0.75 (0.49-1.15)	Age at diagnosis, pre-diagnostic observation time, tumor stage, region of residence, year at diagnosis before and after 1995 and BMI
Hellmann (2010)	Copenhagen City Heart Study Denmark	Study recruitment:1976; Study follow up: until 2007	Cancer survivors of a population-based prospective cohort study	528 participants 66.9 years (mean) 33.1 - 95.4 years 16.1% premenopausal, 83.9% postmenopausal HRT use: 71.2% unexposed, 28.8% exposed	7.8 years	Primary breast cancer, one sarcoma, 527 carcinomas; TNM; 56.2% local, 33.7 regional, 6.3 metastatic, 3.8% unknown		7.4% radiotherapy, 7.4% chemotherapy, 22.4% hormonal therapy	74% at the 1st, 70% at the 2nd , 61% at the 3rd and 50% at the 4th examination / 1%lost	Measured at study baseline	528 participants 323 deaths, 174 breast cancer mortality, 126 other causes of death including 43.6% death from cardiovascular disease and 25.6% other cancers	Cancer registry	>4 vs. 0h/w	1.01 (0.62-1.63)	Alcohol, smoking, physical activity, body mass index, hormone replacement therapy, age, disease stage, menopausal status, parity, education, and adjuvant treatment
Friedenreich CM (2009)	Alberta Cancer Registry Follow-up Study Canada	Cancer diagnosis: 1995-1997; Study follow up: until 2008	Prospective cohort study of breast cancer survivors	1225 participants 56 years (mean) 62.4% postmenopausal HRT use: 34% 47.3% with comorbidities	8.3 years	Incident in situ and invasive breast cancer; 9% stage 0, 42.3% stage I, 39.8% stage II, 8.8% stage III+, 0.2% missing	68.2% ER+ve, 62.7% PR+ve	35.6% chemotherapy, 38.6% hormonal therapy, 54.7% radiotherapy		Self reported at baseline; lifetime PA	1225 participants 341 deaths, 223 breast cancer mortality	SEERS	>19 vs. <=5 MET-h/week	0.54 (0.36-0.79)	Age, tumor stage, treatment (chemotherapy, hormone therapy and radiation therapy), SBR grade, BMI and other comorbidity conditions
West-Wright CN (2009)	California Teachers Study United States	Study recruitment: 1995; Cancer diagnosis: 1995-2004; Study follow up: until 2005	Cancer survivors of a population-based prospective cohort study	3539 participants 58.9 years (mean) 26 - 94 years Mostly white: 89.7%Comorbidities: 111 diabetes, 106 cardiovascular disease; % by menopausal status not reported	9 Years (max)	Incident first primary invasive breast cancer; 68.9% localized, 28.4% regional, 1.86 metastatic, 0.8 % missing	72% ER+ve, 12.7% ERve, 15.3% unknown			Self-reported at baseline; PA within the 3 years prior to cohort entry, prior to diagnosis	3539 participants 460 deaths, 221 breast cancer mortality, 69 death from other causes including 24 death from other cancers, 68 cardiovascular disease deaths; 38 cerebrovascular disease deaths;	Death certificate	>3 vs. 0-0.5 h/week/y	0.53 (0.35-0.80)	Age, for race, BMI, total caloric intake, number of comorbid conditions and estrogen receptor status

											28 cardiopulmonary or pulmonary disease deaths; 4 diabetes death				
Dal Maso L (2008)	Six Italian Regions Follow-up Study Italy	Cancer diagnosis: 1991-1994; Study follow up: until 2005-2006 diagnosed no longer than 1 year before the interview	Follow-up of cases of a case-control study	1453 participants 55 years (mean) 23 - 74 years Among those with data, pre diagnosis data: 45.5 % peri/pre menopausal, 54.9% postmenopausal HRT use: 91.3% never, 8.6% ever	12.6 years	Invasive breast cancer; TNM; 32.7% Stage I, 44.1% stage II, 13.2% stage III-IV, 9.8% unknown	41.5% ER+ve/PR+ve, 3.5% ERve/ PR+ve, 45.6% no node+ve, 44.2% node+ve, 10.1%		2.70% lost	Self-reported (questionnaire) at study baseline	1453 participants 503 deaths, 398 breast cancer mortality, 6.2% death from other cancers, 7.4% from cardiovascular disease	Cancer registry	>=2 vs. <2h/week	0.85 (0.68-1.07)	Region, age at diagnosis, year of diagnosis, TNM stage, receptor status
Enger S (2004)b	University of Southern California Cancer Surveillance Program United States	Cancer diagnosis: 1983-89, Study follow-up: Until 2000	Follow-up of cases of population-based case-control study	717 participants 40 years White or Hispanic Premenopausal	10.4 years	Stages: 9.9% in situ, 47.4% localized, 39.1% regional, 3.6% distant metastasis	41.1% +ve, 57.3% -ve, 1.5% unknown		76.80%	Self-reported data for age 18, a year prior to diagnosis in interview at study baseline	717 participants 251 breast cancer mortality, 2 deaths from coronary/CVD, 10 other causes of deaths	Death certificate	>5 vs. 0h/week	0.78 (0.45-1.34)	Age, tumor stage, BMI

Physical activity less than 12 months after diagnosis and breast cancer mortality

One study (Borugian, 2004) on physical activity less than 12 months after diagnosis and breast cancer mortality was identified. This study found no relationship between different types of physical activity (climbing stairs (RR 1.1; 95%CI 0.5-2.2; >9 vs. none flights), walking (RR 1.0; 95%CI 0.5-1.9; > 9 vs. none blocks), sports (RR 1.0; 95% CI 0.5-3.2; more than once a week vs. none), jogging (RR 1.8; 95% CI 0.4-7.5; more than once a week vs. none), swimming (RR 0.9; 95% CI 0.5-1.5; more than once a week vs. none) or gardening (RR 0.8; 95% CI 0.5-1.4; more than once a week vs. none) and breast cancer mortality.

Physical activity 12 months or more after diagnosis and breast cancer mortality

Total physical activity 12 months or more after diagnosis and breast cancer mortality

The two studies identified (Irwin, 2008; Sternfeld, 2009) showed non-significant associations between total physical 12 months or more after diagnosis and breast cancer mortality. In the HEAL study (Irwin, 2008), the hazard ratio for > 9 MET-h/wk of physical activity two years after diagnosis compared to no physical activity was 0.65; 95% CI 0.23-1.87. In the LACE study, the hazard ratio for > 62 compared to < 29 MET-h/wk was 0.87 (95% CI 0.48-1.59).

Recreational physical activity 12 months or more after diagnosis and breast cancer mortality

Two studies were identified (Rohan, 1995; Holmes, 2005). Only the Nurses' Health Study (Holmes, 2005) showed a protective effective of recreational physical activity against breast cancer mortality, significant for levels above 9-14.9 MET-h/week. The RR was 0.60 (95% CI 0.40-0.89, ≥ 24 vs. < 3 MET-h/week). One study (Fleischauer, 2003) found no association between exercise and breast cancer mortality/breast cancer recurrence.

Figure 77 Highest versus lowest forest plot of physical activity 12 months or more after diagnosis and breast cancer mortality

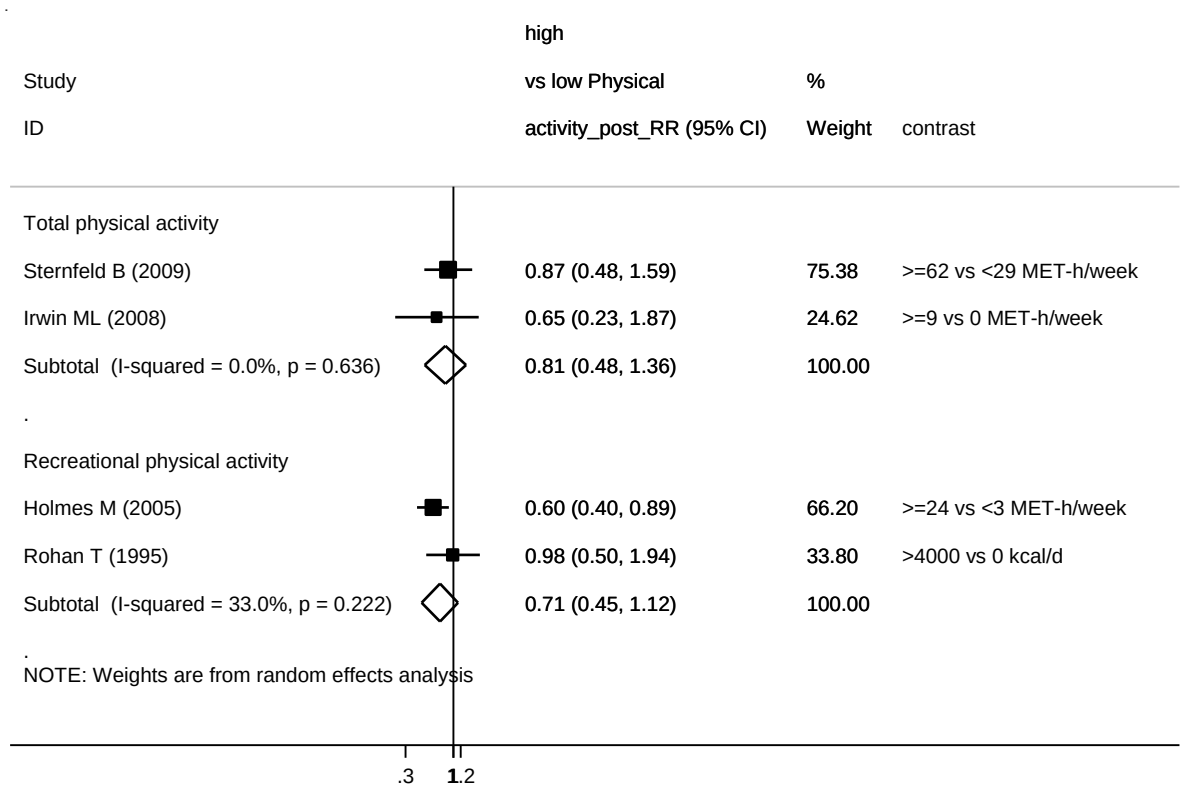


Table 66 Table of included studies on total physical activity 12 months or more after diagnosis breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Sternfeld B (2009)	LACE United States	Cancer diagnosis:1997-2000; Diagnosed within 39 months of enrolment in the original study	Prospective cohort study of breast cancer survivors	1970 participants 18 - 79 years Among those with data: 21 % premenopausal, 65.3% postmenopausal, 13.7% unknown	87 months	Early-stage breast cancer; AJCC; among those with data: 47.6% stage I, 33.4% stage IIa, 16% stage IIb, 2.9% stage IIIa	Among those with data: 68.2% ER+/ PR+, 14.2% ER+/ PR-, 1.8% ER-/ PR+, 15.8% ER-/ PR- / Among those with data: 64.2% node-ve, 35.8% node+ve (25.5 % 1-3 nodes+ve, 10.3% >= 3 nodes +ve)	Among those with data: Surgery: 50.4% conserving, 49.6% mastectomy; Chemotherapy: 56.3% yes, 43.7% no; Radiation therapy: 62.9 % yes, 37.1% no	/ 15 patients lost	Self-reported at baseline; PA after diagnosis (6 month prior to enrolment)	1970 participants 187 deaths, 102 breast cancer mortality	Death certificate	>=62 vs. <29 MET-h/week	0.87 (0.48-1.49)	Age, number of positive nodes, stage, weight at 18 y, education level and smoking status
Irwin ML (2008)	Health Eating Activity and Lifestyle Study United States	Cancer diagnosis:1995-1998; Study follow up: until 2004	Prospective cohort study of breast cancer survivors	933 participants 18 - 64 years Multi-ethnic	6 years	Primary breast cancer				Assessed the year before & 2 years after diagnosis (during baseline interview (approximately 6 months after diagnosis).	933 participants 164 deaths, 115 breast cancer mortality, 56 breast cancer recurrence, 40 new breast cancer primaries.	Cancer register	>=9 vs. 0 MET-h/week	0.65 (0.23-1.87)	Age, race, disease stage, initial treatment, and tamoxifen use

Table 67 Table of included studies on recreational physical activity 12 months or more after diagnosis breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Holmes M (2005)	Nurses' Health Study United States	Cancer diagnosis:1984 and 1998; Study follow up: until June 2002 Recruitment in 1976, Diagnosis in 1984-1998	Cancer survivors of population-based prospective cohort study	2987 participants 30 - 55 years Among those with data: 531 premenopausal and 2242 postmenopausal 986 postmenopausal HRT use:986 postmenopausal women only	96 months	Invasive breast cancer; stage I, II and III		991 patients had chemotherapy		Measured first at 2 years after diagnosis (1986) and reassessed in 1988, 1992, 1994, 1996, 1998, and 2000	2987 participants 463 deaths, 280 breast cancer mortality	Family+ National Death Index	>=24 vs. <3 MET-h/week	0.60 (0.40-0.89)	Age, time from diagnosis to exposure assessment, smoking, BMI, menopausal status, hormonal therapy, age at first birth, parity, oral contraceptive, energy intake, tumor stage, tamoxifen use, chemotherapy
Rohan T (1995)	Diet and Breast Cancer in Australia Follow-up Study Australia	Cancer diagnosis: 1982-1984, Study follow-up: Until 1989	Follow-up of cases of population-based case-control study	451 participants 55.1 years (mean) 20 - 74 years	5.5 years				80.7% (16.7% refused/untraceable, 2.7% died)	The average interval between diagnosis and interview was 4.8 months	451 participants 112 breast cancer mortality, 11 other causes of deaths	Cancer registry	>4000 vs. 0 Kcal/d	0.98 (0.50-1.94)	Age, receptor status, tumor size, education, history of benign breast disease, age at first birth, age of menarche, height, Quetelet Index, energy intake, menopausal status

Physical activity change from before to 12 months or more after diagnosis

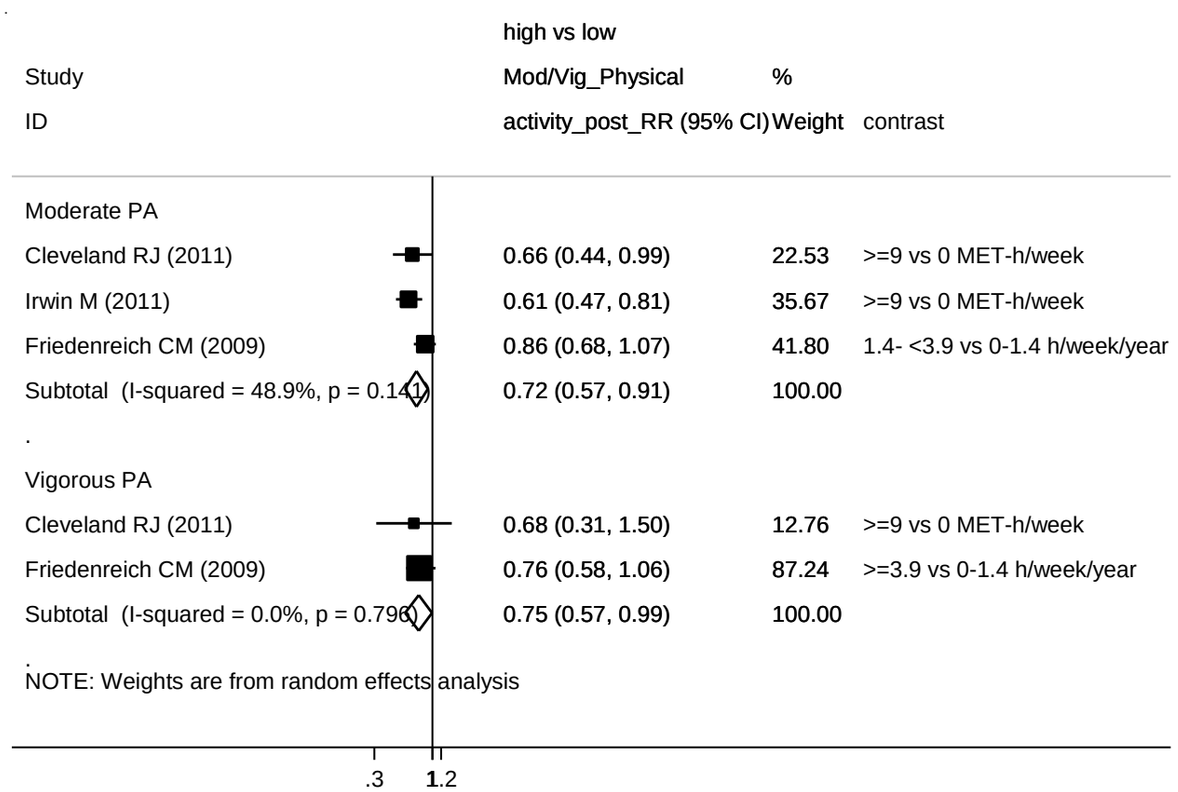
Three studies were identified. The HEAL study (Irwin, 2008) found no association between physical activity change one year before and 2 years after diagnosis and total mortality (RR 0.55; 95% CI 0.22 to 1.38, increased vs. inactive) or breast cancer mortality (RR 0.82;, 95% CI 0.29 to 2.34, increased vs. inactive). The WHI study (Irwin, 2011) found no association between moderate- to vigorous-intensity physical activity change before (4.1 ± 2.3 years) and after diagnosis (1.8 ± 1years) and total mortality (RR 1.06, 95% CI 0.73-1.54, decrease/inactive vs. no change/inactive) or breast cancer mortality (RR 1.06; 95% CI 0.59-1.88; decrease/inactive vs. no change/inactive). The WHEL study (Bertram, 2011) found no association between physical activity change (baseline post-treatment to 1 year after) and total mortality (RR 1.04; 95% CI 0.61-1.77; not meeting guidelines of 10 MET-h/week vs. change to meet the guidelines of 10 MET-h/week) or second primary breast cancer events (RR 1.22; 95% CI 0.81-1.83; not meeting guidelines of 10 MET-h/week vs. change to meet the guidelines of 10 MET-h/week).

Moderate to vigorous physical activity and total mortality

Moderate to vigorous before diagnosis

Three studies were identified and could be included in the high versus low analysis. For moderate physical activity before diagnosis the RR was 0.72 (95% CI 0.57-0.91; 3 studies) and for vigorous physical activity before diagnosis the RR was 0.75 (95% CI 0.57-0.99; 2 studies).

Figure 78 Highest versus lowest forest plot of moderate to vigorous physical activity before diagnosis and total mortality



Cleveland RJ (2011) - Moderate intensity recreational physical activity includes activities that expend ≥ 3.0 or < 6.0 metabolic equivalent task. Vigorous intensity recreational physical activity includes activities that expend ≥ 6.0 metabolic equivalent task.

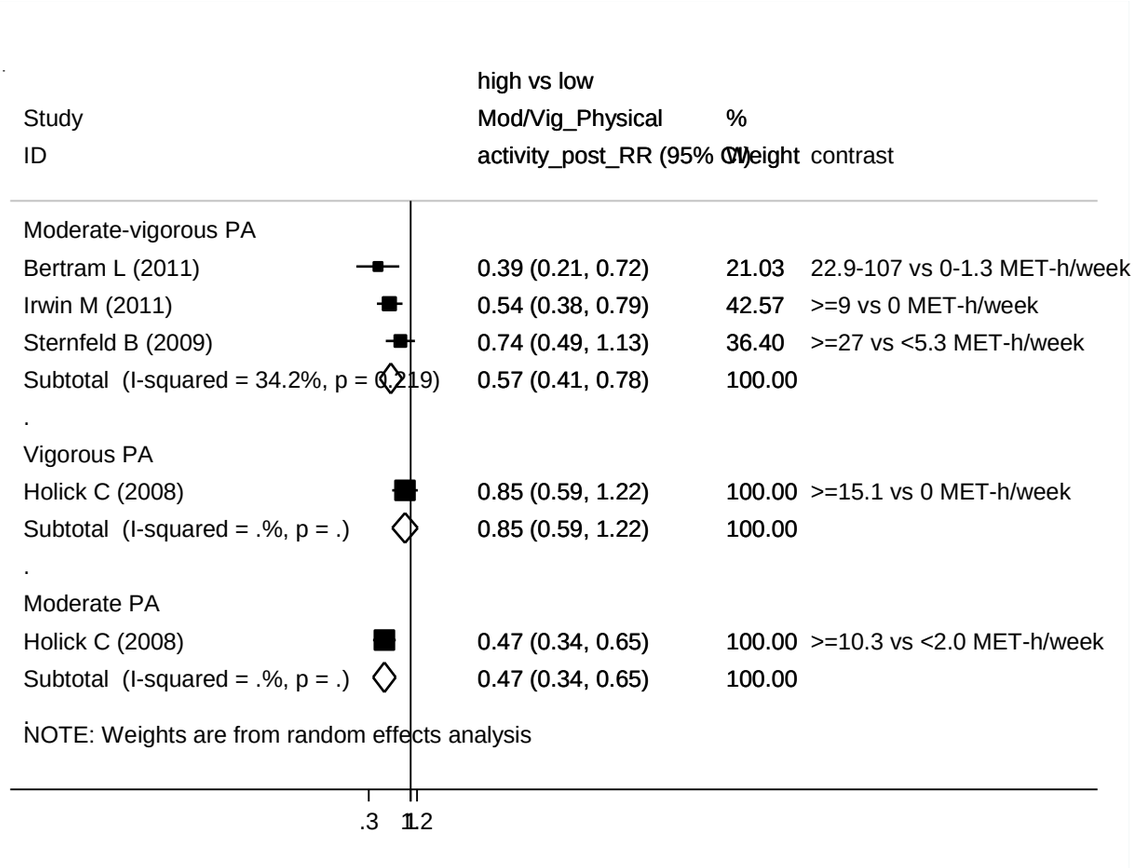
Irwin M (2011) - Moderate-intensity recreational (4 METs), and vigorous-intensity recreational (7 METs) activities. The authors multiplied the MET level for the activity by h/wk to compute a moderate- to vigorous-intensity physical activity variable.

Friedenreich CM (2009) - Moderate intensity (3–6 METs) recreational physical activity (hr/week). Vigorous intensity (> 6 METs) recreational physical activity (hr/week).

Moderate to vigorous physical activity 12 months or more after diagnosis

Four studies were identified and could be included in the high versus low analysis. For moderate physical activity 12 months or more after diagnosis the RR was 0.47 (95% CI 0.34-0.65; 1 study), for moderate-to-vigorous physical activity 12 months or more after diagnosis the RR was 0.57 (95% CI 0.41-0.78; 3 studies) and for vigorous physical activity 12 months or more after diagnosis the RR was 0.85 (95% CI 0.59-1.22; 1 study).

Figure 79 Highest versus lowest forest plot of moderate to vigorous physical activity 12 months or more after diagnosis and total mortality



Bertram L (2011) – Moderate to vigorous physical activity ≥ 3.0 MET-h/week

Irwin M (2011) - Moderate-intensity recreational (4 METs), and vigorous-intensity recreational (7 METs) activities. The authors multiplied the MET level for the activity by h/wk to compute a moderate- to vigorous-intensity physical activity variable.

Sternfeld B (2009) - Moderate to vigorous physical activity ≥ 3.0 MET-h/week.

Holick C (2008) - Moderate-intensity recreational physical activity include activities that expend < 6.0 MET: walking outdoors and stair climbing. Vigorous-intensity recreational physical activity include activities that expend ≥ 6.0 MET: running (≥ 10 min/mile); calisthenics, aerobics, aerobic dance, and rowing machine; tennis, squash, or racquetball; lap swimming; and other aerobic recreation (e.g., lawn mowing).

6 Energy balance

6.1 Total energy intake

Table 68 Summary results of meta-analysis on before diagnosis total energy intake and total mortality*

Comparison	No. of studies	No. of events in studies	RR (95% CI)	I^2, $P_{heterogeneity}$
Per 500 kcal/day	3	542	1.07 (0.80-1.42)	82.1%, p = 0.004

*No studies on breast cancer mortality and second cancers were included in the meta-analyses. Only studies on total energy intake before diagnosis could be included in the dose-response meta-analysis.

Total energy intake and total mortality

Seven studies on total mortality were identified. Four studies examined total energy intake before diagnosis (Zhang, 1995; Saxe, 1999; Goodwin, 2003; West-Wright, 2009), no study examined intake less than 12 months after diagnosis, and three studies examined intake 12 months or more after diagnosis (Pierce, 2007a; Holmes, 1999; Beasley, 2011).

Total energy intake before diagnosis and total mortality

Methods

Four studies were identified. Three studies could be included in the linear dose-response meta-analysis. Goodwin et al. (2003) reported no relationship between total energy intake and breast cancer survival. Data in this study was not sufficient to include in a meta-analysis. Saxe et al. (1999) only reported a dose-response result; a highest versus lowest meta-analysis was not conducted with the remaining two studies (Zhang, 1995; West-Wright, 2009).

Main results and heterogeneity

The summary RR per 500 kcal/day was 1.07 (95% CI 0.80-1.42; 3 studies). There is evidence of high heterogeneity (I^2 = 82.1%, p = 0.004). In an influence analysis, the summary RR ranged from 0.99 (95% CI 0.69-1.41) when Saxe et al. (1999) was omitted to 1.24 (95% CI 1.05-1.46) when West-Wright et al. (2009) was omitted.

Study quality

Numbers of events were low in two studies, with only 26 deaths (Saxe, 1999) and 56 deaths (Zhang, 1995) accrued after a follow-up of 5 years or more and an average of 2.9 years respectively. The study of West-Wright et al. (2009) had 460 deaths from a maximum of 9 years of follow-up. Saxe et al. (1999) was a clinical series study, with recruitment spanned from 1989 to 1991; while the other two studies (Zhang, 1995; West-Wright, 2009) were population cohorts, with cancer diagnosed in 1986-1991 or 1995-2004. Participants in the first study (Saxe, 1999) were assessed close to the time of diagnosis for a diet one year ago; while dietary data was collected before diagnosis in the latter two studies (Zhang, 1995; West-Wright, 2009). Total energy intake was estimated using a FFQ of at least 100 items in the studies (Zhang, 1995; Saxe, 1999; West-Wright, 2009). One study (West-Wright, 2009) included invasive breast cancer only. Two studies (Saxe, 1999; Zhang, 1995) included *in situ* and invasive breast cancers. One study (Zhang, 1995) was restricted to postmenopausal women only. The other two studies (Saxe, 1999; West-Wright, 2009) included both pre- and postmenopausal women. All studies provided multivariate adjusted results, including the adjustment for tumor stage (Saxe, 1999; Zhang, 1995), or comorbidity and ER status (West-Wright, 2009).

Figure 80 Linear dose-response meta-analysis of total energy intake before diagnosis and total mortality

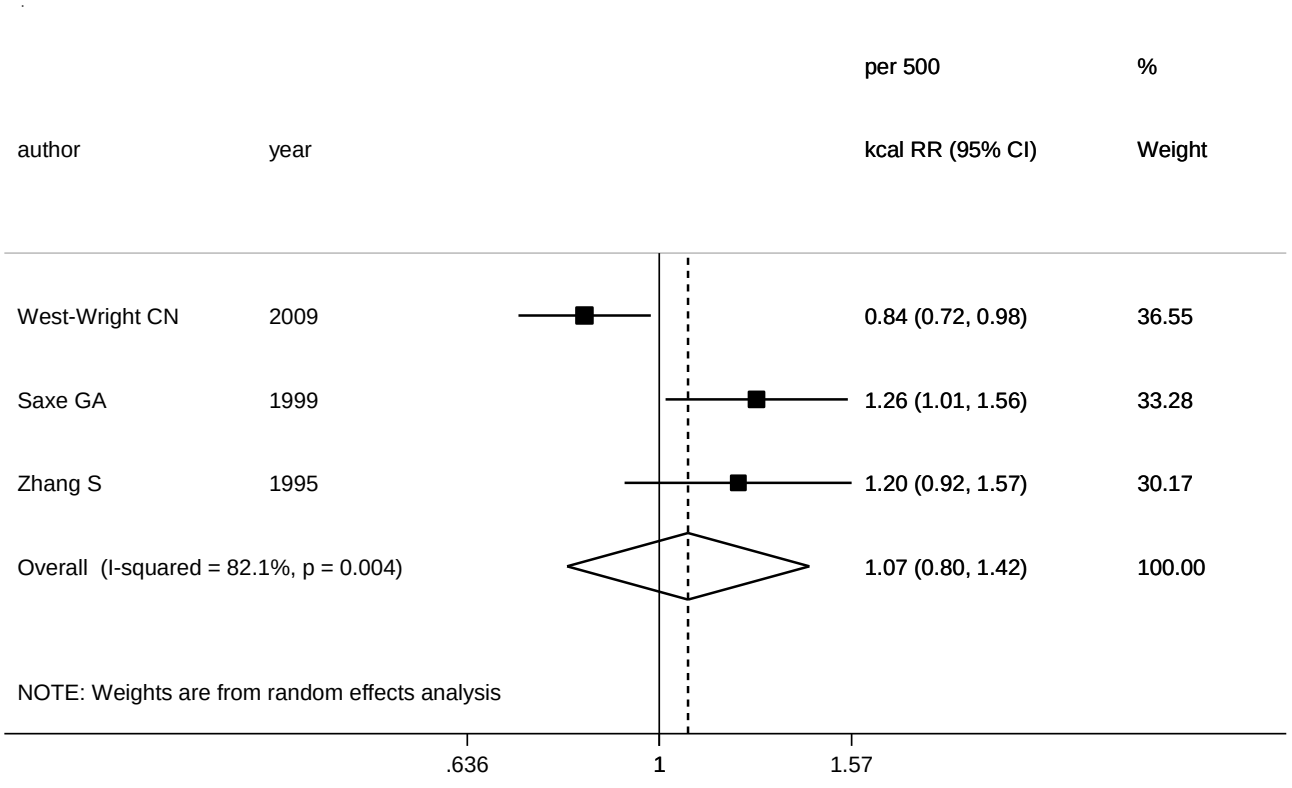


Figure 81 Individual dose-response graph of total energy intake before diagnosis and total mortality

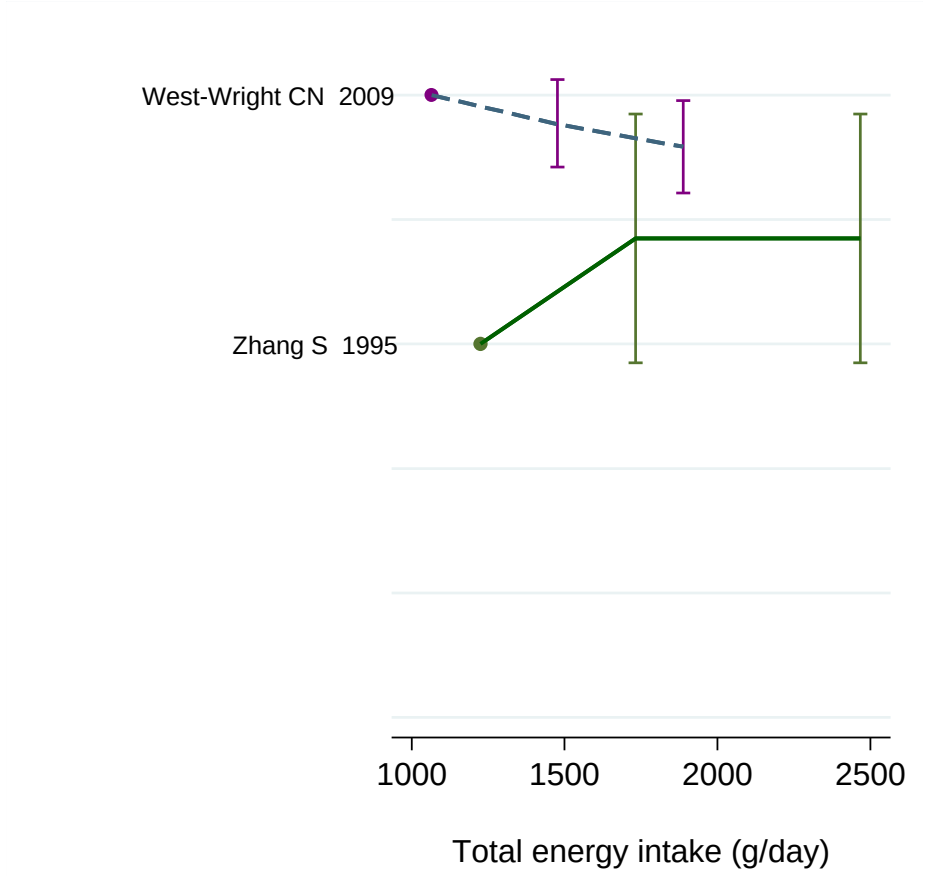


Table 69 Table of included studies on total energy intake before diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
West-Wright CN (2009)	California Teachers Study United States	Study recruitment: 1995; Cancer diagnosis: 1995-2004; Study follow up: until 2005	Cancer survivors of a population-based prospective cohort study	3539 participants 58.9 years (mean) 26 - 94 years Mostly white: 89.7% Comorbidities: 111 diabetes, 106 cardiovascular disease; 24.5 %	9 years (max)	Incident first primary invasive breast cancer; 68.9% localized, 28.4% regional, 1.86 metastatic, 0.8 % missing	72% ER+ve, 12.7% ERve, 15.3% Unknown			Self-reported at baseline; Block FFQ (1995 validated version); 103-item	3539 participants 460 deaths, 221 breast cancer mortality, 69 death from other causes including 24 death from other cancers, 68 cardiovascular disease deaths; 38 cerebrovascular disease deaths; 28 cardiopulmonary or pulmonary disease deaths; 4 diabetes death	Death certificate	>1682 vs. <1271 kcal/d	0.75 (0.58-0.97)	Age, race, BMI, physical activity, number of comorbid conditions and estrogen receptor status
Saxe GA (1999)	Medical Center, Michigan University Follow-up Study United States	Study recruitment: 1989-1991, Recruited during first medical center visit for suspected or newly diagnosed	Prospective cohort of breast cancer survivors	149 participants 57.8 years (mean) 26 - 95 years White: 90.6%, black:7.2% and other: 2.2%, 34.2% premenopausal, 65.8% postmenopausal	5 years (min)	Primary breast cancer, stages: 19.6% in situ, 34.5% I, 34.5% II, 8.8% III, 2.7% IV	73.4% ER+, 26.6% ER- / 43% +ve, 57% -ve		0% lost	Interviewed close to time of diagnosis for diet a year prior to diagnosis, NCI semi-quantitative FFQ; 100-item	149 participants 26 deaths	Hospital records	Per 1000kcal/d increase	1.58 (1.03-2.43)	Tumor stage, body mass index/arm muscle circumference ratio
Zhang S (1995)	Iowa Women's Health Study United States	Study recruitment:1986; Study follow up: until 1991	Cancer survivors of population-based prospective cohort study	698 participants 55 - 69 years Mostly white: 98%, Postmenopausal	2.9 years	Unilateral breast cancer; 10% in situ, 58% local, 28% regional, 3%distant, and 1% unknown; 55% tumour size <2cm, 33% size >= 2cm and 11% unknown	Among those with data: 85% ER+ve and 72% PR+ve		42.60% / < 1% migration rate	Self reported within 6 years before diagnosis, semi-quantitative FFQ; adapted from 126-item questionnaire in NHS	698 participants 56 deaths, 40 breast cancer mortality (among the causes of death) and 2 death from coronary heart disease	Death certificates, National death index	2467vs. 1225 kcal/d	1.80 (0.90-3.60)	Age, smoking, education, tumor stage, ER status, tumor size

Table 70 Table of excluded studies on total energy intake before diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments Exclusion reason
Goodwin P (2003)	University of Toronto Hospitals Follow-up Study, Canada	Study recruitment: 1989-1996,	Prospective cohort of breast cancer survivors	477 participants 50.4 years (mean) <=75 years 57.7% premenopausal, 3.6% perimenopausal, 38.8% postmenopausal	6.1 years	Tumor stages: 55.6% T1, 32.3% T2, 5.2%, 6.9% unknown; Grades: 13% 1, 40.7% 2, 33.1% 3, 13.2% unknown	62.5% ER+, 18.7% ER-, 13.4% unknown; 56.6% PR+, 22.9% PR-, 14.9% unknown 30.6% +ve, 69.4% -ve	Mastectomy: 23.3% yes; Lumpectomy: 76.7% yes; Chemotherapy only: 28.3% yes; Chemotherapy plus tamoxifen 9.6%; Tamoxifen only: 29.6%; None: 32.5% yes	8 patients lost	Block FFQ comleted 9.3 ± 4.6 weeks after diagnosis, reporting intake over preceding 12 months	477 participants, 52 deaths, 2 non-breast cancer related deaths	Medical records		P for linear=0.35, P for non-linear=0.15	BMI,age,tumor stage,nodal status,hormonal therapy,chemotherapy, energy intake Study examined the association of dietary factors with breast cancer survival. HRs were provided from linear and non-linear models, but without 95% CIs or p-values

Total energy intake less than 12 months after diagnosis and total mortality

No study has reported data.

Total energy intake 12 months or more after diagnosis and total mortality

Three studies were identified. Meta-analyses were not conducted because of insufficient data. An undjusted HR of 0.74 (no 95% CI or p-value; p_{trend} = 0.24) for 1981-3553 versus 584-1435 kcal/day was reported by Pierce et al. (2007a). In addition, Holmes et al. (1999) and Beasley et al. (2011) both observed a HR of 0.89 (95% CI 0.64-1.23, p_{trend} = 0.97 and 95% CI 0.68-1.15, p_{trend} = 0.33 respectively) for the highest to the lowest quartile comparison.

Table of studies on total energy intake 12 months or more after diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Beasley JM (2011)	Collaborative Women's Longevity Study United States	Study recruitment: 1998-2001, Study follow-up: Until 2005 On average 5 years (range 1-16 years) post-diagnosis	Follow up of cases of population-based case-control studies	4441 participants 20 - 79 years Mostly white 22.8% premenopausal, 73.3% postmenopausal among those with data HRT use: 33.2% yes, 56.9% no	5.5 years	Primary invasive breast cancer; Stages: 72.8% local, 27.2% regional		Surgery: 97.9% yes; Radiotherapy: 49.8% yes; Hormonal therapy: 57.8% yes; Chemotherapy: 31.9% yes	42%	Assessed on average 5 years (range 1–16) after diagnosis, usual intake over the past year; 126-item FFQ used in NHS	4441 participants 525 deaths, 137 breast cancer mortality, 132 deaths from cardiovascular disease	Death certificate	2407 vs 1077 kcal/day	0.89 (0.68-1.15)	Age, residence, menopausal status, smoking, stage, alcohol intake, hormonal therapy, interval between diagnosis and baseline interview, BMI, physical activity , breast cancer treatment
Pierce J (2007)a	Women's Healthy Eating and Living Study United States	Cancer diagnosis:1991-2000; Study follow up: until 2005 Within 48 months of diagnosis (average, 24 months)	Randomised controlled trial of dietary intervention; ancillary analysis	1490 participants 50 years (mean)	6.7 years	Early stage breast cancer; AJCC; 40% Stage I (>=1cm), 45% Stage II, 15% stage III, 15.9% grade I, 39.8% grade II, 35.8% grade III, 8.3% unknown	63.1% ER+ve/PR+ve, 10.8% ER+ve/PR-ve, 5.1%ER-ve/PR+ve, 20.8% ER-ve/PR-ve	31.4% none-chemotherapy, 25.7% nonanthracycline , 42.8% anthracycline; 42% adjuvant tamoxifen, 58% no adjuvant tamoxifen	7 patients lost	Measured on average 2 y, and a maximum of 4 y after diagnosis; four 24-hr dietary recalls	1490 participants 135 deaths, 118 breast cancer mortality, 10 death from other cancers, 7 death from non-cancer, 236 breast cancer events	Death certificate	1981-3553 vs 584-1435 kcal/day	0.74, p for trend=0.24	
Holmes MD (1999)	Nurses' Health Study United States	Cancer diagnosis: 1976–1990, Study follow-up: Until 1994	Cancer survivors of population-based prospective cohort study	1982 participants 54 years (mean) 35.1% premenopausal, 64.9% postmenopausal, among those with data	157 months	Invasive breast carcinoma; Grade 1-3			95% / 5% lost	On average 24 months (SD 18m) after diagnosis; from the FFQ followed most closely after diagnosis	1978 participants 378 deaths, 326 breast cancer mortality	Death certificate	Q5 vs Q1	0.89 (0.64-1.23)	Age, time between exposure assessment and cancer diagnosis,year of diagnosis,oral contraceptive,hormonal therapy,smoking,age at first birth,nodal status,tumor size,BMI,menopausal status

Total energy intake and breast cancer mortality

Five studies from six publications on breast cancer mortality were identified. Two studies from three publications (Jain, 1994a; Jain 1997; West-Wright, 2009) examined before diagnosis total energy intake, one study (Borugian, 2004) examined intake less than 12 months after diagnosis, and two studies (Rohan 1993; Beasley, 2011) examined intake 12 months or more after diagnosis.

Total energy intake before diagnosis and breast cancer mortality

Two studies from three publications were identified. Meta-analyses were not conducted because of insufficient data. The two articles by Jain et al. were from the same study (Jain, 1994a; Jain 1997). Jain et al. (1994a) reported no association (HR per 500 kcal/day = 1.00; 95% CI 0.84-1.19). West-Wright et al. (2009) observed a statistically non-signficant decreased risk (RR 0.79; 95% CI 0.56-1.11) for > 1682 vs. < 1271 kcal/day.

Total energy intake less than 12 months after diagnosis and breast cancer mortality

Only one study reported data. Borugian et al. (2004) reported a RR of 0.8 (95% CI 0.5-1.3; p_{trend} = 0.26) for ≥ 1890 versus ≤ 1262 kcal/day intake.

Total energy intake more than 12 months after diagnosis and breast cancer mortality

Only two studies reported data. For the highest to the lowest quartile comparison, Rohan et al. (1993) reported a statistically non-significant decreased risk (HR for ≥ 10322 vs. < 6045 kj/day = 0.65; 95% CI 0.37-1.14; p_{trend} = 0.09), while Beasley et al. (2011) observed no association (HR for 2407 vs. 1077 kcal/day = 1.02; 95% CI 0.61-1.71; p_{trend} = 0.89).

Table 71 Table of studies on total energy intake before diagnosis and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
West-Wright CN (2009)	California Teachers Study United States	Study recruitment: 1995; Cancer diagnosis: 1995-2004; Study follow up: until 2005	Cancer survivors of a population-based prospective cohort study	3539 participants 58.9 years (mean) 26 - 94 years Mostly white: 89.7%Comorbidities: 111 diabetes, 106 cardiovascular disease; 24.5 %	9 Years (max)	Incident first primary invasive breast cancer; 68.9% localized, 28.4% regional, 1.86 metastatic, 0.8 % missing	72% ER+ve, 12.7% ERve, 15.3% unknown			Self-reported at baseline; Block FFQ (1995 validated version); 103-item	3539 participants 460 deaths, 221 breast cancer mortality, 69 death from other causes including 24 death from other cancers, 68 cardiovascular disease deaths; 38 cerebrovascular disease deaths; 28 cardiopulmonary or pulmonary disease deaths; 4 diabetes death	Death certificate	>1682 vs. <1271 kcal/day	0.79 (0.56-1.11)	Age,Race,estrogen receptor level,Tumor stage,Physical activity ,Comorbidity,BMI
Jain M (1997)	National Breast Screening Study Canada	Cancer diagnosis: 1982-1985, Study follow-up: Until 1992 Recruited between1980-1985 and diagnosed after July 1982	Randomised controlled trial of mammography screening trial; ancillary analysis	676 participants 49.9 years (mean) 40 - 59 years 90% Caucasian 57% postmenopausal (at enrollment) 48.4% cases detected through mammography	7.7 years	Invasive breast cancer; any stage				Self-administered diet history questionnaire for diet in the previous months; 86-item	83 deaths, 76 breast cancer mortality, 7 other causes of deaths	Death certificate	With ER status With PR status With nodal status With tumour size Per 500 kcal/day increase	1.64 (0.89-3.05) 0.75 (0.41-1.36) 0.76 (0.46-1.24) 0.75 (0.44-1.26)	Age at diagnosis, weight, smoking, fat intake, when appropriate ER status PR status, nodal statu tumour size
Jain M (1994)a	National Breast Screening Study Canada	Cancer diagnosis: 1982-1992	Randomised controlled trial of mammography screening trial; ancillary analysis	678 participants 52.7 years (mean) Mostly white 37.3% premenopausal 62.7% postmenopausal, 55.6% allocated to mammography group	7.7 years	Tumor size (cm): 50.6% 0.1-1.5, 49.4% >1.5 among those with data	75.7% ER+, 24.3% ER-; 69.3% PR+, 30.7% PR- 70.5% 0, 17.8% 1-3, 11.7% >3 among those with data			Self-administered diet history questionnaire for diet in the previous months; 86-item	678 participants 83 deaths, 76 breast cancer mortality, 7 other causes of deaths	Death certificate	Per 500 kcal/day increase	1.00 (0.84-1.19)	Age at diagnosis, smoking, weight

Table 72 Table of studies on total energy intake less than 12 months after diagnosis and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Borugian M (2004)	Vancouver Cancer Centre of the British Columbia Cancer Agency Canada	Study recruitment: 1991-1992, Recruited 2 months after surgery but before adjuvant treatment	Prospective cohort of breast cancer survivors	603 participants 54.5 years (mean) 19.0 - 75.0 years; 39% premenopausal, 61% postmenopausal; 88.4% Caucasian	10.0 years	Tumor grades: 7.6% well differentiated, 46.4% moderately differentiated, 46% poorly differentiated	76.4% ER+ / 11.1% no axillary dissection, 57.5% no +ve, 27.9%	40.1% no systemic treatment, 21.9% tamoxifen only, 14.7% chemotherapy only, 21.4% both hormonal and chemotherapies, 1.9% other hormonal therapy; 4.6% lumpectomy, 14.6% lumpectomy and radiation therapy, 59.6% mastectomy, 10.0% mastectomy and radiation therapy, 11.2% other local treatment	89%	Block semi-quantitative FFQ at diagnosis/study baseline	603 participants 146 deaths, 112 breast cancer mortality	Cancer registry + death certificate	>=1890 vs. <=1262kcal/day	0.8 (0.5-1.3)	Age, tumor stage

Table 73 Table of studies on total energy intake 12 months or more after diagnosis and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Beasley JM (2011)	Collaborative Women's Longevity Study United States	Study recruitment: 1998-2001, Study follow-up: Until 2005	Follow up of cases of population-based case-control studies	4441 participants 20 - 79 years Mostly white 22.8% premenopausal, 73.3% postmenopausal among those with data HRT use: 33.2% yes, 56.9% no	5.5 years	Primary invasive breast cancer; Stages: 72.8% local, 27.2% regional		Surgery: 97.9% yes; Radiotherapy: 49.8% yes; Hormonal therapy: 57.8% yes; Chemotherapy: 31.9% yes	42%	Assessed on average 5 years (range 1–16) after diagnosis, usual intake over the past year; 126-item FFQ used in NHS	4441 participants 525 deaths, 137 breast cancer mortality, 132 deaths from cardiovascular disease	Death certificate	2407 vs 1077 kcal/day	1.02 (0.61-1.71)	Age, residence, menopausal status, smoking, stage, alcohol intake, hormonal therapy, interval between diagnosis and baseline interview, BMI, Physical activity , breast cancer treatment
Rohan T (1993)	Diet and Breast Cancer in Australia Follow-up Study Australia	Cancer diagnosis: 1982-1984, Study follow-up: Until 1989	Follow-up of cases of population-based case-control study	412 participants 55.1 years (mean) 20 - 74 years 30.7% premenopausal, 5.4% perimenopausal, 64%	5.5 years	Primary breast cancer, any stages			80.70% / 39 patients lost	Interval between diagnosis and interview was 4.8months; quantitative FFQ; 176-item	412 participants 112 breast cancer mortality, 11 other causes of deaths	Cancer registry + death certificate	>=10322 vs. <=6044 kj/day	0.65 (0.37-1.14)	age of menarche, Quetelet Index

				postmenopausal, among those with data											

6.2 Percentage of energy intake from fat

Table 74 Summary results of meta-analysis on before diagnosis percentage energy intake from fat and total mortality*

Comparison	No. of studies	No. of events in studies	RR (95% CI)	I^2, $P_{heterogeneity}$
Per 10% energy	3	178	1.82 (1.41-2.36)	0%, p = 0.38

*No studies on breast cancer mortality and second cancers were included in the meta-analyses. Only studies on percentage of energy intake from fat before diagnosis could be included in the dose-response meta-analysis.

Percentage energy intake from fat and total mortality

Five studies on total mortality were identified. Three studies examined before diagnosis percentage energy intake from fat (Zhang, 1995; Saxe, 1999; McEligot, 2006), no study examined percentage intake less than 12 months after diagnosis, and two studies examined percentage intake 12 months or more after diagnosis (Pierce, 2007a; Beasley, 2011).

Percentage energy intake from fat before diagnosis and total mortality

Methods

Three studies were identified and all studies could be included in the linear dose-response meta-analysis. A highest versus lowest meta-analysis was not conducted as only two studies could be included. Saxe et al. (1999) only reported a dose-response result.

Main results and heterogeneity

The summary RR per 10% energy intake was 1.82 (95% CI 1.41-2.36; I^2 = 0%; p = 0.38; 3 studies). In an influence analysis, the summary RR ranged from 1.49 (95% CI 0.97-2.29) when McEligot et al. (2006) was omitted to 1.99 (95% CI 1.49-2.66) when Saxe et al. (1999) was omitted.

Study quality

All studies had less than 100 events, with only 26 deaths (Saxe, 1999) and 56 deaths (Zhang, 1995) accrued after a follow-up of 5 years or more and an average of 2.9 years respectively. The study of McEligot et al. (2006) had 96 deaths after an average of 80 months of follow-up. Saxe et al. (1999) was a clinical series study, with recruitment spanning from 1989 to 1991. McEligot et al. (2006) identified cases diagnosed between

1994 and 1995 from a cancer registry. Zhang et al. (1995) was a population study, with cancer diagnosed in 1986-1991. All studies included *in situ* and invasive breast cancers. Dietary data was collected at or near to diagnosis for the diet a year prior in two studies (McEligot, 2006; Saxe, 1999). One study collected the data before diagnosis (Zhang, 1996). Two studies (Zhang, 1995; McEligot, 2006) were restricted to postmenopausal women only. Saxe et al. (1999) included both pre- (34%) and postmenopausal (66%) women. Two studies (Zhang, 1995; McEligot, 2006) adjusted for tumor stage in addition to other risk factors. Model adjustment was unclear in Saxe et al. (1999).

Figure 82 Linear dose-response meta-analysis of percentage energy intake from fat before diagnosis and total mortality

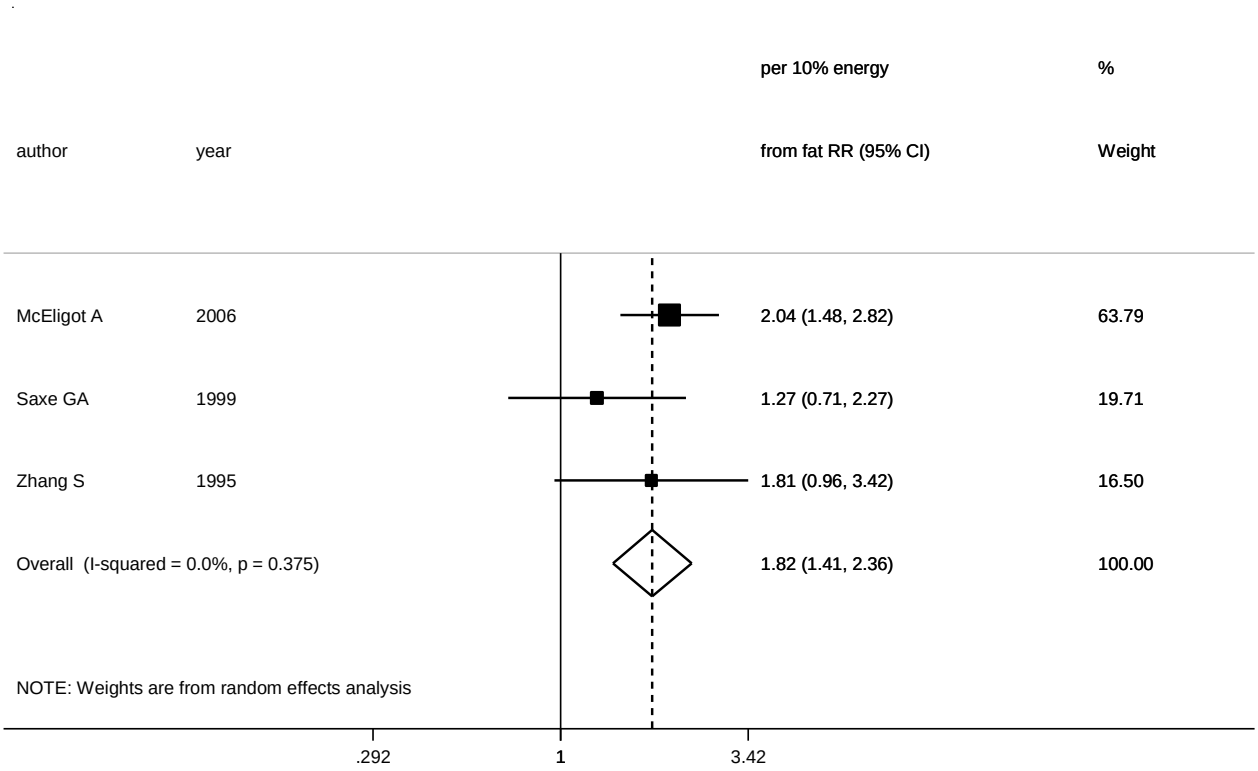


Figure 83 Individual dose-response graph of percentage energy intake from fat before diagnosis and total mortality

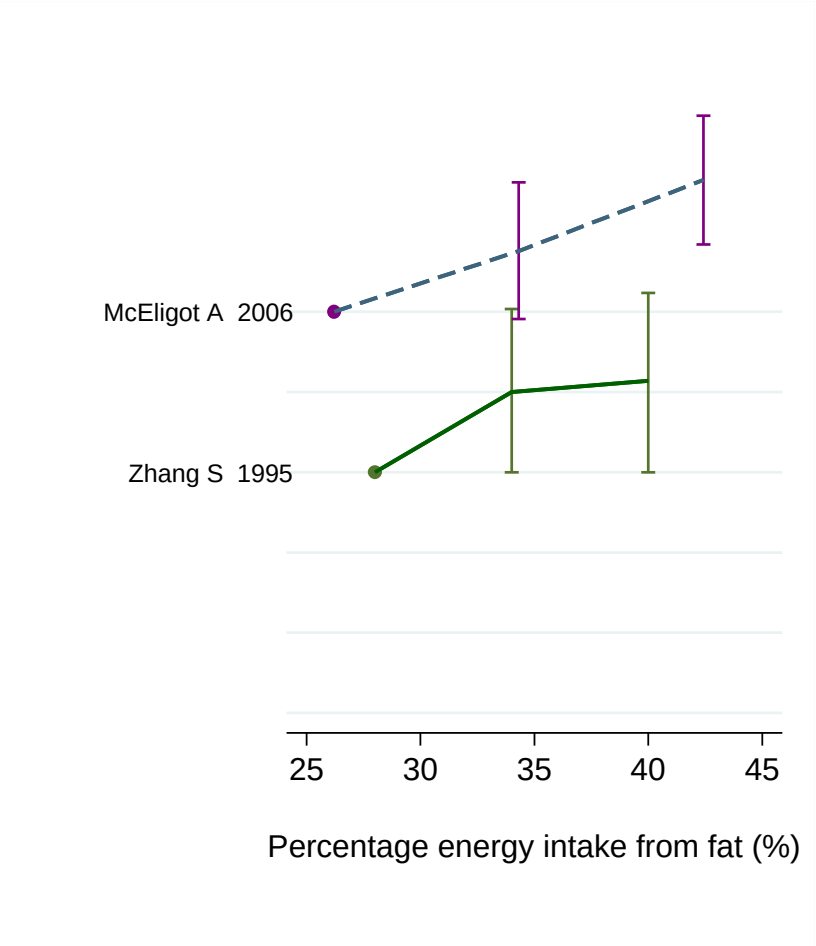


Table 75 Table of included studies on percentage energy intake from fat before diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
McEligot A (2006)	Orange County California Study United States	Cancer diagnosis: 1994-1995, Study follow-up: Until 2003 Recruited within 6 months of diagnosis	Prospective cohort of breast cancer survivors	516 participants 64.78 years (mean) Postmenopausal 92.3% non-Hispanic white HRT use: 36.2% estrogen only, 1.9% progesterone only, 35.1% estrogen and progesterone, 26.7% non-users	80 months	Stages: 14.9% in situ, 59.3% localized, 24.2% regional, 1.55% metastatic			98% / 2% lost	Self-reported at diagnosis for dietary habits 1 year prior to diagnosis, FFQ	516 participants 96 deaths, 41 breast cancer mortality, 13 deaths from cardiovascular disease, 31 other causes of deaths, 11 unknown causes of deaths	Cancer registry + National Death Index	>=38.37 vs. <=30.26 % energy/day	3.12 (1.79-5.44)	Tumor stage, age at diagnosis, BMI, parity, HRT, alcohol intake, multivitamins, energy intake
Saxe GA (1999)	Medical Center, Michigan University Follow-up Study United States	Study recruitment: 1989-1991, Recruited during first medical center visit for suspected or newly diagnosed	Prospective cohort of breast cancer survivors	149 participants 57.8 years (mean) 26 - 95 years White: 90.6%, black:7.2% and other: 2.2%, 34.2% premenopausal, 65.8% postmenopausal	5 years (min)	Primary breast cancer, stages: 19.6% in situ, 34.5% I, 34.5% II, 8.8% III, 2.7% IV	73.4% ER+, 26.6% ER- / 43% +ve, 57% -ve		0% lost	Interviewed close to time of diagnosis for diet a year prior to diagnosis, semi-quantitative FFQ	149 participants 26 deaths	Hospital records	Per 10 % energy increase	1.27 (0.71-2.27)	Energy intake
Zhang S (1995)	Iowa Women's Health Study United States	Study recruitment:1986; Study follow up: until 1991	Cancer survivors of population-based prospective cohort study	698 participants 55 - 69 years Mostly white: 98%, Postmenopausal	2.9 years	Unilateral breast cancer; 10% in situ, 58% local, 28% regional, 3%distant, and 1% unknown; 55% tumour size <2cm, 33% size >= 2cm and 11% unknown	Among those with data: 85% ER+ve and 72% PR+ve		42.60% / < 1% migration rate	Self reported within 6 years before diagnosis, semi-quantitative FFQ	698 participants 56 deaths, 40 breast cancer mortality (among the causes of death) and 2 death from coronary heart disease	Death certificates, National death index	40 vs. 28 % energy/day from fat	2.2 (1.0-4.7)	Age, smoking, education, tumor stage, ER status, tumor size

Percentage energy intake from fat 12 months or more after diagnosis and total mortality

Two studies reported data. Pierce et al. (2007a) reported a 39% increased risk for 33.42-58.86% compared with 9.04-23.87% energy from fat (unadjusted result; no 95% CI; p_{trend} = 0.10). Beasley et al. (2011) reported no association (HR for 39 vs. 23% = 1.05; 95% CI 0.79-1.39; p_{trend} = 0.98).

Percentage energy intake from fat and breast cancer mortality

Three studies from four publications on breast cancer mortality were identified. Two publications on the same study (Jain, 1994a; Jain, 1997) examined percentage energy intake from fat before diagnosis, one study (Borugian, 2004) examined less than 12 months after diagnosis, and another study (Beasley, 2011) examined 12 months or more after diagnosis.

Percentage energy intake from fat before diagnosis and breast cancer mortality

Two publications on the same study (Jain, 1994a; Jain, 1997) were identified. Jain et al. (1994a) observed a statistically non-signficant increased risk (HR for 45.20 vs. 38.08% = 1.89; 95% CI 0.96-3.7).

Percentage energy intake from fat less than 12 months after diagnosis and breast cancer mortality

Only one study reported data. No association was observed (RR per 1% increase =1.02; 95% CI 0.99-1.04) (Borugian, 2004).

Percentage energy intake from fat 12 months or more after diagnosis and breast cancer mortality

Only one study reported data. No significant association was observed (HR for 39 vs. 23% = 0.92; 95% CI 0.53-1.60; p_{trend} = 0.39) (Beasley, 2011).

7 Anthropometry

7.1 Body Mass Index

Table 76 Summary results of meta-analysis on body mass index (BMI) and total mortality, breast cancer mortality, and second primary breast cancer*

Comparison	Total mortality			Breast cancer mortality			Second primary breast cancer		
	No. of studies	No. of events in studies	RR (95% CI) I^2, $P_{heterogeneity}$	No. of studies	No. of events in studies	RR (95% CI) I^2, $P_{heterogeneity}$	No. of studies	No. of events in studies	RR (95% CI) I^2, $P_{heterogeneity}$
BMI before breast cancer diagnosis									
Highest vs. lowest	20	8318	1.41 (1.29-1.54) 40.6%, p = 0.03	21	9888	1.35 (1.24-1.46) 35.2%, p = 0.06	3	701	1.43 (0.87-2.34) 66.7%, p=0.05
Underweight vs. normal weight	10	4944	1.10 (0.92-1.31) 48.2%, p = 0.04	8	4479	1.02 (0.85-1.21) 31.1%, p = 0.18	-	-	-
Per 5 kg/m^2	14	6261	1.17 (1.13-1.21) 13.0%, p = 0.31	17	6634	1.18 (1.11-1.24) 47.8%, p = 0.02	3	701	1.21 (1.04-1.40) 20.8%, p=0.28
BMI less than 12 months after diagnosis									
Highest vs. lowest	26	16831	1.27 (1.16-1.39) 76.6%, P<0.0001	11	10157	1.35 (1.23-1.48) 8.6%, p = 0.36	8	3478	1.30 (1.14-1.48) 0%, p=0.64
Underweight vs. normal weight	9	2598	1.23 (0.93-1.63) 69.4%, p =0.001	4	1455	1.52 (1.26-1.84) 0%, p = 0.42	-	-	-
Per 5 kg/m^2	10	5875	1.11 (1.06-1.17) 60.5%, p = 0.01	5	1918	1.18 (1.11-1.25) 0%, p = 0.57	7	3186	1.13 (1.06-1.21) 15.2%, p=0.31
BMI 12 months or more after breast cancer diagnosis									
Highest vs. lowest	5	2289	1.21 (1.06-1.38) 0%, p = 0.70	-	-	-	-	-	-
Underweight vs. normal weight	3	1361	1.29 (1.02-1.63) 0%, p = 0.39	-	-	-	-	-	-

Per 5 kg/m^2	4	1703	1.08 (1.01-1.15) 0%, P=0.52	-	-	-	-	-	-

* No studies on BMI 12 months or more after breast cancer diagnosis and breast cancer mortality and second primary breast cancer were included in the meta-analyses.

Table 77 Summary results of meta-analysis on BMI less than 12 months after diagnosis, mortality not related to breast cancer and second primary endometrial cancer

	Mortality not related to breast cancer			**Second primary endometrial cancer**		
Comparison	**No. of studies**	**No. of events in studies**	**RR (95% CI) I^2, $P_{heterogeneity}$**	**No. of studies**	**No. of events in studies**	**RR (95% CI) I^2, $P_{heterogeneity}$**
BMI less than 12 months after diagnosis						
Highest vs. lowest	4	2617	1.37 (1.14-1.66) 37.2%, p = 0.19	4	634	1.94 (1.45-2.59) 0%, p = 0.84

Table 78 Table for subgroup analysis of before diagnosis BMI and total mortality

Comparison	No. of studies	No. of events in studies	RR (95% CI)	I^2, $P_{heterogeneity}$
Menopausal status				
Highest vs. lowest				
Premenopausal	7	3468	1.75 (1.26-2.41)	69.7%, p=0.003
Postmenopausal	9	3954	1.34 (1.18-1.53)	27.0%, p=0.20
Per 5 kg/m^2				
Premenopausal	3	644	1.25 (1.10-1.43)	47.4%, p = 0.15
Postmenopausal	3	1103	1.16 (1.01-1.34)	56.4%, p = 0.10
Estrogen receptor status				
Highest vs. lowest				
ER negative	2	1778	1.18 (0.92-1.52)	0%, p = 0.72
ER positive	2	1680	1.43 (1.16-1.78)	0%, p = 0.32

Table 79 Table for subgroup analysis of BMI less than 12 months after diagnosis and total mortality

Comparison	No. of studies	No. of events in studies	RR (95% CI)	I^2, $P_{heterogeneity}$
Per 5 kg/m^2				
Geographic location				
North America	4	1097	1.19 (1.12-1.28)	0%, p = 0.55
Europe	2	3693	1.01 (0.90-1.12)	66.8%, p = 0.08
Asia Pacific	2	682	1.17 (1.04-1.31)	0%, p = 0.34
International	2	403	1.10 (1.02-1.20)	57.9%, p = 0.12
Source of study population				
Case-series	4	4168	1.04 (0.98-1.11)	32.8%, p = 0.22

Randomised controlled trial	3	744	1.14 (1.05-1.24)	68.9%, p = 0.04
Population-based studies	3	963	1.21 (1.11-1.32)	0%, p = 0.43
Method of exposure assessment				
Measured	5	1399	1.20 (1.14-1.27)	0%, p = 0.74
Medical records	4	4034	1.05 (1.01-1.10)	32%, p = 0.22
Self-reported	1	442	1.13 (0.99-1.29)	-
Time of exposure assessment				
At-diagnosis	3	783	1.05 (0.93-1.20)	61.8%, p = 0.07
Shortly after diagnosis	6	5092	1.16 (1.07-1.26)	68.1%, p = 0.01
Timing unclear	1	-	1.07 (1.02-1.12)	-
Menopausal status				
Highest vs. lowest				
Premenopausal	7	4604	1.28 (1.16-1.42)	0%, p = 0.51
Postmenopausal	6	4520	1.13 (1.03-1.23)	0%, p = 0.77
Estrogen receptor status				
Highest vs. lowest				
ER negative	5 (6 results)	5358	1.29 (1.06-1.56)	56.6%, p = 0.04
ER positive	5 (6 results)	5521	1.19 (1.06-1.33)	31.4%, p = 0.20

Table 80 Table for subgroup analysis of before diagnosis BMI and breast cancer mortality

Comparison	**No. of studies**	**No. of events in studies**	**RR (95% CI)**	**I^2, $P_{heterogeneity}$**
Menopausal status				
Highest vs. lowest				
Premenopausal	8	4891	1.50 (1.13-2.00)	69.7%, p=0.002
Postmenopausal	12	6363	1.34 (1.21-1.48)	15.0%, p = 0.30

Per 5 kg/m^2				
Premenopausal	5	1830	1.12 (0.92-1.35)	72.3%, p = 0.01
Postmenopausal	7	2866	1.15 (1.05-1.25)	53.6%, p = 0.04
Estrogen receptor status				
Highest vs. lowest				
ER negative	3	1675	1.01 (0.79-1.30)	0%, p = 0.38
ER positive	4	2276	1.42 (1.15-1.75)	0%, p = 0.84

Table 81 Table for subgroup analysis of BMI less than 12 months after diagnosis and breast cancer mortality

Comparison	**No. of studies**	**No. of events in studies**	**RR (95% CI)**	**I^2, $P_{heterogeneity}$**
Menopausal status				
Highest vs. lowest				
Premenopausal	2	586	0.96 (0.45-2.06)	77.4%, p = 0.04
Postmenopausal	4	1161	1.54 (1.29-1.84)	0%, p = 0.72
Estrogen receptor status				
Highest vs. lowest				
ER negative	1	624	1.13 (0.85-1.50)	-
ER positive	2	1076	1.31 (1.03-1.67)	34.6%, p = 0.22

BMI and total mortality

Before diagnosis BMI and total mortality

Methods

Twenty-three studies from 27 publications were identified. Three publications (Vatten, 1991; Holmes, 1999; Daling, 2001) were superseded by other publications of the same studies (Emaus, 2010; Kroenke, 2005; Reding, 2008). The study populations in Reeves et al. (2000) and Greenberg et al. (1985) overlapped. The former was included in the overall meta-analysis, whereas the latter was reviewed for its results on premenopausal women. Fourteen studies could be included in the linear dose-response meta-analysis and 20 studies could be included in the highest versus lowest meta-analysis.

Three studies were excluded from the highest versus lowest and dose-response analyses. Allemani et al. (2011) was excluded because it reported relative excess risk (RER for ≥ 25 vs. < 25 kg/m^2 = 2.20; 95% CI 1.01-4.70). Eley et al. (1994) reported an unadjusted result of 2.5-fold (95% CI 1.8-3.4) increased risk in total mortality for the comparison of high to low/normal BMI. Gregorio et al. (1985) observed no association between Quetelet Index (kg/cm^2 x 1000) and total mortality. Only p > 0.05 was provided with the result. Six studies that were included in the highest versus lowest meta-analysis were not in the dose-response meta-analysis, due to insufficient data for the analysis (Buck, 2011a; Keegan, 2010; Reeves, 2007; Bernstein, 2002; Reeves, 2000) and results by two BMI categories only (Cleveland, 2007).

Ten studies reported results separately on the underweight group and were included in the underweight versus normal weight meta-analysis. We included the BMI categories as defined by the studies. The reference category in most studies was the normal weight group, but may include underweight women. BMI could be assessed at different times before diagnosis, e.g. age at 20 years (Abrahamson, 2006) or of an adult BMI (Bernstein, 2002).

Main results and heterogeneity

The summary RR per 5 kg/m^2 was 1.17 (95% CI 1.13-1.21, 14 studies). Low heterogeneity was observed (I^2 = 13.0%, p = 0.31). Visual inspection of the funnel plot suggested small studies with an inverse association were missing (Egger's test p = 0.04) and that the asymmetry may also be explained by two small studies that reported strong positive associations. There is no evidence of strong influence from any individual study on the summary estimate, which remained statistically significant when each study was omitted in turn in the influence testing, ranging from 1.16 (95% CI 1.12-1.20) when Conroy et al. (2011) was omitted to 1.18 (95% CI 1.14-1.22) when Lu et al. (2011) was omitted.

When stratified by menopausal status, the summary RRs per 5 kg/m^2 were 1.25 (95% CI 1.10-1.43; I^2 = 47.4%; p = 0.15; 3 studies) for premenopausal women and 1.16 (95% CI 1.01-1.34; I^2 = 56.4%; p = 0.10; 3 studies) for postmenopausal women.

In the highest versus lowest meta-analysis, the summary RR was 1.41 (95% CI 1.29-1.54, 20 studies). Moderate heterogeneity was observed (I^2 = 40.6%, p = 0.03). When stratified by menopausal status, premenopausal women with breast cancer had a higher risk of total mortality compared with postmenopausal women, but a high heterogeneity was observed between the premenopausal studies (summary RR for highest vs. lowest = 1.75; 95% CI 1.26-2.41; I^2 = 69.7%; p = 0.003, 7 studies; and RR 1.34, 95% CI 1.18-1.53, I^2 = 27%, p = 0.20, 9 studies). The study on premenopausal women by Greenberg et al. (1985) could not be included in the analysis because of the missing 95% CIs. An increased risk was reported in this study (RR for QI $\geq$ 2.7vs. $\leq$ 2.0 = 1.8, p_{trend} = 0.12).

When stratified by estrogen receptor status, a statistically significant increased risk of total mortality was observed in ER positive breast cancer patients, but not in ER negative breast cancer patients (summary RR for highest vs. lowest = 1.43; 95% CI 1.16-1.78; I^2 = 0%; p = 0.32; 2 studies; and RR 1.18; 95% CI 0.92-1.52; I^2 = 0%; p = 0.72; 2 studies respectively).

For the comparison of underweight to normal weight, the summary RR was 1.10 (95% CI 0.92-1.31; I^2 = 48.2%; p = 0.04). When stratified by the exclusion of subjects with underlying diseases, the summary RRs remained similar (data not shown). When all data including those from the underweight subjects were modelled in a non-linear dose-response analysis, a slight J-shape relation, with the normal weight (~20-<25 kg/m^2) group associated with the lowest risk of total mortality was observed ($p_{non\text{-}linearity}$ < 0.001). When studies with or without a separate underweight group were analysed seperately, the non-linear relationship was only observed in the former studies (data not shown).

Study quality

Number of events ranged from 56 deaths to 1053 deaths. The population cohort conducted by Zhang et al. (1995) had only 56 deaths (40 died from breast cancer) after an average of 2.9 years of follow-up. Holmberg et al. (1994), a follow-up of case-control studies in Sweden and Norway, had 94 deaths (92 died from breast cancer) after 5 years of follow-up. Four studies (Bernstein, 2002; Cleveland, 2007; Caan, 2008; Buck, 2011a) had under 200 deaths. Eight studies had between 200-500 deaths (Abrahamson, 2006b; Reeves, 2007; Reding, 2008; Nichols, 2009; West-Wright, 2009; Chen, 2010; Emaus, 2010; Hellmann, 2010). Six studies had over 500 deaths (Reeves, 2000; Kroenke, 2005; Dal Maso, 2008; Keegan, 2010; Conroy, 2011; Lu, 2011). Apart from four studies (Reeves, 2007; Nichols, 2009; West-Wright, 2009; Conroy, 2011), most studies had more than half of the deaths attributed to breast cancer. Death from cardiovascular disease was reported in some studies (Zhang, 1995; Cleveland, 2007; Reeves, 2007; Dal Maso, 2008; Nichols, 2009; West-Wright, 2009; Emaus, 2010; Hellmann, 2010; Buck, 2011a). Reeves et al. (2007) had 45 breast cancer deaths among 206 deaths. Other causes of death in this cohort of older women (mean age at diagnosis = 78 years) included death from

cardiovascular disease (56 deaths) or death from other cancers (68 deaths). Most studies had more than 6 years of average follow-up. Loss to follow-up was mostly minimal in the studies reported data. The most being Reding et al. (2008), with 6.9% lost and also in Cleveland et al. (2007). Of the cases identified in this study, 410 cases were without follow-up data due to nonresponse, refusal, untraceability, or death without an identifiable, leaving 1508 participants.

Six studies included *In situ* and invasive breast cancers (Zhang, 1995; Bernstein, 2002; Reeves, 2007; Cleveland, 2007; Chen, 2010; Buck, 2011a) and 13 studies included invasive only breast cancer (Holmberg, 1994; Reeves, 2000, Kroenke, 2005; Abrahamson, 2006b; Reding, 2008; Dal Maso, 2008; Caan, 2008; West-Wright, 2009; Nichols, 2009; Keegan, 2010; Emaus, 2010; Lu, 2010; Conroy, 2011). All women in the study by Bernstein et al. (2002) had a second primary breast cancer. Cancer diagnosis dated as early as from 1968 to 1984 (Reeves, 2000), and from 1975 to 2005 (Emaus, 2010) or 1976 to 2000 (Kroenke, 2005). Four studies included cases diagnosed in the 1980s (Holmberg, 1994; Bernstein, 2002), or up until the 1990s (Reding, 2008; Nichols, 2009). Eight studies recruited cases diagnosed in the 1990s (Abrahamson, 2006b; Reeves, 2007; Cleveland, 2007; Dal Maso, 2008; Caan, 2008; Keegan, 2010; Lu, 2011), or up until 2004 (West-Wright, 2009). Cancer diagnosis dated from 2002 in two studies (Chen, 2010; Buck, 2011a).

Eleven studies were follow-up of case-control studies (Holmberg, 1994; Reeves, 2000; Bernstein, 2002; Abrahamson, 2006b; Cleveland, 2007; Reding, 2008; Dal Maso, 2008; Nichols, 2009; Lu, 2011; Buck, 2011a) or health screening cohort (Emaus, 2010). Three studies were cohorts of breast cancer survivors (Caan, 2008; Chen, 2010; Keegan, 2010). Cases in these studies were identified from hospitals or cancer registries. Six studies were population cohorts (Zhang, 1995; Kroenke, 2005; Reeves, 2007; West-Wright, 2009; Hellmann, 2010; Conroy, 2011). The Life After Cancer Epidemiology (LACE) cohort was a cohort of breast cancer survivors that consisted of cases identified from cancer registries and those rejected participation in a dietary intervention trial (Caan, 2008). Anthropometric data were measured in three studies (Reeves, 2007; Hellmann, 2010; Emaus, 2010), self-reported in 16 studies (Holmberg, 1994; Zhang, 1995; Bernstein, 2002; Kroenke, 2005; Abrahamson, 2006b; Cleveland, 2007; Reding, 2008; Dal Maso, 2008; Caan, 2008; West-Wright, 2009; Nichols, 2009; Keegan, 2010; Chen, 2010; Buck, 2011a; Lu, 2011; Conroy, 2011 and taken from records in one study (Reeves, 2000). Anthropometric data referenced to the time prior to cancer diagnosis were retrospectively collected in the follow-up studies or the cohorts of breast cancer survivors, while the data was collected prospectively in the population cohorts.

Holmberg et al. (1994) and Reding et al. (2008) were a premenopausal women only study, while Zhang et al. (1995), Reeves et al. (2007) Conroy et al. (2011) and Buck et al. (2011a) were a postmenopausal women only study. Cleveland et al. (2007) only included postmenopausal women in the analysis. Most results were adjusted for multiple confounders, including tumour stage and treatment**.** Result in Reding et al. (2008) was adjusted for age, year of diagnosis and mammogram. For the studies of Holmberg et al. (1994), Reeves et al. (2000), Abrahamson et al. (2006b) and Cleveland et al. (2007), only

few variables were included in the final statistical model because other factors did not change the estimate materially. Reeves et al. (2007) reported results by age groups.

Published pooled analysis

The After Breast Cancer Pooling Project (ABCPP) published results on before diagnosis BMI and total, breast cancer, and non-breast cancer mortality risks (Kwan, 2012).

Data from four prospective studies of breast cancer survivors (Shanghai Breast Cancer Survival Study, Life After Cancer Epidemiology, Women's Healthy Eating and Living, and Nurses' Health Study) were pooled in the project. After a mean follow-up of 7.8 years, 2140 deaths (1423 breast cancer mortality, 717 deaths because of other causes) from 14948 participants with stage I-IV invasive breast cancer were accrued.

Compared with the normal weight, statistically significant increased risks in total mortality were observed for the obese (multivariate-adjusted HR for ≥ 30 vs. 18.5-24.9 kg/m^2 = 1.17; 95% CI 1.04-1.32), and the underweight (HR for <18.5 vs. 18.5-24.9 kg/m^2 = 1.59; 95% CI 1.18-2.13); while no association was observed for the overweight (HR for 25.0-29.9 vs. 18.5-24.9 kg/m^2 = 1.01; 95% CI 0.91-1.12). The association was non-linear ($p_{non\text{-}linearity}$ = 0.025).

Similar increased risks by menopausal status and hormone receptor status were observed. The HRs for obese versus normal weight were 1.29 (95% CI 0.98-1.69) and 1.16 (95% CI 1.01-1.33) in the pre- and postmenopausal women respectively ($p_{interaction}$ = 0.99), and 1.14 (95% CI 0.99-1.31) and 1.22 (95% CI 0.94-1.60) ($p_{interaction}$ = 0.88) in women with ER+ and/or PR+ and ER-and PR- cancers respectively. There were also no significant effect modifications with comorbidity or smoking (all $p_{interaction}$ > 0.05).

Further analysis using different BMI cutpoints suggested differential risk associations of total mortality with the level of obesity. Statistically significant increased risk was observed for the morbidly obese (≥ 40 kg/m^2), but not for obese (30.0-34.9 kg/m^2) or severely obese (35.0-39.9 kg/m^2) when compared with normal weight women (18.5-24.9 kg/m^2). The HRs for overweight, obese, severely obese, and morbidly obese were 1.01 (95% CI 0.91-1.12), 1.11 (95% CI 0.97-1.27), 1.09 (95% CI 0.88-1.36), and 1.81 (95% CI 1.42-2.32) respectively.

The dose-response and highest vs. lowest meta-analyses in this report included results from the Shanghai Breast Cancer Survival Study (Chen, 2010), Life After Cancer Epidemiology (Caan, 2008), and the Nurses' Health Study (Kroenke, 2005), but not the Women's Healthy Eating and Living RCT as in the ABCPP. In addition, the Shanghai Breast Cancer Survival Study (Chen, 2010) and the Nurses' Health Study (Kroenke, 2005) were included in the underweight vs. normal weight meta-analysis.

Figure 84 Highest versus lowest forest plot of before diagnosis BMI and total mortality

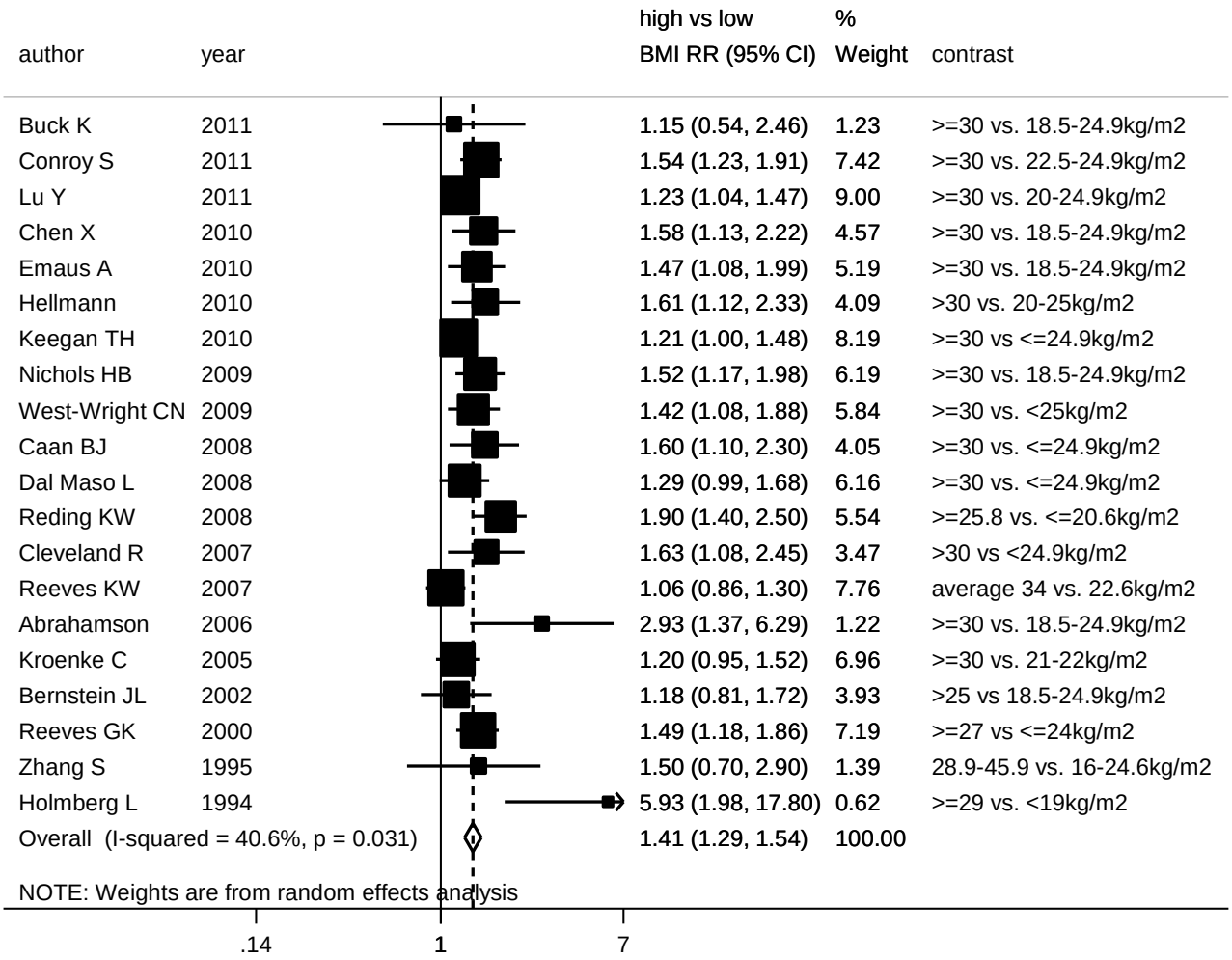


Figure 85 Highest versus lowest forest plot of before diagnosis BMI and total mortality by menopausal status

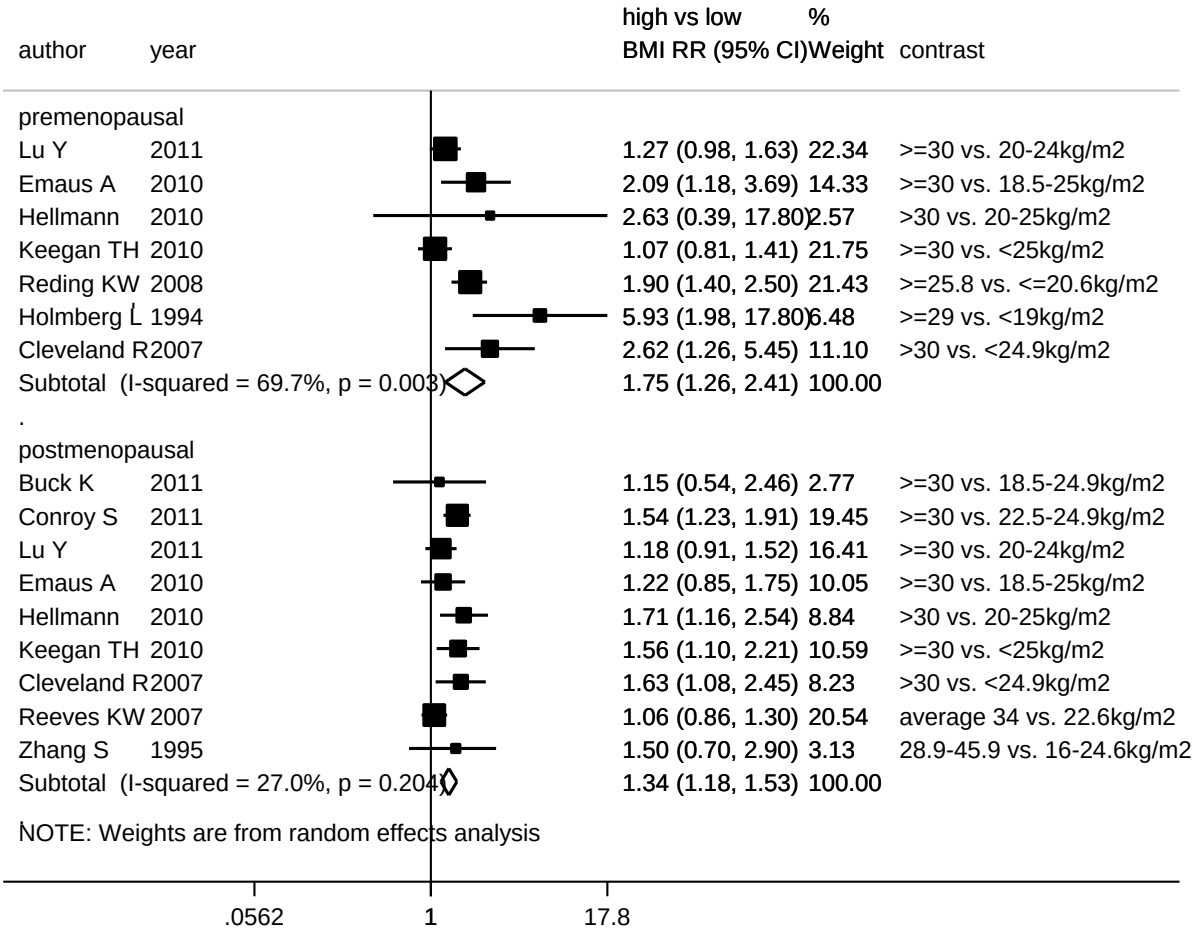


Figure 86 Highest versus lowest forest plot of before diagnosis BMI and total mortality by estrogen receptor status

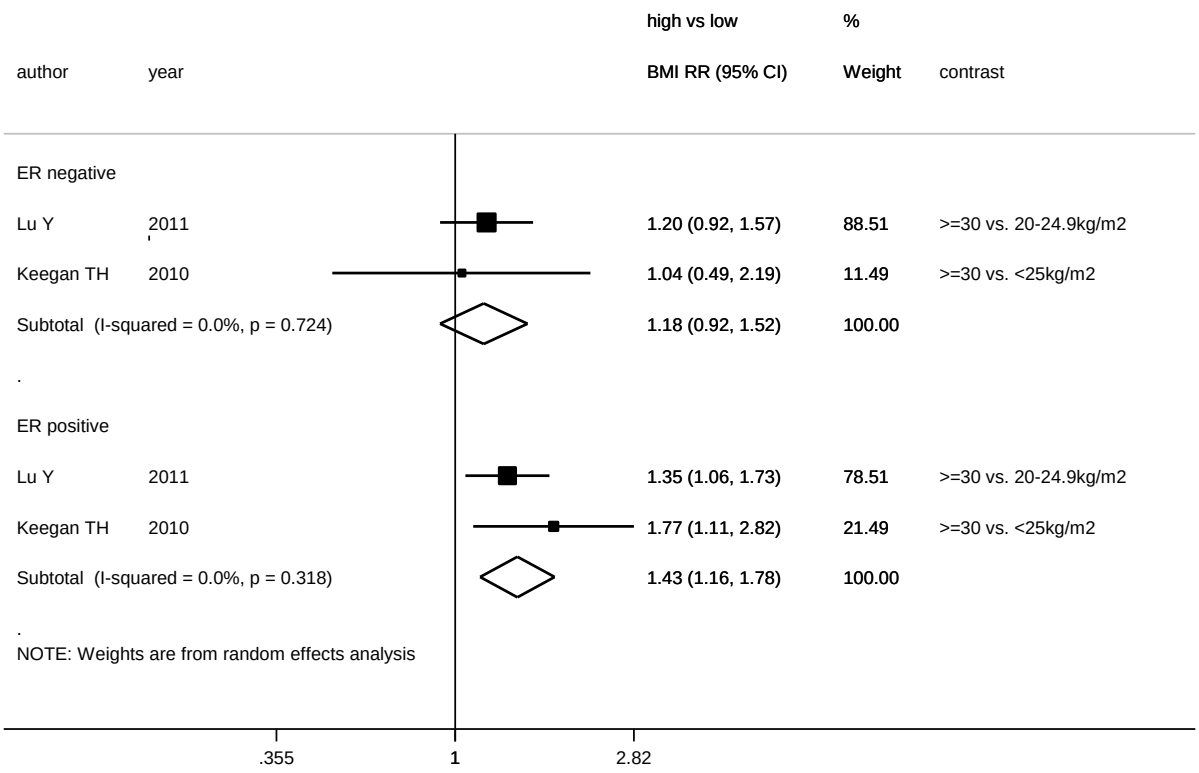


Figure 87 Forest plot of before diagnosis underweight versus normal weight and total mortality

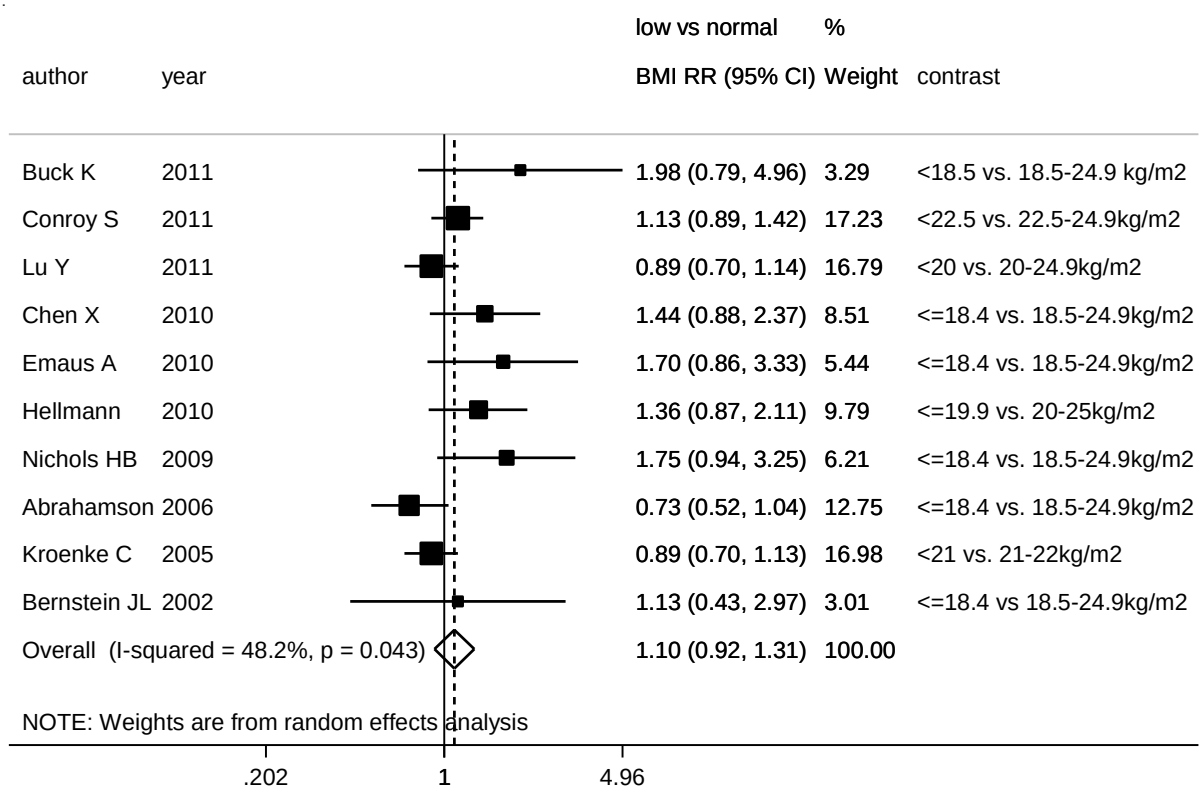


Figure 88 Linear dose-response meta-analysis of before diagnosis BMI and total mortality

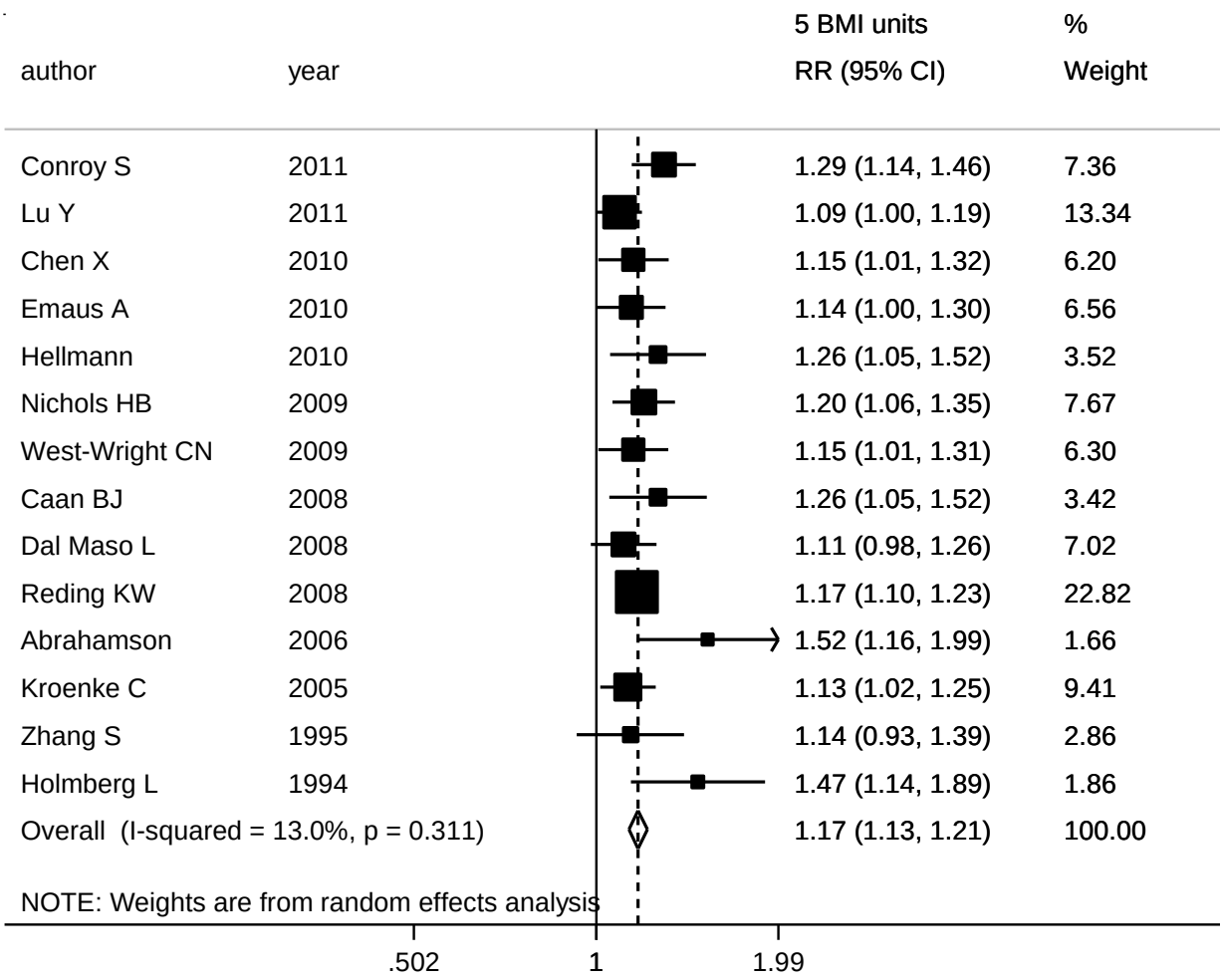
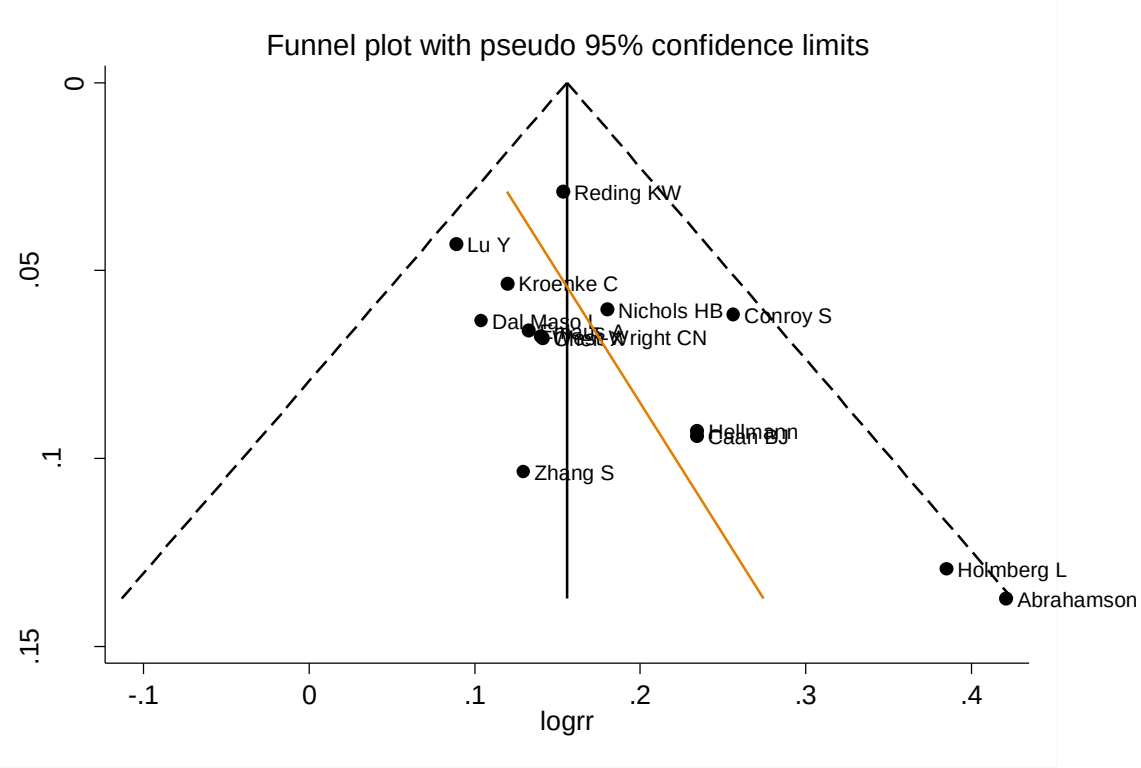


Figure 89 Funnel plot of studies of before diagnosis BMI and total mortality



Each dot represents the logarithm of relative risk estimate against standard error as a measure of study size. Solid line is the logarithm of summary risk estimate from the meta-analysis. Dashed lines are its 95% confidence interval.

Egger's test p = 0.038

Figure 90 Individual dose-response graph of before diagnosis BMI and total mortality

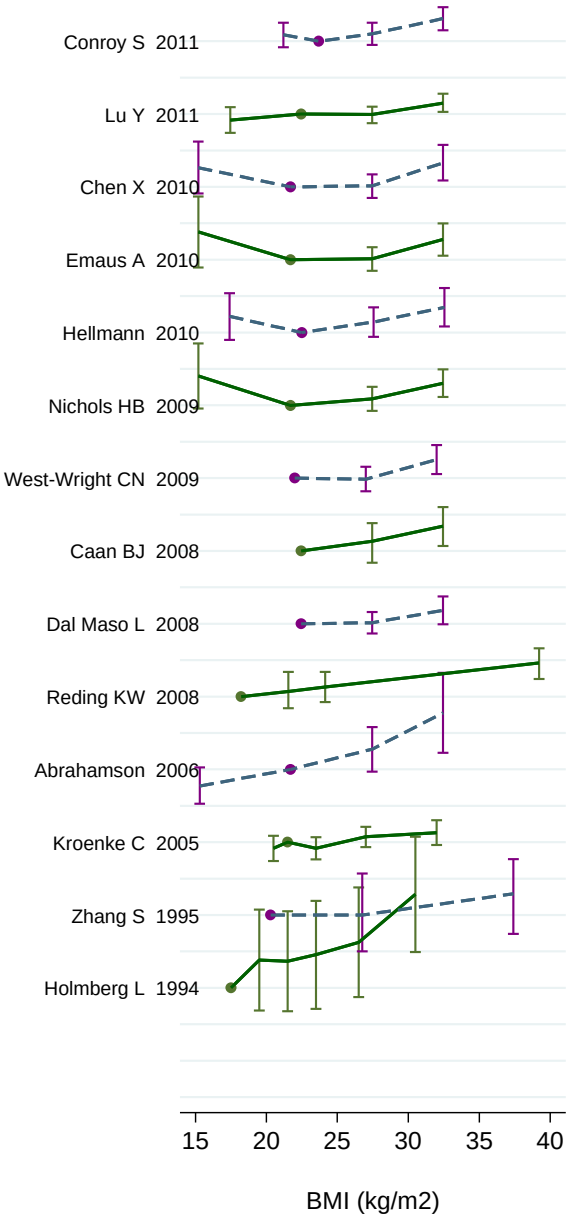


Figure 91 Linear dose-response meta-analysis of before diagnosis BMI and total mortality by menopausal status

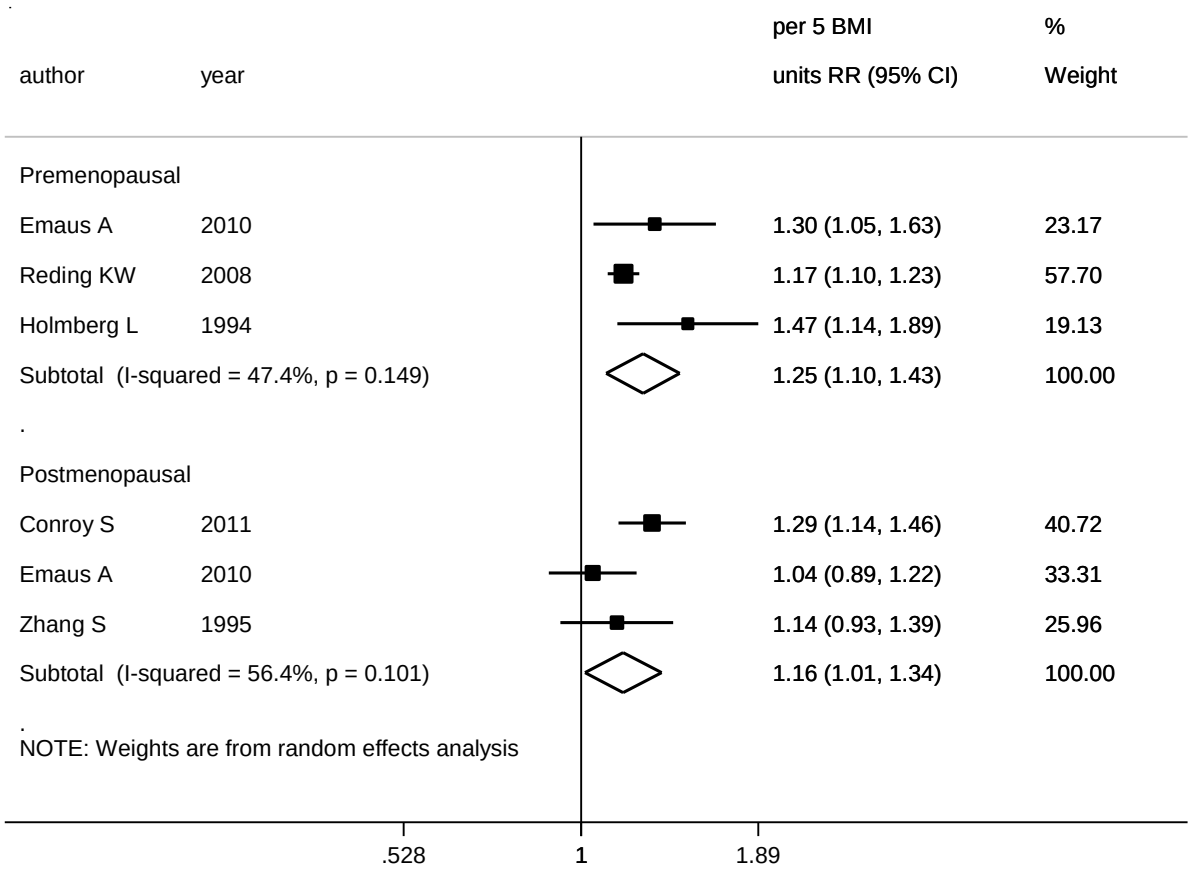
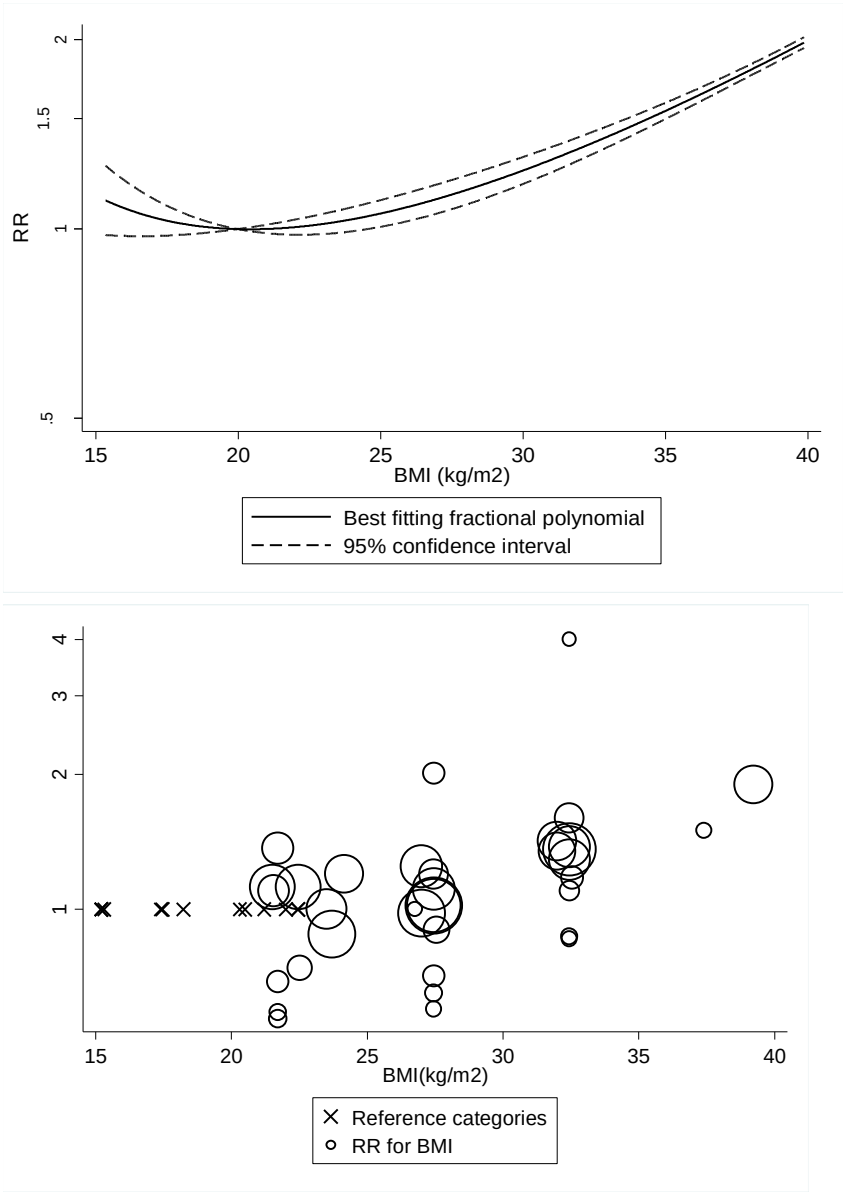


Figure 92 Non-linear dose-response meta-analysis of before diagnosis BMI and total mortality



$p_{non\text{-}linearity} < 0.001$

Table 82 Table with BMI values and corresponding RRs (95% CIs) for non-linear analysis of before diagnosis BMI and total mortality

BMI kg/m^2	RR (95%CI)
16	1.08 (0.98-1.19)
20	1
25	1.06 (1.01-1.11)
30	1.24 (1.18-1.30)
35	1.54 (1.50-1.59)

Table 83 Table of included studies on BMI before diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments Remarks
Buck K (2011)a	Hamburg and Rhein-Neckar-Karlsruhe, Germany Follow-up Study Germany	Cancer diagnosis: 2002-2005, Study follow-up: Until 2009	Follow-up of cases of population-based case-control study	1140 participants 50 - 74 years Postmenopausal HRT use:39.8% current, 59.2% past/ever Diabetes: 10.5% yes, 89.4% no; Cardiovascular disease: 51.2% yes, 48.8% no	6.1 years	5.9% In situ, Grades: 63.7% 1-2, 24.1% 3, 17.7% HER2+, 66.3% HER2-, 3.9% metastasis, 6% unknown	54% ER+/PR+, 17.8% ER+/PR- or ER-/PR+, 16.2% ER-/PR- 29.8% +ve, 58.1% -ve	Surgery: 2.6% ablation, 26.4% ablation + axilla, 11.4% breast conserving surgery, 58.5% breast conserving surgery + axilla; Chemotherapy: 39% adjuvant, 6% neoadjuvant, 54.1% no; Radiotherapy: 76% yes, 23.9% no; Tamoxifen use: 59.8% yes, 30.4% no		At baseline, interview	1140 participants 162 deaths, 124 breast cancer mortality, 15 deaths from cardiovascular disease, 23 other causes of deaths	Death certificate	>=30 vs. 18.5-24.9 Kg/m^2	1.15 (0.54-2.46)	Age at diagnosis, tumor size, nodal status, metastasis, tumor grade, ER status, detection type, diabetes, HRT, physical activity Highest vs lowest analysis only; missing number of events per category
Conroy S (2011)	The Multiethnic Cohort Study Hawai	Study recruitment: 1993-1996, Study follow-up: Until 2007	Cancer survivors of population-based prospective cohort study	3842 participants 68.8 years (mean) 50 - 89 years Multi-ethnic Postmenopausal Comorbidities: Heart disease/stroke: 9% yes; Hypertension: 37% yes	6.2 years	Incident, invasive breast cancer; SEER stages: 71% local, 25% regional, 3% distant; Size (cm): 61% <=2 61%, >2 24%, 16% unknown	45% ER+ PR+, 13% ER- PR-, 10% ER+PR-/ER-PR+, 31% other/unknown	Surgery: 56% conserving surgery, 38% mastectomy, 6% none/unknown; Chemotherapy: 24% yes; Radiotherapy: 47% yes		Self-reported BMI at cohort baseline on average 6.5 years before diagnosis	3842 participants 804 deaths, 376 breast cancer mortality	Death certificate	>=30 vs. 22.5 -24.9 Kg/m^2	1.54 (1.23-1.91)	Stage, hormonal receptor status, smoking, years between diagnosis and study entry
Lu Y (2011)	The Women's Contraceptive and Reproductive Experiences (CARE) Study United States	Cancer diagnosis: 1994-1998, Study follow-up: Until 2005/2007	Follow-up of cases of population-based case-control study	4538 participants 35 - 64 years White: 64.7%, Black: 35.3%, 46.2% premenopausal, 42.2% postmenopausal, 11.6% unknown 62.8% comorbidity free, 29.7% one, 7.5% >=2 of either hypertension, myocardial infraction, stroke, diabetes, or other cancers excluding nonmelanoma skin cancers	8.6 years	SEER stages: 60.3% localized, 38.5% non-localized, 1.2% unknown; Invasive breast cancer	58.7% ER+, 28.8% ER-, 12.5% unknown	No info on breast cancer therapies	76.50% 2 patients lost	Self-reported on average 5.1 months post-diagnosis; BMI of 5 years before diagnosis	4538 participants 1053 deaths, 828 breast cancer mortality	SEER record	>=30 vs. 20 -24.9 Kg/m^2	1.23 (1.04-1.47)	Age at diagnosis, education, Study centre, tumor stage, ER status, number of comorbidities, race
Chen X (2010)	Shanghai Breast Cancer Survival Study China	Study recruitment: 2002-2006; Recruited on average 6 months after	Prospective cohort of breast cancer survivors	5042 participants 53.5 years (mean) 20 - 75 years 51.1% postmenopausal	46 months	TNM; 36.4% stage 0-I, 32.6% IIA, 16.6% IIB, 9.8% IIIIV, 4.6% unknown	49.9% ER+ve/PR+ve, 27.6% ER-ve/PR-ve, 20.4% mixed (ER+ve PR-	Mastectomy:93.9% ; Chemotherapy: 91.2%; Radiotherapy: 32.1% ; Tamoxifen usage: 52%	80%	Self-reported weight 1 year prior to diagnosis and at diagnosis, measured at	5042 participants 442 deaths	Cancer register	>=30 vs. 18.5-24.9 Kg/m^2	1.58 (1.13, 2.22)	Age at diagnosis, education, income, marital status, exercise, meat intake, cruciferous vegetables, soy protein, time from diagnosis to

		diagnosis					ve/ER-ve PR+ve), 2.1% unknown			baseline interview approximately 6 months after diagnosis					study enrollment, menopausal status, menopausal symptoms, chemotherapy, surgery type, radiotherapy, tamoxifen use, nodal status, immunotherapy, TNM stage, comorbidity, estrogen/progesterone receptor status
Emaus A (2010)	Norwegian Health Surveys Follow-up Study, three counties Norway	Cancer diagnosis: 1975–2005	Cancer survivors of a population-based prospective cohort study	1364 participants 57.5 years (mean) 27 - 79 years 61% postmenopausal HRT use: 30 patients, only measured in 3rd survey. Participants of a health screening cohort. Comorbidities: 8 diabetic patients	8.2 years	Invasive breast cancer; TNM; 49% Stage 1, 41% Stage 2, 4.5% stage 3, 5.3% stage 4			91% in the 1st, 91% in the 2nd and 88% in the 3rd survey Complete follow up	Measured during health screening, prior to diagnosis	1364 participants 429 deaths, 355 breast cancer mortality, 27 death from other cancers, 23 death from cardiovascular disease, and 24 from other causes	Death record	>=30 vs. 18.5-24.9 Kg/m^2	1.47 (1.08-1.99)	Age at diagnosis, pre-diagnostic observation time, tumor stage, area of residence, year of diagnosis, physical activity
Hellmann (2010)	Copenhagen City Heart Study Denmark	Study recruitment:1976; Study follow up: until 2007	Cancer survivors of a population-based prospective cohort study	528 participants 66.9 years (mean) 33.1 - 95.4 years Mostly Caucasian 16.1% premenopausal, 83.9% postmenopausal HRT use: 71.2% unexposed, 28.8% exposed	7.8 years	Primary breast cancer, one sarcoma, 527 carcinomas; TNM; 56.2% local, 33.7 regional, 6.3 metastatic, 3.8% unknown		7.4% radiotherapy, 7.4% chemotherapy, 22.4% hormonal therapy	74% at the 1st, 70% at the 2nd , 61% at the 3rd and 50% at the 4th examination 1% lost	Measured at study baseline	528 participants 323 death, 174 breast cancer mortality, 126 other causes of death including 43.6% death from cardiovascular disease and 25.6% other cancers	Cancer registry	>=30 vs. 20-25 Kg/m^2	1.61 (1.12–2.33)	Age, smoking, physical activity , alcohol intake, hormonal therapy, tumor stage, menopausal status, parity, education, treatment
Keegan TH (2010)	Australia, Canada and the US Registries Follow-up Study Australia, Canada, United States	Cancer diagnosis:1991-2000; Study follow up: ranged from Jan 1994 - July 2007 Newly diagnosed patients recruited	Prospective population-based cohort study of cancer survivors	4153 participants Multi-ethnic	7.8 years	Invasive breast cancer; 62% tumor size <=20 mm, 31% size>20 mm, 7% missing; 19% grade 1, 36% grade 2, 37% grade 3, 8% unknown	24% ER-ve, 65% ER+ve, 11% unknown; 26% PR-ve, 63% PR+ve, 11% unknown 54% none, 23% 1-3nodes, 12% >=4 nodes, 11% missing	Chemotherapy: 34% no, 49% yes, 18% unknown; Tamoxifen: 47% no, 39% yes, 14% missing		Self reported at baseline; height and weight 1 year prior to diagnosis, lifetime PA and 3 yrs prior to diagnosis	4153 participants 725 deaths	Cancer registry + death certificate	>=30 vs. <=24.9 Kg/m^2	1.21 (1.0-1.48)	Study centre, age at diagnosis, race/ethnicity, number of axillary invaded nodes,time since last full term pregnancy, ER status, PR status, tumor grade,tumor size,tumor type, physical activity Highest vs lowest analysis only; missing number of events per category
Nichols HB (2009)	Collaborative Women's Longevity Study United States	Study recruitment: 1988-2001; Cancer diagnosis: 1988-1999; Study follow up: until 2005 Recruited 5.8 years after breast cancer diagnosis	Follow-up of cases of case-control studies	3993 participants 58.4 years (mean) 20 - 79 years Mostly white: 98%, 28.1% premenopausal; 71.9% postmenopausal HRT use: 38.9% (postmenopausal hormone use)	6.3 years	Invasive nonmetastatic breast cancer; 64.1% local, 24.7% regional, 0.6% distant, 10.6% unknown			40%	Self-reported body weight 1-5 years before diagnosis at study baseline	3993 participants 421 deaths, 121 breast cancer mortality, 95 deaths from cardiovascular disease	Death record	>=30 vs. 18.5-24.9 Kg/m^2	1.52 (1.17-1.98)	Age, tumor stage, time from diagnosis to exposure assessment, family history, smoking, physical activity, menopausal status

West-Wright CN (2009)	California Teachers Study United States	Study recruitment: 1995; Cancer diagnosis: 1995-2004; Study follow up: until 2005	Cancer survivors of a population-based prospective cohort study	3539 participants 58.9 years (mean) 26 - 94 years Mostly white: 89.7% Comorbidities: 111 diabetes, 106 cardiovascular disease; 24.5 %	9 years	Incident first primary invasive breast cancer; 68.9% localized, 28.4% regional, 1.86 metastatic, 0.8 % missing	72% ER+ve, 12.7% ERve, 15.3% unknown			Self-reported at baseline; PA within the 3 years prior to cohort entry, prior to diagnosis	3539 participants 460 deaths, 221 breast cancer mortality, 69 death from other causes including 24 death from other cancers, 68 cardiovascular disease deaths; 38 cerebrovascular disease deaths; 28 cardiopulmonary or pulmonary disease deaths; 4 diabetes death	Death certificate	>=30 vs. <25 Kg/m^2	1.42 (1.08-1.88)	Age,Race,estrogen receptor level,Energy intake,Tumor stage,Physical activity ,Comorbidity
Caan BJ (2008)	LACE United States	Cancer 46% diagnosis:1997-2000; Study follow up: until 2007 Diagnosed 11–39 months before study enrolment	Prospective cohort study of breast cancer survivors	1692 participants 58.3 years (mean) 18 - 70 years 22.8% premenopausal, 63.8% postmenopausal	83.9 months	Early stage invasive breast cancer; AJCC; 46.7% Stage I, 50.2% Stage II, 3.1% Stage IIIA	69.2% ER+/PR+, 13.6% ER+/ PR-, 1.7% ER-/ PR+, 15.5% ER-/ PR- 63.2% o node+ve, 26.3% 1-3 nodes+ve, 5.7% 4-6 nodes+ve, 1.7% 7-9 nodes+ve, 3.1% >=10 nodes+ve	19% chemotherapy; 24.8% radiotherapy; 38.4% chemo- and radiotherapy; 49.2% mastectomy; 50.8% breast-conserving surgery; 70.9% current tamoxifen users, 6.7% past tamoxifen users	46%	Self-reported at baseline; one year pre-diagnosis and also after diagnosis at baseline	1689 participants 162 deaths, 99 breast cancer mortality, 160 deaths included in the analysis,	Medical records	>=30 vs. <=24.9 Kg/m^2	1.60 (1.10-2.30)	Tumor stage, age at diagnosis, tamoxifen use, treatment, nodal status, estrogen receptor level, progesterone receptor level, smoking, physical activity
Dal Maso L (2008)	Six Italian Regions Follow-up Study Italy	Cancer diagnosis: 1991-1994; Study follow up: until 2005-2006 diagnosed no longer than 1 year before the interview	Follow-up of cases of a case-control study	1453 participants 55 years (mean) 23 - 74 years Among those with data, pre diagnosis data: 45.5 % peri/pre menopausal, 54.9% postmenopausal HRT use: 91.3% never, 8.6% ever	12.6 years	Invasive breast cancer; TNM; 32.7% Stage I, 44.1% stage II, 13.2% stage III-IV, 9.8% unknown	41.5% ER+ve/PR+ ve, 3.5% ERve/ PR+ve, 45.6% no node+ve, 44.2% node+ve, 10.1%		2.70% lost	Self-reported at study baseline; height, weight 1 year before cancer diagnosis and at different ages; hip and waist measured at interview	1453 participants 503 deaths, 398 breast cancer mortality, 6.2% death from other cancers, 7.4% from cardiovascular disease	Cancer registry	>=30 vs. <=24.9 Kg/m^2	1.29 (0.99–1.68)	Region, age at diagnosis, year of diagnosis, TNM stage, receptor status
Reding KW (2008)	Fred Hutchinson Cancer Research Center Follow-up study United States	Cancer diagnosis: 1983-1992, Study follow-up: Until 2002 Recruited at diagnosis	Follow-up of cases of case-control studies	1286 participants <=45 years White: 95.2%, Black: 1.7%, Othes: 3.1% Premenopausal HRT use: 41.4% ever had, 58.6% had not among those with data	9 Years (max)	First primary invasive breast cancer; 57.94% local, 409% regional, 1.97% distant	59.3% ER+ve, 40.7% ER-ve, 60.5% PR+ve, 39.5% PR-ve 41.1% +ve, 58.9% -ve, among those with data	Chemotherapy: 68.9% yes, 31.1% no; Radiotherapy 53.8% yes, 46.2% no; Hormone therapy 35.3% yes, 64.7% no, among those with data	83.3%, 83.9% in original studies 93.1% contacted within 12 months of end of F/U, 6.9% loss	5 years before diagnosis were recalled at interview	1286 participants 364 deaths, 335 breast cancer mortality, 22 other causes of deaths, 7 unknown causes of deaths	Medical records	>=25.8vs. <=20.6 Kg/m^2	1.90 (1.40-2.50)	Age, diagnosis year, and mammography.
Cleveland R (2007)	Long Island Breast Cancer Study Project United States	Cancer diagnosis:1996-1997; Study follow up: 2002- 2004	Follow up of cases of a case-control study	1508 participants 58.8 years (mean) 25 - 98 years Mostly white 32.2% premenopausal, 67.8% postmenopausal HRT use: 86.8%	66.7 months	84.4% invasive and 15.6% In situ	26.7% ER-ve, 73.3% ER +ve, 35.8% PR-ve, 64.2% PR+ve 73.7% no nodes involved, 26.3% nodes involved	Radiation therapy, chemotherapy, hormone therapy	410 patients lost	Self-reported shortly after diagnosis; weight and height at each decade of life from age 20 years until	1508 participants 196 deaths (of which 21% from cardiovascular disease), 127 breast cancer mortality, 9 death from brain and lung metastases Analysis included	National Death Index	>30 vs. <24.9 Kg/m^2	1.63 (1.08-2.45)	Age at diagnosis, hypertension Highest vs. lowest analysis only; two BMI categories only

				ever, 13.2% never						1 year before diagnosis	postmenopausal women only				
Reeves KW (2007)	Study of Osteoporotic Fractures United States	Study recruitment:1986-1988; Study follow up: until 2006 Diagnosed 7.5 years on average after enrolling into SOF	Cancer survivors of a population-based prospective cohort study	533 participants 78 years (mean) >=65 years Caucasian All postmenopausal 6.3% diabetes, Comorbidities: 0.9% history of congestive heart failure	8.1 years	15% In situ, 75.2% Stage I or II, 5.1% Stage III/IV, 4.7% unknown	68.9% ER+ve, 10.5% ER-ve, 20.6% unknown; 54% PR+ve, 23.5% PR-ve, 22.5% unknown		1% lost	Measured at clinical examinations at study baseline 128 participants	533 participants 206 deaths, 45 breast cancer mortality, 68 deaths from any cancer, 56 deaths from cardiovascular disease	Death certificate	Age 65 years Age 70 years Age 75 years Age 80 years Age 85 years 34 vs. 22.6 Kg/m^2	2.41 (1.07-5.45) 1.71 (0.97-3.02) 1.21 (0.82-1.77) 0.86 (0.60-1.23) 0.61 (0.36-1.02)	Age,smoking,hypertension, tumor stage, ER status,diabetes Highest vs lowest analysis only; missing number of events and at-risk per category
Abrahamson (2006)b	Atlanta, Seattle, New Jersey Follow-up Study United States	Cancer diagnosis:1990-1992; Study follow up: until 2000	Follow-up of cases of a population-based case-control study	1254 participants 20 - 54 years 75% white 25% nonwhite 78% premenopausal, 22% postmenopausal and unknown <1%	9.8 Years (max)	Invasive breast cancer; AJCC; any stage ; 57% local, 40% regional, 3% distant, <1% unknown	56% ER+ve, 35%ER-ve, 3% borderline, 6% unknown		86% <2% lost	Measured 4.2 months after diagnosis; self-reported weight and height at age 20 years and the year before diagnosis	1217 participants 290 deaths, 280 deaths included in analysis	Cancer registry + National Death Index	>=30 vs. 18.5-24.9 Kg/m^2 at age 20	2.93 (1.37-6.29)	Tumor stage, income (Result further adjusted for waist-hip-ratio was also provided in the article)
Kroenke C (2005)	Nurses' Health Study United States	Cancer diagnosis: 1976 - 2000, Study follow-up: Until 2002	Cancer survivors of population-based prospective cohort study	5204 participants 30 - 55 years	9 years	Invasive non metastatic breast cancer, any stages; 86.9% tumor size >2cm	73.2% ER+ 85.2% +ve	Chemotherapy: 63.9% yes; Tamoxifen: 64.8% yes		Self-reported at cohort baseline; pre and post-diagnosis weight	5204 participants 860 deaths, 533 breast cancer mortality	Family+ National Death Index	>=30 vs. 21-22 Kg/m^2	1.20 (0.95-1.52)	Age, oral contraceptive, birth index, menopausal status, age at menopause, hormonal therapy, smoking, tumor size, nodal status, chemotherapy, tamoxifen use, protein intake
Bernstein JL (2002)	Cancer and Steroid Hormone Study United States	Cancer diagnosis:1980-1982 (1st breast cancer) and before 1999 (2nd breast cancer); Study follow up: until 1998	Follow-up of cases of a population-based case-control study	369 participants 20 - 54 years Multi-ethnic	18 Years (max)	First primary breast cancer and a second primary in the contralateral breast; any stages including In situ breast cancer		81 and 71 patients had radiation treatment following first and second primary breast cancer respectively	28 patients lost	Interviewed within 6 months of diagnosis of primary cancer for data at age 18 years and adulthood	369 participants 160 deaths (90% death from cancer including 87% breast cancer mortality)	Cancer registry	>=25 vs. 18.5-24.9 Kg/m^2	1.18 (0.81-1.72)	Age at diagnosis, education, tumor stage, time between primary cancers Highest vs lowest analysis only; missing number of events per category
Reeves GK (2000)	Six London Hospitals Follow-up Study UK	Study recruitment: 1968-1984; Cancer diagnosis: 1968-1980 for 1st study and 1980-1984 for 2nd study; Study follow up: until 1994	Follow-up of cases of case-control studies	1208 participants 24 - 59 years 74% premenopausal, 26% postmenopausal HRT use: Among those with data: 5% yes, 95% no use	25 Years (max)	TNM; 49.6% Stage I, 32% stage II, 17.2% stage III, 1.2% stage IV	36% node-ve, 47.8% node+ve, 16.2% unknown		39 women, 3% lost	from records of original studies	1208 participants 608 deaths	Medical records	>=27 vs. <=24 Kg/m^2	1.49 (1.18-1.86)	Age at diagnosis, year of diagnosis, hospital Highest vs lowest analysis only; missing number of events and at-riak per category

Zhang S (1995)	Iowa Women's Health Study United States	Study recruitment:1986; Study follow up: until 1991	Cancer survivors of population-based prospective cohort study	698 participants 55 - 69 years Mostly white: 98%, Postmenopausal	2.9 years	Unilateral breast cancer; 10% in situ, 58% local, 28% regional, 3%distant, and 1% unknown; 55% tumour size <2cm, 33% size >= 2cm and 11% unknown	Among those with data: 85% ER+ve and 72% PR+ve		42.60% < 1% migration rate	Self reported questionnaire within 6 years before diagnosis	698 participants 56 deaths, 40 breast cancer mortality (among the causes of death) and 2 death from coronary heart disease	Death certificates, National death index	28.9-45.9 vs. 16-24 Kg/m^2	1.50 (0.7-2.90)	Age, smoking, education, tumor stage, ER status, tumor size
Holmberg L (1994)	Swedish and Norwegian Cancer Registries Follow-up Study Sweden and Norway	Cancer diagnosis: original studies 1984-1985, Study follow-up: Until 1989	Follow-up of cases of case-control study	422 participants <=45 years Premenopausal	5 Years (max)	Invasive breast cancer; any stages			88.3%, 92.1% in original studies 0% lost	Self-reported BMI 18 months prior to diagnosis during interview 3-12 months after diagnosis	422 participants 94 deaths, 92 breast cancer mortality	Cancer registry + National Death Index	1 Kg/m^2 increase >=29 vs. <19 Kg/m^2	1.08 (1.03-1.14) 5.93 (1.98-17.80)	Age, study centre

Table 84 Table of excluded studies on BMI before diagnosis and total mortality

Author Year	**Study name**	**Diagnosed / recruitment dates End of follow-up**	**Study type**	**Study characteristics**	**Follow-up time**	**Tumour characteristics**	**Hormone receptor status** **Nodal status**	**Treatment info**	**Response rate** **Loss to follow-up**	**Exposure assessment Timeframe**	**Outcome events Number in analysis**	**Outcome confirmation**	**Contrast**	**RR (95% CI)**	**Adjustments** **Exclusion reason**
Vatten LJ (1991)	Norwegian Health Screening Examination Cohort Study Norway	Study recruitment:1974-1978; Study follow up: until 1989	Cancer survivors of population-based prospective cohort study	242 participants 50.0 years (mean) 36.0 - 63.0 years White 93.8% participated in health screening	5 years	40% stage I, 33% stage II, 7.5% stage III or IV, 20% unspecified stage					242 participants 61 deaths	Death certificate	30 vs. 21 Kg/m^2	2.1 (1.2-3.8)	Age at diagnosis, tumor stage,total serum cholesterol Superseded by Emaus, 2010
Holmes MD (1999)	Nurses' Health Study United States	Cancer diagnosis: 1976–1990, Study follow-up: Until 1994	Cancer survivors of population-based prospective cohort study	1982 participants 54 years (mean) 35.1% premenopausal, 64.9% postmenopausal, among those with data	157 months	Invasive breast carcinoma; Grade 1-3			95% 5% lost	On average 24 months (SD 18m) after diagnosis	1978 participants 378 deaths, 326 breast cancer mortality	Death certificate	>29 vs. <21 Kg/m^2	1.39 (0.97-2.0)	Age, diet interval, calendar year of diagnosis, body mass index, oral contraceptive use, menopausal status, postmenopausal hormone use, smoking, age at first birth and parity, number of metastatic lymph nodes, tumor size, energy intake Superseded by Kroenke, 2005
Daling JR (2001)	Fred Hutchinson Cancer Research Center Follow-up	Cancer diagnosis: 1983-1992, Study follow-up: Until	Follow-up of cases of case-control studies	1177 participants years (mean) 45.0 years Premenopausal	17 years	Invasive incident ductal breast carcinoma, histologic grades: 19.9%	60.2% ER+, 39.8% ER-, 60.7% PR+, 39.3% PR-, among those with data	Info on adjuvant therapy, radiation, chemotherapy, hormone therapy, doxorubicin were	83.3% and 83.9%	Post-diagnosis; weight 1 year before diagnosis	1177 participants 317 deaths, 283 breast	Cancer registry	25.8 -52.5 vs. 15.8–20.6 Kg/m^2	2.1 (1.5–2.9)	Age, year of diagnosis, tumor size, nodal status, PR status, ER status, other factors

	study United States	2000 Post-diagnosis				low, 38% intermediate, 42% high, among those with data	58.8% +ve, 41.2% -ve, among those with data	abstracted from the medical records	Less than 4% lost within 3 years of June 2000	was used to determine BMI	cancer mortality, 9 deaths from leukemia or other neoplasm, 2 deaths from other causes, and 23 unknown causes of deaths				Superseded by Reding 2008
Greenberg (1985)	Six London Hospitals Follow-up Study United Kingdom	Study recruitment:1968-1977; Study follow up: until December 1982	Follow up of cases of a hospital-based case-control study	582 participants 40.0 years (mean) 24.0 - 50.0 years All premenopausal	14 years	TNM; 62% Stage I, 20% Stage II, 19% Stage III+IV	40% node +ve		18 patients lost	Reported at the time of diagnosis	582 participants 228 deaths	Hospital records	QI>= 2.70 vs. <=2.0	1.8 P for trend=0.115	Tumor stage, age, social class, reproductive history, family history, smoking, oral contraceptive, year of diagnosis, hospital of diagnosis Superseded by Reeves 2000 in the overall analysis; reviewed in the highest vs. lowest meta-analysis of premenopausal breast cancer
Allemani C (2011)	ORDET (Hormones and Diet in the Etiology of Breast Cancer) & UROCARE (European Cancer Registry-based Study of Survival and Care of cancer patients	Cancer diagnosis: 1987-2001, Study follow-up: Until 2005	Prospective cohort of breast cancer survivors	264 participants 34 - 70 years	7.6 years	Tumor stages: 47.7% T1N0M0 ,9.8% T2-3N0M0, 42.4% T1-3N+M0/T4/M1				Possibly collected during baseline interview; alcohol intake over the 12 months prior to recruitment	264 participants 43 deaths	Clinical records	>= 25 vs. <25 Kg/m2	Relative excess risk (2.20 1.01-4.70)	Non alcohol energy intake Reported relative excess risk and not relative risk
Eley JW (1994)	Black/White Cancer Survival Study United States	Cancer diagnosis: 1985-1986, Study follow-up: Until 1990 Post-diagnosis	Retrospective cohort study	1130 participants 20.0 - 79.0 years Black and White 55% comorbidity free	5 years	Invasive breast cancer, AJCC stages: 25.5% I, 46.2% II, 17.1% III, 6.5% IV, 4.8% unknown	38.5% +ve, 48.2% -ve, 13.3% unknown		2 patients lost	Self reported post-diagnosis BMI at baseline or from medical records	1130 participants 350 deaths, 237 breast cancer mortality	Active follow-up and review	High vs. low-normal	2.5 (1.8-3.4)	Unadjusted result
Gregorio DI (1985)	Roswell Park Memorial Institute Review Study United States	Cancer diagnosis: 1957-1965; Study follow up: until 1983	Prospective cohort of breast cancer survivors (historical prospective cohort)	854 participants White2		Among those with data: 29.8% local, 45.6% regional and 24.5% distant			83 patients lost	Assessed at diagnosis by interview; fat consumption prior to diagnosis and onset of symptoms			Per 1 QI (kg/cm2 x 1000)	0.99, p>0.05	Age,Tumor stage,Treatment delay,Fat intake Insufficient data

BMI less than 12 months after diagnosis and total mortality

Methods

We identified 49 publications. Six publications (Anderson, 2009; Goodwin, 2002; Jung, 2011; Eralp, 2009; Bayraktar, 2012; Shu, 2009) were superseded by other publications of the same studies (Litton, 2008; Dawood, 2008; Dignam, 2003; Dignam, 2006; Goodwin, 2012; Jung, 2012; Chen, 2010). One publication had two studies (Moon, 2009). This resulted 44 different studies (43 publications) on BMI less than 12 months after diagnosis and total mortality, of which 15 studies could not be included in the meta-analyses beause of insufficient data (Abe, 1976; Donegan, 1978; Mohle-Boetani, 1988; Suissa, 1989; Taylor, 1989; Kimura, 1990; Kyogoku, 1990; Albain, 1992; Lethaby, 1996; Singh, 2011) or unadjusted results (Gordon, 1992; Menon, 1999; Saxe, 1999; Schuetz, 2007; Allin, 2011).

Four of the ten studies with insufficient data observed poorer survival with obesity (Abe, 1976; Taylor, 1989; Kimura, 1990; Singh, 2011), three observed an increased risk with mortality (Suissa, 1989; Kyogoku, 1990; Mohle-Boetani, 1988), and three observed no significant associations (Donegan, 1978; Albain, 1992; Lethaby, 1996). For the three studies reported on relative risk - Suissa et al. (1989) reported a relative risk of 3.35 ($p = 0.002$) for each 1 unit of Quetelet Index (0.01 x lbs/inches^2) increase from a quadratic model. Such result could not be included in our linear analysis. The stuies by Kyogoku et al. (1990) and Mohle-Boetani et al. (1988) also observed a positive association (RR for > 25 vs. < 20 kg/m^2 = 2.51 and for > 34.7 vs. ≤ 30.4 lb/inch^2 = 1.4, respectively), with a dose-response trend ($p < 0.01$ and $p = 0.02$, respectively), but a 95% CI or p-value was missing for the association. Data was not available for the Donegan et al. study, a hospital-based study of 83 women, in which 5-year survival rates were not significantly lower for obese women (measured by an obesity index of weight (lb)/height (inch)). For the five studies with unadjusted results, Saxe et al. (1999) observed a statistically non-significant decreased risk between BMI and total mortality (RR for >27 vs. ≤ 27 kg/m^2=0.74, 95% CI 0.32-1.71), while Gordon et al. (1992) and Allin et al. (2011) reported a significant increased risk (RR for >36 vs. ≤ 19 kg/m^2 = 1.43, 95% CI 1.09-1.88 and RR for ≥ 30 vs 18.5-24.9 kg/m^2 = 1.45, 95% CI 1.01-2.09 respectively). Schuetz et al. (2007) and Menon et al. (1999) reported no association in postmenopausal women and overall respectively. In addition, Allin et al. (2011) reported an increased risk for underweight versus normal weight (unadjusted HR for < 18.5 vs. 18.5-24.9 kg/m^2 = 2.21; 95% CI 1.37-3.57).

Hence, 29 studies (28 publications) were included in the meta-analyses. There were 26 studies included in the highest vs. lowest meta-analysis as, two studies (Vitolins, 2008; Baumgartner, 2011) reported dose-response results only, and one study (Gonzalez-Angulo, 2005) was included in the highest vs. lowest meta-analysis by menopausal status only. Nine studies reported results separately on the underweight group and were included in the underweight versus normal weight meta-analysis.

We included the BMI categories as defined by the studies. The reference category in most studies was the normal weight group, but may include underweight women. BMI could be

assessed at or around diagnosis, e.g. several months but less than a year after diagnosis or just before cancer treatment.

Main results and heterogeneity

The summary RR per 5 kg/m^2 was 1.11 (95% CI 1.06-1.17; 10 studies). High heterogeneity was observed (I^2 = 60.5%, p = 0.01). There is no evidence of small study/publication bias (Egger's test p = 0.11). There is no evidence of strong influence from any individual study on the summary estimate, which remained statistically significant when each study was omitted in turn in the influence testing, ranging from 1.10 (95% CI 1.05-1.15) when Abrahamson et al. (2006b) was omitted to 1.13 (95% CI 1.06-1.20) when Majed et al. (2008) was omitted. All studies except Baumgartner et al. (2011) comprised pre- and postmenopausal women, when excluding this postmenopausal study, the summary RR became 1.13 (95% CI 1.08-1.19).

In the highest versus lowest meta-analysis, the summary RR was 1.27 (95% CI 1.16-1.39; 26 studies). High heterogeneity between studies was observed (I^2 = 76.6%; p < 0.0001). When stratified by menopausal status, a higher risk of total mortality was observed in premenopausal women compared with postmenopausal women (summary RR for highest vs. lowest = 1.28; 95% CI 1.16-1.42; I^2 = 0%, p = 0.51; 7 studies, and RR 1.13; 95% CI 1.03-1.23; I^2 = 0%; p = 0.77; 6 studies, respectively). Mohle-Boetani et al. (1988) could not be included in the analysis. The RRs for BMI (1000 x weight (lb)/height (inches)) ≥ 34.7 vs. 〈 30.4 were 1.6 and 1.3 (no 95% CI or p-value) respectively in pre- and postmenopausal women.

When stratified by estrogen receptor status, an increased risk of total moratily was observed in both ER negative and ER positive breast cancer patients (summary RR for highest vs. lowest = 1.29; 95% CI 1.06-1.56; I^2 = 56.6%; p = 0.04, and RR = 1.19, 95% CI 1.06-1.33; I^2 = 31.4%; p = 0.20, respectively). Five studies were included in each stratum. One study (Azambuja, 2010) reported separately on ER-PR- and ER-PR+ breast cancers.

In the underweight versus normal weight meta-analysis, the summary RR was 1.23 (95% CI 0.93-1.63; 9 studies). High heterogeneity between studies was observed (I^2 = 69.4%; p = 0.001).

When all data including those from the underweight subjects were modelled in a non-linear dose-response analysis, non-linearity was observed ($p_{non\text{-}linearity}$ = 0.02). There was a slight J-shape relation, with the lowest total mortality risk associated with the normal weight group (~20-<24 kg/m^2). When studies with or without a separate underweight group were analysed seperately, the non-linear relationship was only observed in the former studies, but the number of studies were limited (data not shown).

Dose-response meta-analysis by subgroups and meta-regression analyses were performed on factors such as study design, length of study follow-up, geographic location, number of outcome events, exposure assessment method, exposure levels, and covariate adjustments to explore heterogeneity between studies that were included in the linear

dose-response meta-analysis. Exploration by menopausal status was not possible due to limited data.

Meta-regression suggested that European studies were weaker in association compared with North American studies ($p_{heterogeneity}$ = 0.03). Summary RRs were 1.01 (95% CI 0.90-1.12; I^2 = 66.8%; p = 0.08; 2 studies) and 1.19 (95% CI 1.12-1.28; I^2 = 0%; p = 0.55; 4 studies) respectively.

However, these two European studies were also hospital-based case-series that assessed BMI from medical records, as observed when exploring heterogeneity by these factors. When comparing studies that used medical records to assess BMI with studies that used measured data, summary RRs were 1.05 (95% CI 1.01-1.10; I^2 = 32%; p = 0.22; 4 studies) and 1.20 (95% CI 1.14-1.27; I^2 = 0%; p = 0.74; 5 studies) respectively, and p for heterogeneity of meta-regression was 0.01. When comparing hospital-based case-series with population-based studies, summary RRs were 1.04 (95% CI 0.98-1.11; I^2 = 32.8%; p = 0.22; 4 studies) and 1.21 (95% CI 1.11-1.32; I^2 = 0%; p = 0.43; 3 studies) respectively, and $p_{heterogeneity}$ of meta-regression = 0.06.

Study quality

Number of events ranged from 57 to 983 deaths. Thivat et al. (2010) accrued 57 deaths from 111 breast cancer patients who had been treated by anthracycline-based chemotherapy after an average of 20.4 years (between 1976-1989) of follow-up. Three other studies (Kumar, 2000; Labidi, 2008; Ademuyiwa, 2011) had less than 100 deaths. Four studies had between 100 and 200 deaths (Loi, 2005; Litton, 2008; Maskarinec, 2011; Goodwin, 2012). Seven studies had between 200 and 500 deaths (Abrahamson, 2006b; Tao, 2006; Dawood, 2008; Vitolins, 2008; Azambuja, 2010; Chen, 2010; Lung, 2012). Three studies had over 500 deaths (Dignam, 2003; Dignam, 2006; Sparano, 2012). For the studies reported data, more than half of the deaths were attributed to breast cancer (Dignam, 2003; Dignam, 2006; Litton, 2008; Vitolins, 2008; Azambuja, 2010; Goodwin, 2012; Sparano, 2012); one exception was Maskarinec et al. (2011), in which 43 out of 115 deaths were from breast cancer.

Average follow-up ranged from 37.2 months to 20.4 years. Ademuyiwa et al. (2011) had an average follow-up of 37.2 months. Only triple-negative breast cancer patients, diagnosed in 1996-2010, were recruited in this study. Chen et al. (2010) also had a short average follow-up of 46 months. Four studies (Loi, 2005; Tao, 2006; Azambuja, 2010; von Drygalski, 2011) had average follow-up of approximately 5 years. Tao et al. (2006) reported that the vital status of 126 patients were unconfirmed and assumed living by the end of follow-up. Camoriano et al. (1990), Vitolins et al. (2008) and Azambuja et al. (2010) included lymph node-positive breast cancer cases only. The latter study involved only stage II and III breast cancers. The trials conducted by Dignam et al. consisted only of ER-negative and lymph node-negative breast cancer cases (Dignam et al. 2006), ER-positive and lymph node-negative breast cancer cases (Dignam et al. 2003). Labidi et al. (2008) included nonmetastatic inflammatory breast cancer cases, while Dawood et al. (2008) included stage III locally advanced breast cancer cases. Participants in von Drygalski et al.

(2011) had metastatic breast cancer and received high-dose chemotherapy with autologous stem cell support (HD-ASCT) as part of their treatment. Jung et al. (2012) also included metastatic breast cancer cases.

Three studies (Tao, 2006; Chen, 2010; Maskarinec, 2011) included *In situ* and invasive breast cancers and 24 studies (Camoriano, 1990; Kumar, 2000; Dignam, 2003; Camichael, 2004; Berclaz, 2004; Loi, 2005; Dignam, 2006; Abrahamson, 2006b; Vitolins, 2008; Majed, 2008; Litton, 2008; Labidi, 2008; Dawood, 2008; Moon, 2009; Thivat, 2010; Clough-Gorr, 2010; Azambuja, 2010; Baumgartner, 2011; von Drygalski, 2011; Ewertz, 2011; Ademuyiwa, 2011; Sparano, 2012; Jung, 2012; Goodwin, 2012) included invasive breast cancer only. Case diagnosis dated as early as 1963-1999 in Camichael et al. (2004). Three studies included cases diagnosed from the 1970s (Berclaz, 2004; Dawood, 2008; Thivat, 2010). Most studies included cases diagnosed from the 1980s (Dignam, 2003; Dignam, 2006; Vitolins, 2008; Majed, 2008; Moon, 2009; Baumgartner, 2011; von Drygalski, 2011; Goodwin, 2012) or from the 1990s (Loi, 2005; Tao, 2006; Abrahamson, 2006b; Litton, 2008; Labidi, 2008; Azambuja, 2010; Maskarinec, 2011; Ademuyiwa, 2011; Sparano, 2012; Jung, 2012). Chen et al. (2010) included cases diagnosed in 2002-2006. There were four follow-up of case-control studies (Kumar, 2000; Loi, 2005; Abrahamson, 2006b; Tao, 2006) and 15 cohorts of breast cancer survivors (Camichael, 2004; Dawood, 2008; Labidi, 2008; Litton, 2008; Majed, 2008; Moon, 2009; Chen, 2010; Clough-Gorr, 2010; Thivat, 2010; Ademuyiwa, 2011; Maskarinec, 2011; von Drygalski, 2011; Baumgartner, 2011; Goodwin, 2012; Jung, 2012), of which 13 were case-series (Kumar, 2000; Camichael, 2004; Dawood, 2008 and Litton, 2008; Labidi, 2008;; Majed, 2008; Thivat, 2010; Ademuyiwa, 2011; Maskarinec, 2011; von Drygalski, 2011; Baumgartner, 2011; Goodwin, 2012; Jung 2012) and six (Loi, 2005; Abrahamson, 2006b; Tao, 2006; Moon, 2009; Chen, 2010; Clough-Gorr, 2010) were population-based studies. There were eight ancillary analyses of randomised controlled trials (Camoriano, 1990; Dignam, 2003; Berclaz, 2004; Dignam, 2006; Vitolins, 2008; Azambuja, 2010; Ewertz, 2011; Sparano, 2012).

Eight studies (Camoriano, 1990; Kumar, 2000; Tao, 2006; Abrahamson, 2006b; Vitolins, 2008; Azambuja, 2010; Thivat, 2010; Goodwin, 2012) used measured anthropometric data. Five studies (Camichael, 2004; Loi, 2005; Clough-Gorr, 2010; Chen, 2010; Sparano, 2012) used self-reported data. Eleven studies (Berclaz, 2004; Majed, 2008; Litton, 2008; Dawood, 2008; Labidi, 2008; Moon, 2009; Baumgartner, 2011; von Drygalski, 2011; Maskarinec, 2011; Ewertz, 2011; Ademuyiwa, 2011; Jung, 2012) used data from medical records. Anthropometric data assessment methods in Dignam et al. (2003; 2006) were unclear. Anthropometric data were assessed in breast cancer patients, either at diagnosis (Camichael, 2004; Majed, 2008; Litton, 2008; Labidi, 2008; Dawood, 2008; Moon, 2009; Chen, 2010 Baumgartner, 2011; Maskarinec, 2011; Ewertz, 2011; Ademuyiwa, 2011; Jung, 2012), or a few months but less than a year after diagnosis or before cancer treatment (Camoriano, 1990; Kumar, 2000; Dignam, 2003; Loi, 2005; Tao, 2006; Dignam, 2006; Abrahamson, 2006b; Vitolins, 2008; Thivat, 2010; Clough-Gorr, 2010; Azambula, 2010; von Drygalski, 2011; Sparano, 2012; Goodwin, 2012). The timing of assessment in Berclaz, et al. (2004) was unclear.

The study by Clough-Gorr et al. (2010) was in postmenopausal women only. The study by von Drygalski et al. (2011) was mostly postmenopausal. All other studies included women of all ages. Adjustment was unclear in Camicahel et al. (2004). Vitolins et al. (2008) and Azambuja et al. (2010) provided unadjusted results but the analyses were based on data from randomised controlled trials of adjuvant treatment, in stage II and III (Vitolins, 2008) and lymph-node positive (Azambuja, 2010) breast cancer patients respectively. Kumar et al. (2000) adjusted for tumour stage only. Labidi et al. (2008) adjusted for chemo- and hormonal therapies only. Von Drygalski et al. (2010) adjusted for tumour stage and metastasis only. Sparano et al. (2012) adjusted for race only. The result of Abrahamson et al. (2006b) was adjusted for tumour stage and income. Other factors like age, race and menopausal status were not included in the final model in this study, as they did not make an appreciable change to the estimate. Results in other studies were multivariated adjusted. The analysis conducted by Baumgartner et al. (2011) was stratified by menopausal status.

Published meta-analysis

Two meta-analyses on obesity less than 12 months after diagnosis and total and breast cancer moralities were published in recent years (Protani, 2010; Niraula, 2012).

Protani et al (2010) reported a summary RR of 1.33 (95% CI 1.21-1.47) for obese versus non-obese (measured by BMI or waist-hip-ratio) in the risk of total mortality, with high heterogeneity between studies (I^2 = 72.7%; p < 0.0001; 33 studies). When stratified by menopausal status, the summary RRs for pre- and postmenopausal women were 1.47 (95% CI 1.19-1.83; I^2 = 68%) and 1.22 (95% CI 0.95-1.57; I^2 = 70%) ($p_{heterogeneity}$ = 0.25) respectively. The summary estimate remained similar when only BMI data was used (RR 1.33; 95% CI 1.23-1.44; I^2 = 70.0%).

Niraula et al. (2012) also observed statistically significant increased risks for obesity and total mortality by hormone receptor status or menopausal status. The summary RRs for obese versus non-obese were 1.31 (95% CI 1.17-1.46; 13 studies) and 1.18 (95% CI 1.06-1.31; 12 studies) in women with ER/PR positive cancers and ER/PR negative cancers respectively ($p_{heterogeneity}$ = 0.31), and 1.23 (95% CI 1.07-1.42; 7 studies) and 1.15 (95% CI 1.06-1.26; 9 studies) in pre- and postmenopausal women respectively ($p_{heterogeneity}$ = 0.57).

All studies reviewed by Protani et al. (2010) were identified and included in the report. Majority of the studies were reviewed under BMI less than 12 months after diagnosis and total mortality, or breast cancer mortality. Some studies were in a different section (waist-hip-ratio), or under different timeframes (BMI before or 12 months or more after diagnosis). Studies reviewed by Niraula et al. (2012) were also included in the report, except Fetting et al. (1998) and Davidson et al. (2005) which data were possibly obtained by author's contacts. It is reported in Niraula's review that Fetting et al. (1998), a study of hormone receptor-negative breast cancer cases, observed no statistically significant association with total mortality (HR for obese vs. non-obese = 0.85 (95% CI 0.18-4.12); and that Davidson et al. (2005), a study of hormone receptor-positive breast cancer cases,

observed a significant increased risk (HR for obese vs. non-obese = 1.52; 95% CI 1.18-1.95).

Figure 93 Highest versus lowest forest plot of BMI less than 12 months after diagnosis and total mortality

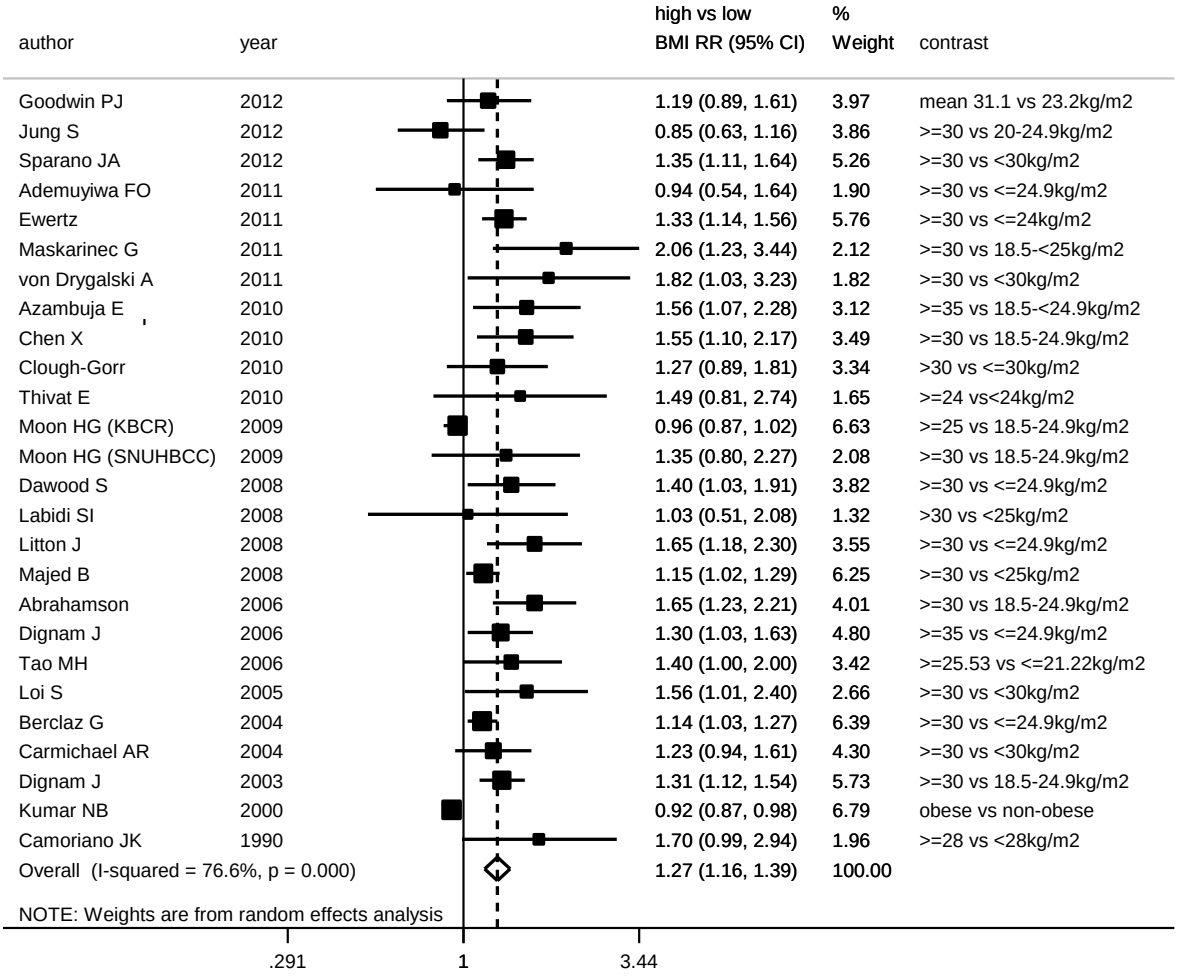


Figure 94 Highest versus lowest forest plot of BMI less than 12 months after diagnosis and total mortality by menopausal status

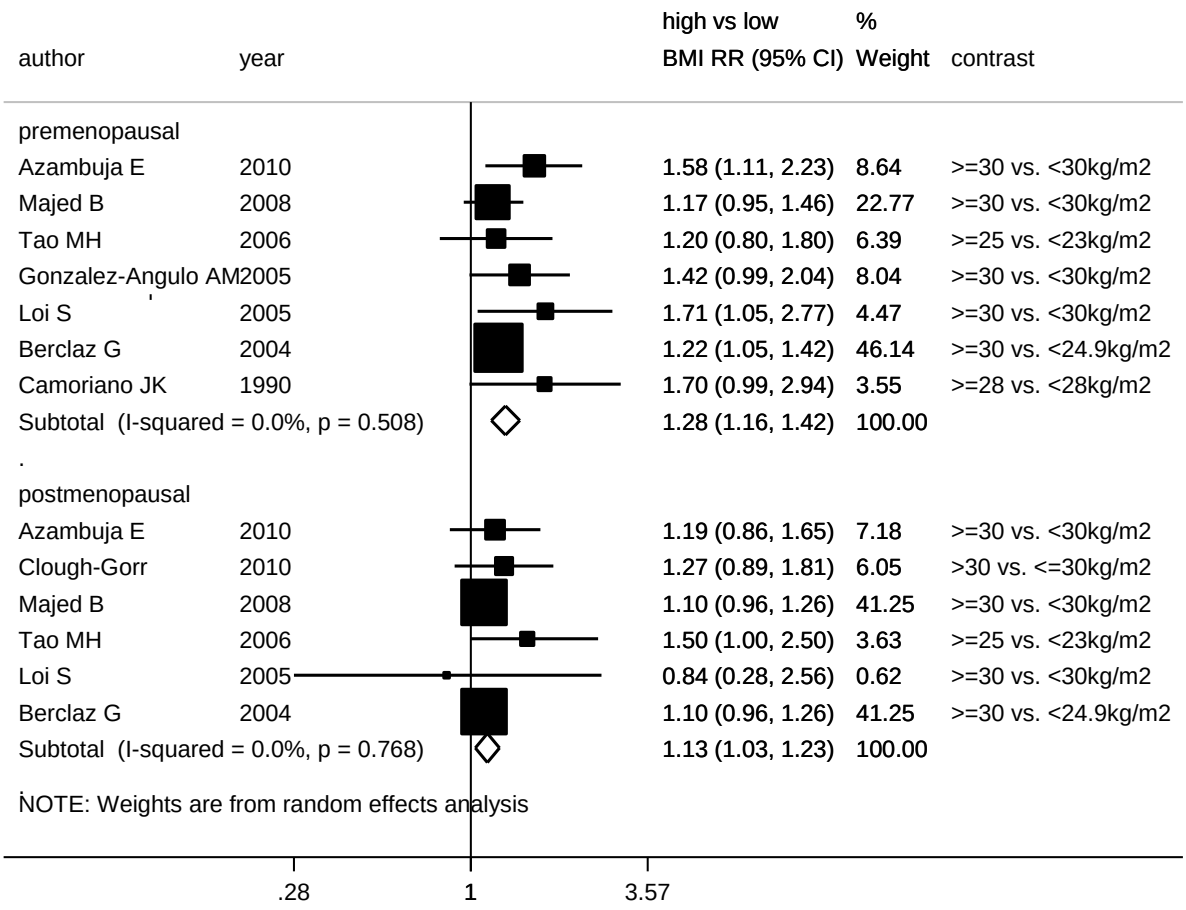


Figure 95 Highest versus lowest forest plot of BMI less than 12 months after diagnosis and total mortality by estrogen receptor status

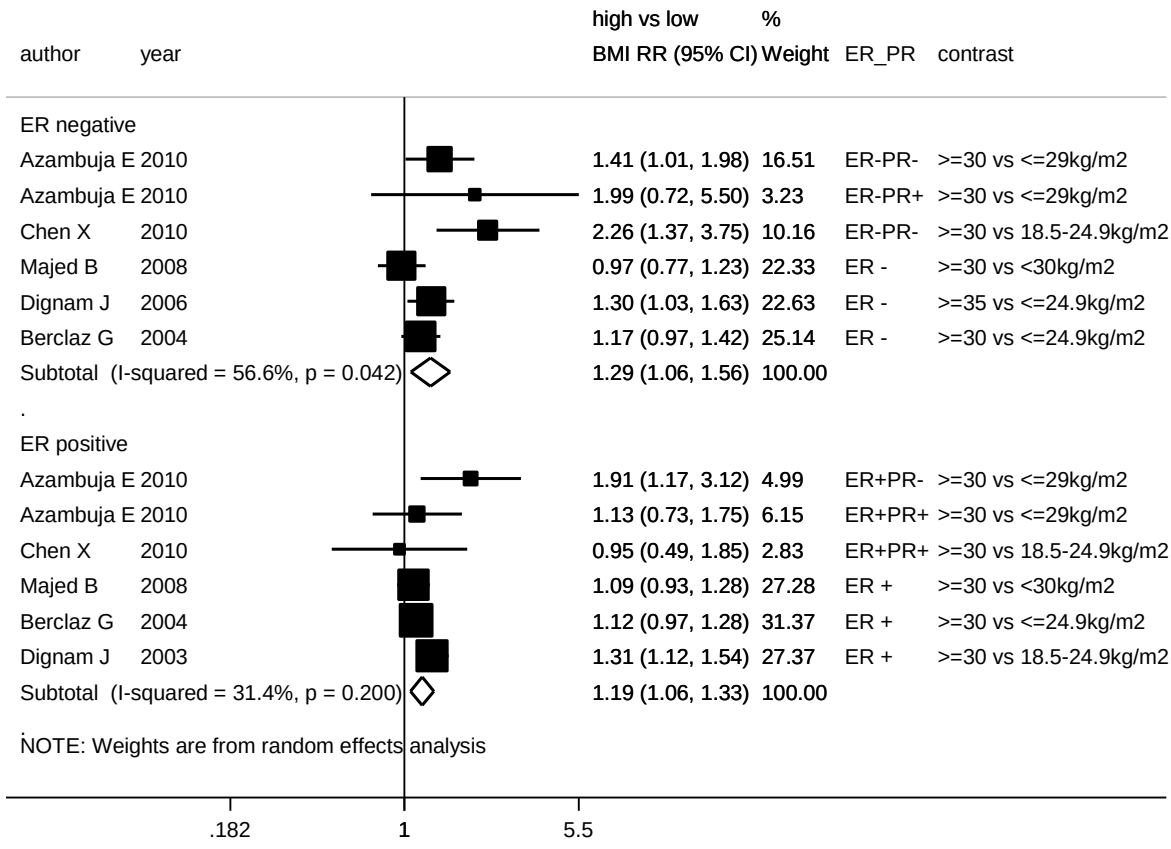


Figure 96 Forest plot of underweight versus normal weight less than 12 months after diagnosis and total mortality

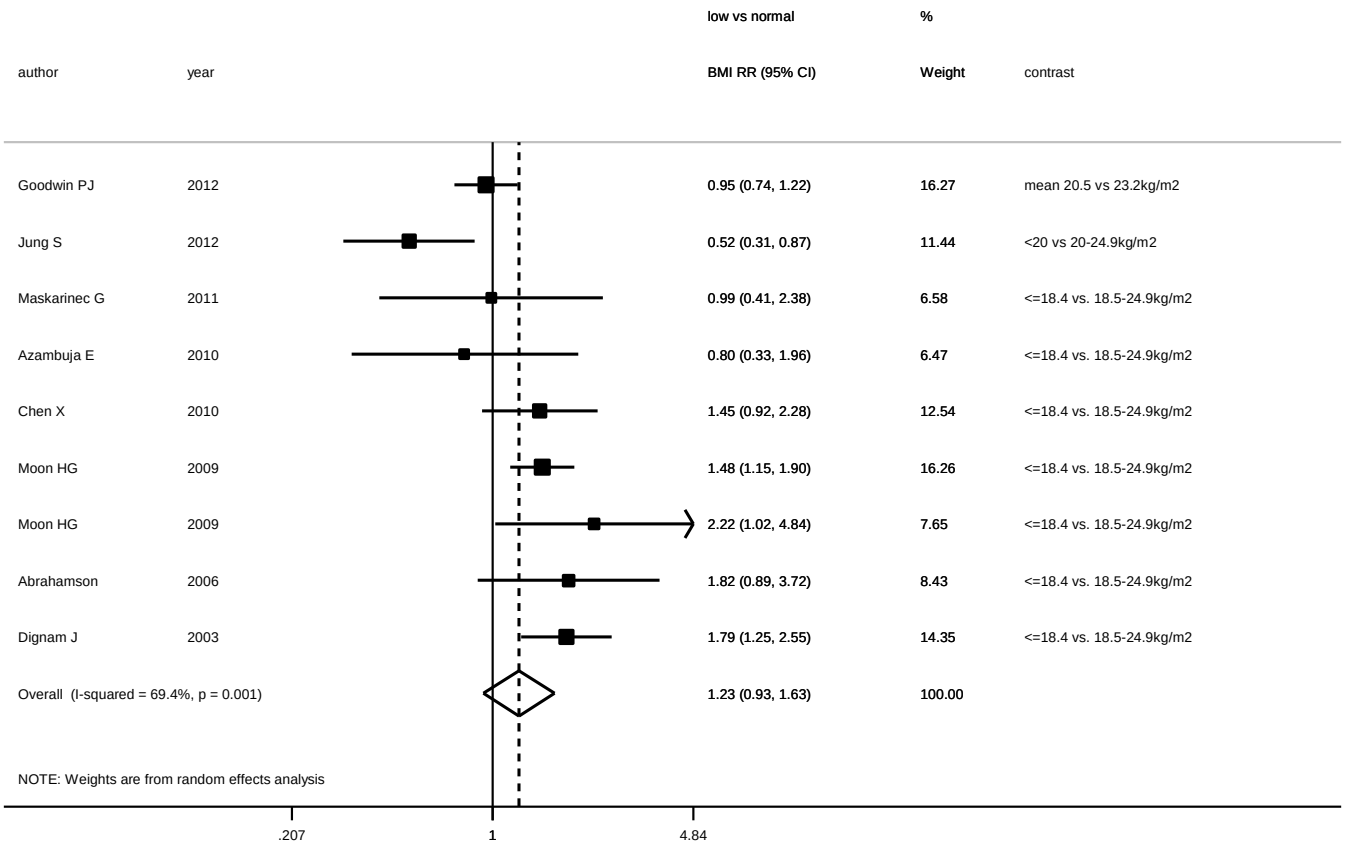


Figure 97 Linear dose-response meta-analysis of BMI less than 12 months after diagnosis and total mortality

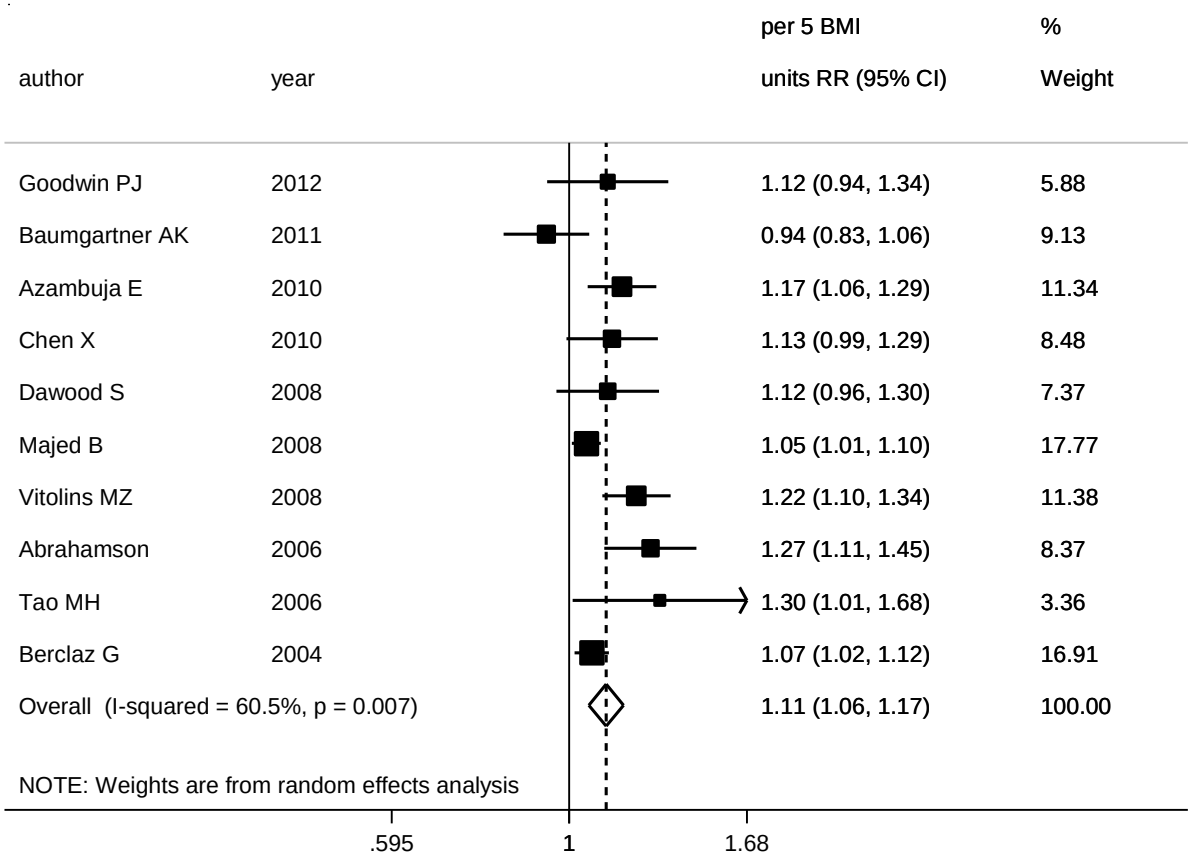
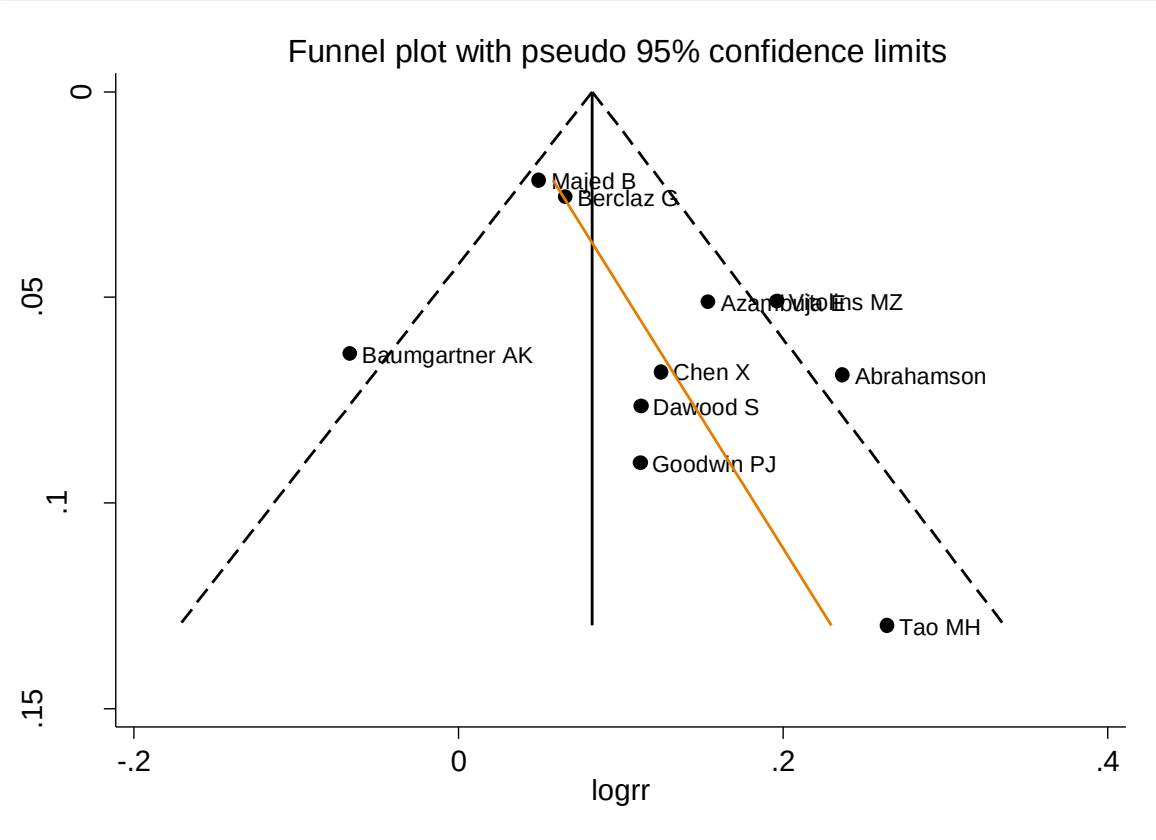


Figure 98 Funnel plot of BMI less than 12 months after diagnosis and total mortality



Each dot represents the logarithm of relative risk estimate against standard error as a measure of study size. Solid line is the logarithm of summary risk estimate from the meta-analysis. Dashed lines are its 95% confidence interval.

Egger's test p = 0.11

Figure 99 Individual dose-response graph of BMI less than 12 months after diagnosis and total mortality

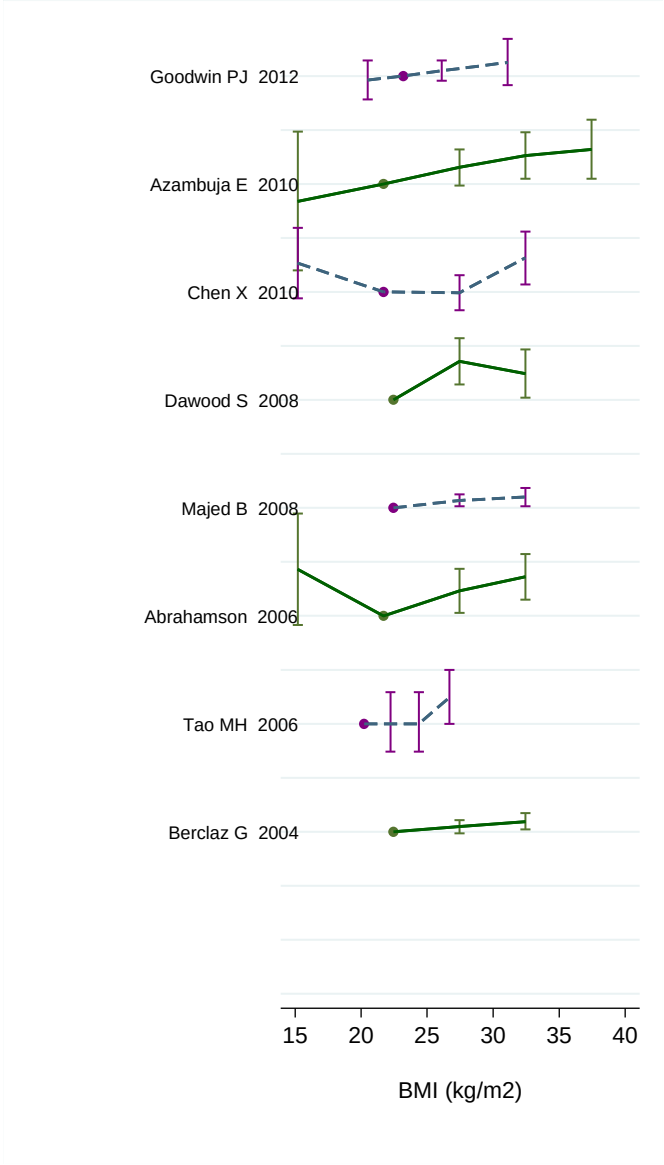


Figure 100 Linear dose-response meta-analysis of BMI less than 12 months after diagnosis and total mortality by country

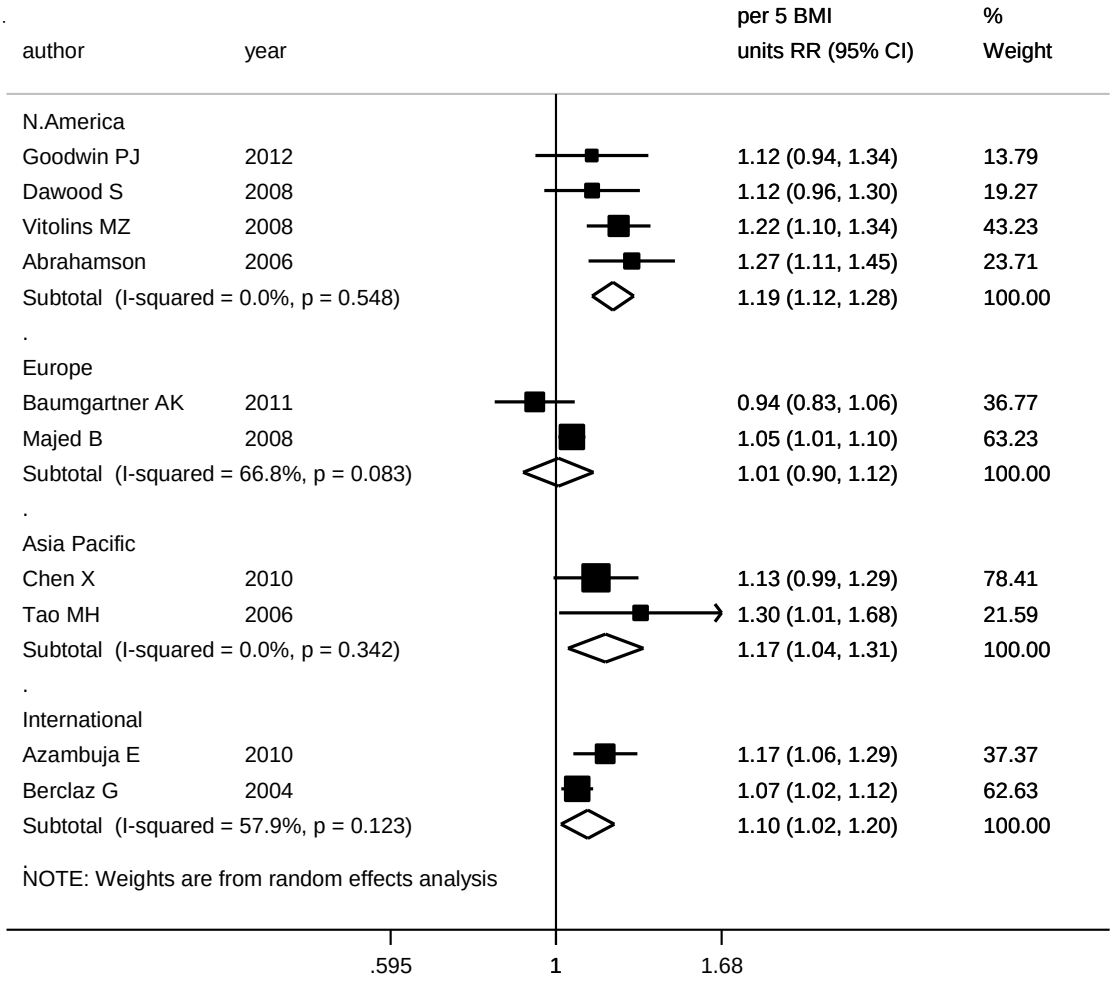


Figure 101 Linear dose-response meta-analysis of BMI less than 12 months after diagnosis and total mortality by study design

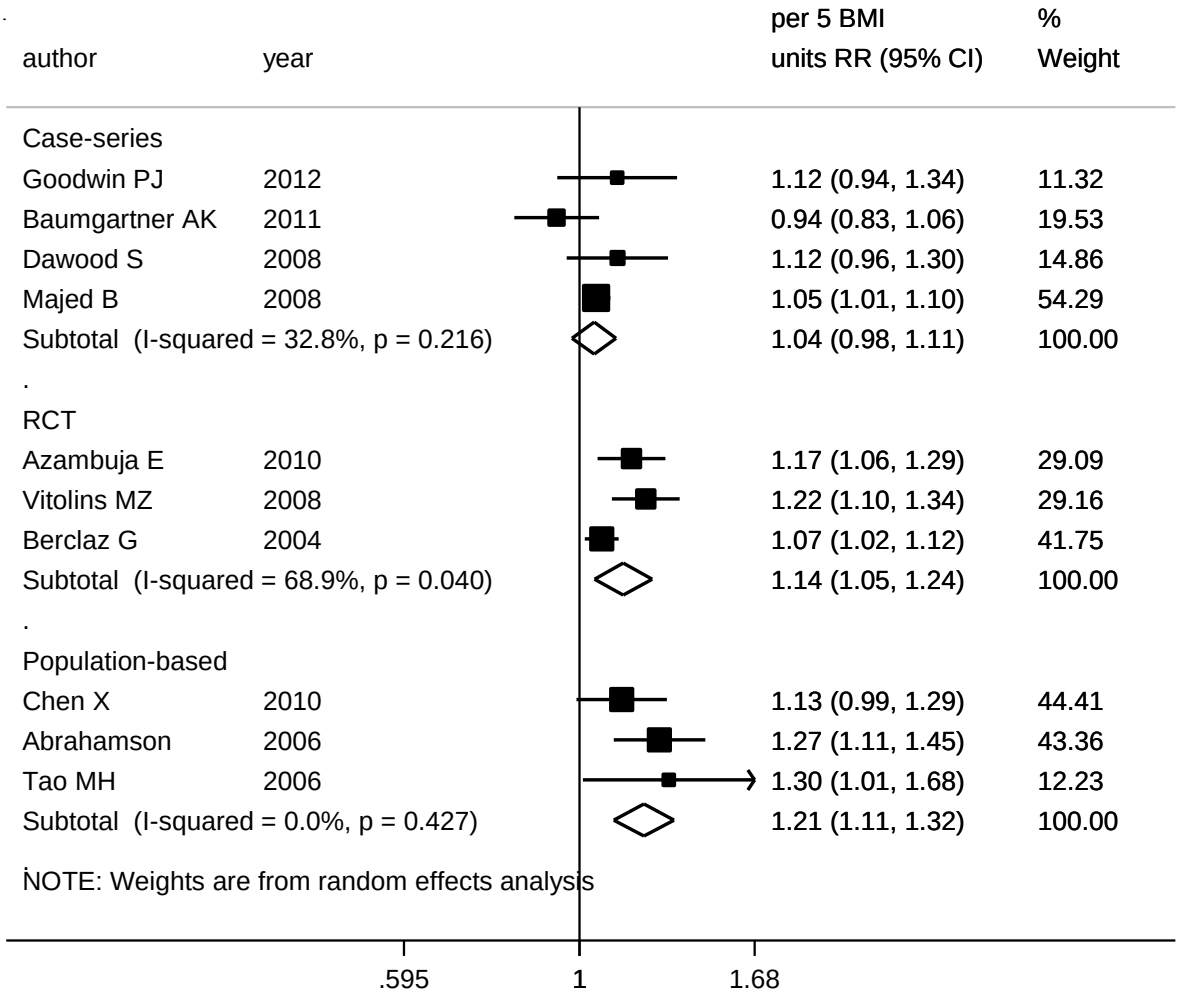


Figure 102 Linear dose-response meta-analysis of BMI less than 12 months after diagnosis and total mortality by exposure assessment method

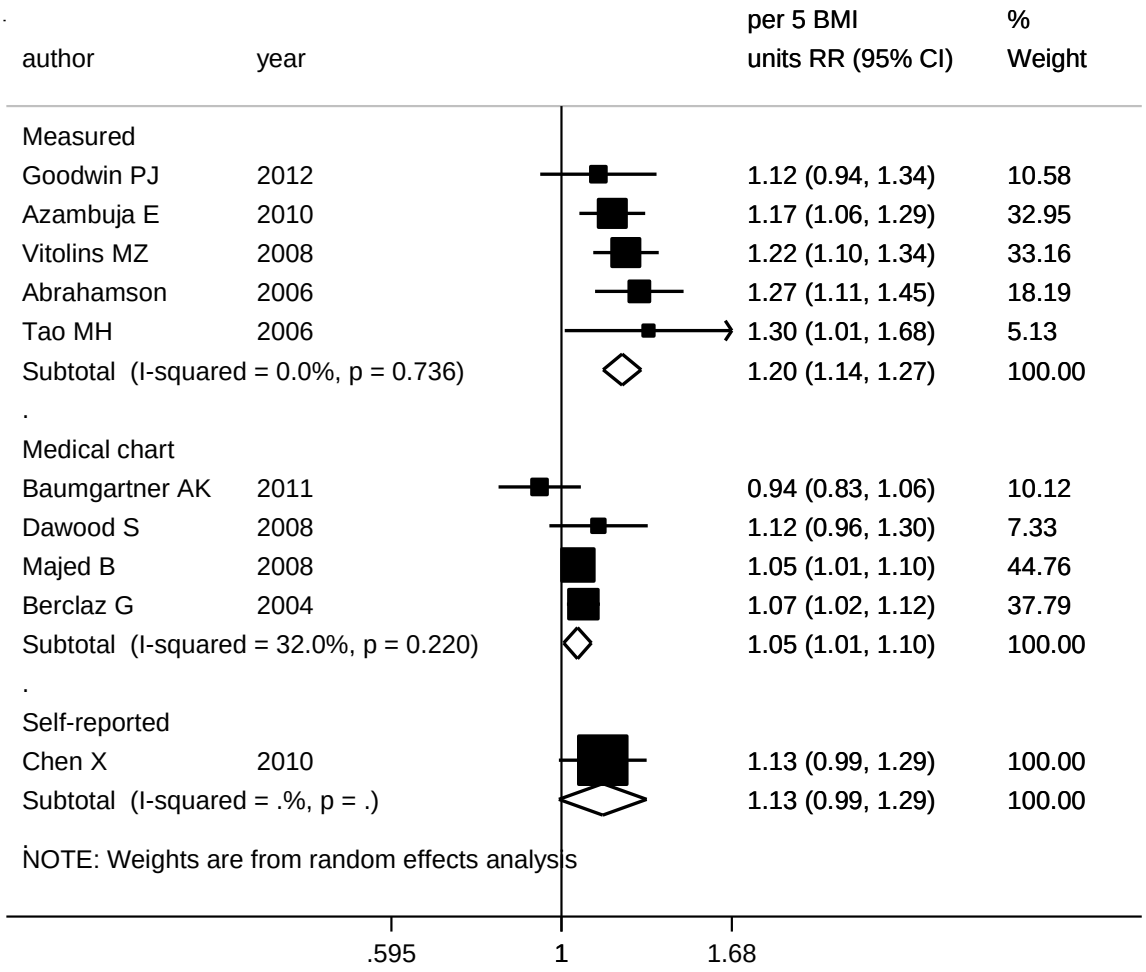


Figure 103 Linear dose-response meta-analysis of BMI less than 12 months after diagnosis and total mortality by time of exposure assessment

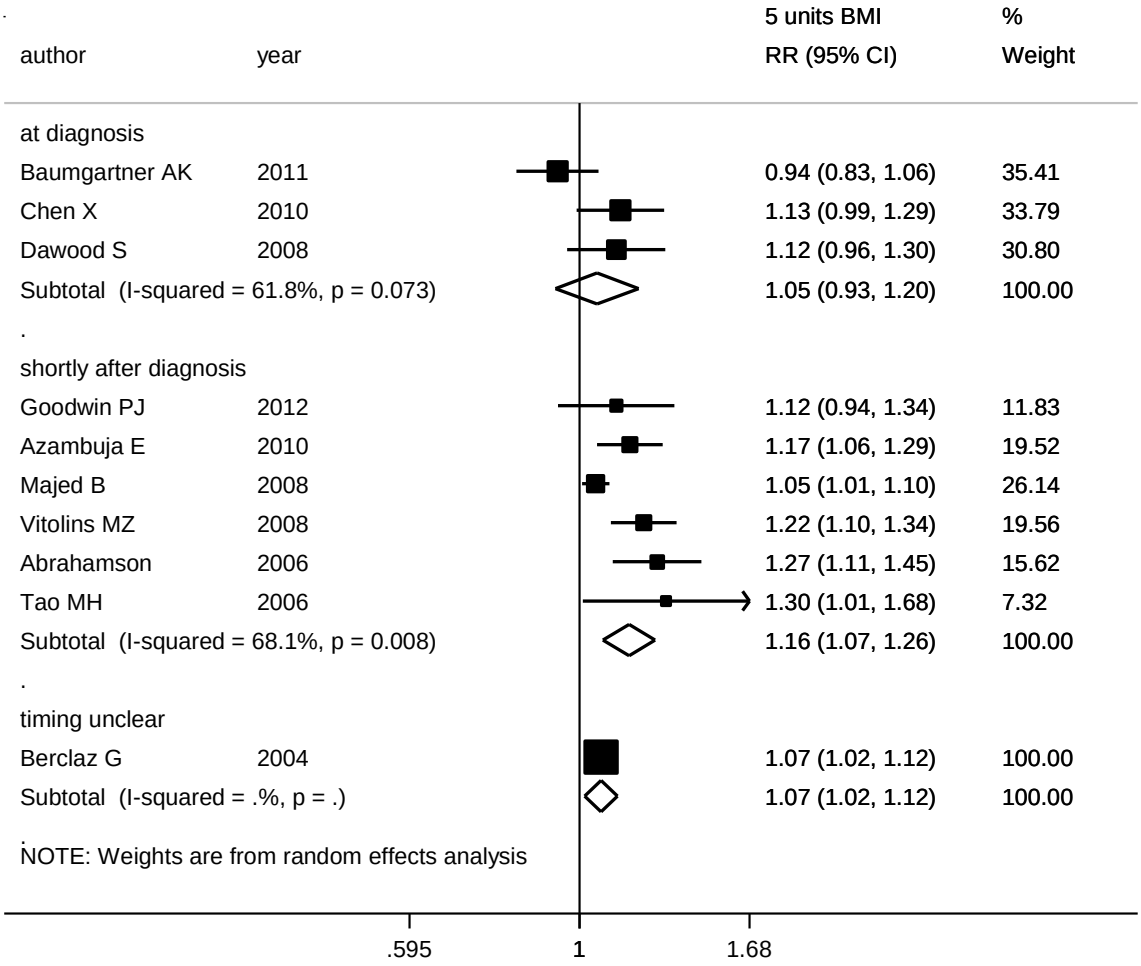
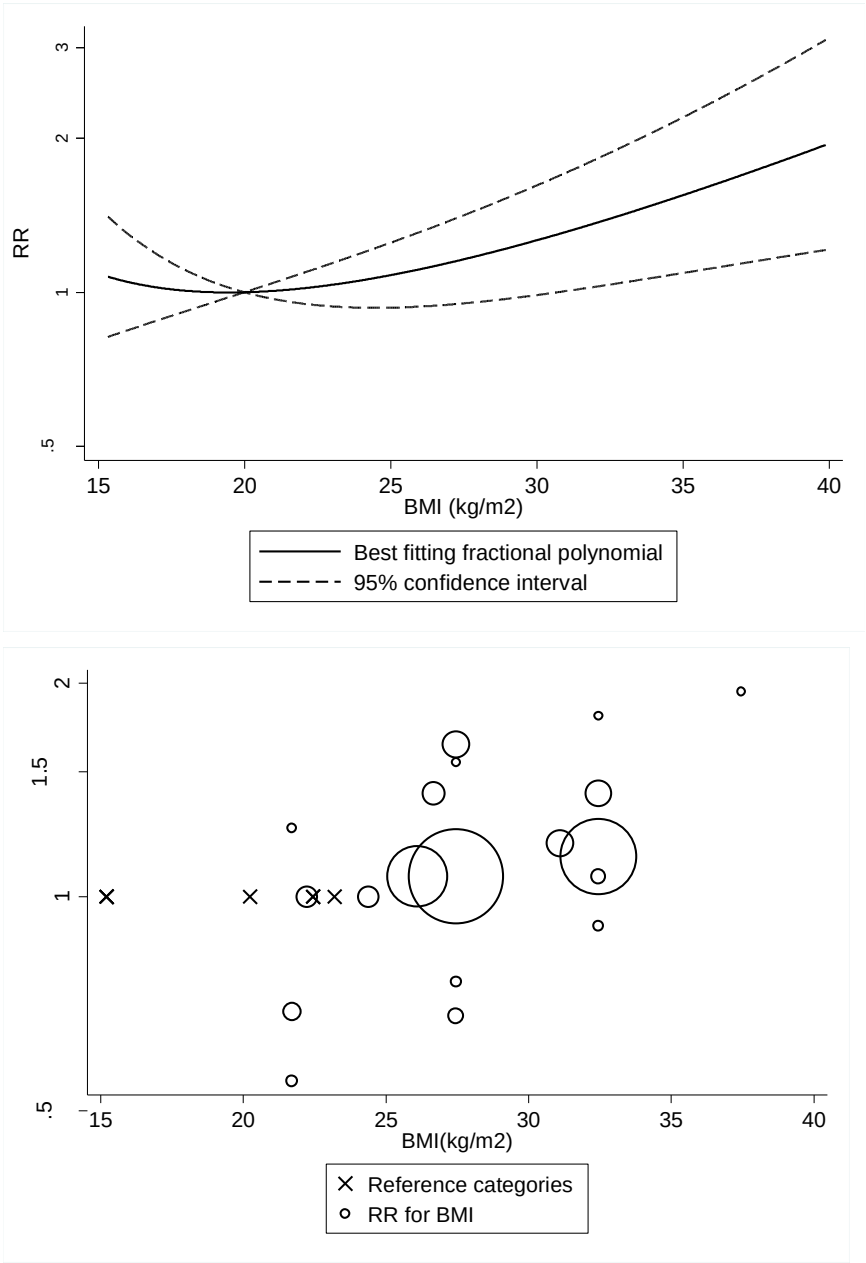


Figure 104 Non-linear dose-response meta-analysis of BMI less than 12 months after diagnosis and total mortality



$p_{non\text{-}linearity} = 0.02$

Table 85 Table with BMI values and corresponding RRs (95% CIs) for non-linear analysis of BMI less than 12 months after diagnosis and total mortality

BMI kg/m^2	RR (95%CI)
16	1.05 (0.84-1.30)
20	1
25	1.08 (0.93-1.25)
30	1.26 (0.99-1.62)
35	1.55 (1.09-2.20)

Table 86 Table of included studies on BMI less than 12 months after diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments Remarks
Goodwin PJ (2012)	University of Toronto Hospitals Follow-up Study Canada	Cancer diagnosis:1989-1996; Study follow up: until 2007	Prospective cohort of breast cancer survivors	535 participants 50.3 years (mean) <=75 years Multi-ethnic 57.2% premenopausal, 4.9% perimenopausal, 37.9% postmenopausal	12.1 years	Early M0 invasive breast cancer; non-diabetic women; 55.5% T1, 32.5% T2, 5% T3, 6.9% Tx, N0-1,	67.7% ER+ve, 18.7% ER-ve, 13.6% unknown; 61.7% PR+ve, 23.4% PR-ve, 15% unknown 69.2% N0, 30.8% N1	22.8% mastectomy, 77.2% lumpectomy; adjuvant chemotherapy: 39.8% yes, 60.2% no; hormone therapy: 39.1% yes, 60.9% no	23 women, 4.3%	Measured post diagnosis; median, 7 weeks postoperatively before systemic therapy	535 participants 134 deaths, 113 breast cancer mortality, 21 deaths from other causes	Hospital records	31.1 vs. 23.2 Kg/m^2	1.19 (0.89-1.61)	Age, tumor stage, tumor grade, hormone receptor status, adjuvant chemotherapy, hormonal therapy
Jung S (2012)	UPMC, UPCI Breast Cancer Program Review Study United States	Cancer diagnosis: 1999-2008; Study follow up: until 2010	Retrospective cohort study of breast cancer survivors, a hospital clinic-based	557 participants 55 years (mean) 26 - 88 years Majority non-black: 93.5%, Black:6.6%, 25.5% premenopausal, 74.5% postmenopausal 79.5% Charlson comorbidity condition free; 6.6% diabetes, 2.3% heart failure	9 years	Metastatic breast cancer; 34.5% HER2 +ve, 65.5% HER2 -ve, and metastatic at only one site (69.8%)	73.2% ER/PR +ve, 26.8% ER/PR –ve			From medical records, assessed at diagnosis	557 participants 403 deaths	National Death Index	>=30 vs. 20-24.9 Kg/m^2	0.85 (0.63-1.16)	Age, race, education, menopausal status, hypertension, comorbidity, heart failure, chronic pulmonary disease, mild liver disease, diabetes, receptor status, metastasis-free survival, metastasis location Highest vs. lowest analysis only; missing number of events per category
Sparano JA (2012)	Phase III Taxanebased Drug Trial E1199 United States	Study recruitment: 1999-2002	Randomised controlled trial of chemotherapy; ancillary analysis	4817 participants 22 - 84 years Black and White	95 months	AJCC; 31.9% of black patients, 17.2% of non-blacks patients have triple-negative disease; Stage I-III	71.4% ER/PR+ve, 27.1% ER/PR-ve, 1.5% unknown 11.5% 0node+ve, 55.4% 1-3 nodes+ve, 22.7% 4-9 nodes+ve, 9.6% >=10 nodes+ve, 0.6% unknown	Surgery (among those with data): 99% breast-sparing surgery, 1% mastectomy; Radiation therapy: 56.1% given, 43.9% not-given; Endocrine therapy given (among those with data): 32.8% tamoxifen alone, 56.3% tamoxifen and then aromatase inhibitor,		Self-reported at the time of registration for trials	4817 participants 904 deaths, 704 breast cancer mortality (577 deaths from BC and 127 deaths after breast cancer recurrence), 119 deaths from other causes, 81 unknown causes of death	Active follow-up and review	>=30 vs. <30 Kg/m^2	1.35 (1.11-1.64)	Race Highest vs. lowest analysis only; two BMI categories only
Ademuyiwa FO (2011)	Roswell Park Cancer Institute, Buffalo Review Study United States	Cancer diagnosis: 1996-2010	Retrospective cohort study	418 participants 54 years (mean) 26 - 92 years 77.8% Caucasian, 22.2$ others	37.2 months	Triple-negative breast cancer; AJCC stages: 36.8% I, 47.6% II, 15.6% III; Grades: 9.6% 1/2, 85.2% 3, 5.3% unknown; Histology: 90% ductal, 2.2% inflammatory,	38.5% +ve, 61.5% -ve	Breast conserving surgery: 72% yes; Chemotherapy: 80.6% yes, 19.4% no		From medical records; BMI at diagnosis	418 participants 87 deaths	Medical records	>=30 vs. <=24.9 Kg/m^2	0.94 (0.54-1.64)	Age at diagnosis, race, chemotherapy, year of diagnosis, grade, histology, stage, lymphovascular invasion Highest vs. lowest analysis only; missing numbers of events and at risk per category

						3.6% lobular, 4.1% other									
Ewertz (2011)	Danish Breast Cancer Cooperative Group Denmark	Study follow up: until 2008	Follow up of cases of randomised controlled trials of adjuvant treatment	18967 participants 39 - 70 years 18688 (34.7%) premenopausal and 35128 (65.3%) postmenopausal	7.1 years	Early stage - 14077 patients had ductal grade 1, 19456 grade 2, 9282 grade 3, 5532 lobular breast cancer	9780 ER-ve, 32276 ER+ve, 11760 unknown 29660 with 0 +ve node, 15486 with 1-3 +ve nodes, 8666 with 4+ nodes, 4 unknown	22968 patients had no adjuvant treatment, 10230 chemotherapy, 16148 endocrine therapy, 4470 combined therapy	Complete follow-up for first events (loco regional recurrences and distant metastases)	From medical records; weight and height at diagnosis	For those with BMI data, 18967 participants 5868 death from breast cancer and 1529 death from unknown causes	Death certificate	>=30 vs. <=24.9 Kg/m^2 >10 years follow-up	1.33 (1.14-1.56)	Age, menopausal status, tumor size, nodal status, tumor grade, histology , ER status, fascia invasion, protocol year, systemic therapy Highest vs. lowest analysis only; missing numbers of events and at risk per category
Maskarinec G (2011)	Patterns of Care and Outcomes Breast Cancer Follow-up Study Hawai	Cancer diagnosis: 1995-1996, Study follow-up: Until 2009	Prospective cohort of breast cancer survivors	382 participants 59.3 years (mean) Multi-ethnic Close to 30% had either CVD, pulmonary disease, liver disease, neuromuscular/skeletal disorders, or kidney disease	13.2 years	Stages 0-IV		Adhered to treatment guidelines according to Physicians Data Query, no other details	48.20%	From medical records	382 participants 115 deaths, 43 breast cancer mortality, 72 other causes of deaths	Cancer registry	>=30 vs. 18.5-<25 Kg/m^2	2.06 (1.23-3.44)	Ethnicity, age at diagnosis, menopausal status, adherence to treatment guidelines, tumor stage, hormone receptor status, toxicity, comorbidity, health insurance Highest vs. lowest analysis only; missing numbers of events and at risk per category
von Drygalski A (2011)	University of California San Diego Metastatic Breast Cancer Review Study United States	Cancer treatment: 1989-1999; Study follow up: 65 mo (median) from diagnosis	Retrospective cohort study	96 participants 43 years (mean) Multi-ethnic Mostly postmenopausal	65 months	Metastatic breast cancer; 21.9% stage I, 44.8% stage II, 24% stage III, 8.3% stage IV, 1% unknown	37.5% ERve, 59.4% ER+ve, 3.1% unknown	Received high-dose chemotherapy with autologous stem cell support (HD-ASCT) as part of their treatment		From records; BMI at the time of treatment	96 participants	Hospital records	>=30 vs. <30 Kg/m^2	1.82 (1.03-3.23)	Tumor stage, metastasis Highest vs. lowest analysis only; two BMI categories only
Baumgartner AK (2011)	Munchen University Breast Cancer Center Review Study Germany	Cancer diagnosis: 1984-2006 Recruited after diagnosis	Retrospective cohort study	1053 participants 27 - 94 years 18.8% premenopausal, 12% perimenopausal, 69.2% postmenopausal HRT use:37.1% yes, 51.5% no, 11.4% unknown	88 months	Primary invasive, nonmetastatic breast cancers; Tumor stages: 55.1% T1, 33.1% T2, 5.4% T3, 6.5% T4 among peri-postmenopausal women with data	36.8% +ve, 63.2% -ve among peri-postmenopausal women with data	Mastectomy: 37.1% yes; Breast conserving surgery: 62.9% yes; Chemotherapy: 48.2% yes; Radiotherapy: 74.5% yes; Hormonal therapy: 87.6% yes among peri-postmenopausal women with data		From medical records	1053 participants At ten years 79% of the HRT users and 67% of the non-users were free of distant metastases. No number of events reported for other outcomes	Medical records	Perimenopausal Postmenopausal Per 1 Kg/m^2 increase	1.31 (1.11-1.54) 0.98 (0.96-1.01)	Age, tumor stage, nodal status, hormonal therapy, Histology, tumor grade, surgery, adjuvant therapy, adjuvant chemotherapy Dose-response analysis only; only continuous results
Azambuja E (2010)	BIG 02-98 adjuvant study null	Study recruitment: 1998-2001;	Randomised controlled trial of chemotherapy; ancillary	2887 participants 18 - 70 years 53.7% premenopausal, 40.6% postmenopausal,	62.5 months	Node+ve breast cancer; 39.6% pTumour size <= 2cm, 52.7% size 2.1-5 cm, 7.1%	75.5% at least 1 ER+ve, 24.5% ER-ve; among those with	Surgery: among those with data 42.4% breast conservation, 57.6% mastectomy;		Measured at trial baseline, after surgery, before first cycle of chemotherap	2887 participants 403 deaths, 368 breast cancer mortality and 35 other causes of	Trial medical staff	>=35 vs. 18.5-24.9 Kg/m^2 5-year survival	1.56 (1.07-2.28)	

			analysis	5.6% others Comorbidities: 15.7% cardiac, 2.6% diabetes		size >5cm and 0.4% unknown	data 51% ER+ve and PR+ve, 20.5% ER+ve and PR-ve, 42% ER-ve and PR+, 24.5%ER-ve and PR -ve All node+ve: 54.3% 1-3 nodes+ve, 32.8% 4-10 nodes+ve and 12.8% >10 nodes+ve	Adjuvant endocrine therapy: 73.6% yes		y	death; 70 second primary tumour including 20 second primary breast tumour				
Chen X (2010)	Shanghai Breast Cancer Survival Study China	Study recruitment: 2002-2006, Recruited on average 6 months after diagnosis	Prospective cohort of breast cancer survivors	5042 participants 53.5 years (mean) 20 - 75 years 51.1% postmenopausal	46 months	TNM; 36.4% stage 0-I, 32.6% IIA, 16.6% IIB, 9.8% IIIIV, 4.6% unknown	49.9% ER+ve/PR+ve, 27.6% ER-ve/PR-ve, 20.4% mixed (ER+ve PR-ve/ER-ve PR+ve), 2.1% unknown	Mastectomy:93.9% ; Chemotherapy: 91.2%; Radiotherapy: 32.1% ; Tamoxifen usage: 52%	80%	Self-reported weight 1 year prior and at diagnosis, measured at baseline interview approximately 6 months after diagnosis	5042 participants 442 deaths	Cancer registry	>=30 vs. 18.5-24.9 Kg/m^2	1.55 (1.10-2.17)	Age at diagnosis, education, Income, marital status, comorbidity, exercise, meat intake, cruciferous vegetables, soy protein, time from diagnosis to study enrollment, menopausal status, menopausal symptoms, chemotherapy, surgery type, radiotherapy, tamoxifen use, receptor status, nodal status, immunotherapy
Clough-Gorr (2010)	Follow-up of Older Breast Cancer Survivors, Four US Regions United States	Study recruitment: 1997-2006,	Prospective cohort of breast cancer survivors	660 participants => 65 years Postmenopausal 94% white, 6.1% others Comorbidities: 13% 0, 52% 1-2, 26% 3-4, 8.7% 5 or more	7 years	Primary breast cancer; TNM stages: 51% I, 45% II, 3.8% III		Mastectomy: 49% yes, breast-conserving surgery with radiation: 33% yes, without radiation: 16% yes, other: 2.6% yes; Chemotherapy: 22% yes; Tamoxifen: 75% yes		Self reported weight and height at interview 3 months after definitive surgery	660 participants	Cancer registry + National Death Index	>30 vs<=30 Kg/m^2	1.27 (0.89-1.81)	Age, tumor stage, social class, comorbidity, physical function, mental health index Highest vs. lowest analysis only; two BMI categories only
Thivat E (2010)	Jean Perrin Center, Clermont-Ferrand Review Study France	Cancer treatment:1976-1989; Study follow up: until 2009	Hospital-based retrospective cohort study of cancer survivors	111 participants 54 years (mean) 32 - 74 years 45% premenopausal, 55% post-menopausal	20.4 years	Early stage and locally advanced breast cancer; 19% T1, 44% T2, 15% T3, 22% T4; 8% patients had Scarff-Bloom-Richardson Grade I, 55% II, 20% III	42% ER+ve, 44% ER-ve, 35% PR+ve, 47% PR-ve 50% N0, 44% N1, 5% N2, 1% N3	Anthracycline-based chemotherapy: all patients; Tumourectomy: 66 patients; Mastectomy: 44 patients; Radiation: 97% (after chemotherapy); Hormonal therapy: 44% (90% with tamoxifen)	0% lost	Measured at the beginning of treatment and in the last chemotherapy cycle	111 participants 57 deaths	Hospital records	>=24 vs.<24 Kg/m^2	1.49 (0.81-2.74)	Nodal status, tumor stage, menopausal status, hormonal therapy, weight variation Highest vs. lowest analysis only; two BMI categories only

Moon HG (2009)	KBCR, SNUHBCC Database Study, Korea Korea	Breast surgery: 1982-2006	Retrospective cohort study	29043 participants 48 years (mean)		Nonmetastatic, invasive breast cancer; histologic grades of KBCR patients: 62.8% 1-2, 37.2% 3; histologic grades of SNUHBCC patients: 57.1% grade 1-2, 42.9% grade 3	KBCR: 59% ER+, 41% ER-, 53.7% PR+, 46.3% PR-; SNUHBCC: 58% ER+, 42% ER-, 46.6% PR+, 53.4% PR-	Among those with data: Chemotherapy: 79.6% yes, 20.4% no KBCR patients, 73.4% yes, 26.6% no SNUHBCC; Hormonal treatment: 62.5% yes, 37.5% no KBCR patients, 50.7% yes, 49.3% no SNUHBCC		From hospital records	29043 participants	Cancer registry	SNUHBCC data >=30 vs. 18.5-24.9 Kg/m^2	1.35 (0.80-2.27)	Age, tumor size, tumor stage, nodal status, ER status, PR status, tumor grade, lymphovascular invasion, chemotherapy, hormonal therapy
													KBCR data >=25 vs. 18.5-24.9 Kg/m^2	0.96 (0.87-1.02)	Age,Tumor size,Tumor stage,Nodal status,ER status,PR status,Tumor grade,Lymphovascular invasion
							KBCR: 43% +ve, 57% -ve; SNUHBCC: 42.3% +ve, 57.7% -ve								Highest vs. lowest analysis only; SNUHBCC data were missing numbers of events and at risk per category KBCR data were only for two BMI categories
Dawood S (2008)	MD Anderson Cancer Center, Texas Review Study	Cancer diagnosis:1974-2000	Retrospective cohort study of breast cancer survivors	606 participants 44.4% premenopausal, 44.9% postmenopausal and 10.7% unknown	6 years	18% nonmetastatic inflammatory(IBC), 82% noninflammatory locally advanced breast cancers (non-IBC LABC); AJCC stage III; 1.98% grade 1, 23.4% grade 2, 51% grade 3 and 23.6% unknown	26.7% HR-ve, 39.3% HR+ve and 34% unknown	Surgery: 115% BCS, 79.9% mastectomy, 6.6% none, 2.4% unknown; Chemotherapy: 794% A, 20.95% A+T; X-ray therapy: 794% adjuvant, 4.6% neoadjuvant, 9.6% none, 6.7% unknown		From medical records; height and weight at time of initial diagnosis	606 participants 341 death, 325 recurrence	Trial medical staff	>=30 vs. <=24.9 Kg/m^2	1.40 (1.03-1.91)	Tumor type, year of diagnosis, number of positive lymph nodes, menopausal status, pathological complete response, age, chemotherapy
Labidi SI (2008)	Salah Azaiz Institute Tunisia Review Study Tunisia	Cancer treatment: 1994-2000	Retrospective study	100 participants 44 years (mean) 23 - 71 years Among those with data: 70% premenopausal, 30% postmenopausal	6 Years (max)	Nonmetastatic inflammatory breast cancer; AJCC; 30% tumor size <= 5cm, 46% size >5 cm, 24% unknown; Scarf and Bloom: 4% grade 1, 39% grade 2, 37% grade 3, 20% unknown	40% ER-ve, 17 %ER +ve, 43% unknown; 27% PR-ve, 12 %PR +ve, 61% unknown	99% neo-adjuvant chemotherapy, 93% mastectomy, 83% radiotherapy, 84% adjuvant chemotherapy, 60% hormone therapy		From medical records: height and weight at the time of diagnosis, before treatment;	100 participants 70 deaths	Medical records	>30 vs. <25 Kg/m^2 3-year survival	1.032 (0.511-2.084)	Chemotherapy, hormonal therapy
							91% axillary node+ve: 23% 1-3 nodes+ve, 60% >4 nodes+ve, 9% unknown; 8% node-ve								Highest vs. lowest analysis only; missing numbers of events per category
Litton J (2008)	MD Anderson Cancer Center, Texas Review Study United States	Cancer diagnosis: 1990-2004 Recruited after treatment with NC and before surgical treatment	Retrospective cohort study	1169 participants 50 years (mean) white: 70%, Hispanic: 12.3%, African American: 12.1%, Asian/others: 5.6%, 44.9% premenopausal, 3.8% perimenopausal, 51.3% postmenopausal	14 years	Cancer stages: 4.1% I, 63% II, 32.9% III; Tumor stages: 0.2% T0, 11.5% T1, 56.5% T2, 17.7% T3; 14.1% T4; Histology: 92.9% ductal, 7.1% lobular	60.1% ER+, 39.9% ER-; 51.2% PR+, 48.8% PR-; 22.8% HER-2+, 77.2% HER-2-	Mastectomy: 61% yes; Breast-conserving surgery: 38% yes; No surgery: 1% yes; Anthracycline-based regimen: 91% yes		From medical records	1169 participants 194 deaths, 167 breast cancer mortality, 18 other causes of deaths, 9 unknown causes of deaths	Cancer registry	>=30 vs. <=24.9 Kg/m^2	1.65 (1.18-2.30)	Race, age, menopausal status, chemotherapy, receptor status, nodal status, pathological complete response, time from chemo to surgery, nuclear grade
							56.4% +ve, 43.6% -ve								Highest vs. lowest analysis only; two BMI categories only

Majed B (2008)	Curie Institute Breast Cancer Study France	Breast cancer treatment: 1981-1999, Study follow-up: Until 2004	Prospective cohort of breast cancer survivors	14709 participants 44.8% premenopausal, 55.2% postmenopausal Obesity: 7.9% yes 20.2% cancers detected by mammography	8 years	Stages: 36.2% I, 51.1% II, 12.6% III; SBR grades: 22.9% I, 23% II weak, 18.8% II strong, 16.2% III, 9.4% non gradation, 9.7% NA; Tumor size (cm): 12% <=1, 23.9% 1-2, 44.4% 2-5, 13.5% >5, 6.2% NA; Tumor histology: 73.7% ductal, 8.5% lobular, 6.9	50.9% ER+, 17.4% ER-, 31.7% NA; 50.2% PR+, 24.2% PR-, 25.6% NA Clinical node involvement: 82.1% N0-N1a, 17.9% N1b-N3	Conservative surgery: 57.2% yes; Non-conservative surgery: 29% yes; Non surgical local treatment: 13.8% yes; Hormonal therapy: 33.1% yes; Chemotherapy: 30.8%; Radiotherapy: 86.6% yes		From medical records	14709 participants 3693 deaths, 555 second cancers	Cancer registry	Per 1 Kg/m^2 increase >=30 vs. <25 Kg/m^2	1.01 (1.002-1.019) 1.15 (1.02-1.29)	Age, tumor dimension, clinical node development, menopausal status, year of diagnosis, tumor estrogen, progesterone receptor level, clinical tumor extension, number of axillary invaded nodes, Scarf-Bloom-Richardson grade
Vitolins MZ (2008)	Phase II Doxorubicin-Based Drug Trial for Node-Positive Breast Cancer United States	Study recruitment: 1980-1985, Study follow-up: Until 1999 Post-diagnosis, post-surgery	Randomised controlled trial of adjuvant treatment trial; ancillary analysis	636 participants 52 years (mean) 25 - 73 years Caucasian: 90%, African-American: 10% 41% premenopausal, 59% postmenopausal	13.7 years	Stages II-III; lymphnode positive breast cancer	62% ER+ve, 38% ER-ve; 49% PR+ve, 51% PR-ve among those with data 52% 1-3 +ve, 32% 4-9 +ve, 16% 10+ +ve	Participants of doxorubicin-based multidrug regimen as adjuvant therapy trial; had mastectomy		Measured at time of enrolment for trial	636 participants 341 deaths, 303 breast cancer mortality, 38 other causes of deaths	Active follow-up and review	Per 1 Kg/m^2 increase	1.04, p-value=0.0001	 Dose-response analysis only; only continuous results
Abrahamson (2006)b	Atlanta, Seattle, New Jersey Follow-up Study United States	Cancer diagnosis:1990-1992; Study follow up: until 2000	Follow-up of cases of a population-based case-control study	1254 participants 20 - 54 years 75% white 25% nonwhite 78% premenopausal, 22% postmenopausal and unknown <1%	9.8 Years (max)	Invasive breast cancer; AJCC; any stage ; 57% local, 40% regional, 3% distant, <1% unknown	56% ER+ve, 35%ER-ve, 3% borderline, 6% unknown		86% <2% lost	Measured 4.2 months after diagnosis; self-reported weight and height at age 20 years and the year before diagnosis	1217 participants 290 deaths, 281 deaths included in analysis	Cancer registry + National Death Index	>=30 vs. 18.5-24.9 Kg/m^2	1.65 (1.23-2.21)	Tumor stage, income (Result further adjusted for waist-hip-ratio was also provided in the article)
Dignam J (2006)	National Surgical Adjuvant Breast and Bowel Project B-13, B-19, B-23 Trials United States	Study recruitment:1981-1988; Study follow up: until 2005	Follow up of cases of a randomised controlled trial of adjuvant treatment trial	4077 participants white: 81.7%, black: 12%, others/unknown: 6.3%, 54.5% pre/perimenopausal, 45.5% postmenopausal		Node-negative, ER-negative breast cancer; 54.9% tumour size<=2cm, 38.2% size 2.1-4cm, 6.9% size >=4.1cm	All ER-ve All node -ve	Participants of different adjuvant therapy trials		Measurement obtained only at baseline and during treatment; BMI at diagnosis was used	4077 participants 820 deaths, 624 deaths following a BC events,196 other causes of death, 242 total second primary contralateral breast cancer	Medical records	>=35 vs. <=24.9 Kg/m^2	1.30 (1.03-1.63)	Treatment, tumor size, age, ethnicity Highest vs. lowest analysis only; missing numbers of events per category
Tao MH (2006)	Shanghai Breast Cancer Study China	Cancer diagnosis: 1996-1998; Study follow up: until 2002 Recruited/interview on average 67 days after diagnosis	Follow-up of cases of a population-based case-control study	1455 participants 25 - 64 years 62% aged <50 years	5.1 years	Primary breast cancer; TNM; 24.6% Stage 0-I, 34.9% stage IIA, 21.9% stage IIB, 11.3% stage III-IV, 7.1% unknown	44.4% ER+ve, 25.5% ER-ve, 30% unknown; 43.5% PR+ve, 25.2% PR-ve, 31.1% unknown	Surgery: 99%; Adjuvant chemotherapy: 94% ; adjuvant chemotherapy and traditional Chinese medicine: 63%; radiotherapy: 38.9% yes, 47.4% no, 13.6% unknown; tamoxifen use: 63.2% yes, 18 no, 18.6% unknown	91% 126 patients lost (assumed to be still living)	Measured at or soon after diagnosis at study baseline	1455 participants 240 deaths	Death certificate	>=25.53 vs. <=21.22 Kg/m^2	1.40 (1.0-2.0)	Age at diagnosis, education, menopausal status, tumor stage, chemotherapy, tamoxifen use, radiotherapy, estrogen receptor level, progesterone receptor level

Gonzalez-Angulo AM (2005)	MD Anderson Cancer Center, Texas Review Study United States	Cancer diagnosis:1990-2002	Prospective cohort of breast cancer survivors	452 participants 32.0 years (mean) 17.0 - 35.0 years Multi-ethnic 93.6 % premenopausal, 3.3% Postmenopausal (due to surgery)	36 months	Primary breast cancer; any AJCC Stages (0-X), 63% Stage II-IIIA	52.3% ER+ve, 47.7% ER-ve, 47.5% PR+ve, 52.4% PR-ve	Anthracycline-based chemotherapy: all patients; additional taxane: 35%; Mastectomy: 75.4% (341 patients); node dissection: 75%		From medical records; at diagnosis	452 participants 84 deaths	Medical records	>=30 vs. <30 Kg/m2	1.42 (0.99-2.04)	Adjustment unclear Highest vs. lowest analysis by menopausal status only; two BMI categories only
Loi S (2005)	Australian Breast Cancer Family Study Australia	Study recruitment: from 1992	Follow-up of cases a population-based case-control study	1101 participants 42.7 years (mean) 23 - 69 years 74% premenopausal, 26% postmenopausal	5 years	Nonmetastatic primary breast cancer; 15% grade 1, 37% grade 2, 40% grade 3, 8% unknown	34% ER-ve, 61% ER+ve, 5% unknown; 30% PR-ve, 65% PR+ve, 5% unknown 55% 0 axillary node, 27% 1-3 nodes, 14% >3 nodes, 4% unknown	62% chemotherapy, 34% tamoxifen, 21% did not have treatment	69% of original study 31% lost including 2% deceased	Self reported up to 8 months after diagnosis in the interview; and of weight and height 1 year before diagnosis	1101 participants 184 deaths	Medical records	>=30 vs. <30 Kg/m^2	1.56 (1.01-2.40)	Age, tumor grade, nodal status, progesterone receptor level Highest vs. lowest analysis only; two BMI categories only
Berclaz G (2004)	International Breast Cancer Study Group Switzerland	Study recruitment:1978 - 1993;	Follow up of cases of a randomised controlled trial of adjuvant treatment	6370 participants years (mean) 55% pre/perimenopausal, 45% postmenopausal	14 years	43% tumor size <=2 cm, 53% size >2 cm, 4% unknown; 14% tumour grade 1, 44% grade 2, 35% grade 3 and 7% unknown	28% ER-ve, 57% ER+ve, 15% unknown; 33.6% PR-ve, 47.6% PR+ve and 18.8% unknown 20% node -ve, 80% node +ve	Hormone therapy with or without chemotherapy: 32% ;Chemotherapy only: 58% and 10% no adjuvant therapy		Height and weight previously recorded in database	6370 participants 55% overall survival in obese group, 57% in intermediate weight group and 61% in normal weight group	Death record	>=30 vs. <=24.9 Kg/m^2 10-year survival	1.14 (1.03-1.27)	ER status, menopausal status, nodal status, tumor size, treatment, chemotherapy, hormone+chemotherapy
Carmichael AR (2004)	William Harvey Hospital, Kent Follow-up Study UK	Breast cancer treatment: 1963-1999	Prospective cohort of breast cancer survivors	1579 participants	6 years	Tumor grades: 23% I, 34.5% II, 18.8% III, 23.8% <3.4				Self-reported at diagnosis	1579 participants	Hospital records	<30 vs. >=30 Kg/m^2	0.81 (0.62-1.06)	Adjustment unclear Highest vs. lowest analysis only; two BMI categories
Dignam J (2003)	National Surgical Adjuvant Breast and Bowel Project B-14 Trial United States	Study recruitment:1982-1988; Study follow up: until 2001	Randomised controlled trial of adjuvant treatment trial	3385 participants white: 91.1%, black: 4.3%, unknown: 4.6% 30.6% peri/premenopausal, 69.4% postmenopausal	166 months	Early stage breast cancer; 60.7% tumour size <= 2cm, 34.6% size 2.1-4 cm, 4.7% size >= 4 cm	All ER +ve All node -ve	64.9% tamoxifen, 35.1% placebo		From the records of original study	3385 participants 983 deaths, 595 deaths following a BC events, 388 other causes of death,, 193 contralateral breast cancer, 232 other second primary cancers (plus 51 endometrium cancer)	Trial medical staff (blinded)	>=30 vs. 18.5-24.9 Kg/m^2	1.31 (1.12-1.54)	Age, menopausal status, ethnicity, tumor size, estrogen receptor level, progesterone receptor level, treatment Highest vs. lowest analysis only; missing numbers of events per category
Kumar NB (2000)	H.Lee Moffitt Cancer Center and Research Institute Follow-up Study United States	Study follow-up: Until 1997 Diagnosed within 3 months of entry to the study	Follow-up of a cases of case-control study	166 participants white: 92%, black: 4%, others/Hispanic:4% 17% premenopausal, 83% postmenopausal	10 Years (min)	Stages: 33% I, 41% II, 9% III, 3% IV, 14% unknown	 36% +ve, 64% -ve		100%	Measured within 3 months of diagnosis for exposures at diagnosis and self-reported prediagnosis from	166 participants 83 deaths	Medical notes	Obese vs. non-obese	0.92 (0.87-0.98)	Tumor stage Highest vs. lowest analysis only; two BMI categories only

										adolescence to adulthood					
Camoriano JK (1990)	Review of Adjuvant Chemotherapy Trials of Node-Positive Breast Cancer United States		Randomised controlled trial of adjuvant treatment trial; ancillary analysis	545 participants 20 - 75 years 60.5% premenopausal, 39.5% postmenopausal	6.6 years	Node-positive breast cancer; mastectomy; any stages	All node +ve			BMI measured at randomisation, within 8 weeks of primary breast surgery	545 participants Included 330 premenopausal women only in analysis	Active follow-up and review	>28 vs. <=28 Kg/m^2	1.70 (0.99-2.94)	Age, nodal status, estrogen receptor level, tumor size, weight change, nuclear grade Highest vs. lowest analysis only; two BMI categories only

Table 87 Table of excluded studies on BMI less than 12 months after diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments Exclusion reason
Bayraktar S (2012)	MD Anderson Cancer Center, Texas Review Study United States	Cancer treatment: 1995-2007	Retrospective cohort study, clinical series	1448 participants 21.0 - 87.0 years Multi-ethnic 44.9% premenopausal, 55.1% postmenopausal Comorbidities: 91% non-diabetic, 9% diabetic, 17 patients coronary artery disease or heart	62 months	Triple-negative breast cancer; AJCC; Clinical T classification: 49.4% T1, 44.5% T2, 6.1% T3/4	Among those with data: 56.6%N0, 29.9% N1, 8.9% N2, 6.6% N3	51% breast-conserving surgery, 49% mastectomy; all received adjuvant chemotherapy; none received adjuvant endocrine therapy				Medical records	Normal/underweight Overweight Obese	5-year survival = 0.67, 0.64, 0.71 Log-rank test p-value=0.33	Superseded by Litton, 2008; Dawood, 2008
Allin KH (2011)	Copenhagen Breast Cancer Study, Denmark	Cancer diagnosis: 2002-2008/2009	Prospective cohort of breast cancer survivors	2910 participants 26-99 years 21.36% premenopausal, 78.64% postmenopausal	3 years	Invasive breast cancer; Tumour grade: 23.54% well differentiated, 43.37% moderate, 17.35% poorly/un-differentiated, 15.74% unknown; Distant metastases: 95.53% no, 1.37% yes, 3.09% unknown; HER2 status: 27.73% +ve, 7.56% -ve, 64.71% unknown	ER status: 76.74% +ve, 14.98% -ve, 8.28% unknown; PR status: 47.53% +ve, 27.04% -ve, 25.43% unknown 46.21% node –ve, 45.56% node +ve, 8.23% unknown		93%	Self-reported at diagnosis/study baseline	2910 participants, 383 deaths, 225 (64%) breast cancer deaths, Other causes of death: 11% other cancer, 11% cardiovascular disease, 4% respiratory disease, 11% other disease,	Death registry	>=30 vs. 18.5-24.9 kg/m^2	1.45 (1.01-2.09)	Unadjusted results

											1% unknown				
Jung S (2011)	UPMC, UPCI Breast Cancer Program Review Study United States	Cancer diagnosis and study follow up:1999-2008		553 participants 55.0 years (mean) 26.0 - 88.0 years Majority non-black 74.9% postmenopausal Comorbidities: 79.4% Charlson condition-free	9 years	Metastatic breast cancer; 65.5% HER2-ve	73.1% ER/PR +ve			From medical records	553 participants 288 death	Hospital records	>=30 vs. <20 Kg/m^2	1.46 (0.83-2.58)	Superseded by Jung, 2012
Singh A (2011)	Breast Cancer Study, India India	Breast surgery: 2005-2009 Recruited before surgery	Case series study	309 participants 47.54 years (mean)	4 years	Primary invasive breast cancer: 86.3%; Benign breast disease: 13.7%				During treatment; BMI measured at hospital admission for surgery		Hospital records	Underwt Normal Overweight Obese I Obese II	Mean survival 656.628 days 649.327 days 516.551 days 326.501 days 305.325 days Obesity is a significant risk factor for 3-year mortality in patients; normal and underweight may confer survival benefit	Length of survival comparison only and result in text only
Anderson SJ (2009)	National Surgical Adjuvant Breast and Bowel Project B-13, B-14, B-19, B-20, B-23 Trials United States	Cancer treatment:1981-1991, Study followup: Until 2007 At diagnosis; after treatment by lumpectomy, node dissection	Randomised controlled trial of adjuvant treatment trial; ancillary analysis	3799 participants White, black and other	16.1 years	Node-negative breast cancer	Node-negative breast cancer	Underwent lumpectomy and whole breast irradiation; with or without adjuvant systemic therapy in RCT trials			3799 participants	Active follow-up and review	After ipsilateral breast tumor recurrence (IBTR) After locoregional recurrence (oLRR) Q4 vs. Q1	1.30 (1.05-1.60) 1.31 (1.06-1.61)	Age,ER status,Race,Tumor size Superseded by Dignam 2003; 2006
Eralp (2009)	MD Anderson Cancer Center, Texas Review Study null		Retrospective cohort study of cancer survivors	32.0 years (mean) 22.0 - 35.0 years All premenopausal	43 months	51% stage II, 49% stage III, 75% grade III	59% +ve, 39% -ve 26.1% 0 +ve node, 38.7% 1-3 +ve nodes, 18.9% 4-10% nodes, 11.7%	Treated with neoadjuvant chemotherapy consisting of anthracycline-based combinations, with or without taxanes		From medical records post-diagnosis, diagnosis at initiation of chemotherapy	17 deaths	Medical records	18.1-22.1 22.2-24.6 24.7-29.1 29.2-48.7 Kg/m^2	5-year survival rate = 79.6%, 96%, 81.4%, 73.7% p-value=NS	Superseded by Litton, 2008; Dawood, 2008

							>10 +ve nodes								
Shu X (2009)	Shanghai Breast Cancer Survival Study China	Cancer diagnosis: 2002-2006, Study follow-up: Until 2008 6.5 months Post-diagnosis	Prospective cohort of breast cancer survivors	5042 participants 20 - 75 years 48.9% premenopausal, 51.1% postmenopausal HRT use: 6.8% yes, 93.2% among those with data	3.9 years	TNM stages: 85.8% 0-II, 9.8% III-IV, 4.4% Unknown	63.2% ER+, 35.2% ER-, 1.6% missing; 57.5% PR+, 40.6% PR-, 1.9% missing	Radical mastectomy: 92.6% yes, 7.4% no; Radiotherapy: 32.1% yes, 67.9% no; Chemotherapy: 91.2% yes, 8.8% no; Tamoxifen: 52.1% yes, 47.9% no among those with data	80% 88.2 % is completed after 36 months interview, interview after 60 months is still ongoing	6.5 months post-diagnosis; diet over the preceding 6 months for the baseline survey, the preceding 12 months for the 18-month survey, and the preceding 18 months for the 36-month survey	5042 participants 444 deaths and 534 recurrences or breast cancer-related deaths	Vital statistics registry	<25 25-29 >=30 Kg/m^2	5-year survival rate = 90.3%, 88.7%, 83.9%, p-value=0.01	Superseded by Chen, 2010
Schuetz F (2007)	University Hosptial of Heidelberg, Germany Review Study Germany	Breast surgery: 1990 -1999	Retrospective hospital-based cohort study	1072 participants 54.0 years (mean) 45.0 - 70.0 years 26% premenopausal, 74% postmenopausal HRT use: 40.4% yes, 59.6% no	73.2 months	Primary breast cancer, grades: 12.3% 1, 52.5% 2, 27.9% 3	67.2% ER +ve, 59.4% PR +ve 42.2% +ve	Breast conserving surgery: 74.6% yes; Primary chemotherapy: 9.8% yes; Adjuvant radiation therapy: 80.5% yes; Adjuvatnt systemic therapy 84.2% yes; Endocrine therapy 45.5% yes; Chemotherapy: 25.7% yes; Endocrine and chemotherapy: yes 13.1%	9% lost	From medical records	1072 participants 163 deaths Included in analysis: 793 postmenopausal women and 124 deaths	Medical records	Per 1kg/m^2 increase	1.01 (0.96-1.05)	Unadjusted results
Goodwin PJ (2002)	University of Toronto Hospitals Follow-up Study Canada	Study recruitment: 1989-1996, Post-surgery	Prospective cohort of breast cancer survivors	512 participants 50.4 years (mean) 26.0 - 74.4 years 56.4% premenopausal, 5.1% perimenopausal, 38.5% postmenopausal 100% comorbidity free	50 months	Early stage, 56.3% T1, <=2cm, 32% T2, 2-5cm, 4.7% T3>5cm, 7% unknown	61.3% ER+ve, 19.1% ER-ve, 5.5% ER equivocal, 14.1% unknown; 55.7% PR+ve, 23.2% PR -ve, 5.7% PR equivocal, 15.4% unknown 30.5% +ve, 69.5% -ve	Mastectomy: 22.1% yes; Lumpectomy: 77.9% yes; Chemotherapy only: 28.7% yes; Chemotherapy plus tamoxifen: 9.0% yes; Tamoxifen: 29.5% yes; None: 32.8% yes	8 patients lost	Measured between 4 and 12 weeks post-operation, before adjuvant therapy	512 participants 45 deaths, 42 breast cancer mortality	Medical records	31.1 vs. 20.5 Kg/m^2	1.78 (1.25-2.53)	Superseded by Goodwin 2012
Menon KV (1999)	William Harvey Hospital, Kent Follow-up Study UK	From cancer diagnosis until 1997	Randomised controlled trial of adjuvant treatment trials; ancillary analysis	448 participants 7% premenopausal, 93% postmenopausal	6 years	Invasive primary breast cancer; any stages				Self-reported height; BMI calculated at the time of diagnosis	448 participants 162 deaths	Hospital records	Per 1kg/m^2 increase	1.00 (0.968-1.034)	Unadjusted results

Saxe GA (1999)	Medical Center, Michigan University Follow-up Study United States	Study recruitment: 1989-1991, Recruited during first medical center visit for suspected or newly diagnosed	Prospective cohort of breast cancer survivors	149 participants 57.8 years (mean) 26 - 95 years White, black and other 34.2% premenopausal, 65.8% postmenopausal	5 years	Primary breast cancer, stages: 19.6% in situ, 34.5% I, 34.5% II, 8.8% III, 2.7% IV	73.4% ER+, 26.6% ER- 43% +ve, 57% -ve		0% lost	Measured close to time of diagnosis; alcohol a year prior to diagnosis	149 participants 26 deaths	Hospital records	>27 vs. <=27 kg/m^2	0.74 (0.32, 1.71)	Unadjusted results
Lethaby AE (1996)	Auckland Breast Cancer Study Group New Zealand	Cancer diagnosis: 1976-1985	Cancer survivors of population-based prospective cohort study	1138 participants		Among those with data: women aged <50 yrs: 59.6% PR+ve, 40.4% PR-ve, 55.5% ER+ve, 44.5% ER-ve; women aged >= 50 yrs: 55.5 PR+ve, 44.4 PR_ve, 73.2 ER+ve, 26.7% ER-ve All node -ve	Adjuvant treatment: 9.6% among women aged <50 yrs and 6.2% in women >= 50 yrs of age					Hospital records	Age <50 years Age >=50 years <28 vs. >=28 kg/m^2	Log-rank test p=0.29 Log-rank test p=0.13	Insufficient data – log rank test p-value only
Albain KS (1992)	Southwest Oncology Group Node-positive Adjuvant Trials United States	Breast cancer treatment: 1975-1989 Enrolled on 1-year adjuvant CMFVP arms of clinical trials; no later than 42 days after	Randomised controlled trial of chemotherapy; ancillary analysis	768 participants Multi-ethnic 37% premenopausal, 63% postmenopausal		Tumor size: 89% T1 or T2 (<=5cm), 9% T3 (>5cm), 2% unknown	54% ER+, 25% ER-, 21% unknown 100% +ve	Undergoing adjuvant treatment		Pre-treatment BMI	768 participants 263 deaths	Active follow-up and review	>28 vs. <=28 kg/m^2	No independent prognostic significance as shown in the cox multivariate models for overall survival	Result in text only
Gordon N (1992)	Case Western Reserve University, Cleveland Follow-up Study United States	Study recruitment: 1974-1985, Study follow-up: Until 1990 Post-diagnosis, before adjuvant treatment	Randomised controlled trial of adjuvant treatment trials; ancillary analysis	1392 participants 76 years (mean) Black and White	16 years	Any stages; Tumor diameter (cm): 44.4% T1:<=2, 48.1% T2:>2-<=5, 7.5% T3:>5, among those with data	76.4% ER+, 23.6% ER-	All had mastectomy; some are randomised into adjuvant therapy trials	2.90% lost	BMI measured atdiagnosis		Medical records	>=36 vs. <=19 kg/m^2	1.43 (1.09-1.88)	Unadjusted results
Kimura M (1990)	Gunma Cancer Center Review Study Japan	Cancer treatment: 1972-1988	Retrospective cohort of breast cancer survivors	593 participants 55.99% premenopausal 44.01% postmenopausal	16 years (max)	Stage I-III		Had radical operation		From medical records	593 participants	From medical records	<21 21.1-23.0 >23.1 kg/m^2 5-year survival 10-year survival	Not significant P<0.05	Survival rates comparison only

Kyogoku S (1990)	Fukuoka Hospitals, Japan Follow-up Study Japan	Study recruitment:1975-1978; Study follow up: until 1987 Newly diagnosed patients recruited	Follow up of cases of a hospital-based case-control study	213 participants 55.5 years (mean) 32.3% pre-menopausal, 67.6% post-menopausal	12 years	80 patients had TNM Stage I, 102 Stage II, 13 Stage III	87 patients had N0, 91 had N1, 17 had N2, 17 had N3 and N4	16 patients had radiation therapy, 87 chemotherapy, 130 endocrine therapy	95.80% 9 patients lost	Assessed by an interview 1-3 after operation	213 participants 64 deaths, 47 breast cancer mortality, 6 second primary cancer mortality, 4 death from cardiac failures and 3 death from cerebro-vascular diseases and 4 other causes of death	Death certificate	QI>25 vs. <20 (kg/m^2)	2.51, p for trend<0.01	Tumor stage, age of menarche, age at first birth, menopausal status, history of abortion, smoking, radiotherapy, chemotherapy, hormonal therapy, type of operative procedure, history of benign breast disease Insufficient data – missing 95% CI
Suissa S (1989)	National Surgical Adjuvant Breast project protocol B-04 Canada	Study recruitment: 1971-1973; Study follow up: until Jan 1986	Retrospective cohort study of cases of a randomised controlled trial	68 participants 52.7 years (mean) 29.0 - 72.0 years 38% premenopausal	13 years	31% stage II		From the patients records; weight and height at the time of mastectomy	1 patient lost	From the patients records; weight and height at the time of mastectomy	68 participants	Active follow-up and review	Per 1 QI unit increase (0.01 x weight in lbs/height^2 in inches)	3.35, p-value=0.002	Age, tumor stage, menopausal status, treatment Insufficient data – unable to convert to BMI
Taylor SG IV (1989)	Eastern Cooperative Oncology Group trial United States	Study recruitment: Until 1981, Study follow-up: 6 years Recruited after diagnosis and had surgery within 8 weeks of randomization in	Randomised controlled trial of adjuvant treatment; ancillary analysis	265 participants <=65.0 years Postmenopausal	74 months		All node+ve	Trial arm: Adjuvant cyclophosphamide, methotrexate, fluorouracil, and prednisone (CMFP) or CMFP plus tamoxifen (CMFPT) for 1 year; all undergone mastectomy and axillary node dissection; no postoperative radiation therapy			265 participants	Active follow-up and review	<24 24-28 >28 kg/m^2	Obesity was a significant independent risk factor for survival	Results in text only
Mohle-Boetani J (1988)	San Francisco-Oakland Bay Area Follow-up Study United States	Cancer diagnosis: 1973-1982	Follow-up of cases of case-control study	838 participants 56 years (mean) 22 - 74 years 27.2% premenopausal, 71.7% postmenopausal,1.1% unknown	6 years	AJCC Stages: 24% I, 32% II, 34% II or IIIA, 5% IIIA, 4% IIIB, 2% IV				BMI obtained at diagnosis	838 participants 257 deaths	SEER record	>34.7 vs. <=30.4 lb/in^2	1.4, p for trend=0.02	Age at diagnosis, tumor stage, follow up time Insufficient data – missing 95% CI
Abe R (1976)	Breast Cancer Survivors Study, Sendai Japan	Breast cancer treatment: within past 10 years,	Prospective cohort of breast cancer	134.0 participants 47.0 years (mean)	At 5 years	Stages: 31.3% I, 42.5% II, 19.4% III,				At-diagnosis	82 participants, 21 deaths	Hospital records	Obese vs. non-obese (>20% standard	55.6% vs 79.9%	

	Japan	Study follow-up: minimum 5 years Post-treatment	survivors	59.7% premenopausal, 40.3% postmenopausal Obesity: 24.6%		6.7% IV; Tumor grades: 22.4% T1, 53% T2, 17.2% T3, 7.5% T4	65% +ve, 35.1% -ve		52 patients				weight vs <=20% standard weight) 5-year survival		Obesity – percentage of standard weight; 5-year survival rates only
Donegan (1978)	Milwaukee hospital-based study United States		Hospital-based study	83 participants 56.4 years (mean)	At 5 years			Had mastectomy		At-diagnosis	83 participants	Hospital records	>2.45 <=2.45 lb/inch	5-year survival rates were not signficaintly lower for obese women	Obesity index; 5-year survival rates only

12 months or more after diagnosis BMI and total mortality

Methods

Five studies from seven publications were identified. Four studies could be included in the linear dose-response meta-analysis, while all five studies could be included in the highest versus lowest meta-analysis. The publication by Ewertz et al. in 1991 superseded the publication in 1993 (RR for > 30 vs. 20-24.9 kg/m^2 = 0.98; p = non-signficant) with more sufficient data for the highest versus lowest and dose-response analyses. The study (Barnett, 2008) not included in the dose-response meta-analysis reported unadjusted dose-response results. Three studies reported results separately on the underweight group and were included in the underweight versus normal weight meta-analysis. Two publications from Women's Healthy Eating and Living (WHEL) Randomised Trial were included in the analyses – Flatt (2010) was included in the highest versus lowest and dose-response meta-analyses and Pierce (2007) was included in the underweight versus normal weight meta-analysis.

We included the BMI categories as defined by the studies. The reference category in most studies was the normal weight group, but may include underweight women. BMI could be assessed anytime but at least a year after diagnosis.

Main results and heterogeneity

The summary RR per 5 kg/m^2 was 1.08 (95% CI 1.01-1.15; I^2 = 0%; p = 0.52; 4 studies). Statistically non-significant summary RRs were observed when three of the studies (Flatt, 2010; Nichols, 2009; Caan, 2008) were omitted in turn in the influence analysis. Summary RRs ranged from 1.06 (95% CI 0.98-1.15) when Flatt et al. (2010) was omitted to 1.11 (1.03-1.20) when Ewertz (1991) was omitted. All studies comprised pre- and postmenopausal women.

In the highest versus lowest meta-analysis, the summary RR was 1.21 (95% CI 1.06-1.38; 5 studies). No evidence of heterogeneity was observed (I^2 = 0%; p = 0.70). In the underweight versus normal weight meta-analysis, the summary RR was 1.29 (95% CI 1.02-1.63; I^2 = 0%; p = 0.39; 3 studies).

In addition, Barnett et al. (2008) reported that BMI was associated with a poorer prognosis in ER positive breast cancer patients (HR per 1 kg/m^2 = 1.05 (95% CI 1.03-1.08) for ER+ve, and HR 0.99 (95% CI 0.96-1.03) for ER-ve cases).

Study quality

Number of events ranged from 135 deaths to 805 deaths. Pierce, et al. (2007a) performed an ancillary analysis using data from the comparison group of a dietary intervention trial, reported 135 deaths (118 breast cancer deaths) after an average of 6.7 years of follow-up, with minimal lost (7 patients). Flatt et al. (2010) also published data using the same but the whole of the dietary intervention trial (315 deaths, 3088 participants, 7.3 years average follow-up). More than half of the deaths were attributed to breast cancer deaths in two studies that reported data (Caan, 2008; Flatt, 2010). In the study by Nichols et al. (2009),

out of a total of 421 deaths, 121 and 95 deaths were respectively from breast cancer and cardiovascular disease. Average follow-up was more than 6 years in most study. Ewertz et al. (1991) had a maximum of seven years of follow-up. Two studies were follow-up of case-control studies (Ewertz, 1991; Nichols, 2009). Two studies were cohort of breast cance survivors (Barnett, 2008; Caan, 2008). Anthropometric data 12 months or more after diagnosis were either measured (Pierce, 2007a; Flatt, 2010) or self-reported (Ewertz, 1991; Caan, 2008; Barnett, 2008; Nichols, 2009). All studies included invasive breast cancer only. Cases were diagnosed in the 1980s (Ewertz, 1991) or through to the 1990s (Nichols, 2009), and in the 1990s (Pierce, 2007a; Caan, 2008; Flatt, 2010) or through to the 2000s (Barnett, 2008). All studies included women of all ages. Most results were adjusted for multiple confounders, including tumour stage or hormone receptor status**.** Results in Barnett, et al. (2008) were adjusted for age, tumour stage and grade.

Figure 105 Highest versus lowest forest plot of BMI 12 months or more after diagnosis and total mortality

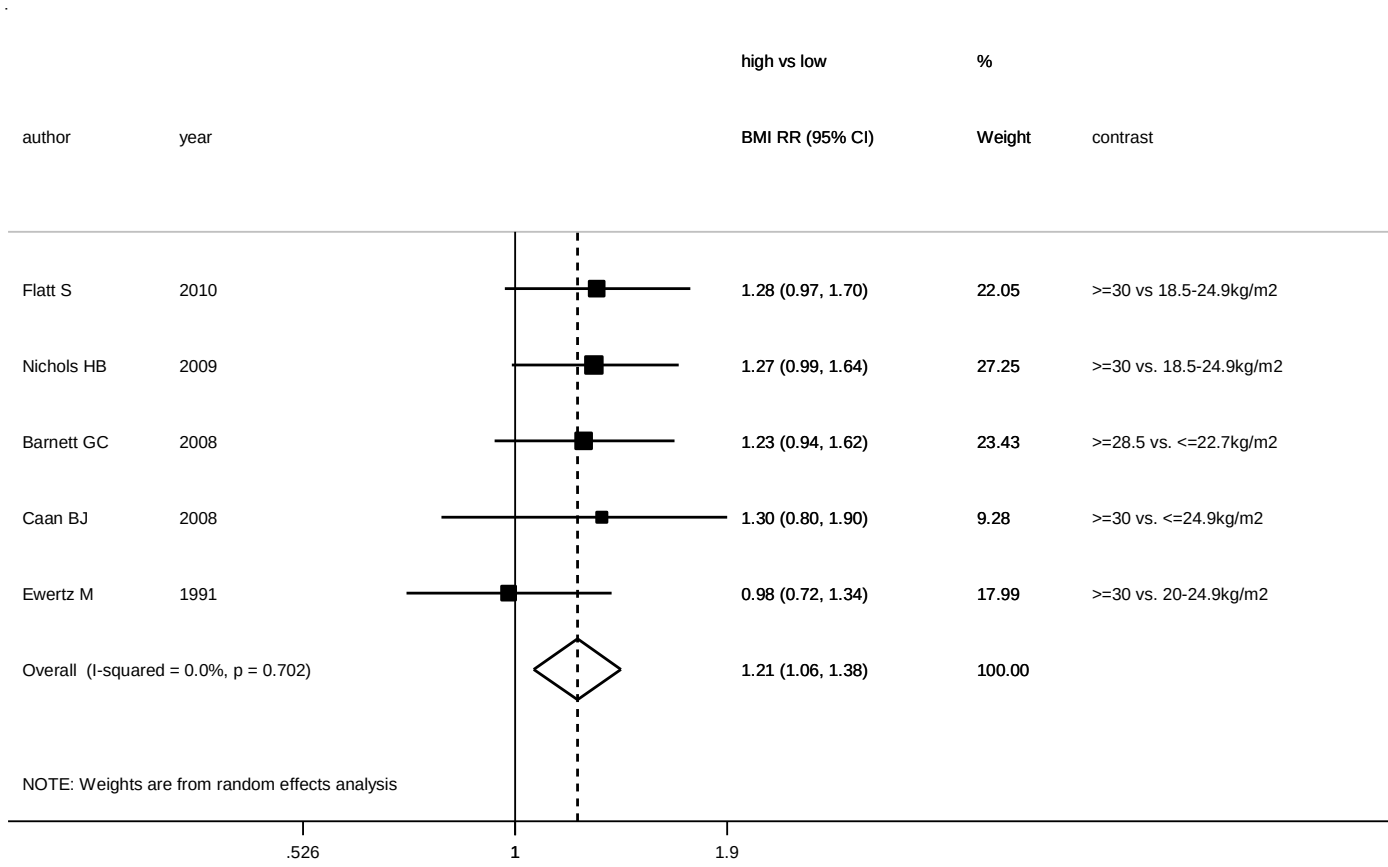


Figure 106 Forest plot of underweight versus normal weight 12 months or more after diagnosis and total mortality

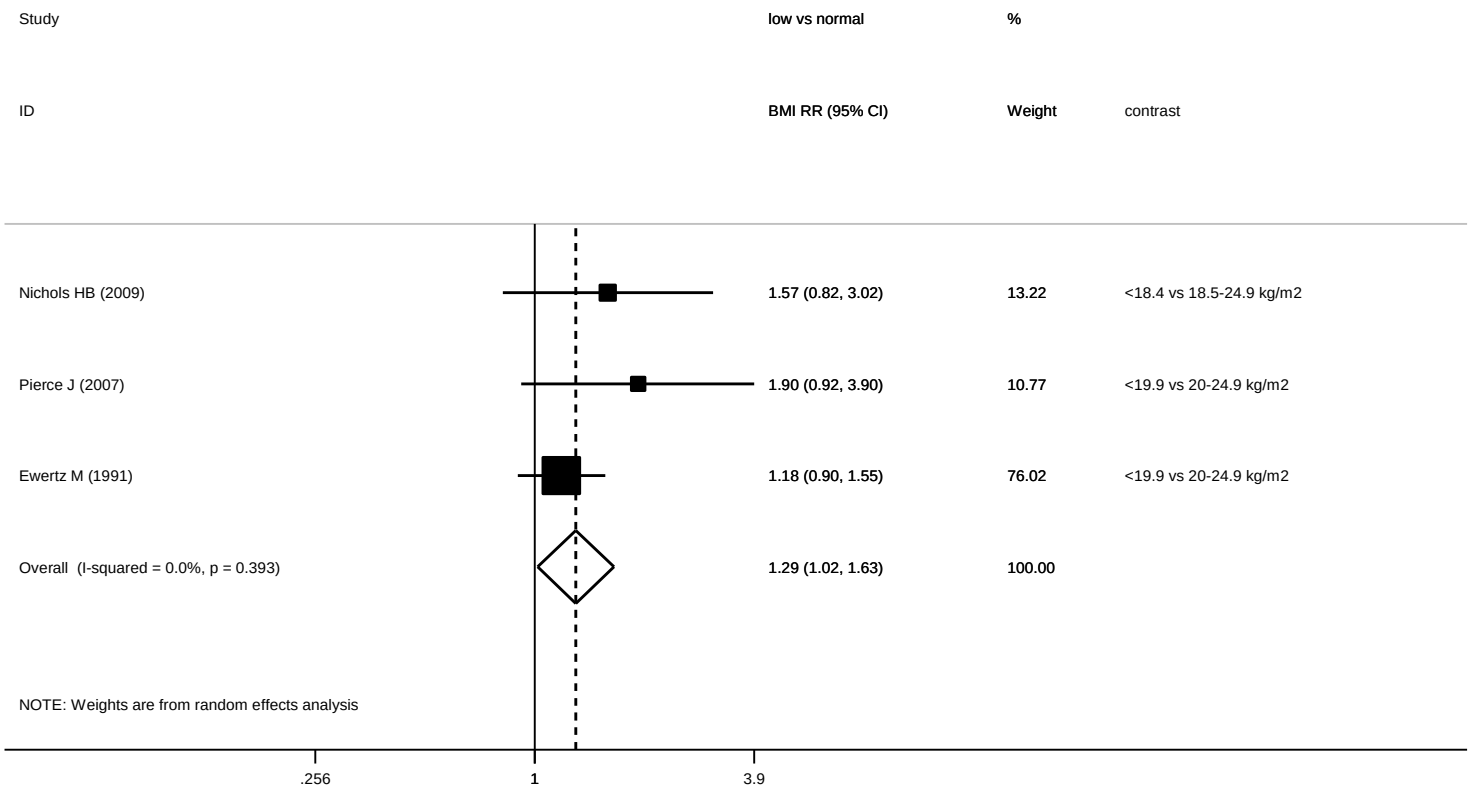


Figure 107 Linear dose-response meta-analysis of BMI 12 months or more after diagnosis and total mortality

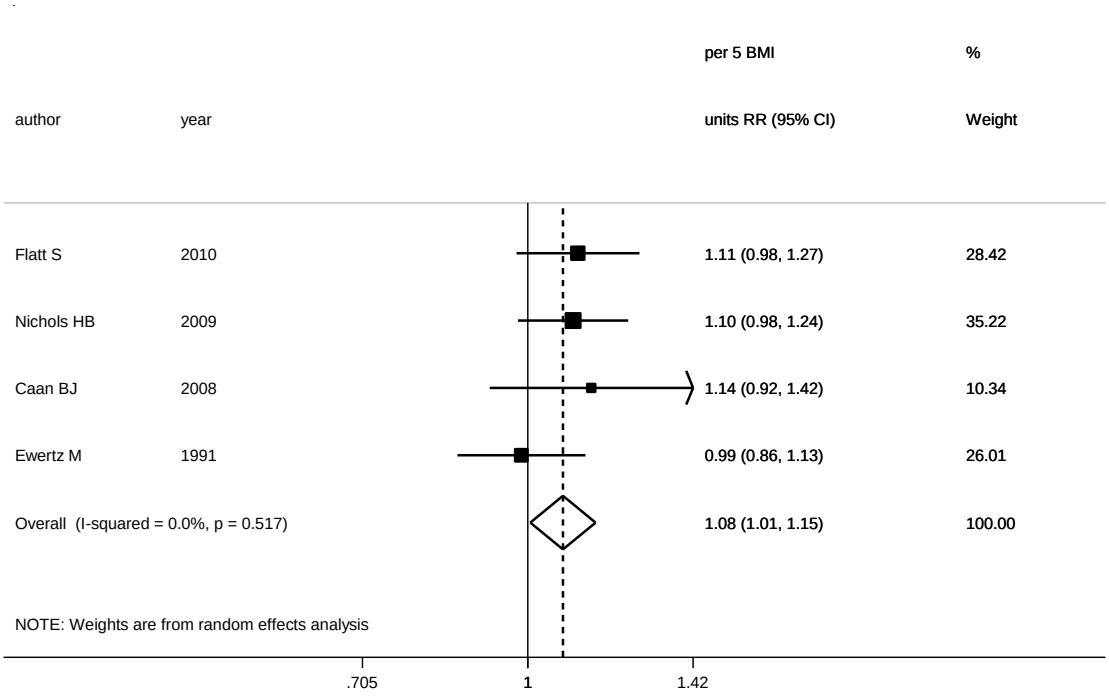


Figure 108 Individual dose-response graph of BMI 12 months or more after diagnosis and total mortality

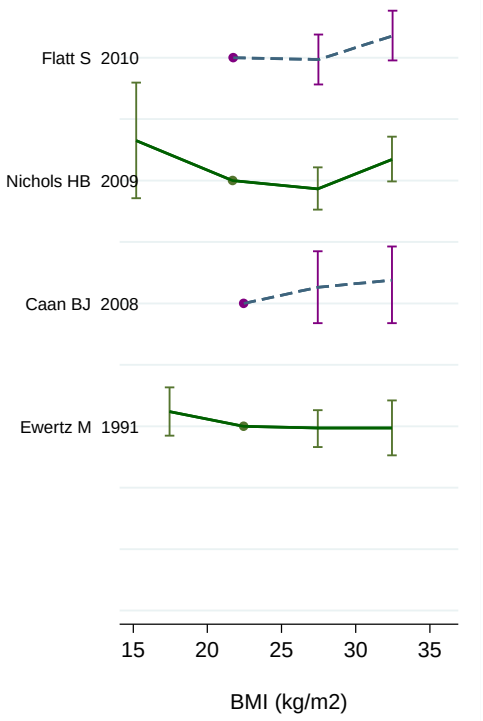


Table 88 Table of included studies on BMI 12 months or more after diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments / Remarks
Flatt S (2010)	Women's Healthy Eating and Living Study United States	Cancer diagnosis: 1991-2000; Study recruitment:1995-2000, Follow up: until June 2006 Up to 4 years; 1698 patients <2y and 1390 patients 2-4 y	Randomised controlled trial of dietary intervention; ancillary analysis	3088 participants 52 years (mean) 18 - 70 years	7.3 years	Invasive breast cancer: 38.5% stage I (=1 cm), 45.5% stage II, 15.9% stage III; 15.7% grade 1, 40.1% grade2, 35.9% grade 3, 8.2% unspecified	Among those with data: 24.8% ER-ve, 75.1%		96%	Measured on average 2 y, and a maximum of 4 y after diagnosis	3088 participants 315 deaths (83% of which were BC–related, and only 8% of which were not from any cancer), 518 breast cancer events (69% of which were distal recurrences)	Death certificate	>=30 vs. 18.5-24.9 Kg/m^2	1.28 (0.97-1.70)	Tumor grade, tumor stage, years between diagnosis and study entry, alcohol intake, education, ethnicity, smoking, parity, physical activity
Nichols HB (2009)	Collaborative Women's Longevity Study United States	Study recruitment: 1988-2001; Cancer diagnosis: 1988-1999; Study follow up: until 2005 Recruited 5.8 years after breast cancer diagnosis	Follow-up of cases of case-control studies	3993 participants 58.4 years (mean) 20 - 79 years Mostly white: 98%, 28.1% premenopausal; 71.9% postmenopausal HRT use: 38.9% (postmenopausal hormone use)	6.3 years	Invasive nonmetastatic breast cancer; 64.1% local, 24.7% regional, 0.6% distant, 10.6% unknown			40%	Self-reported body weight 1-5 years before diagnosis at study baseline	3993 participants 421 deaths, 121 breast cancer mortality, 95 deaths from cardiovascular disease	Death record	>=30 vs. 18.5-24.9 Kg/m^2	1.27 (0.99-1.64)	Age, tumor stage, time from diagnosis to exposure assessment, family history, smoking, physical activity, menopausal status
Barnett GC (2008)	Studies of Epidemiology and Risk Factors in Cancer Heredity Breast Cancer Study UK	Cancer diagnosis: 1991-2005	Prospective cohort study of breast cancer survivors	4560 participants 51.5 years (mean) 23 - 69 years 98% white Among those with data: 55.2% pre-menopausal, 44.7% postmenopausal HRT use: 62 % never usage, 37.9% ever usage	6.82 years	Invasive breast cancer; 73% incident and 27% prevalent; among those with data: 49.7% stage I, 45.8% stage II, 3.3% stage III, 1.1% stage IV; 24.1% grade 1, 47.2% grade 2, 28.6% grade 3	18.7% ERve, 81.2% ER+ve		67%	Self-reported at study baseline	4346 participants, 586 deaths included in analysis	Cancer registry + death certificate	>28.5 vs. <=22.7 Kg/m^2	1.23 (0.94 - 1.62)	Age at diagnosis, tumor stage, tumor grade Highest vs. lowest analysis only; adjusted result for upper vs. lower quartile comparison only
Caan BJ (2008)	LACE United States	Cancer diagnosis:1997-2000; Study follow up: until 2007 Diagnosed 11–39 months before study enrolment	Prospective cohort study of breast cancer survivors	1692 participants 58.3 years (mean) 18 - 70 years 22.8% premenopausal, 63.8% postmenopausal	83.9 months	Early stage invasive breast cancer; AJCC; 46.7% Stage I, 50.2% Stage II, 3.1% Stage IIIA	69.2% ER+/PR+, 13.6% ER+/ PR-, 1.7% ER-/ PR+, 15.5% ER-/ PR- 63.2% o node+ve, 26.3% 1-3 nodes+ve, 5.7% 4-6 nodes+ve, 1.7% 7-9	19% chemotherapy; 24.8% radiotherapy; 38.4% chemo- and radiotherapy; 49.2% mastectomy; 50.8% breast-conserving surgery; 70.9% current tamoxifen users,	46%	self-reported at baseline; one year pre-diagnosis and also after diagnosis at baseline	1689 participants 162 deaths, 160 deaths included n analysis, 99 breast cancer mortality	Medical records	>=30 vs. <=24.9 Kg/m^2	1.30 (0.80-1.90)	Tumor stage, age at diagnosis, tamoxifen use, treatment, nodal status, estrogen receptor level, progesterone receptor level, smoking, physical activity

							nodes+ve, 3.1% >=10 nodes+ve	6.7% past tamoxifen users							
Ewertz M (1991)	Danish Breast Cancer Cooperative Group Denmark	Cancer diagnosis:1983-1984; Study follow up: until 1990	Follow up of cases of population-based case-control study	2445 participants <=70 years Among those with data, HRT use: 66.1% never usage, 33.8% ever usage	7 Years (max)	Primary Invasive breast cancer; 44.8%Grade I, 42.3% Grade II, 12.8% Grade III breast cancer	58.5% none node+ve, 28.6% 1-3 node+ve, 12.8% >4 node+ve		87%	Self-reported 1 year after diagnosis	2445 participants 805 deaths	Cancer registry	>=30 vs. 20-24.9 Kg/m^2	0.98 (0.72 - 1.34)	Age, tumor size, nodal status, tumor grade, skin invasion, area of residence
Pierce J (2007)a	Women's Healthy Eating and Living Study United States	Cancer diagnosis:1991-2000; Study follow up: until 2005 Within 48 months of diagnosis (average, 24 months)	Randomised controlled trial of dietary intervention; ancillary analysis	1490 participants 50 years (mean)	6.7 years	Early stage breast cancer; AJCC; 40% Stage I (>=1cm), 45% Stage II, 15% stage III, 15.9% grade I, 39.8% grade II, 35.8% grade III, 8.3% unknown	63.1% ER+ve/PR+ve, 10.8% ER+ve/PR-ve, 5.1%ER-ve/PR+ve, 20.8% ER-ve/PR-ve	31.4% none-chemotherapy, 25.7% nonanthracycline, 42.8% anthracycline; 42% adjuvant tamoxifen, 58% no adjuvant tamoxifen	7 patients lost	Measured on average 2 y, and a maximum of 4 y after diagnosis	1490 participants 135 deaths, 118 breast cancer mortality, 10 death from other cancers, 7 death from non-cancer, 236 breast cancer events	Death certificate	<19.9 vs. 20-24.9 Kg/m^2	1.90 (0.92-3.90)	Age, alcohol intake, receptor status, time from diagnosis to randomization (Incliuded only in the analysis of underweight versus normal weight)

Table 89 Table of excluded studies on BMI 12 months or more after diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments / Exclusion reason
Ewertz M (1993)	Danish Breast Cancer Cooperative Group Denmark	Cancer diagnosis: 1983-1984; Study follow up: until 1990	Follow up of cases of a population based case-control study	2445 participants	7 years	Primary invasive breast cancer; 44.8% grade I, 42.3% grade II, 12.8% grade III 58.5% none node +ve, 28.6% 1-3 nodes +ve, 12.7% >= 4 nodes+ve		Adjuvant therapy	3 patients emigrated	From the recorded data one year after the diagnosis		Death record	>30 vs. 20-24.9 kg/m^2 Advanced disease	0.98, p=ns	Tumor size,Nodal status,Tumor grade,Skin invasion Superseded by Ewertz, 1991, missing 95% CI

Body Mass Index (BMI) and breast cancer mortality

Before diagnosis BMI and breast cancer mortality

Methods

Twenty-five studies from 27 publications were identified**.** Jain et al. (1997), and Maehle et al. (1996) were superseded by other publications of the same studies (Jain, 1994b; Maehle, 2004). Nomura et al. (1991) reported results on obesity index that was calculated by weight in kg divided by height in $m^{1.5182}$, therefore it is excluded in the meta-analyses. For high vs. low obesity index, the RRs were 1.15 (95% CI 0.51-2.62) in Caucasian cases and 3.53 (95% CI 1.25-10.0) in Japanese cases in this study (Nomura, 1991).

Seventeen studies could be included in the linear dose-response meta-analysis and 21 studies could be included in the highest versus lowest meta-analysis. Three studies were excluded from the highest versus lowest and dose-response analyses. Eley et al. (1994) and Den Tonkelaar et al. (1995) were excluded because unadjusted results were reported. The former study observed a 2.2-fold (95% CI 1.5-3.2) increased risk in dying of breast cancer for the comparison of high to low/normal BMI. The latter study on postmenopausal women reported no significant association (incident density ratio (IDR) for ≥ 26 vs. < 26 kg/m^2 = 0.95; 95% CI 0.51-1.78). Zhang et al. (1995) reported an increased risk of 1.8-fold, with no 95% CI or p value in postmenopausal women. Four studies that were included in the highest versus lowest meta-analysis were not in the dose-response meta-analysis due to insufficient data for the analysis (Emaus, 2010; Reeves, 2007; Tretli, 1990; Maehle, 2004).

Eight studies reported results separately on the underweight group and were included in the underweight versus normal weight meta-analysis. BMI could be assessed at different times before diagnosis, or of an adult BMI (Whiteman, 2005)

Main results and heterogeneity

The summary RR per 5 kg/m^2 was 1.18 (95% CI 1.11-1.24; 17 studies). Low to moderate heterogeneity was observed (I^2 = 47.8%; p = 0.02). There is no evidence of small study/publication bias. Egger's test is not statistically significant (p = 0.32). There is no evidence of strong influence from any individual study on the summary estimate, which remained statistically significant when each study was omitted in turn in the influence testing, ranging from 1.16 (95% CI 1.10-1.23) when Tornberg (1993) was excluded to 1.19 (95% CI 1.12-1.25) when Jain (1994b) was excluded. When stratified by menopausal status, the summary RRs were 1.12 (0.92-1.35; I^2 = 72.3%; p = 0.01; 5 studies) for premenopausal women and 1.15 (1.05-1.25; I^2 = 53.6%; p = 0.04; 7 studies) for postmenopausal women.

In the highest versus lowest meta-analysis, the summary RR was 1.35 (95% CI 1.24-1.46; I^2 = 35.2%; p = 0.06; 21 studies). When stratified by menopausal status, an increased risk of dying of breast cancer was observed in both pre- and postmenopausal women

(summary RR for highest vs. lowest = 1.50; 95% CI 1.13-2.00, and RR 1.34; 95% CI 1.21-1.48 respectively). High heterogeneity was observed in the studies on premenopausal women (I^2 = 69.7%; p = 0.002; 8 studies, and I^2 = 15.0%; p = 0.30; 12 studies, respectively).

When stratified by estrogen receptor status, a statistically significant increased risk of breast cancer mortality was observed in ER positive breast cancer patients (RR for highest vs. lowest = 1.42; 95% CI 1.15-1.75; I^2 = 0%; p=0.84; 4 studies). No association was observed in ER negative breast cancer patients (RR 1.01, 95% CI 0.79-1.30; I^2 = 0%; p = 0.38; 3 studies). Dal Maso et al. (2008) also reported results on a group of ER-PR+, ER+ PR-, and ER- PR- breast cancers that was not included in the analysis. A non-significant increased risk was reported (HR for ≥30 vs. < 25 kg/m^2 = 1.35, 95% CI 0.77-2.38). In addition, Jain et al. (1994) reported a RR per 1 unit increase of BMI of 1.02 (95% CI 0.97-1.08) in ER positive breast cancer patients and 0.98 (95% 0.88-1.08) in ER negative breast cancer patients. For QI ≥ 26 vs. < 26, the unadjusted IDR reported by den Tonkelaar et al. (1995) were 0.59 (95% CI 0.26-1.32) and 3.60 (95% 0.53-24.67) respectively.

For the comparison of underweight to normal weight, the summary RR was 1.02 (95% CI 0.85-1.21; I^2 = 31.1%; p = 0.18; 8 studies). When stratified by the exclusion of subjects with underlying diseases, the summary RRs remained similar (data not shown). Non-linear dose-response analysis did not show a non-linear relationship when all data including those from the underweight subjects were modelled ($p_{non\text{-}linearity}$ = 0.21).

Dose-response metaanalysis by subgroups and meta-regression analyses were performed on factors such as study design, length of study follow-up, geographic location, number of outcome events, exposure assessment methods, exposure levels, menopausal status, and covariate adjustments to explore heterogeneity between studies that were included in the linear dose-response meta-analysis. None of these factors could significantly explain heterogeneity (p for meta-regression ranged from 0.07 (adjusted for tumour stage) to 0.97 (adjusted for cancer treatment).

Study quality

Number of events ranged from 34 to 2383 breast cancer deaths. The study by Galanis et al. (1998) reported 34 breast cancer deaths. The cohort of breast cancer survivors conducted by Caan et al. had 99 breast cancer deaths from an average of 83.9 months of follow-up. In addition, four studies (Jain, 1994b; Cleveland, 2007; Nichols, 2009; Hellmann, 2010) had less than 200 breast cancer deaths. Nine studies (Tornberg, 1993; Schairer, 1999; Enger, 2004; Maehle, 2004; Dal Maso, 2008; West-Wright, 2009; Rosenberg, 2009; Emaus, 2010; Conroy 2011) had between 200-500 breast cancer deaths. Five studies (Tretli, 1990; Kroenke, 2005; Whiteman, 2005; Alsaker, 2011; Lu, 2011) had over 500 deaths.

Average follow-up ranged from 4.3 to 14.9 years. The studies of a health screening cohort, with cancer diagnosed in 1963-1975 (Tretli, 1990) or pre-1983 (Tornberg, 1993) had

follow-up of an average 4.3 years or a maximum of 4 years respectively. Loss to follow-up was minimal in the studies reported data. The most being Whiteman et al. (2005), with 4.1% lost and also in Cleveland et al. (2007). Of the cases identified in this study, 410 cases were without follow-up data due to nonresponse, refusal, untraceability, or death without an identifiable, leaving 1508 participants.

Maehle et al. (2004), Emaus et al. (2010) and Alsaker, et al. (2011) were also a health screening cohort, while the studies of Jain et al. (1994b) and Schairer (1999) involved breast cancer screening/mammography**.** Jain et al. (1994b) was originally a randomised controlled trial of mammography screening. A total of seven studies were follow-up of case-control studies (Enger, 2004b; Whiteman, 2005; Cleveland, 2007; Dal Maso, 2008; Nichols, 2009; Rosenberg, 2009; Lu, 2011). Cases in these studies were identified from hospitals or cancer registries. The Life After Cancer Epidemiology (LACE) cohort was a cohort of breast cancer survivors, identified from cancer registries and those rejected participation in a dietary intervention trial (Caan, 2008). Overall, seven studies were population cohorts (Galanis, 1998; Tretli, 1990; Tornberg, 1993; Schairer, 1999; Maehle, 2004; Kroenke, 2005; Reeves, 2007; West-Wright, 2009; Emaus, 2010; Hellmann, 2010; Alsaher, 2011; Conroy, 2011).

Four studies included *In situ* and invasive breast cancers (Schairer, 1999; Enger, 2004b; Reeves, 2007; Cleveland, 2007) and 14 studies included invasive only breast cancer (Tretli, 1990; Tornberg, 1993; Jain, 1994b; Whiteman, 2005; Kroenke, 2005; Dal Maso, 2008; Caan, 2008; West-Wright, 2009; Rosenberg, 2009; Nichols, 2009; Emaus, 2010; Lu, 2011; Conroy, 2011; Alsaker, 2011). Cancer diagnosis dated as early as from the 1960s, with Alsaker et al. (2011) spanned from 1961 to 2007 and Tretli et al (1990), from 1963 to 1975. Five studies recruited cancer diagnosed from the 1970s (Galanis, 1998; Schairer, 1999; Maehle, 2004; Kroenke, 2005; Emaus, 2010) to various years – 1980 (Galanis, 1998), 1981 (Schairer, 1999), 1990 (Maehle, 2004), 2000 (Kroenke, 2005) and 2005 (Emaus, 2010). Five studies included cancer diagnosed in the 1980s (Jain, 1994b; Enger, 2004b; Whiteman, 2005), or in the 1980s and 90s (Reeevs, 2007; Nichols, 2009). Tornberg et al. (1993) included cases diagnosed before 1983. Six studies recruited cases diagnosed in the 1990s (Cleveland, 2007; Caan, 2008; Dal Maso, 2008; Rosenberg, 2009; Lu, 2011), or up until the 2000s (West-Wright, 2009).

Anthropometric data were measured in eight studies (Tretli, 1990; Tornberg, 1993; Jain, 1994b; Maehle, 2004; Reeves, 2007; Hellmann, 2010; Emaus, 2010; Alsaker, 2011) and self-reported in 13 studies (Galanis, 1998; Schairer, 1999; Enger, 2004b; Whiteman, 2005; Kroenke, 2005; Cleveland, 2007; Dal Maso, 2008; Caan, 2008; West-Wright, 2009; Rosenberg, 2009; Nichols, 2009; Lu, 2011; Conroy, 2011). Anthropometric data referenced to the time prior to cancer diagnosis were retrospectively collected in the follow-up studies or the cohort of breast cancer survivors, while the data was collected prospectively in the population cohorts. The referenced assessment period or when measurement was made varied in the studies. Alsaker et al. (2011) used BMI on average taken 19 years prior to diagnosis. Lu et al. (2011) used BMI five years prior to diagnosis.

Enger et al. (2004b) was a study in premenopausal women. Schairer et al. (1999), Reeves, et al. (2007), Rosenberg et al. (2009), Conroy et al. (2011), Alsaker et al. (2011)

were studies in postmenopausal women. Tretli, et al. (1990) reported results on age-specific Quetelet's Index by tumour stage. Tornberg (1993) reported age-adjusted results. Other results were mostly adjusted for multiple confounders, with some studies having fewer adjustments – Jain et al. (1994b) (age and nodal status), Schairer et al. (1999) (tumour stage, race), Maehle et al. (2004) (tumour size, nodal status, nuclear grade), Enger et al. (2004b) (age, tumour stage, physical activity), Reeves et al. (2007) (smoking, tumour stage, ER status), Cleveland et al. (2007) (age, hypertension) and Alsaker et al. (2011) (age, time-period at diagnosis).

Published pooled analysis

The After Breast Cancer Pooling Project (ABCPP) published results on before diagnosis BMI and total, breast cancer, and non-breast cancer mortality risks (Kwan, 2012b).

Data from four prospective studies of breast cancer survivors (Shanghai Breast Cancer Survival Study, Life After Cancer Epidemiology, Women's Healthy Eating and Living, and Nurses' Health Study) were pooled in the project. After a mean follow-up of 7.8 years, 2140 deaths (1423 breast cancer mortality, 717 deaths because of other causes) from 14948 participants with stage I-IV invasive breast cancer were accrued.

Underweight or obesity was not associated with breast cancer mortality in this study. Multivariate- adjusted HRs for underweight (<18.5 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (≥ 30 kg/m^2) versus normal weight women (18.5-24.9 kg/m^2) were 1.33 (95% CI 0.92-192), 1.04 (95% CI 0.92-1.18), and 1.10 (95% CI 0.95-1.28) respectively. P for non-linearity was 0.97. Further analysis using different BMI cutpoints showed a borderline significant increased risk for the morbidly obese (≥ 40 kg/m^2) compared with the normal weight (18.5-24.9 kg/m^2) (HR 1.40; 95% CI 1.00-1.96). No significant associations were found for the overweight (HR 1.04; 95% CI 0.92 1.18), obese (HR 1.12; 95% CI 0.94 1.32), or severely obese (HR 0.92; 95% CI 0.68 1.24).

The dose-response and the highest vs. lowest meta-analyses in this report included results from the Life After Cancer Epidemiology (Caan, 2008) and the Nurses' Health Study (Kroenke, 2005), but not the Shanghai Breast Cancer Survival Study and the Women's Healthy Eating and Living RCT as in the ABCPP. In addition, the Nurses' Health Study (Kroenke, 2005) was included in the underweight vs. normal weight meta-analysis in this report.

Figure 109 Highest versus lowest forest plot of before diagnosis BMI and breast cancer mortality

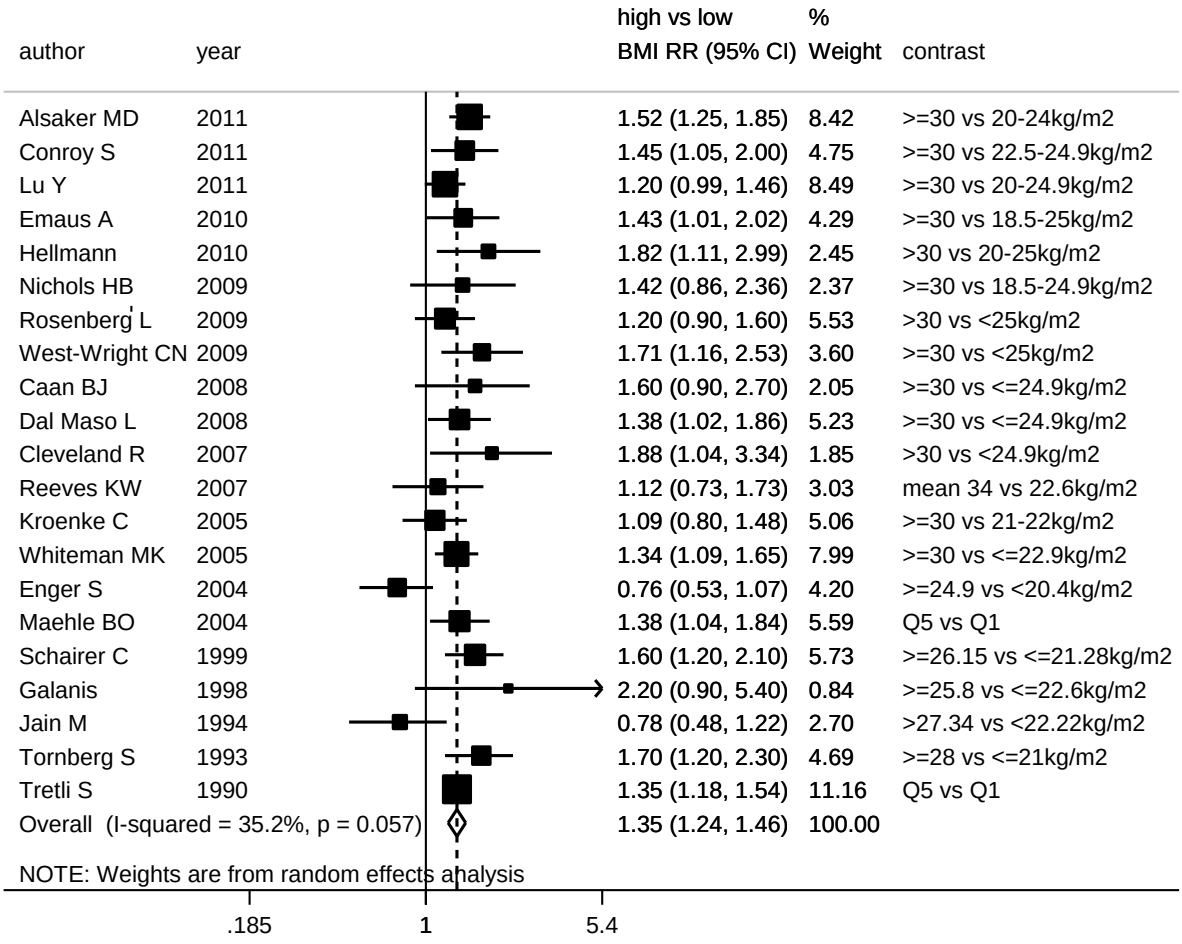


Figure 110 Highest versus lowest forest plot of before diagnosis BMI and breast cancer mortality by menopausal status

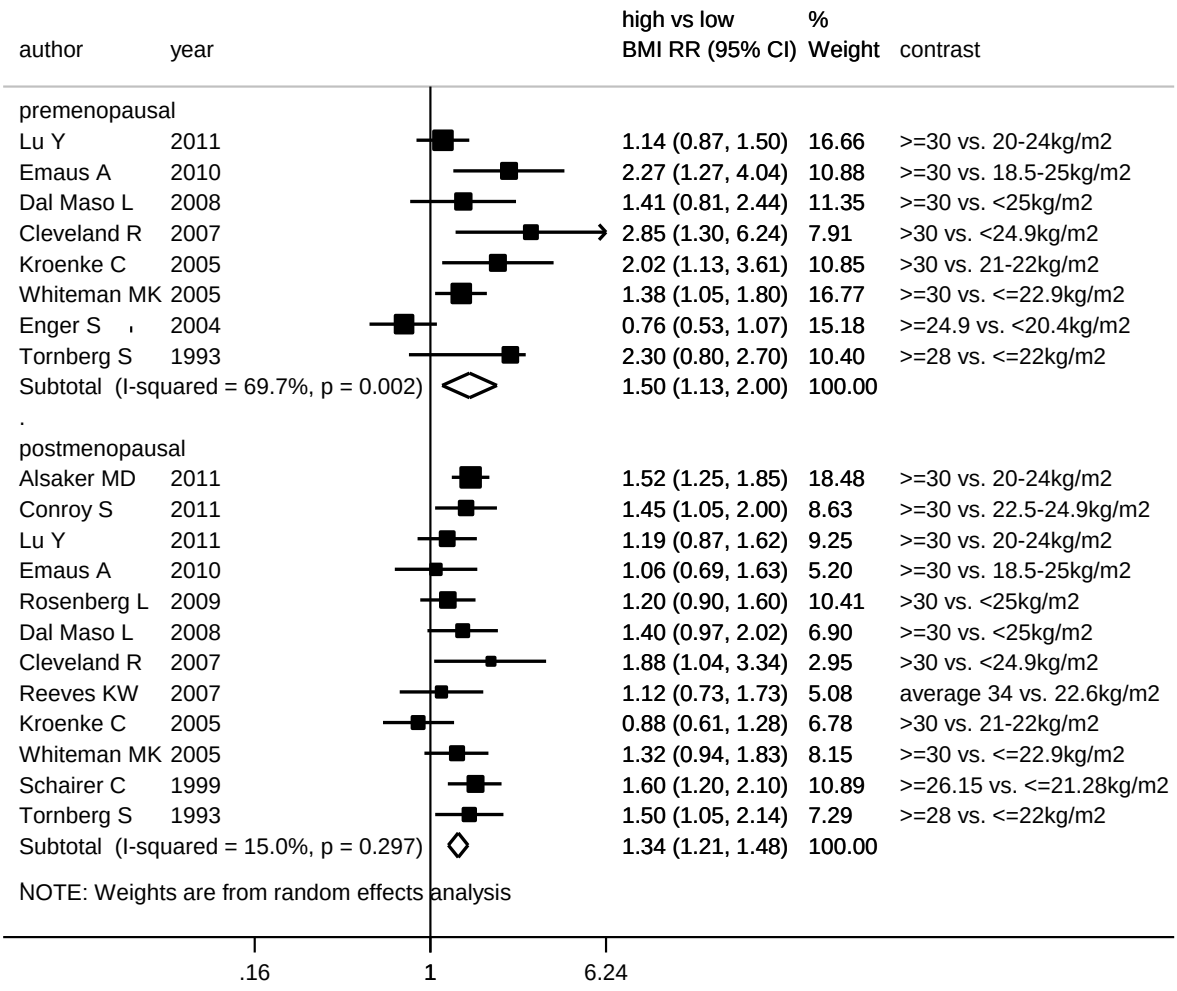


Figure 111 Highest versus lowest forest plot of before diagnosis BMI and breast cancer mortality by estrogen receptor status

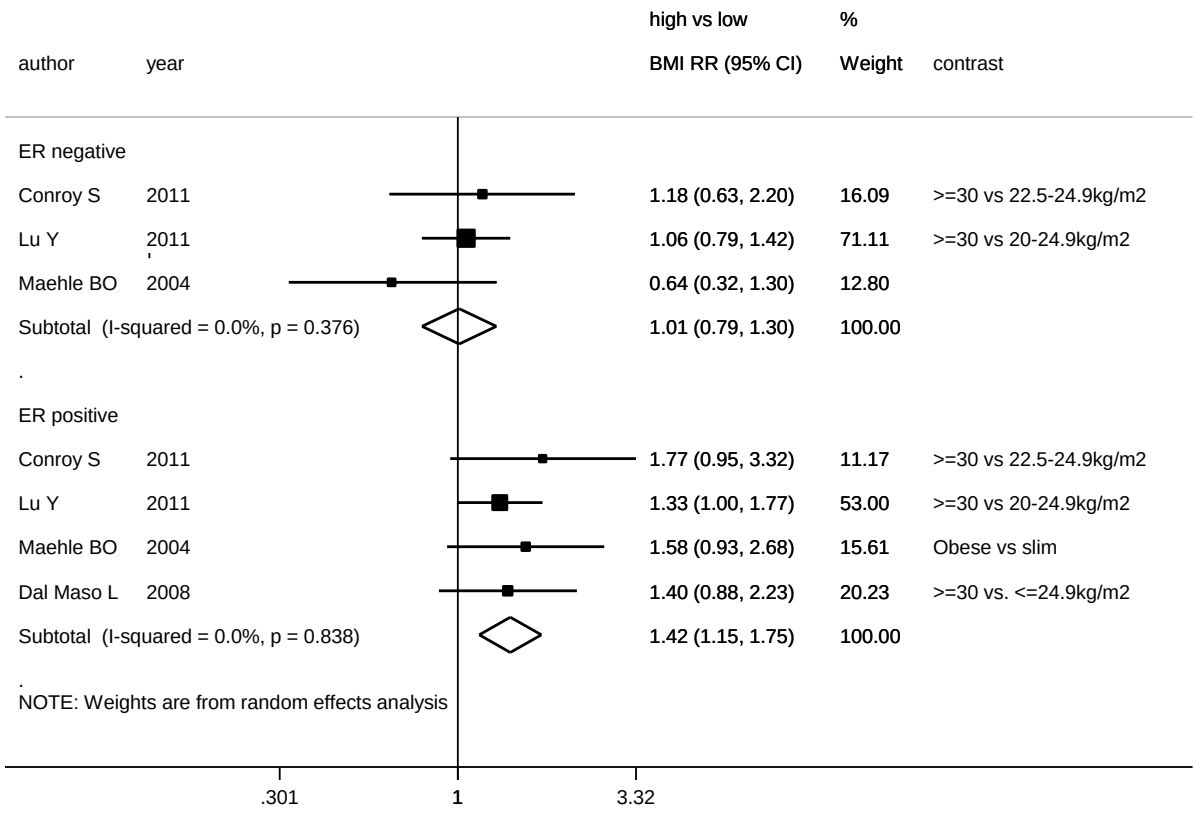


Figure 112 Forest plot of before diagnosis underweight versus normal weight and breast cancer mortality

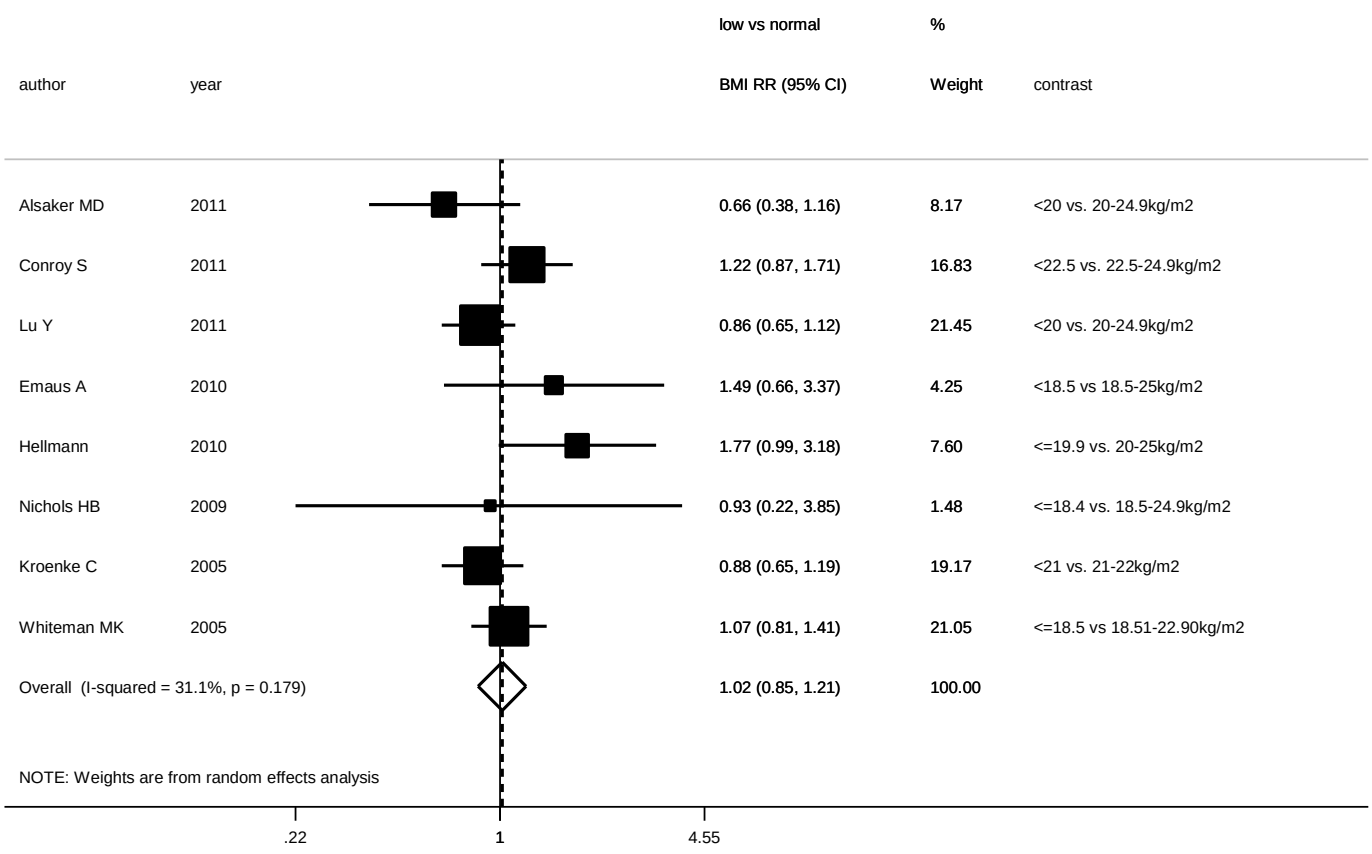


Figure 113 Linear dose-response meta-analysis of before diagnosis BMI and breast cancer mortality

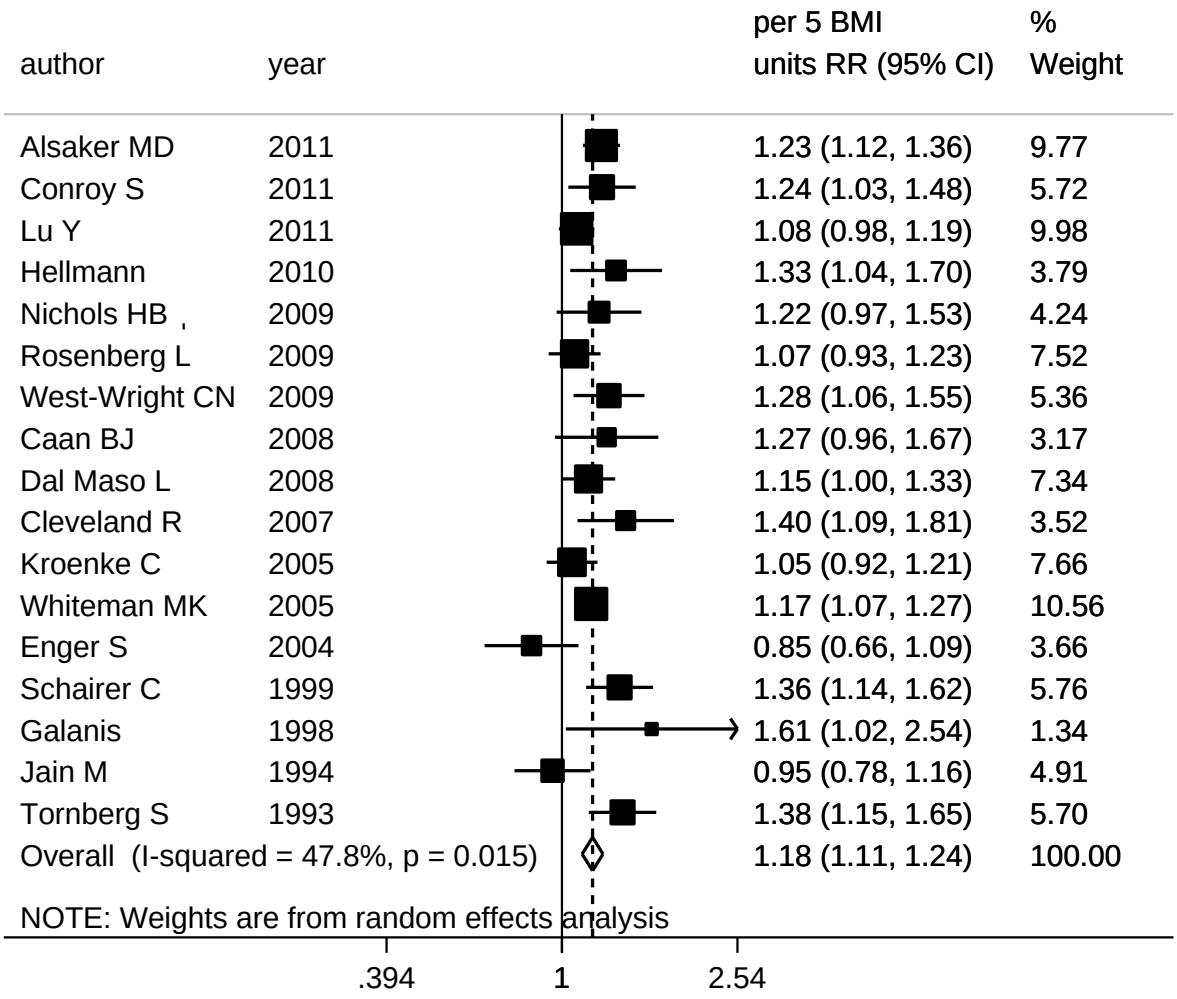
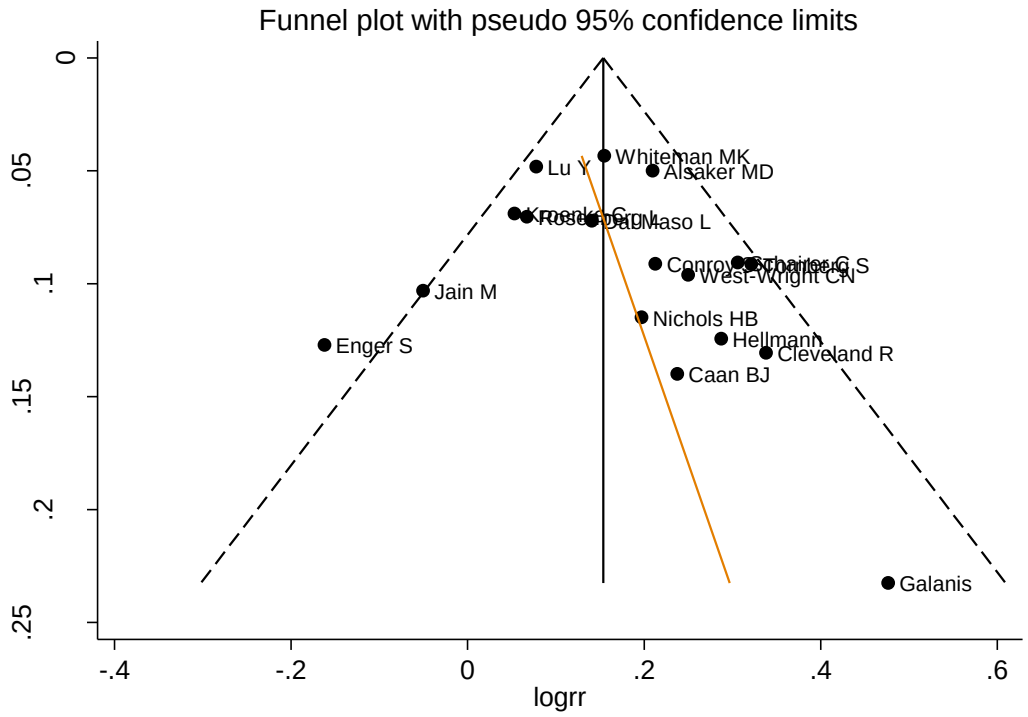


Figure 114 Funnel plot of studies of before diagnosis BMI and breast cancer mortality



Each dot represents the logarithm of relative risk estimate against standard error as a measure of study size. Solid line is the logarithm of summary risk estimate from the meta-analysis. Dashed lines are its 95% confidence interval.

Egger's test p = 0.32

Figure 115 Individual dose-response graph of before diagnosis BMI and breast cancer mortality

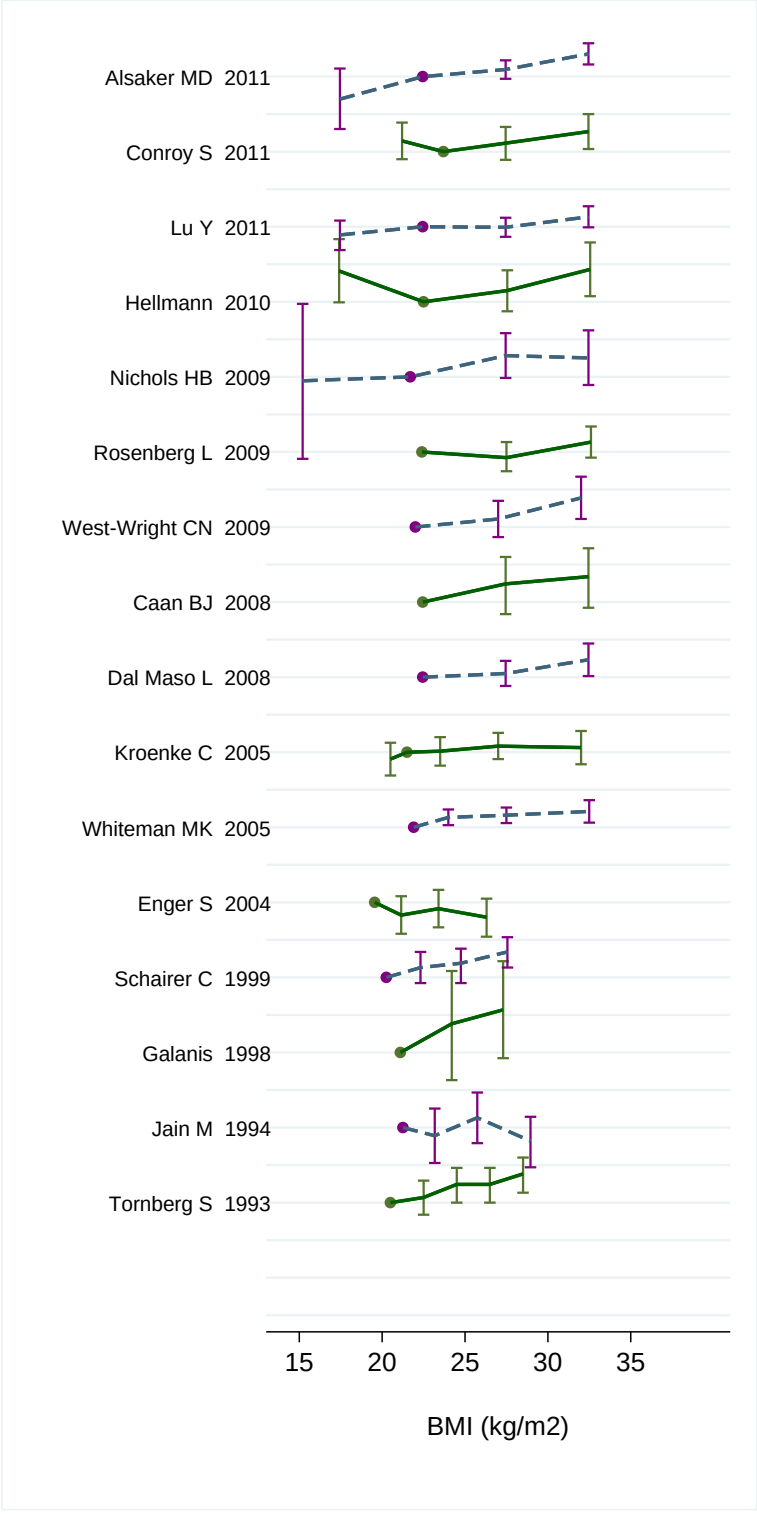


Figure 116 Linear dose-response meta-analysis of before diagnosis BMI and breast cancer mortality by menopausal status

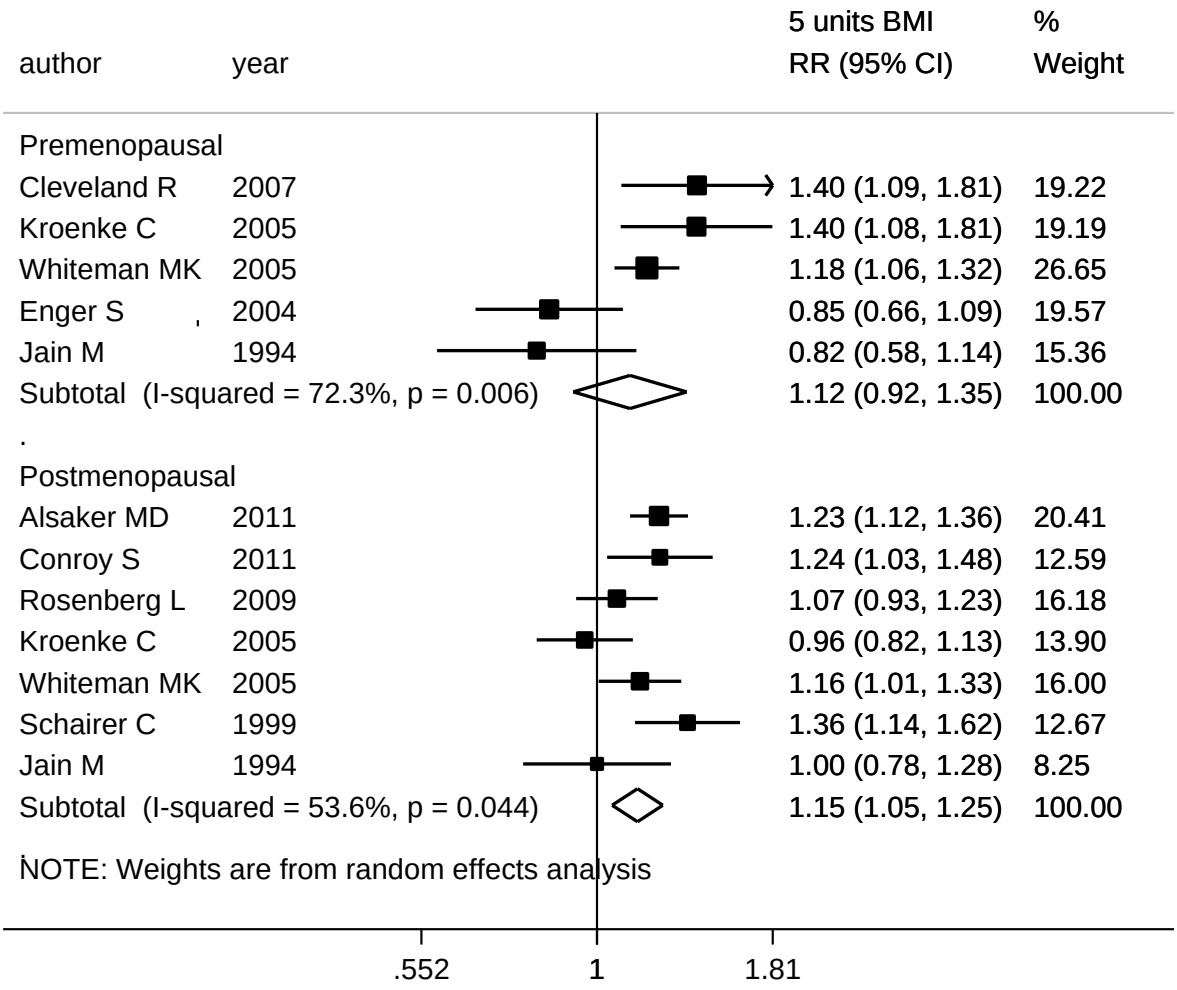


Table 90 Table of included studies on BMI before diagnosis and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments / Remarks
Alsaker MD (2011)	Norwegian Breast Cancer Screening Cohort Study Norway	Study recruitment:1956-1959, Cancer diagnosis: 1961-2007, Study follow-up: Until 2007 Recruited on average 23.9 years before diagnosis	Cancer survivors of population-based prospective cohort study	2640 participants; >=55 years Postmenopausal, participants of breast cancer screening cohort	5.75 years	Stages: 53% I, 34% II, 6% III, 6% IV, 1% unknown			74.20%	Measured at screening on average 19 years prior to diagnosis	2640 participants, 2301 deaths, 1022 breast cancer mortality, 745 breast cancer deaths from 1992 participants, age >=55 years were included in analysis	Death certificate	>=30 vs. 20-24 Kg/m^2 >= age 55 years	1.52 (1.25-1.85)	Age at diagnosis, time-period at diagnosis
Conroy S (2011)	The Multiethnic Cohort Study Hawai	Study recruitment: 1993-1996, Study follow-up: Until 2007	Cancer survivors of population-based prospective cohort study	3842 participants 68.8 years (mean) 50 - 89 years Multi-ethnic Postmenopausal Comorbidities: Heart disease/stroke: 9% yes; Hypertension: 37% yes	6.2 years	Incident, invasive breast cancer; SEER stages: 71% local, 25% regional, 3% distant; Size (cm): 61% <=2 61%, >2 24%, 16% unknown	45% ER+ PR+, 13% ER- PR-, 10% ER+PR-/ER-PR+, 31% other/unknown	Surgery: 56% conserving surgery, 38% mastectomy, 6% none/unknown; Chemotherapy: 24% yes; Radiotherapy: 47% yes		Self-reported BMI at cohort baseline on average 6.5 years before diagnosis	3842 participants 804 deaths, 376 breast cancer mortality	Death certificate	>=30 vs. 22.5 - 24.9 Kg/m^2	1.45 (1.05-2.0)	Stage, hormonal receptor status, smoking, years between diagnosis and study entry
Lu Y (2011)	The Women's Contraceptive and Reproductive Experiences (CARE) Study United States	Cancer diagnosis: 1994-1998, Study follow-up: Until 2005/2007	Follow-up of cases of population-based case-control study	4538 participants 35 - 64 years White: 64.7%, Black: 35.3%, 46.2% premenopausal, 42.2% postmenopausal, 11.6% unknown 62.8% comorbidity free, 29.7% one, 7.5% >=2 of either hypertension, myocardial infraction, stroke, diabetes, or other cancers excluding nonmelanoma skin cancers	8.6 years	SEER stages: 60.3% localized, 38.5% nonlocalized, 1.2% unknown; Invasive breast cancer	58.7% ER+, 28.8% ER-, 12.5% unknown	No info on breast cancer therapies	76.50% / 2 patients lost	Self-reported on average 5.1 months post-diagnosis; BMI of 5 years before diagnosis	4538 participants 1053 deaths, 828 breast cancer mortality	SEER record	>=30 vs. 20 -24.9 Kg/m^2	1.20 (0.99-1.46)	Age at diagnosis, education, study centre, tumor stage, ER status, number of comorbidities, race
Emaus A (2010)	Norwegian Health Surveys Follow-up Study, three	Cancer diagnosis: 1975–2005	Cancer survivors of a population-based prospective cohort	1364 participants 57.5 years (mean) 27 - 79 years 61% postmenopausal	8.2 years	Invasive breast cancer; TNM; 49% Stage 1, 41% Stage 2, 4.5% stage 3, 5.3%			91% in the 1st, 91% in the 2nd and 88% in the 3rd survey	Measured during health screening, prior to diagnosis	1364 participants 429 deaths, 355 breast cancer mortality, 27	Death record	>=30 vs. 18.5-25 Kg/m^2	1.43 (1.01-2.02)	Age at diagnosis, pre-diagnostic observation time, tumor stage, region of residence, year at diagnosis before and after 1995, physical

	counties Norway		study	HRT use: 30 patients, only measured in 3rd survey. Participants of a health screening cohort. Comorbidities: 8 diabetic patients		stage 4			Complete follow-up	(usual level of physical activity during leisure time in the year preceding each survey)	death from other cancers, 23 death from cardiovascular disease, and 24 from other causes				activity Highest vs. lowest analysis only; missing number of events per category
Hellmann (2010)	Copenhagen City Heart Study Denmark	Study recruitment:1976; Study follow up: until 2007	Cancer survivors of a population-based prospective cohort study	528 participants 66.9 years (mean) 33.1 - 95.4 years Mostly Caucasian 16.1% premenopausal, 83.9% postmenopausal HRT use: 71.2% unexposed, 28.8% exposed	7.8 years	Primary breast cancer, one sarcoma, 527 carcinomas; TNM; 56.2% local, 33.7 regional, 6.3 metastatic, 3.8% unknown		7.4% radiotherapy, 7.4% chemotherapy, 22.4% hormonal therapy	74% at the 1st, 70% at the 2nd, 61% at the 3rd and 50% at the 4th examination 1% lost	Measured at study baseline	528 participants 323 death, 174 breast cancer mortality, 126 other causes of death including 43.6% death from cardiovascular disease and 25.6% other cancers	Cancer registry	>=30 vs. 20-25 Kg/m^2	1.82 (1.11–2.99)	Age, smoking, physical activity , alcohol intake, hormonal therapy, tumor stage, menopausal status, parity, education, treatment
Nichols HB (2009)	Collaborative Women's Longevity Study United States	Study recruitment: 1988-2001; Cancer diagnosis: 1988-1999; Study follow up: until 2005 Recruited 5.8 years after breast cancer diagnosis	Follow-up of cases of case-control studies	3993 participants 58.4 years (mean) 20 - 79 years Mostly white: 98%, 28.1% premenopausal; 71.9% postmenopausal HRT use: 38.9% (postmenopausal hormone use)	6.3 years	Invasive nonmetastatic breast cancer; 64.1% local, 24.7% regional, 0.6% distant, 10.6% unknown			40%	Self-reported body weight 1-5 years before diagnosis at study baseline	3993 participants 421 deaths, 121 breast cancer mortality, 95 deaths from cardiovascular disease	Death record	>=30 vs. 18.5-24.9 Kg/m^2	1.42 (0.86-2.36)	Age, tumor stage, time from diagnosis to exposure assessment, family history, smoking, physical activity, menopausal status
Rosenberg L (2009)	Swedish Hormone Replacement Therapy Follow-up Study Sweden	Cancer diagnosis: 1993-1995, Study follow-up: Until 2003 Recruited at diagnosis	Follow-up of cases of population-based case-control study	2640 participants 63.7 years (mean) 50 - 74 years Postmenopausal	9.5 years	Invasive breast cancer, any stages; Tumor grades: 15.3% 1, 41.7% 2, 43% 3 among those with data. About 33% of cases missing data	78.3% ER+, 21.7% ER-; 66.7% PR+, 33.3% PR - among those with data. About 33% of cases missing data 31.8% +ve, 68.2 -ve among those with data		84%	Self-reported data for 1 year before questionnaire, filled in about 4.3 months after diagnosis	2640 participants 354 breast cancer mortality	Death certificate	>30 vs. <25 Kg/m^2	1.20 (0.90-1.60)	Age at diagnosis, alcohol intake, tumor size, nodal status
West-Wright CN (2009)	California Teachers Study United States	Study recruitment: 1995; Cancer diagnosis: 1995-2004; Study follow up: until 2005	Cancer survivors of a population-based prospective cohort study	3539 participants 58.9 years (mean) 26 - 94 years Mostly white: 89.7% Comorbidities: 111 diabetes, 106	9 years	Incident first primary invasive breast cancer; 68.9% localized, 28.4% regional, 1.86 metastatic, 0.8 % missing	72% ER+ve, 12.7% ERve, 15.3% unknown			Self-reported at baseline; PA within the 3 years prior to cohort entry, prior to diagnosis	3539 participants 460 deaths, 221 breast cancer mortality, 69 death from other causes including 24	Death certificate	>=30 vs. <25 Kg/m^2	1.71 (1.16-2.53)	Age, race, tumor stage, total caloric intake, physical activity, number of comorbid conditions and estrogen receptor status

				cardiovascular disease; 24.5 %							death from other cancers, 68 cardiovascular disease deaths; 38 cerebrovascular disease deaths; 28 cardiopulmonary or pulmonary disease deaths; 4 diabetes death				
Caan BJ (2008)	LACE United States	Cancer diagnosis:1997-2000; Study follow up: until 2007 Diagnosed 11–39 months before study enrolment	Prospective cohort study of breast cancer survivors	1692 participants 58.3 years (mean) 18 - 70 years 22.8% premenopausal, 63.8% postmenopausal	83.9 months	Early stage invasive breast cancer; AJCC; 46.7% Stage I, 50.2% Stage II, 3.1% Stage IIIA	69.2% ER+/PR+, 13.6% ER+/ PR-, 1.7% ER-/ PR+, 15.5% ER-/ PR- 63.2% o node+ve, 26.3% 1-3 nodes+ve, 5.7% 4-6 nodes+ve, 1.7% 7-9 nodes+ve, 3.1% >=10 nodes+ve	19% chemotherapy; 24.8% radiotherapy; 38.4% chemo- and radiotherapy; 49.2% mastectomy; 50.8% breast-conserving surgery; 70.9% current tamoxifen users, 6.7% past tamoxifen users	46%	self-reported at baseline; one year pre-diagnosis and also after diagnosis at baseline	1692 participants 162 deaths, 99 breast cancer mortality	Medical records	>=30 vs. <=24.9 Kg/m^2	1.60 (0.90-2.70)	Tumor stage, age at diagnosis, tamoxifen use, treatment, nodal status, estrogen receptor level, progesterone receptor level, smoking, physical activity
Dal Maso L (2008)	Six Italian Regions Follow-up Study Italy	Cancer diagnosis: 1991-1994; Study follow up: until 2005-2006 diagnosed no longer than 1 year before the interview	Follow-up of cases of a case-control study	1453 participants 55 years (mean) 23 - 74 years Among those with data, pre diagnosis data: 45.5 % peri/pre menopausal, 54.9% postmenopausal HRT use: 91.3% never, 8.6% ever	12.6 years	Invasive breast cancer; TNM; 32.7% Stage I, 44.1% stage II, 13.2% stage III-IV, 9.8% unknown	41.5% ER+ve/PR+ve, 3.5% ERve/ PR+ve 45.6% no node+ve, 44.2% node+ve, 10.1%		2.70% lost	Self-reported at study baseline; height, weight 1 year before cancer diagnosis and at different ages; hip and waist measured at interview	1453 participants 503 deaths, 398 breast cancer mortality, 6.2% death from other cancers, 7.4% from cardiovascular disease	Cancer registry	>=30 vs. <=24.9 Kg/m^2	1.38 (1.02-1.86)	Region, age at diagnosis, year of diagnosis, TNM stage, receptor status
Cleveland R (2007)	Long Island Breast Cancer Study Project United States	Cancer diagnosis:1996-1997; Study follow up: 2002- 2004	Follow up of cases of a case-control study	1508 participants 58.8 years (mean) 25 - 98 years Mostly white 32.2% premenopausal, 67.8% postmenopausal HRT use: 86.8% ever, 13.2% never	66.7 months	84.4% invasive and 15.6% In situ	26.7% ER-ve, 73.3% ER +ve, 35.8% PR-ve, 64.2% PR+ve 73.7% no nodes involved, 26.3% nodes involved	Radiation therapy, chemotherapy, hormone therapy	410 patients lost	Self-reported shortly after diagnosis; weight and height at each decade of life from age 20 years until 1 year before diagnosis	1508 participants 196 deaths (of which 21% from cardiovascular disease), 127 breast cancer mortality, 9 death from brain and lung metastases, analysis included postmenopausal women only	National Death Index	Per 1 Kg/m^2 increase >30 vs. <24.9 Kg/m^2	1.07 (1.02-1.13) 1.88 (1.04-3.34)	Age at diagnosis, hypertension

Reeves KW (2007)	Study of Osteoporotic Fractures United States	Study recruitment:1986-1988; Study follow up: until 2006 Diagnosed 7.5 years on average after enrolling into SOF	Cancer survivors of population-based prospective cohort study	533 participants 78 years (mean) >=65 years Caucasian All postmenopausal 6.3% diabetes, Comorbidities: 0.9% history of congestive heart failure	8.1 years	15% In situ, 75.2% Stage I or II, 5.1% Stage III/IV, 4.7% unknown	68.9% ER+ve, 10.5% ER-ve, 20.6% unknown; 54% PR+ve, 23.5% PR-ve, 22.5% unknown		1% lost	Measured at clinical examinations at study baseline 128 participants	533 participants 206 deaths, 45 breast cancer mortality, 68 deaths from any cancer, 56 deaths from cardiovascular disease	Death certificate	Age 65 years Age 70 years Age 75 years Age 80 years Age 85 years 34 vs. 22.6 Kg/m^2	4.93 (1.12-21.7 2.44 (0.90-6.64) 1.21 (0.59-2.49) 0.60 (0.25-1.43) 0.30 (0.08-1.09)	Smoking, tumor stage, ER status Highest vs lowest analysis only; missing number of events and at-risk per category
Kroenke C (2005)	Nurses' Health Study United States	Cancer diagnosis: 1976 - 2000, Study follow-up: Until 2002	Cancer survivors of population-based prospective cohort study	5204 participants 30 - 55 years	9 years	Invasive non metastatic breast cancer, any stages; 86.9% tumor size >2cm	73.2% ER+ 85.2% +ve	Chemotherapy: 63.9% yes; Tamoxifen: 64.8% yes		Self-reported at cohort baseline; pre and post-diagnosis	5204 participants 860 deaths, 533 breast cancer mortality	Family+ National Death Index	>=30 vs. 21-22 Kg/m^2	1.09 (0.80-1.48)	Age, oral contraceptive, birth index, menopausal status, age at menopause, hormonal therapy, smoking, tumor size, nodal status, chemotherapy, tamoxifen use, protein intake
Whiteman MK (2005)	Cancer and Steroid Hormone Study United States	Cancer diagnosis:1980-1982; Study follow up: until 1997	Follow-up of cases of a population-based case-control study	3924 participants 20 - 54 years White: 87.5%, black: 12.5% and other 47% premenopausal, 18% postmenopausal Comorbidities: 37.2% due to diabetes, high blood pressure, blood clots, kidney disease, gallbladder disease, heart attack, paralysis, rheumatoid arthritis, stroke, other cancer	14.6 years	Primary invasive incident breast cancer; 51.4% local, 45.4% regional, 3.2% distant		22.4% radiation therapy; info on adjuvant treatment not available	80.40% 4.10% lost	Self-reported at interview on average 2.5 months of diagnosis; BMI at age 18 years and after diagnosis	3924 participants 1671 deaths, 1, 347 breast cancer mortality	SEER record	>=30 vs. <=22.9 Kg/m^2 adult BMI	1.34 (1.09-1.65)	Age at diagnosis, race, radiotherapy, history of benign breast disease, education, menopausal status, tumor stage
Enger S (2004)b	University of Southern California Cancer Surveillance Program United States	Cancer diagnosis: 1983-89, Study follow-up: Until 2000	Follow-up of cases of population-based case-control study	717 participants years (mean) <=40 years White or Hispanic Premenopausal	10.4 years	Stages: 9.9% in situ, 47.4% localized, 39.1% regional, 3.6% distant metastasis	41.1% +ve, 57.3% -ve, 1.5% unknown		76.80%	Self-reported data for age 18, a year prior to diagnosis in interview at study baseline	717 participants 251 breast cancer mortality, 2 deaths from coronary/CVD, 10 other causes of deaths	Cancer registry + death certificate	>=24.9 vs. <20.4 Kg/m^2	0.76 (0.53-1.07)	Age, tumor stage, physical activity
Maehle BO (2004)	Norwegian Health Surveys Follow-up Study Norway	Study recruitment:1963-1975; Cancer diagnosis: 1970-1990; Study	Cancer survivors of a population-based prospective cohort study	1211 participants 60.85 years (mean) 28 - 90 years, participants of a health screening cohort	189 months		42% node+ve metastases	Detailed information about adjuvant treatment was not available	Few patients lost	Measured at screening programme; on average 12.5 years before diagnosis	1211 participants 471 breast cancer mortality, 275 deaths from other	Death record	Q5 vs. Q1	1.38 (1.04-1.84)	Tumor size, nodal status, nuclear grade Highest vs lowest analysis only; missing number of events per category

		follow up: until 2000									causes				
Schairer C (1999)	Breast Cancer Detection Demonstration Project United States	Study rec ruitment: 1973-1980 Cancer diagnosis: 1973-1981, Study follow-up: Until 1995	Follow-up of a breast cancer screening cohort	2614 participants years (mean) Multi-ethnic Postmenopausal HRT use: 122 (15.3%) current users, 82 (8.3%) non-users, 72(10.4%) past users	14.1 years	Incident breast cancer, any stages including in situ cancer			72.3%, 87% at different occasions	Self-reported at baseline of screening study	2614 participants 978 deaths, 486 breast cancer mortality	Death certificate	>=26.15 vs. <=21,28 Kg/m^2	1.60 (1.20-2.10)	Tumor stage, race
Galanis (1998)	Multiethnic Cohort in Hawai, 75-80	Study recruitment: 1975-1980; Study follow up: until 1994	Prospective cohort study of cancer survivors	378 participants 43 years (mean) 86 (22.75%) premenopausal cases, 292 (77.25%) postmenopausal cases	14.9 years					Self-reported; height and weight before diagnosis	378 participants 34 breast cancer mortality	Cancer registry	>25.8 vs. <22.6 kg/m^2	2.2 (0.9-5.4)	Age, ethnicity, tumor stage, education, alcohol intake
Jain M (1994)b	National Breast Screening Study Canada	Study recruitment: 1980-1985; Cancer diagnosis:1981-1982; Study follow up: until 1988	Randomised controlled trial of mammography screening trial	1033 participants 52.2 years (mean) 40 - 66 years Trial group screened; 48% detected by screening	5.2 years	Invasive breast cancer; any stage	341 node+ve women			Measured during screening prior to diagnosis	1033 participants 133 breast cancer mortality	Death certificate	Per 1 Kg/m^2 increase >27.34 vs. <22.22 Kg/m^2	0.99 (0.95-1.03) 0.78 (0.48-1.22)	Age at diagnosis, nodal status
Tornberg S (1993)	Swedish General Health Screening Cohort Sweden	Study recruitment: 1963-1965, Cancer diagnosis: before 1983, Study follow-up: Until 1987	Follow-up of a health screening cohort	1170 participants 62.4 years (mean) White	4 Years (max)	Stages I-IV			80%	Before diagnosis; examined during health screening	1170 participants 407 breast cancer mortality	Death record	>=28 vs. <=21 Kg/m^2	1.70 (1.20-2.30)	Age
Tretli S (1990)	Norwegian Health Surveys Follow-up Study Norway	Cancer diagnosis: 1963-1975; Study follow up: until 1981	Cancer survivors of a population-based prospective cohort study	8427 participants 30 - 69 years, participants of a health screening cohort	4.3 years	Any TNM stages I-IV; 47.7% stage I, 33.3% stage II, 5.5% stage III, 7.5% stage IV			85%	Measured during screening	8427 participants 2383 breast cancer mortality, 430 death from other causes	Death certificate	Stage I Stage II Stage III Stage IV Q5 vs. Q1	1.70 (1.29-2.25) 1.42 (1.17-1.73) 0.97 (0.63-1.47) 1.09 (0.82-1.45)	Highest vs lowest analysis only; missing exposure values

Table 91 Table of excluded studies on BMI before diagnosis and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments / Exclusion reason
Jain M (1997)	National Breast Screening Study Canada	Cancer diagnosis: 1982-1985, Study follow-up: Until 1992 Recruited between1980-1985 and diagnosed after July 1982	Randomised controlled trial of mammography screening trial; ancillary analysis	676 participants 49.9 years (mean) 40 - 59 years 57% postmenopausal (at enrollment) 48.4% cases detected through mammography	7.7 years	Invasive breast cancer; any stage				Pre-diagnosis; diet history completed at enrollment	83 deaths, 76 breast cancer mortality, 7 other causes of deaths	Death certificate	With ER status With PR status With nodal status With tumour size Per 1 kg/m^2 increase	1.03 (0.97-1.10) 1.06 (0.98-1.13) 0.98 (0.92-1.03) 0.97 (0.91-1.03)	Age at diagnosis, smoking, when appropriate ER status, PR status, nodal status, tumour size Superseded by Jain, 1994b
Maehle (1996)	Norwegian Health Surveys Haukeland Hospital Study Norway	Study recruitment: 1963-1975; Cancer diagnosis: 1970-1990; Study follow up: until 1990	Cancer survivors of a population-based prospective cohort study	1238 participants 63 years (mean) 28 – 91 years, participants of a health screening cohort	95 months	Any stages breast cancer		Tamoxifen: 1/3 of cases with hormone receptor +ve after 1982		Measured 12.5 years before presentation of the disease	339 breast cancer mortality and 123 death from other diseases	Vital statistics registry	Q5 vs. Q1	1.37 (0.99-1.90)	Nodal status, tumor size, mean Nuclear Area (MNA) Superseded by Maehle, 2004
Eley JW (1994)	Black/White Cancer Survival Study United States	Cancer diagnosis: 1985-1986, Study follow-up: Until 1990 Post-diagnosis	Retrospective cohort study	1130 participants 20.0 - 79.0 years Black and White 55% comorbidity free	5 years	Invasive breast cancer, AJCC stages: 25.5% I, 46.2% II, 17.1% III, 6.5% IV, 4.8% unknown	38.5% +ve, 48.2% -ve, 13.3% unknown		2 patients lost	Self reported post-diagnosis BMI at baseline or from medical records	1130 participants 350 deaths, 237 breast cancer mortality	Active follow-up and review	High vs. low-normal	2.2 (1.5-3.2)	Unadjusted results
den Tonkelaar I (1995)	DOM-project The Netherlands	Cancer diagnosis:1974-1988; Study follow up: until 1990	Cancer survivors of a population-based prospective cohort study	241 participants All postmenopausal	9.1 years	Any stages breast cancer;72.2% tumour diameter < 2.0 cm, 22.8% tumour diameter > 2 cm, 5% unknown	53.5% ER+ve, 14.9% PR-ve, 31.5% unknown 62.7% axillary node-ve, 32.4% axillary node+ve, 5.0% unknown	94% of patients were operated before 1986, when adjuvant anti-estrogen therapy was not generally used	1.7% emigrated	Measured during screening			>=26 vs. <26 kg/m^2	Incident density ratio 0.95 (0.51-1.78)	Unadjusted results
Zhang S (1995)	Iowa Women's Health Study United States	Study recruitment:1986; Study follow up: until 1991	Cancer survivors of population-based prospective cohort study	698 participants 55 - 69 years Mostly white All postmenopausal	2.9 years	Unilateral breast cancer; 10% in situ, 58% local, 28% regional, 3%distant, and 1% unknown; 55% tumour size <2cm, 33% size >=	Among those with data: 85% ER+ve and 72% PR+ve		42.60% <1% migration rate	Self reported questionnaire within 6 years before diagnosis	698 participants 56 deaths, 40 breast cancer mortality (among the causes of death) and 2 death from coronary heart	Death certificates, National death index	28.9-45.9 vs. 16-24.6 Kg/m^2	1.8	Age, smoking, education, tumor stage, ER status, tumor size Insufficient data – highest vs. lowest comparison only, missing CI

						2cm and 11% unknown					disease				
Nomura AM (1991)	Hawaiian Caucasian, Japanese Follow-up Study, United States	Cancer diagnosis:1975-1980; Study follow up: until 1987	Follow-up of cases of a hospital-based case-control study	343.0 participants 45.0 - 74.0 years Japanese; Caucasian	12.5 years (max)	Japanese: 12% in situ, 63% localized, 24%regional, 1% distant; Caucasian: 5% in situ, 56% localized, 36% regional, 3% distant			82.70% 10% of the Caucasian cases and 3% of the Japanese	Interviewed after diagnosis in mean of 2.2 months;	161 Caucasian, 182 Japanese; 78.6% and 86.6% survival rate	Cancer registry	High vs low Caucasian Japanese	1.15 (0.51-2.62) 3.53 (1.25-10.00)	Tumor stage,menopausal status,Hormonal therapy, total fat intake Obesity index

BMI less than 12 months after diagnosis and breast cancer mortality

Methods

Twenty studies were identified. Only five studies could be included in the linear dose-response meta-analysis and ten studies could be included in the highest versus lowest meta-analysis. Four studies reported results separately on the underweight group and were included in the underweight versus normal weight meta-analysis. This included Moon et al. (2009) that reported on the comparison of underweight to normal weight only.

Three studies (Rohan, 1993; Majed, 2008; Allin, 2011) provided unadjusted results and were not included in the analyses, all of which reported a statistically significant increased risk in dying of breast cancer (RR for ≥ 30 vs. < 23 kg/m^2 = 3.39; 95% CI 1.84-6.25, RR for ≥ 30 vs. < 30 kg/m^2 = 1.35, 95% CI 1.19-1.54; and RR for ≥ 30 vs. 18.5-24.9 kg/m^2 = 1.62, 95% CI 1.05-2.52, respectively). In addition, Allin et al. (2011) observed a non-significant association with underweight when compared to normal weight (HR for < 18.5 vs. 18.5-24.9 kg/m^2 = 1.10; 95% CI 0.48-2.52). Coates et al. (1990) and Litton et al. (2008) were excluded from the analyses because only breast cancer survival rates by BMI groups were presented (Wilcoxon test p < 0.001and log rank test p = 0.048, respectively). Bastarrachea et al. (1994), assessed obesity by percentage ideal weight, was also excluded from the analyses on BMI. In this study, a statistically significant increased risk was observed (RR for >20% ideal weight vs. ≤ 20% ideal weight = 1.36; 95% CI 1.06-1.76). Two studies (Hebert, 1998; Vitolins, 2008) reported dose-response results and were unable to include in the highest versus lowest meta-analysis. Other eight studies that were included in the highest versus lowest meta-analysis but not in the dose-response meta-analysis because numbers of events and/or non-events per BMI category were missing (Dignam, 2003; Dignam, 2006; Ewertz, 2011; Maskarinec, 2011) and results were on two BMI categories only (Mason, 1990; Katoh, 1994 Chang, 2000; Sparano, 2012).

We included the BMI categories as defined by the studies. The reference category in most studies was the normal weight group, but may include underweight women. BMI could be assessed at or around diagnosis, e.g. several months but less than a year after diagnosis or just before cancer treatment.

Main results and heterogeneity

The summary RR per 5 kg/m^2 was 1.18 (95% CI 1.11-1.25; 5 studies). No evidence of heterogeneity was observed (I^2 = 0%; p = 0.57). Visual inspection of the funnel plot suggested small studies with an inverse association are missing (Egger's test p = 0.18), but the number of studies is very small. There is no evidence of strong influence from any individual study on the summary estimate, which remained statistically significant when each study was omitted in turn in the influence testing, ranging from 1.16 (95% CI 1.08-1.25) when Vitolins et al. (2008) was excluded to 1.19 (95% CI 1.12-1.28) when Olsson et al. (2009) was excluded. All studies except Sestak et al. (2010) comprised pre- and postmenopausal women, when excluded this postmenopausal study, the summary RR became 1.19 (95% CI 1.10-1.29).

Summary RRs were not materially different in a sensitivity analysis by timing of exposure assessment (RR 1.19; 95% CI 1.04-1.36; I^2 = 17.1%; p = 0.30; 3 studies for BMI assessed at diagnosis, and RR 1.18, 95% CI 1.09-1.27; I^2 = 0.0%; p = 0.46; 2 studies for BMI assessed shortly after diagnosis/before treatment).

In the highest versus lowest meta-analysis, the summary RR was 1.35 (95% CI 1.23-1.48; I^2 = 8.6%; p = 0.37; 11 studies). When stratified by menopausal status, no significant association was observed in premenopausal women, but only two studies had provided data (RR for highest vs. lowest = 0.96; 95% CI 0.42-2.06; I^2 = 77.4%; p = 0.04). For postmenopausal women, a significant increased risk of dying of breast cancer was observed (RR 1.54; 95% CI 1.29-1.84; I^2=0%; p = 0.72; 4 studies).

Two studies could be included in the highest vs. lowest meta-analysis of ER positive breast cancer patients. A statistically increased risk was observed (RR for highest vs. lowest = 1.31; 95% CI 1.03-1.67; I^2 = 34.6%; p = 0.22). Only one study reported results in ER negative breast cancer patients (Dignam, 2006). A non-significant increased risk (RR for ≥ 35 vs. ≤ 24.9 kg/m^2 = 1.13; 95% CI 0.85-1.50) was observed in this study.

For underweight compared to normal weight, the summary RR was 1.52 (95% CI 1.26-1.84; I^2 = 0%; p = 0.42; 4 studies).

Study quality

Number of events ranged from 43 to 5868 breast cancer deaths. Maskarinec et al. (2011) accrued 43 breast cancer deaths (115 deaths in total) in an average of 13.2 years of follow-up. Hebert et al. had 73 breast cancer deaths (87 deaths in total) while Katoh et al. (1994) had 94 deaths. All other studies had more than 200 breast cancer deaths. Average follow-up ranged from 4.35 years to 13.8 years (166 months), with Newman et al. (1997) being the only study that had less than 5 years (7.3% lost) of average follow-up. Olsson et al. (2009) and Hebert et al. (1998) had a maximum of ten years of follow-up.

Seven studies (Dignam, 2003; Dignam, 2006; Vitolins, 2008; Olsson, 2009; Sestak, 2010; Ewertz, 2011; Sparano, 2012) were ancillary analyses of randomised controlled trials. The other seven studies (Mason, 1990; Katoh, 1994; Newman, 1997; Hebert, 1998; Chang, 2000; Moon, 2009; Maskarinec, 2011) were cohorts of breast cancer survivors. Breast cancer cases were diagnosed in 1961-1991 (Olsson, 2009), from the 1970s (Mason, 1990; Katoh, 1994; Newman, 1997; Chang, 2000), from the 1980s (Hebert, 1998; Dignam, 2003; Dignam, 2006; Vitolins, 2008; Moon, 2009), and from the 1990s (Maskarinec, 2011; Sparano, 2012).

One studies (Maskarinec, 2011) included *in situ* and invasive breast cancers. Twelve studies included invasive breast cancer (Katoh, 1994; Newman, 1997; Hebert, 1998; Chang, 2000; Dignam, 2003; Dignam, 2006; Vitolins, 2008; Olsson, 2009; Sestak, 2010; Moon, 2009; Ewertz, 2011; Sparano, 2012). Chang et al. (2000) involved inflammatory breast cancer cases only. The trials conducted by Dignam et al. consisted only of ER-negative and lymph node-negative breast cancer cases (Dignam et al. 2006) and ER-positive and lymph node-negative breast cancer cases (Dignam et al. 2003). Also, the

trials conducted by Vitolins, et al. (2008) and Sestak et al. (2010) involved stage II-III lymph node-positive cases and ER-positive and/or PR-positive cases respectively.

Anthropometric data were assessed in breast cancer patients. Eight studies (Mason, 1990; Katoh, 1994; Newman, 1997; Hebert, 1998; Chang, 2000; Moon, 2009; Ewertz, 2011; Maskarinec, 2011) assessed BMI at diagnosis. Five studies (Dignam 2003; Dignam 2006; Vitolins, 2008; Sestak, 2010; Sparano, 2012) assessed BMI a few months but less than one year after diagnosis or before cancer treatment. Two studies (Vitolins, 2008; Sestak, 2010) used measured data. Two studies (Hebert, 1998; Sparano, 2012) used self-reported data. Seven studies took data from medical records (Mason, 1990; Katoh, 1994; Newman, 1997; Chang, 2000; Moon, 2009; Maskarinec, 2011; Ewertz, 2011). Olsson et al. (2009) used both measured and self-reported data. Method of assessment was not clear in Dignam et al. (2003; 2006).

Katoh et al. (1994) and Sestak et al. (2010) were studies on postmenopausal women. All other studies included women of all ages. Vitolins et al. (2008) provided unadjusted result but the analysis was based on data from randomised controlled trial of adjuvant treatment in stage II and III breast cancer patients only. Results from Sestak et al. (2010) and Sparano et al. (2012) were adjusted for cancer treatment only and race only respectively. All other results were multivariate adjusted. Olsson et al. (2009) conducted sub-group analysis by mammogram status.

Published meta-analysis

Two meta-analyses on obesity less than 12 months after diagnosis and total and breast cancer mortalities were published in recent years (Protani, 2010; Niraula, 2012).

Protani et al (2010) reported a summary RR of 1.33 (95% CI 1.19-1.50) for obese versus non-obese (measured by BMI or waist-hip-ratio) in the risk of breast cancer mortality, with high heterogeneity between studies (I^2 = 58.1%; p = 0.001; 15 studies; 16 estimates).

Niraula et al. (2012) observed increased risks for obesity and breast cancer mortality by hormone receptor status or menopausal status. The summary RRs for obese versus non-obese were 1.36 (95% CI 1.20-1.54; 7 studies) and 1.46 (95% CI 0.98-2.19; 6 studies) in women with ER/PR positive cancers and ER/PR negative cancers respectively ($p_{heterogeneity}$ = 0.95), and 1.18 (95% CI 0.82-1.70; 4 studies) and 1.38 (95% CI 1.11-1.71; 4 studies) in pre- and postmenopausal women respectively ($p_{heterogeneity}$ = 0.35).

All studies except one, reviewed by Protani et al. (2010) were identified and included in the report. Majority of the studies were reviewed under BMI less than 12 months after diagnosis and total mortality, or breast cancer mortality. Some studies were in a different section (waist-hip-ratio), or under different timeframes (BMI before or after diagnosis). The exception was the breast cancer mortality study by Petrelli et al. (2002). An increased risk for breast cancer mortality (RR for ≥ 40 vs 18.5-20.49 kg/m^2 = 3.08; 95% CI 2.09-4.51; 2852 breast cancer deaths) was observed in this cohort of postmenopausal women who were healthy at study baseline.

All studies reviewed by Niraula et al. (2012) were also included in the report.

Figure 117 Highest versus lowest forest plot of BMI less than 12 months after diagnosis and breast cancer mortality

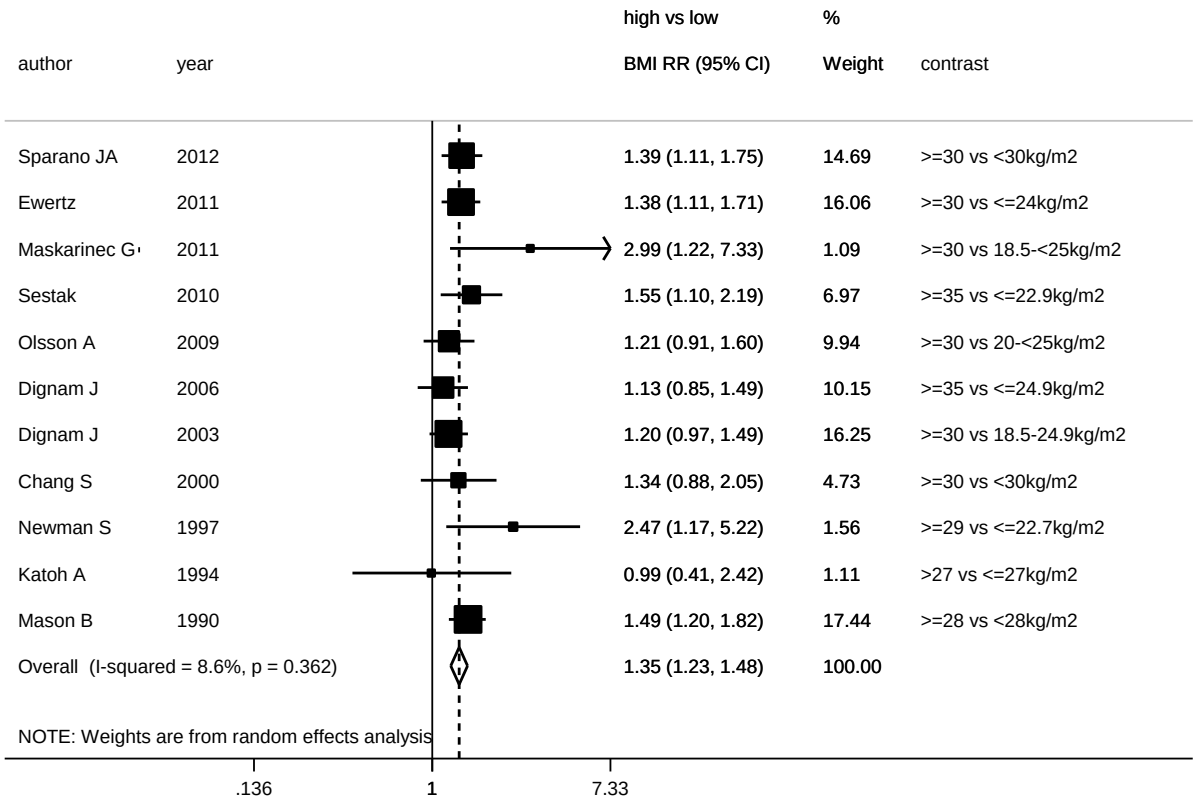


Figure 118 Highest versus lowest forest plot of BMI less than 12 months after diagnosis and breast cancer mortality by menopausal status

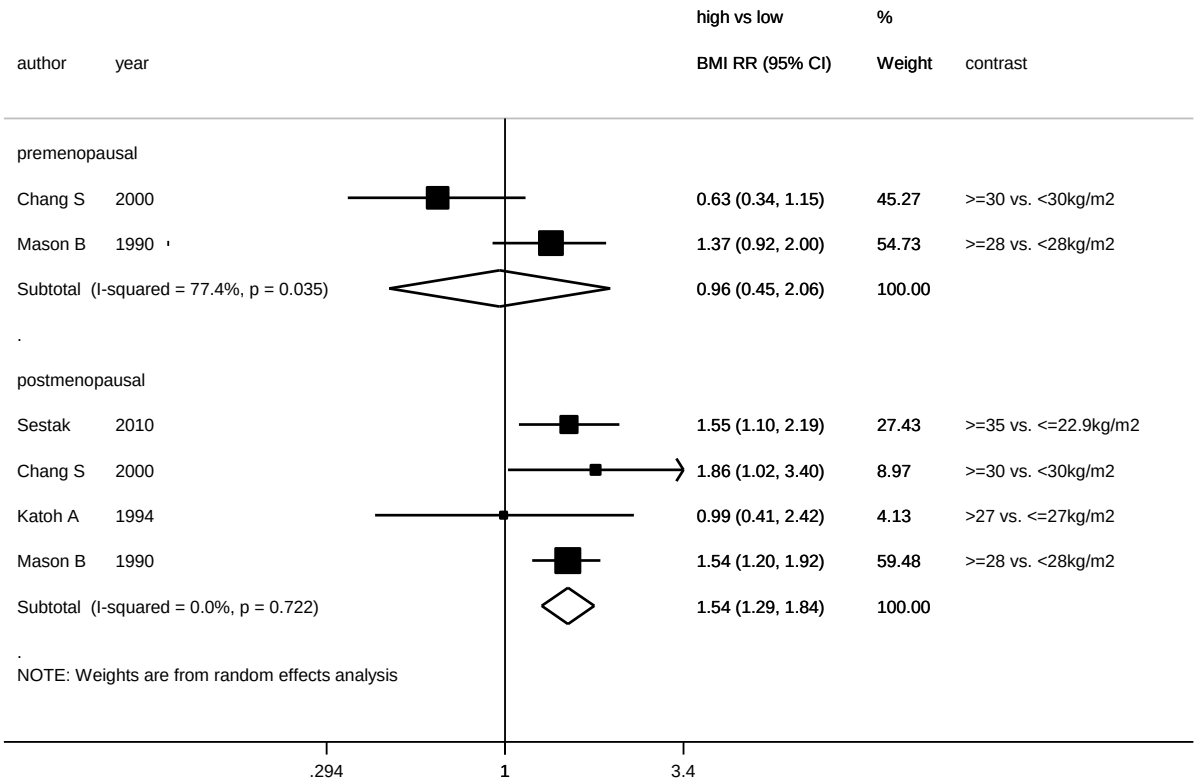


Figure 119 Highest versus lowest forest plot of BMI less than 12 months after diagnosis and breast cancer mortality by estrogen receptor status

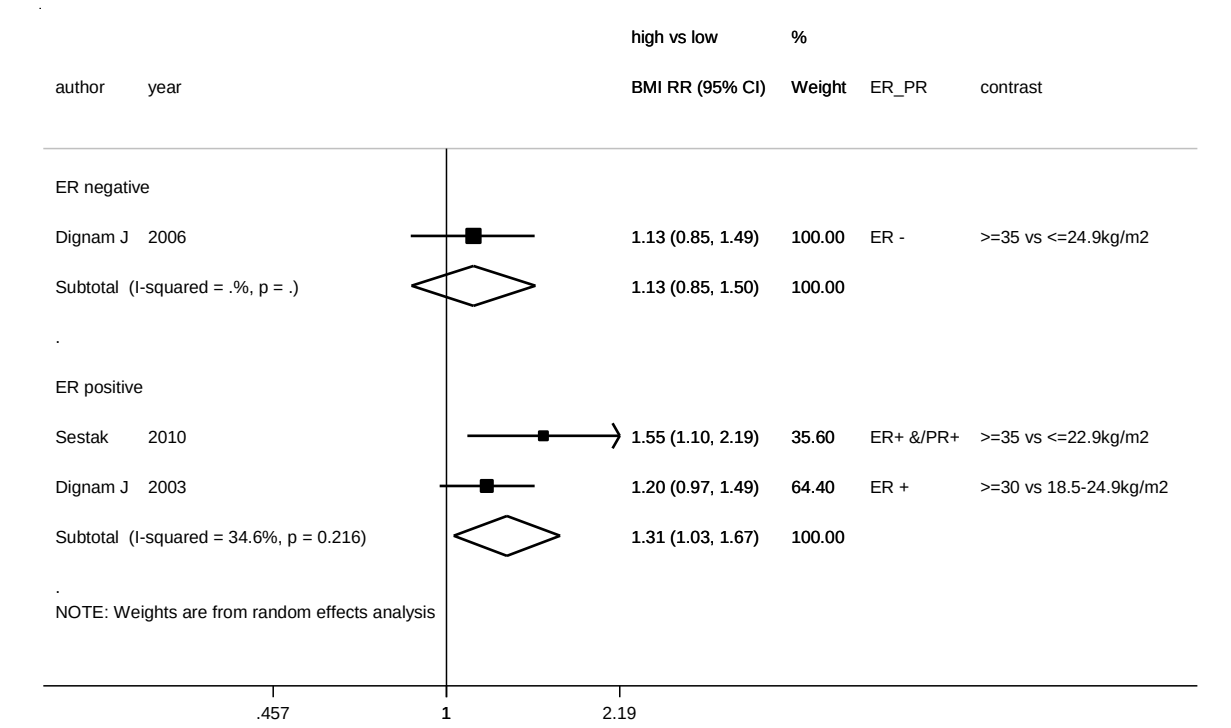


Figure 120 Forest plot of underweight versus normal weight less than 12 months after diagnosis and breast cancer mortality

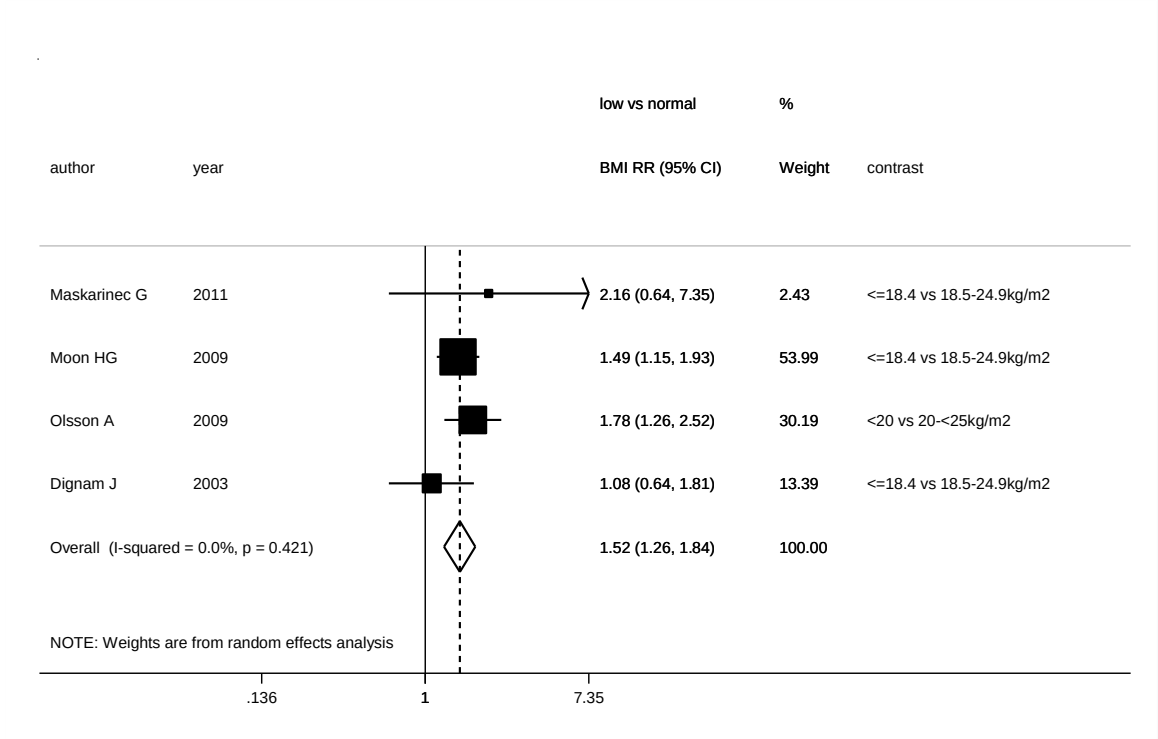


Figure 121 Linear dose-response meta-analysis of BMI less than 12 months after diagnosis and breast cancer mortality

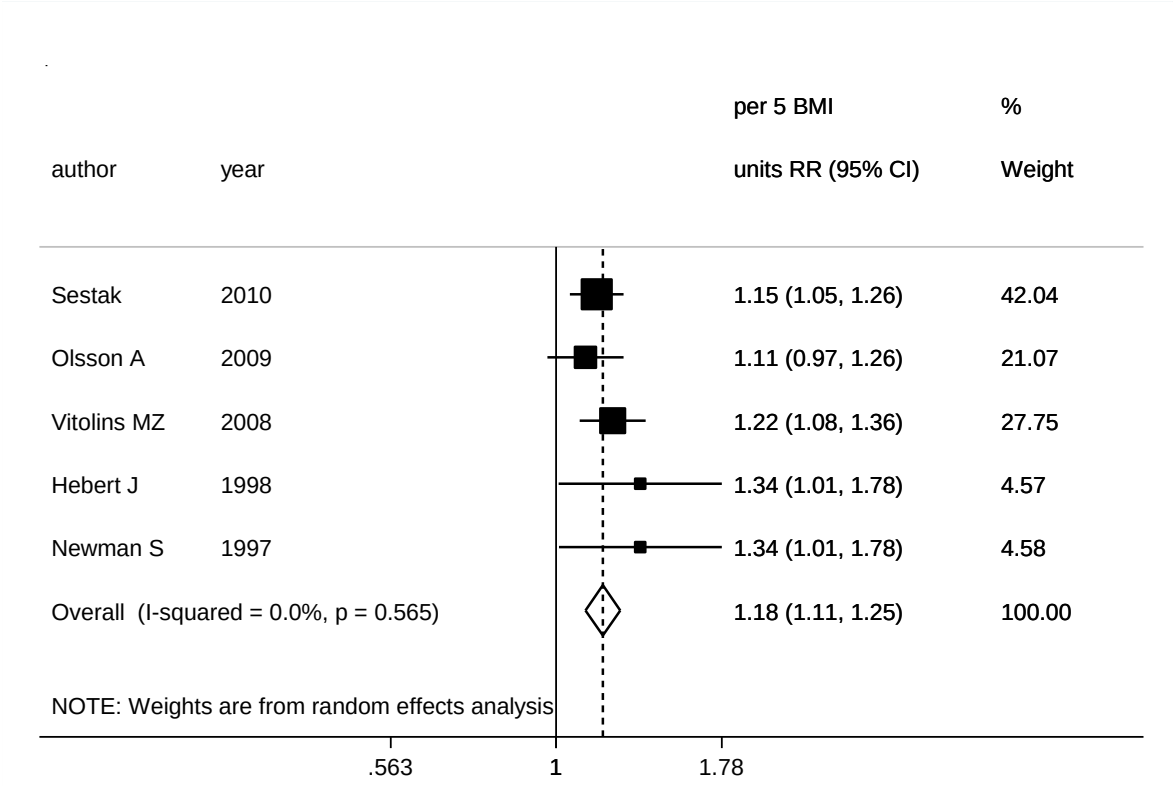
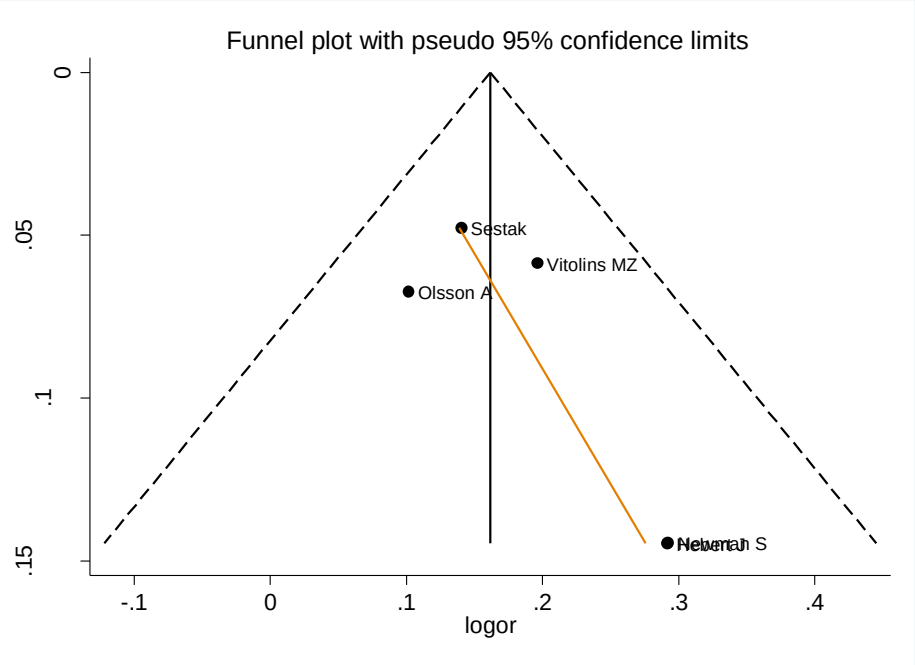


Figure 122 Funnel plot of studies of BMI less than 12 months after diagnosis and breast cancer mortality



Each dot represents the logarithm of relative risk estimate against standard error as a measure of study size. Solid line is the logarithm of summary risk estimate from the meta-analysis. Dashed lines are its 95% confidence interval.

Egger’s test p = 0.18

Figure 123 Individual dose-response graph of BMI less than 12 months after diagnosis and breast cancer mortality

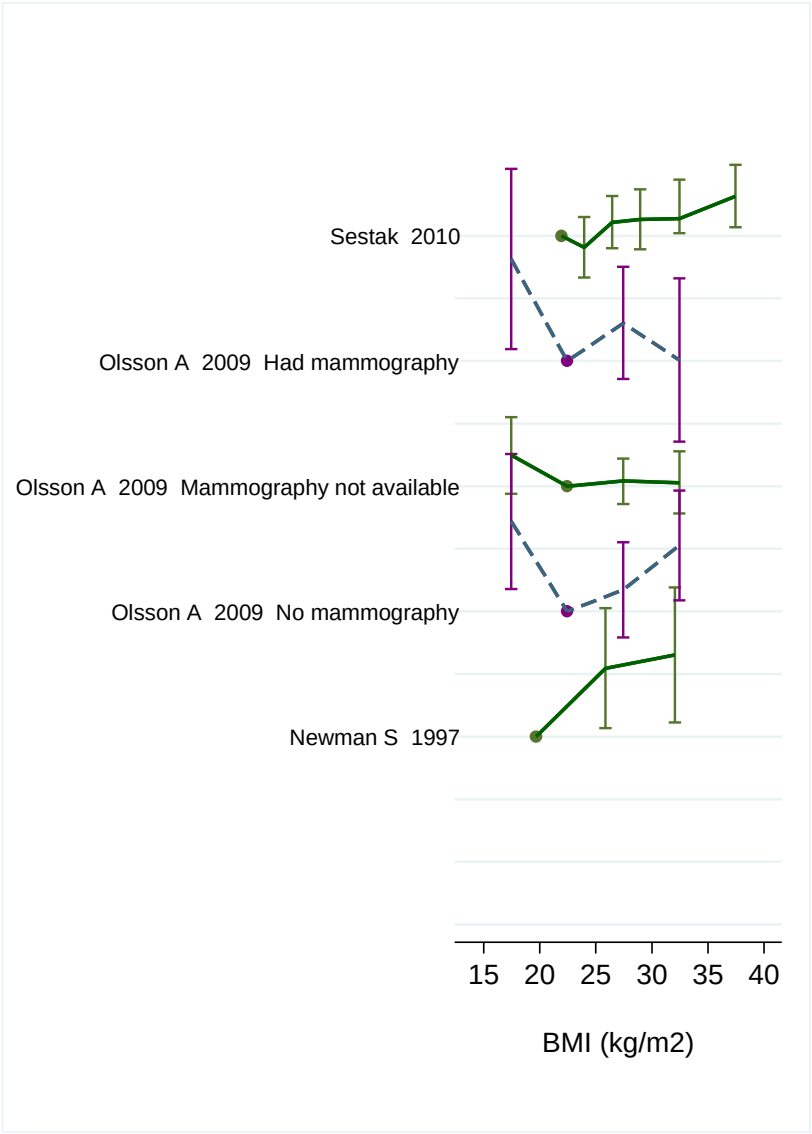


Figure 124 Linear dose-response meta-analysis of BMI less than 12 months after diagnosis and breast cancer mortality

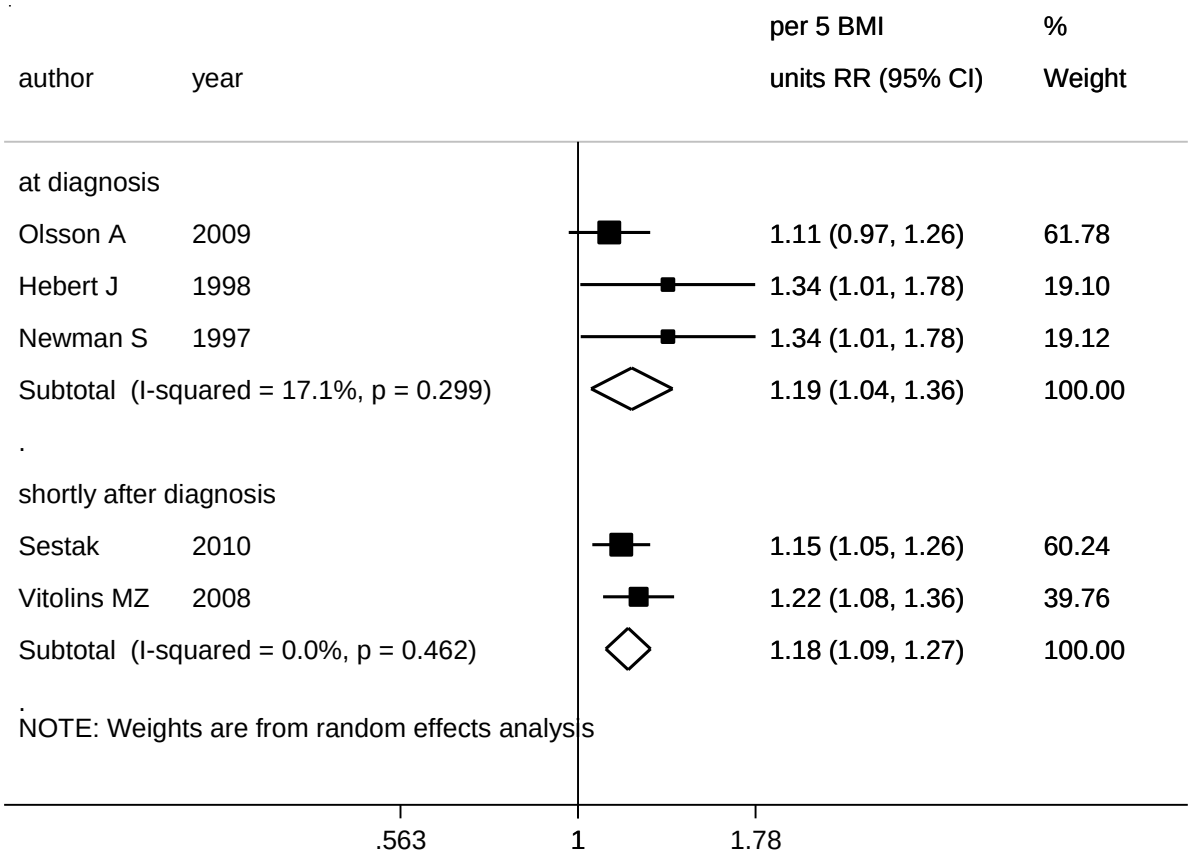


Table 92 Table of included studies on BMI less than 12 months after diagnosis and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments / Remarks
Sparano JA (2012)	Phase III Taxanebased Drug Trial E1199 United States	Study recruitment: 1999-2002	Randomised controlled trial of chemotherapy; ancillary analysis	4817 participants 22 - 84 years Black and White	95 months	AJCC; 31.9% of black patients, 17.2% of non-blacks patients have triple-negative disease; Stage I-III	71.4% ER/PR+ve, 27.1% ER/PR-ve, 1.5% unknown / 11.5% 0node+ve, 55.4% 1-3 nodes+ve, 22.7% 4-9 nodes+ve, 9.6% >=10 nodes+ve, 0.6% unknown	Surgery (among those with data): 99% breast-sparing surgery, 1% mastectomy; Radiation therapy: 56.1% given, 43.9% not-given; Endocrine therapy given (among those with data): 32.8% tamoxifen alone, 56.3% tamoxifen and then aromatase inhibitor,		Self-reported at the time of registration for trials	4817 participants 904 deaths, 704 breast cancer mortality (577 deaths from BC and 127 deaths after breast cancer recurrence), 119 deaths from other causes, 81 unknown causes of death	Active follow-up and review	>=30 vs. <30 Kg/m^2	1.39 (1.11-1.75)	Race / Highest vs. lowest analysis only: two BMI categories only
Ewertz (2011)	Danish Breast Cancer Cooperative Group Denmark	Study follow up: until 2008	Follow up of cases of randomised controlled trials of adjuvant treatment	18967 participants 39 - 70 years 18688 (34.7%) premenopausal and 35128 (65.3%) postmenopausal	7.1 years	Early stage - 14077 patients had ductal grade 1, 19456 grade 2, 9282 grade 3, 5532 lobular breast cancer	9780 ER-ve, 32276 ER+ve, 11760 unknown / 29660 with 0 +ve node, 15486 with 1-3 +ve nodes, 8666 with 4+ nodes, 4 unknown	22968 patients had no adjuvant treatment, 10230 chemotherapy, 16148 endocrine therapy, 4470 combined therapy	Complete follow-up for first events (loco regional recurrences and distant metastases)	From medical records; weight and height at diagnosis	For those with BMI data, 18967 participants 5868 death from breast cancer and 1529 death from unknown causes	Death certificate	>=30 vs. <=24 Kg/m^2 >10 years follow-up	1.38 (1.11-1.71)	Age, menopausal status, tumor size, nodal status, tumor grade, histology , ER status, fascia invasion, protocol year, systemic therapy / Highest vs. lowest analysis only: missing numbers of events and at-risk per category
Maskarinec G (2011)	Patterns of Care and Outcomes Breast Cancer Follow-up Study Hawai	Cancer diagnosis: 1995-1996, Study follow-up: Until 2009	Prospective cohort of breast cancer survivors	382 participants 59.3 years (mean) Multi-ethnic Close to 30% had either CVD, pulmonary disease, liver disease, neuromuscular/skeletal disorders, or kidney disease	13.2 years	Stages 0-IV		Adhered to treatment guidelines according to Physicians Data Query, no other details	48.20%	From medical records	382 participants 115 deaths, 43 breast cancer mortality, 72 other causes of deaths	Cancer registry	>=30 vs. 18.5-<25 Kg/m^2	2.99 (1.22-7.33)	Ethnicity, age at diagnosis, menopausal status, adherence to treatment guidelines, tumor stage, hormone receptor status, toxicity, comorbidity, health insurance / Highest vs. lowest analysis only: missing numbers of events and at-risk per category
Moon HG (2009)	KBCR, SNUHBCC Database Study, Korea Korea	Breast surgery: 1982-2006	Retrospective cohort study	29043 participants 48 years (mean)		Nonmetastatic, invasive breast cancer; histologic grades of KBCR patients: 62.8% 1-2, 37.2% 3; histologic grades of SNUHBCC patients: 57.1%	KBCR: 59% ER+, 41% ER-, 53.7% PR+, 46.3% PR-; SNUHBCC: 58% ER+, 42% ER-, 46.6% PR+, 53.4% PR-	Chemotherapy: 79.6% yes, 20.4% no KBCR patients, 73.4% yes, 26.6% no SNUHBCC; Hormonal treatment: 62.5% yes, 37.5% no KBCR patients,		From hospital records	17278 participants	Cancer registry	KBCR data: <18.4 vs. 18.5-24.9 Kg/m^2	1.49 (1.15-1.93)	. Not included in H vs L because HRs were for unerweght versus normal weight

						grade 1-2, 42.9% grade 3	KBCR: 43% +ve, 57% -ve; SNUHBCC: 42.3% +ve, 57.7% -ve	50.7% yes, 49.3% no SNUHBCC							
Sestak (2010)	The Arimidex, Tamoxifen Alone or in Combination (ATAC) United Kingdom		Randomised controlled trial of adjuvant treatment trial	4939 participants All postmenopausal	100 months	Early-stage breast cancer	All ER+ve and/or PgR +ve)	Participants of adjuvant treatment (anastrozole alone, tamoxifen alone, or combined) trial		Measured at baseline after diagnosis	4939 participants, 481 death after breast cancer recurrence, 504 death without breast cancer recurrence	Trial medical staff (blinded)	>=35 vs. <=22.9 Kg/m^2	1.55 (1.10-2.19)	Age, mastectomy, tumor size, tumor grade, nodal status, chemotherapy, radiotherapy, region
Olsson A (2009)	Malmo Mammographic Screening Trial Sweden	Cancer diagnosis:1961-1991; Study followup: until 2006	Randomised controlled trial of mammography screening	2794 participants 45 - 69 years Mammographic screening trial; 656 women invited to screening	10 Years (max)	Invasive breast cancer; any stages including distant metastasis				Measured (up until 1982 yr) and selfreported (after 1982yr) at diagnosis and recorded in clinical notes	2794 participants 1318 deaths including 862, 210 and 246 in pre-screening group, invited to screening and control groups, respectively; 817 breast cancer mortality including 564 in pre-screening groups, 111 in invited to screening and 142 in control group	Death record	Had mammography Mammography not available (pre-screening) No mammography (controls) >=30 vs. 20-<25 Kg/m^2	1.01 (0.41-2.50) 1.04 (0.74-1.47) 2.08 (1.13-3.81)	Age at diagnosis, menopausal status, histology , tumor size, date of diagnosis, nodal status, clinical site, metastasis
Vitolins MZ (2008)	Phase II Doxorubicin-Based Drug Trial for Node-Positive Breast Cancer United States	Study recruitment: 1980-1985, Study follow-up: Until 1999 Post-diagnosis, post-surgery	Randomised controlled trial of adjuvant treatment trial; ancillary analysis	636 participants 52 years (mean) 25 - 73 years Caucasian: 90%, African-American: 10% 41% premenopausal, 59% postmenopausal	13.7 years	Stages II-III; lymphnode positive breast cancer	62% ER+ve, 38% ER-ve; 49% PR+ve, 51% PR-ve among those with data 52% 1-3 +ve, 32% 4-9 +ve, 16% 10+ +ve	Participants of doxorubicin-based multidrug regimen as adjuvant therapy trial; had mastectomy		Measured at time of enrolment for trial	636 participants 341 deaths, 303 breast cancer mortality, 38 other causes of deaths	Active follow-up and review	Per 1 Kg/m^2 increase	1.04, p-value=0.0009	 Dose-response analysis only; continuous results only
Dignam J (2006)	National Surgical Adjuvant Breast and Bowel Project B-13, B-19, B-23 Trials United States	Study recruitment:1981-1988; Study follow up: until 2005	Follow up of cases of a randomised controlled trial of adjuvant treatment trial	4077 participants white: 81.7%, black: 12%, others/unknown: 6.3%, 54.5% pre/perimenopausal, 45.5% postmenopausal		Node-negative, ER-negative breast cancer; 54.9% tumour size<=2cm, 38.2% size 2.1-4cm, 6.9% size >=4.1cm	All ER-ve All node -ve	Participants of different adjuvant therapy trials		Measurement obtained only at baseline and during treatment; BMI at diagnosis was used	4077 participants 820 deaths, 624 deaths following a BC events, 196 other causes of death, 242 total second primary contralateral breast cancer	Medical records	>=35 vs. <=24.9 Kg/m^2	1.13 (0.85-1.49)	Treatment, tumor size, age, ethnicity Highest vs. lowest analysis only: missing numbers of events and at-risk per category

Dignam J (2003)	National Surgical Adjuvant Breast and Bowel Project B-14 Trial United States	Study recruitment:1982-1988; Study follow up: until 2001	Randomised controlled trial of adjuvant treatment trial	3385 participants white: 91.1%, black: 4.3%, unknown: 4.6% 30.6% peri/premenopausal, 69.4% postmenopausal	166 months	Early stage breast cancer; 60.7% tumour size <= 2cm, 34.6% size 2.1-4 cm, 4.7% size >= 4 cm	All ER +ve All node –ve	64.9% tamoxifen, 35.1% placebo		From the records of original study	3385 participants 983 deaths, 595 deaths following a BC events, 388 other causes of death, 193 contralateral breast cancer, 232 other second primary cancers (plus 51 endometrium cancer)	Trial medical staff (blinded)	>=30 vs. 18.5-24.9 Kg/m^2	1.20 (0.97-1.49)	Age, menopausal status, ethnicity, tumor size, estrogen receptor level, progesterone receptor level, treatment Highest vs. lowest analysis only: missing numbers of events and at-risk per category
Chang S (2000)	MD Anderson Cancer Center, Texas Review Study United States	Cancer diagnosis: 1974-1993	Retrospective cohort study	177 participants 47% premenopausal, 53% postmenopausal	100 months	Inflammatory breast cancer; any stages	11% 0 +ve, 20% 1-3 +ve, 20% 4-10 +ve, 22% >10 +ve, 28% unknown			From medical notes; assessed at the time of diagnosis	177 participants 101 deaths	Hospital records	>=30 vs. <30 Kg/m^2	1.34 (0.88-2.05)	Nodal status, chemotherapy Highest vs. lowest analysis only: two BMI categories only
Hebert J (1998)	Memorial Sloan-Kettering Cancer Center Follow-up Study United States	Cancer diagnosis: 1982-1984; Study follow up: until 1991	Prospective cohort of breast cancer survivors	472 participants 52.2 years (mean) 20 - 80 years 86.8% white 47.3% premenopausal, 52.7% postmenopausal	10 Years (max)	Early-stage breast cancer; TNM; 39, 7% Stage I, 40.6% Stage II, 19.7% Stage III	57.1% ER+ve		Approximately 95% 1 patient lost	Interviewed at the time of diagnosis	472 participants 87 deaths, 73 breast cancer mortality	Cancer registry	Per 1 Kg/m^2 increase	1.06 (1.0-1.12)	Tumor stage, age, meat, butter/margarine/lard, beer, menopausal status, ER status Dose-response analysis only; continuous results only
Newman S (1997)	Northern Alberta Breast Cancer Registry Canada	Cancer diagnosis: 1978-1979, Study follow-up: Until 1990	Prospective cohort of breast cancer survivors	1169 participants 56.1 years (mean) 25 - 98 years 39% premenopausal, 61% postmenopausal	4.35 years	Early stage breast cancer (excluded advanced disease); Stages: 32.1% I, 61.6% II, 6.3% III	67.3% ER+, 32.7% ER- 54.2% 0 +ve, 32.3% 1-3 +ve, 13.5% 4+ +ve		7.30% lost	From cancer registry records	1169 participants 244 breast cancer mortality	Cancer registry	>=29 vs. <=22.7 Kg/m^2	2.47 (1.17-5.22)	Tumor size, nodal status, estrogen receptor level, age
Katoh A (1994)	Mercy Hospital of Pittsburgh, Pennsylvania Review Study United States	Cancer diagnosis:1977-1985	Hospital-based retrospective cohort study	301 participants 72 years (mean) white: 94%, black: 6% All postmenopausal	5 Years (min)	34% Stage I, 51% Stage II, 10% Stage III, 6% Stage IV	78% ER+ve, 22% ER -ve, 56% PR+ve, 44% PR-ve 58% 0 node, 23% 1-2 nodes, 19% >= 4 nodes	62% surgery alone, 38% surgery plus either chemotherapy or radiation therapy		From medical records after diagnosis	301 participants 94 deaths	Cancer registry + National Death Index	>27 vs. <=27 Kg/m^2	0.99 (0.41-2.42)	Age, ER status, PR status, treatment, tumor stage, tumor size, nodal status Highest vs. lowest analysis only; two BMI categories only
Mason B (1990)	Auckland Breast Cancer Study Group Australia	Cancer diagnosis: 1976-1985	Prospective cohort of breast cancer survivors	2706 participants	7 years	Incident breast cancer; any stages				From records	1770 participants 586 breast cancer mortality included in the analysis	Cancer registry	<28 vs. >=28 Kg/m^2	0.67 (0.55-0.83)	Age, age at first birth, age of menarche, parity, lactation, season Highest vs. lowest analysis only: two BMI categories only

Table 93 Table of excluded studies on BMI less than 12 months after diagnosis and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments Exclusion reason
Allin KH (2011)	Copenhagen Breast Cancer Study, Denmark	Cancer diagnosis: 2002-2008/2009	Prospective cohort of breast cancer survivors	2910 participants 26-99 years 21.36% premenopausal, 78.64% postmenopausal	3 years	Invasive breast cancer; Tumour grade: 23.54% well differentiated, 43.37% moderate, 17.35% poorly/un-differentiated, 15.74% unknown; Distant metastases: 95.53% no, 1.37% yes, 3.09% unknown; HER2 status: 27.73% +ve, 7.56% -ve, 64.71% unknown	ER status: 76.74% +ve, 14.98% -ve, 8.28% unknown; PR status: 47.53% +ve, 27.04% -ve, 25.43% unknown 46.21% node –ve, 45.56% node +ve, 8.23% unknown		93%	Self-reported at diagnosis/study baseline	2872 participants, 383 deaths, 225 (64%) breast cancer deaths, Other causes of death: 11% other cancer, 11% cardiovascular disease, 4% respiratory disease, 11% other disease, 1% unknown	Death registry	>=30 vs. 18.5-24.9 kg/m^2	1.62 (1.05-2.52)	 Unadjusted results
Litton J (2008)	MD Anderson Cancer Center, Texas Review Study United States	Cancer diagnosis: 1990-2004 Recruited after treatment with NC and before surgical treatment	Retrospective cohort study	1169 participants 50 years (mean) 44.9% premenopausal, 3.8% perimenopausal, 51.3% postmenopausal	14 years	Cancer stages: 4.1% I, 63% II, 32.9% III; Tumor stages: 0.2% T0, 11.5% T1, 56.5% T2, 17.7% T3; 14.1% T4; Histology: 92.9% ductal, 7.1% lobular	60.1% ER+, 39.9% ER-; 51.2% PR+, 48.8% PR-; 22.8% HER-2+, 77.2% HER-2- 56.4% +ve, 43.6% -ve	Mastectomy: 61% yes; Breast-conserving surgery: 38% yes; No surgery: 1% yes; Anthracycline-based regimen: 91% yes		From medical records	1169 participants 194 deaths, 167 breast cancer mortality, 18 other causes of deaths, 9 unknown causes of deaths	Cancer registry	Normal/underweight Overweight Obese 10-year breast cancer survival	74%, 67%, 62%, log-rank test p-value=0.048	 Insufficient data -log-rank test p-value only
Majed B (2008)	Curie Institute Breast Cancer Study France	Breast cancer treatment: 1981-1999, Study follow-up: Until 2004	Prospective cohort of breast cancer survivors	14709 participants 44.8% premenopausal, 55.2% postmenopausal Obesity: 7.9% yes 20.2% cancers detected by mammography	8 years	Stages: 36.2% I, 51.1% II, 12.6% III; SBR grades: 22.9% I, 23% II weak, 18.8% II strong, 16.2% III, 9.4% non gradation, 9.7% NA; Tumor size (cm): 12% <=1, 23.9% 1-2, 44.4% 2-5, 13.5% >5, 6.2% NA; Tumor histology: 73.7% ductal, 8.5% lobular, 6.9	50.9% ER+, 17.4% ER-, 31.7% NA; 50.2% PR+, 24.2% PR-, 25.6% NA	Conservative surgery: 57.2% yes; Non-conservative surgery: 29% yes; Non surgical local treatment: 13.8% yes; Hormonal therapy: 33.1% yes; Chemotherapy: 30.8%; Radiotherapy: 86.6% yes		From medical records	14709 participants 3693 deaths, 555 second cancers	Cancer registry	>=30 vs. <30 Kg/m^2	1.35 (1.19-1.54)	 Unadjusted result

Bastarrachea J (1994)	MD Anderson Cancer Center, Texas Review Study United States	Study recruitment: 1974-1982; Study follow up: 10.7 yrs (median)	Randomised controlled trial of adjuvant treatment trial; ancillary analysis	735.0 participants 47.7% premenopausal, 52.2% postmenopausal	10.7 years	Primary invasive breast cancer; 69.2% stage II, 30.7% stage III	All node +ve, 38.3% <= 3 nodes +ve, 37.8% 4-10 nodes +ve, 23.5% >10		1%	From medical records	735 participants, 298 breast cancer mortality	Hospital records	Obese vs. non-obese (>20% ideal weight vs <=20% ideal weight)	1.36 (1.06-1.76)	Tumour stage, nodal status, menopausal status Obesity – percentage of ideal weight
Rohan T (1993)	Diet and Breast Cancer in Australia Follow-up Study Australia	Cancer diagnosis: 1982-1984, Study follow-up: Until 1989	Follow-up of cases of population-based case-control study	412 participants 55.1 years (mean) 20 - 74 years 30.7% premenopausal, 5.4% perimenopausal, 64% postmenopausal, among those with data	5.5 years	Primary breast cancer, any stages			80.70% 39 patients lost	Interval between diagnosis and interview was 4.8months	412 participants 112 breast cancer mortality, 11 other causes of deaths	Cancer registry + death certificate	>=30 vs. <23 Kg/m^2	3.39 (1.84-6.25)	 Unadjusted result
Coates RJ (1990)	Georgian Hospital Tumor Registry Review Study Georgia	Cancer diagnosis: 1975-1979	Prospective cohort of breast cancer survivors	1960 participants 23.90% Black 76.10% White 27.30% premenopausal 72.04% postmenopausal	5 years (min)	23.37% Stage 1, 53.93% Stage 2, 16.58% Stage 3, 6.12% Stage 4	52.53% 0 node, 25.07% 1-3 +ve nodes, 22.40% 4 +ve nodes	Surgery: 95.82% yes, 4.18% no; Radiation: 11.37% yes, 88.63% no; Hormonal therapy: 1.79% yes, 98.22% no; Chemotherapy 5.67% yes 94.33% no	11.4%	Measured at study baseline	1924 participants	Cancer registries + SEER records	<=20.5 20.6-24.5 >=24.6 kg/m^2 Cumulative survival at 5-year	73.5% 76.8% 67.4% P<0.001	 Survival rates and Wilcoxon test only

12 months or more after diagnosis BMI and breast cancer mortality

Two studies were identified. One study reported a statistically significant association for the obese compared with normal weight (HR for ≥ 30 vs. 18.5-24.9 kg/m^2 2.28; 95% CI 1.43-3.64) (Nichols, 2009). The other study observed a suggestive increased risk (HR for ≥ 30 vs. ≤ 24.9 kg/m^2 = 1.2; 95% CI 0.7-2.1, p_{trend} = 0.53) (Caan, 2008).

BMI and cardiovascular disease mortality

Before diagnosis BMI and cardiovascular disease mortality

Two studies reported data. One study (Nichols, 2009) reported a significant increased risk (RR for ≥ 30 vs. 18.5-24.9 kg/m^2 2.45; 95% CI 1.46-4.11), while the other postmenopausal study (Reeves, 2007) reported no association (RR for 34 vs. 22.6 kg/m^2 0.99; 95% CI 0.51-1.91).

BMI less than 12 months after diagnosis and cardiovascular disease mortality

Only one study reported data. Lara-Medina et al. (2011) examined 5-year survival rates among those of BMI ≥ 30 and < 30 kg/m^2. No statistically significant difference in survival rates (78.10 vs. 76.1%) was observed between the two groups (p = 0.121).

12 months or more after diagnosis BMI and cardiovascular disease mortality

One study reported data. Nichols et al. (2009) reported a non-significant increased risk (RR for ≥ 30 vs. 18.5-24.9 kg/m^2 1.65; 95% CI 0.97-2.83).

BMI and mortality not related to breast cancer

Before diagnosis BMI and mortality not related to breast cancer

No study has reported data.

Published pooled analysis

The After Breast Cancer Pooling Project (ABCPP) published results on before diagnosis BMI and total, breast cancer, and non-breast cancer mortality risks (Kwan, 2012b).

Data from four prospective studies of breast cancer survivors (Shanghai Breast Cancer Survival Study, Life After Cancer Epidemiology, Women's Healthy Eating and Living, and Nurses' Health Study) were pooled in the project. After a mean follow-up of 7.8 years,

2140 deaths (1423 breast cancer mortality, 717 deaths because of other causes) from 14948 participants with stage I-IV invasive breast cancer were accrued.

Compared with the normal weight, statistically significant increased risks in non-breast cancer mortality were observed for the obese (multivariate-adjusted HR for ≥ 30 vs. 18.5-24.9 kg/m^2 = 1.33, 95% CI1.10-1.62), and the underweight (HR for <18.5 vs. 18.5-24.9 kg/m^2 = 2.12; 95% CI 1.29-3.47); while no association was observed for the overweight (HR for 25.0-29.9 vs. 18.5-24.9 kg/m^2 0.99; 95% CI 0.83-1.18). The association was non-linear ($p_{non\text{-}linearity}$ = 0.0005).

Statistically significant increased risks for the severely obese (35.0-39.9 kg/m^2) or morbidly obese (≥ 40 kg/m^2), but not for the overweight (25.0-29.9 kg/m^2) or obese (30.0-34.9 kg/m^2) when compared with normal weight women (18.5-24.9 kg/m^2) were found in further analysis using different BMI cutpoints. The HRs for overweight, obese, severely obese, and morbidly obese were 0.99 (95% CI 0.83-1.18), 1.13 (95% CI 0.90-1.42), 1.40 (95% CI 1.02-1.92), and 3.01 (95% CI 2.09-4.33) respectively.

BMI less than 12 months after diagnosis and mortality not related to breast cancer

Methods

Six studies were identified. Linear dose-response meta-analysis was not conducted as only Sestak et al. (2010) had sufficient data for the analysis. Four studies were included in the highest versus lowest meta-analysis. Tammemagi et al. (2005) and Majed et al. (2008) reported unadjusted results and was excluded. Both studies reported positive associations between BMI and dying from non-breast cancer related causes (RR for ≥ 35 vs. 18.5-25 kg/m^2 1.35; 95% CI 0.91-2.10; RR for > 30 vs. ≤ 30 kg/m^2 2.14; 95% CI 1.38-3.31 respectively). We included the BMI categories as defined by the studies. The reference category may either be the normal weight group or included underweight women. BMI could be assessed less than 12 months after diagnosis, e.g. several months but less than a year after diagnosis or just before cancer treatment.

Main results and heterogeneity

In the highest versus lowest meta-analysis, the summary RR was 1.37 (95% CI 1.14-1.66; I^2 = 37.2%; p = 0.19; 4 studies). Sestak et al. (2010) is a postmenopausal study.

Study quality

There were 5868 and 504 deaths non-related to breast cancer after an average follow-up of 7.1 years and 100 months respectively in Ewertz et al. (2011) and Sestak et al. (2010). Dignam et al. (2003) had 388 deaths non-related to breast cancer after an average of 166

months of follow-up, while Dignam et al. (2006) had 196 deaths non-related to breast cancer between the study period of 1981 and 2005. The studies by Dignam et al. (2003; 2006) and Sestak et al. (2006) were ancillary analyses using data from randomised controlled trials (RCT) of adjuvant treatment. The trials consisted only of ER-negative and lymph node-negative breast cancer cases (Dignam et al. 2006), ER-positive and lymph node-negative breast cancer cases (Dignam et al. 2003), or ER and/or PR-positive breast cancer cases (Sestak, 2010). Participants in the Ewertz et al. study (2011) also originated from RCTs of adjuvant treatment. Breast cancer cases were of different stages, hormone receptor status and lymph node status in this study. Anthropometric data less than 12 months after diagnosis were either taken from medical record (Ewertz, 2011) or measured (Sestak, 2010). It is unclear with the studies by Dignam. All studies except Sestak et al. (2010) involved pre- and postmenopausal women. Sestak et al. (2010) included postmenopausal women only. All results were multivariate adjusted.

Figure 125 Highest versus lowest forest plot of BMI less than 12 months after diagnosis and mortality not related to breast cancer

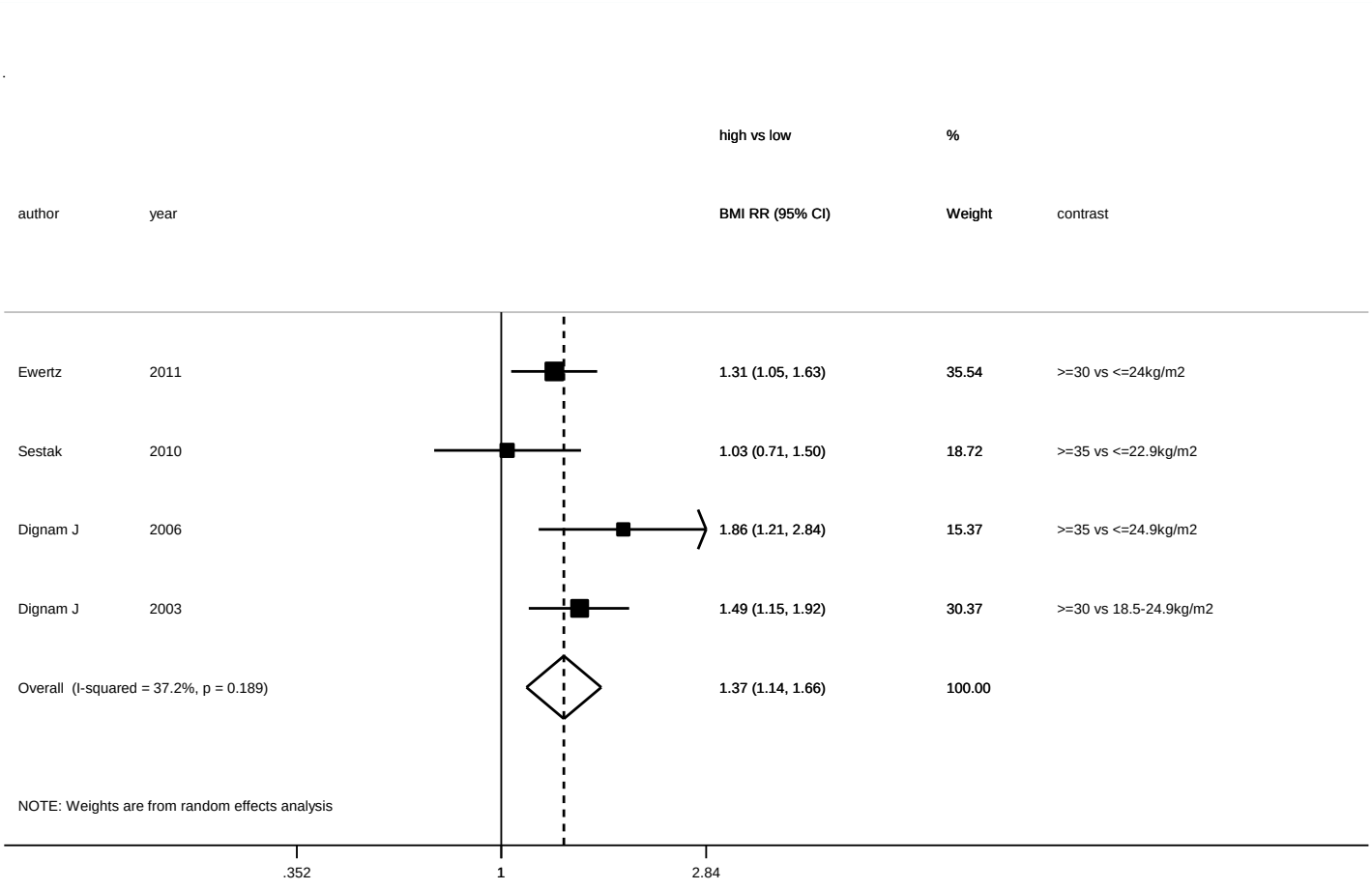


Table 94 Table of included studies on BMI less than 12 months after diagnosis and non-breast related mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Ewertz (2011)	Danish Breast Cancer Cooperative Group Denmark	Study follow up: until 2008	Follow up of cases of randomised controlled trials of adjuvant treatment	18967 participants 39 - 70 years 18688 (34.7%) premenopausal and 35128 (65.3%) postmenopausal	7.1 years	Early stage - 14077 patients had ductal grade 1, 19456 grade 2, 9282 grade 3, 5532 lobular breast cancer	9780 ER-ve, 32276 ER+ve, 11760 unknown / 29660 with 0 +ve node, 15486 with 1-3 +ve nodes, 8666 with 4+ nodes, 4 unknown	22968 patients had no adjuvant treatment, 10230 chemotherapy, 16148 endocrine therapy, 4470 combined therapy	/ Complete follow-up for first events (loco regional recurrences and distant metastases)	From medical records; weight and height at diagnosis	For those with BMI data, 18967 participants 5868 death from breast cancer and 1529 death from unknown causes	Death certificate	>=30 vs. <=24 Kg/m^2 >10 year follow-up	1.31 (1.05-1.63)	Age, menopausal status, tumor size, nodal status, tumor grade, histology , ER status, fascia invasion, protocol year, systemic therapy
Sestak (2010)	The Arimidex, Tamoxifen Alone or in Combination (ATAC) United Kingdom		Randomised controlled trial of adjuvant treatment trial	4939 participants All postmenopausal	100 months	Early-stage breast cancer	All ER+ve and/or PgR +ve)	Participants of adjuvant treatment (anastrozole alone, tamoxifen alone, or combined) trial		Measured at baseline after diagnosis	4939 participants, 481 death after breast cancer recurrence, 504 death without breast cancer recurrence	trial medical staff (blinded)	>=35 vs. <=22.9 Kg/m^2	1.03 (0.71-1.50)	Age, mastectomy, tumor size, tumor grade, nodal status, chemotherapy, radiotherapy, region
Dignam J (2006)	National Surgical Adjuvant Breast and Bowel Project B-13, B-19, B-23 Trials United States	Study recruitment:1981-1988; Study follow up: until 2005	Follow up of cases of a randomised controlled trial of adjuvant treatment trial	4077 participants white: 81.7%, black: 12%, others/unknown: 6.3%, 54.5% pre/perimenopausal, 45.5% postmenopausal		Node-negative, ER-negative breast cancer; 54.9% tumour size<=2cm, 38.2% size 2.1-4cm, 6.9% size >=4.1cm	All ER-ve / All node -ve	Participants of different adjuvant therapy trials		Measurement obtained only at baseline and during treatment; BMI at diagnosis was used	4077 participants 820 deaths, 624 deaths following a BC events, 196 other causes of death, 242 total second primary contralateral breast cancer	Medical records	>=35 vs. <=24.9 Kg/m^2	1.86 (1.21-2.84)	Treatment, tumor size, age, ethnicity
Dignam J (2003)	National Surgical Adjuvant Breast and Bowel Project B-14 Trial United States	Study recruitment:1982-1988; Study follow up: until 2001	Randomised controlled trial of adjuvant treatment trial	3385 participants white: 91.1%, black: 4.3%, unknown: 4.6% 30.6% peri/premenopausal, 69.4% postmenopausal	166 months	Early stage breast cancer; 60.7% tumour size <= 2cm, 34.6% size 2.1-4 cm, 4.7% size >= 4 cm	All ER +ve / All node -ve	64.9% tamoxifen, 35.1% placebo		From the records of original study	3385 participants 983 deaths, 595 deaths following a BC events, 388 other causes of death, 193 contralateral breast cancer, 232 other second primary	trial medical staff (blinded)	>=30 vs. 18.5-24.9 Kg/m^2	1.49 (1.15-1.92)	Age, menopausal status, ethnicity, tumor size, estrogen receptor level, progesterone receptor level, treatment

											cancers (plus 51 endometrium cancer)				

Table 95 Table of excluded studies on BMI less than 12 months after diagnosis and non-breast related mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments / Exclusion reason
Tammemagi CM (2005)	Henry Ford Health System Tumor Registry Review Study, Detroit United States	Cancer diagnosis 1985-1990, Study follow-up: Until 2002	Retrospective cohort study	906 participants Black and White Comorbidites: 28.3% comorbidity free, among those with data 24% had one, 17.2% 2, 11.3% 3, 19.2% 4 to 13 of the 77 specific comorbidities	10 years	ncident breast cancer; stages: 3.6% in situ, 34.3% I, 45.4% II, 10.9% III, 5.9% IV, among those with data		Surgery: 90.8% yes; Chemotherapy: 27.2% yes; Radiotherapy: 28.5% yes; Hormone therapy: 4.4% yes; Tamoxifen: 38.5%	20 patiens lost	From medical records	476 deahts, 179 breast cancer mortality, 297 non-breast cancer deaths	Death certificate	>=35 – 18.5-25 Kg/m^2	1.35 (0.91-2.0)	Unadjusted results
Majed B (2008)	Curie Institute Breast Cancer Study France	Breast cancer treatment: 1981-1999, Study follow-up: Until 2004	Prospective cohort of breast cancer survivors	14709 participants 44.8% premenopausal, 55.2% postmenopausal Obesity: 7.9% yes 20.2% cancers detected by mammography	8 years	Stages: 36.2% I, 51.1% II, 12.6% III; SBR grades: 22.9% I, 23% II weak, 18.8% II strong, 16.2% III, 9.4% non gradation, 9.7% NA; Tumor size (cm): 12% <=1, 23.9% 1-2, 44.4% 2-5, 13.5% >5, 6.2% NA; Tumor histology: 73.7% ductal, 8.5% lobular, 6.9	50.9% ER+, 17.4% ER-, 31.7% NA; 50.2% PR+, 24.2% PR-, 25.6% NA / Clinical node involvement: 82.1% N0-N1a, 17.9% N1b-N3	Conservative surgery: 57.2% yes; Non-conservative surgery: 29% yes; Non surgical local treatment: 13.8% yes; Hormonal therapy: 33.1% yes; Chemotherapy: 30.8%; Radiotherapy: 86.6% yes		From medical records	14709 participants Death from other second cancers	Cancer registry	>30 vs. <=30kg/m^2	2.14 (1.38-3.31)	Unadjusted results

12 months or more after diagnosis BMI and mortality not related to breast cancer

No study has reported data.

BMI and (any) second primary cancer

Before diagnosis BMI and (any) second primary cancer

No study has reported data.

BMI 12 months or more after diagnosis and (any) second primary cancer

Two studies from three publications were identified. Both studies reported increased risk, with one being statistically significant (RR for the highest vs. lowest BMI = 1.46 (95% CI 1.10-1.94, $p_{trend} < 0.05$)) (Majed, 2008) and 1.32 (95% CI 0.96-1.81, $p_{trend} = 0.03$) (Dignam, 2006).

12 months or more after diagnosis BMI and (any) second primary cancer

No study has reported data.

BMI and second primary breast cancer/contralateral breast cancer

Before diagnosis BMI and second primary breast cancer/contralateral breast cancer

Methods

Three studies were identified. Li et al. (2003) reported results on second primary contralateral breast cancer, while Trentham-Dietz et al. (2007) examined second primary breast cancer. All studies could be included in the highest versus lowest and linear dose-response meta-analyses. We included the BMI categories as defined by the studies. The reference category may include underweight women. BMI could be assessed at different times before diagnosis, or of an adult BMI.

Main results and heterogeneity

The summary RR per 5 kg/m^2 was 1.21 (95% CI 1.04-1.40; I^2 = 20.8%; p = 0.28; 3 studies). For the highest versus the lowest comparison, the summary RR was 1.43 (95% CI 0.87-2.34; 3 studies). High heterogeneity (I^2 = 66.7%; p = 0.05) was observed. Li et al. (2003) is a premenopausal study (age < 45 years), the summary RR was 1.13 (95% CI 0.85-1.49) when this study was omitted; Trentham-Dietz et al. (2007) analysed postmenopausal women only, the summary RR was 1.12 (95% CI 0.81-1.55) when this study was omitted.

Study quality

Li et al. (2003) accrued 77 contralateral breast cancer cases after an average of 9 years of follow-up. Bernstein et al. (1992) had 136 contralateral breast cancer cases after an average of 52 months and 5.6% participants lost of follow-up. Trentham-Dietz, et al. (2007) had 351 second breast cancers after an average of 7.1 years of follow-up. All studies were follow-up of case control studies, with first primary breast cancer cases of different stages diagnosed from the 1980s. Bernstein et al. (1992) included *in situ* and invasive breast cancers. Before diagnosis anthropometric data were recall retrospectively. One study (Li, 2003) was of premenopausal women only, while the other two studies (Bernstein, 1992; Trentham-Dietz, 2007) included women of all ages. All results were multivariate adjusted.

Figure 126 Highest versus lowest forest plot of before diagnosis BMI and second primary breast cancer/contralateral breast cancer

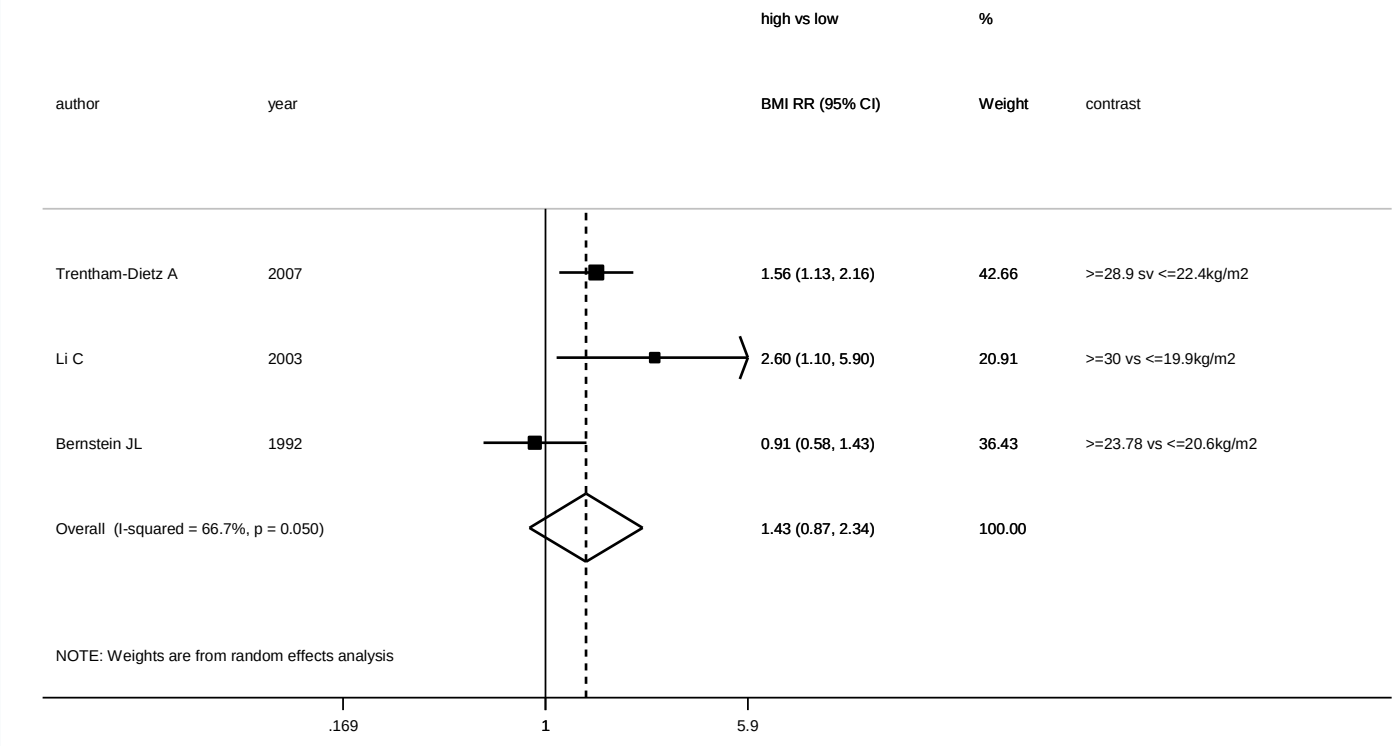


Figure 127 Linear dose-response meta-analysis of before diagnosis BMI and second primary breast cancer/contralateral breast cancer

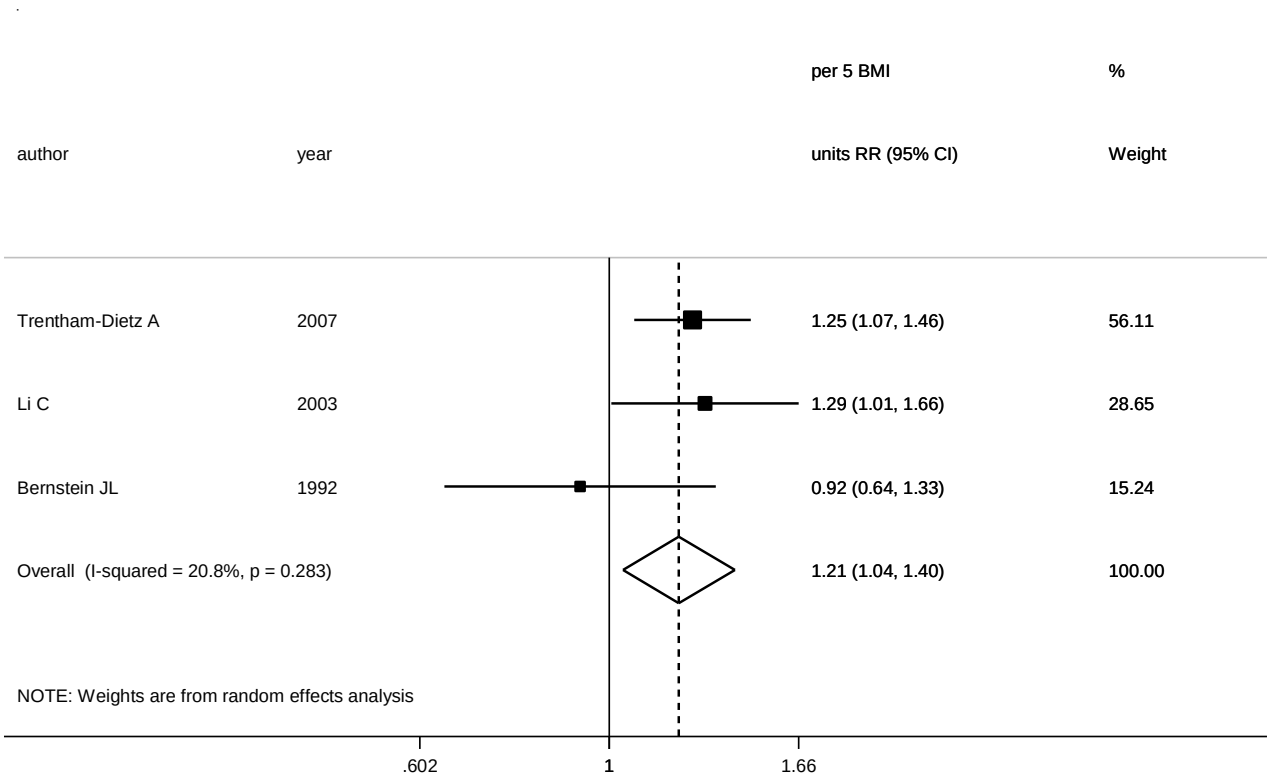


Figure 128 Individual dose-response curves of before diagnosis BMI and second primary breast cancer/contralateral breast cancer

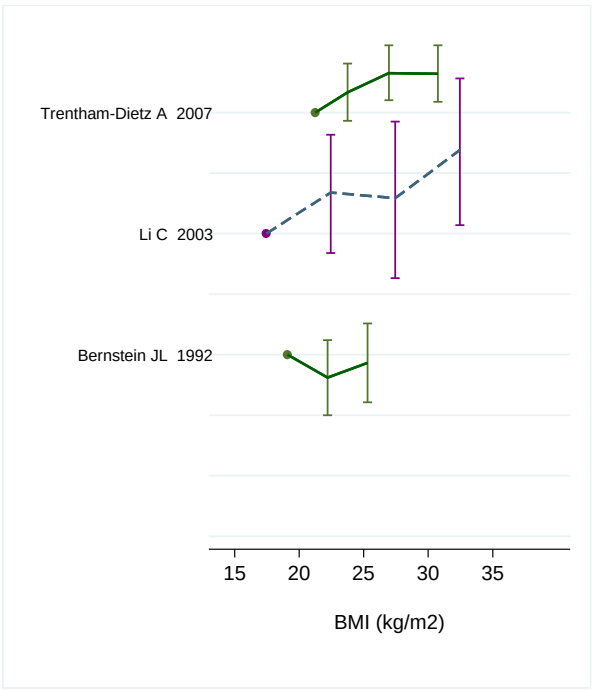


Table 96 Table of included studies on BMI before diagnosis and second primary breast cancer/contralateral breast cancer

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Trentham-Dietz A (2007)	Wisconsin Follow-up Study of Women with Invasive Breast Cancer United States	Cancer diagnosis: 1987-2000, Study follow-up: Until 2002 Recruited approximately 1 year after diagnosis	Follow-up of cases of case-control studies	10953 participants 59.4 years (mean) 18 - 79 years	7.1 years	Stages: 63% local, 28.9% regional, 2.3% distant, 5.8% unknown			83.30%	Self-reported pre-diagnosis weight and height at interview approximatel y1year after diagnosis	10953 participants 1188 second cancers: 488 second breast cancers, 132 colorectal cancers, 113 endometrial cancers, 36 ovarian cancers, 8020 postmenopau sal, 351 second primary breast cancer in analysis only	Cancer registry	>=28.9 vs. <=22.4 Kg/m^2	1.56 (1.13-2.16)	Age, year of diagnosis, tumor stage, family history, smoking, alcohol intake, parity, HRT, menopausal status
Li C (2003)	Fred Hutchinson Cancer Research Center Follow-up study United States	Cancer diagnosis: 1983-1992, Study follow-up: Until 2001	Follow-up of cases of case-control studies	1285 participants 37.7 years (mean) 21 - 44 years Premenopausal	9 years	AJCC stages: 37.5% I, 51% II, 8.7% III, 2.7% IV among those with data (1.9% missing data); tumor size (cm): 52.1% <=2, 39.7% >2-5, 8.1% >5, among those with data	59.4% ER+, 40.6% ER-; 60.4% PR+39.6% PR-, among those with data	Chemotherapy: 71.5% yes, 0.2% missing data; Radiation: 56.8% yes, 0.2% missing data; Tamoxifen: 38.3% yes, 8.7% missing data	83.3% and 83.9% in original studies	Self reported weight 1 year prior to diagnosis	1285 participants 77 contralateral breast cancers	Cancer registry	>=30 VS. <=19.9 Kg/m^2	2.60 (1.10-5.90)	Age at diagnosis, year of diagnosis, tumor stage, chemotherapy, study group
Bernstein JL (1992)	Cancer and Steroid Hormone Study United States	Cancer diagnosis: 1980-1982 (first diagnosis); Study follow up: until 1986 Newly diagnosed patients recruited, within 6 months of diagnosis	Follow-up of cases of a population-based case-control study	4550 participants 44 years (mean) 20 - 54 years 87.5% white, 10.6% black Among those with data: 46.9% premenopausal, 17.5% perimenopausal, 35.6% postmenopausal	52 months	4.5% in situ, 48.4% localised, 44% regional, 3.1% distant first breast cancer		Chemotherapy: 26.8% yes, 8.4% unknown; radiation: 21.4% yes, 1.9% unknown	80% interviewe d / 5.60% lost	From the original study; interviewed within 6 months of the diagnosis of their initial tumor	4550 participants 136 contralateral breast cancer	Cancer registry	>=23.78 vs. <=20.6 Kg/m^2 adult BMI	0.91 (0.58-1.43)	Age at diagnosis, age at first birth, parity, age at menarche, menopausal status, age at menopause, tumor stage, family history, benign breast disease, education

BMI less than 12 months after diagnosis and contralateral breast cancer

Methods

Eight studies (eight publications) and a published meta-analysis were identified. Initially, only four studies (Storm, 1992; Cook, 1996; Li, 2009; Brooks, 2012) could be included in the dose-response meta-analysis. Numbers of events per BMI category were missing in the original articles of two studies (Dignam, 2003; Dignam, 2006) and another two studies (Horn, 1988; Majed, 2011) provided results by two BMI categories. The published meta-analysis (Pecollo, 2012) provided dose-response results on Dignam et al. (2003), Dignam et al. (2006), and Majed et al. (2009) (a publication in French of the same study as Majed, 2011). After including these results from the published meta-analysis, a total of seven studies were included in the dose-response meta-analysis of the present report.

All eight studies could be included in the highest versus lowest meta-analysis. We included the BMI category as defined by the studies. The reference category may include underweight women. Horn et al. (1988) reported in Quetelet index (weight/height^2 x 1000 ≥ 35 vs. ≤ 34). The corresponding comparison in BMI is 24.61 vs. 23.90 kg/m^2.

Main results and heterogeneity

The summary RR per 5 kg/m^2 was 1.13 (95% CI 1.06-1.21; I^2 = 15.2%; p = 0.31; 7 studies). When each study was omitted in turn in an influence analysis, the summary RRs ranged from 1.11 (95% CI 1.04-1.19) when Dignam et al. (2003) was omitted to 1.14 (95% CI 1.06-1.22) when Brooks et al. (2012) was omitted. For the highest versus the lowest comparison, the summary RR was 1.30 (95% CI 1.14-1.48; I^2 = 0%; p = 0.64; 8 studies). All studies comprised pre- and postmenopausal women.

Study quality

Number of contralateral breast cancer cases ranged from 193 to 1370 cases. Follow-up time ranged from an average of 2.9 years to 17 years. First primary breast cancer cases were diagnosed since 1935 in one study (Horn, 1988) and between 1943 and 1978 in another study (Storm, 1992). Most other studies recruited cases (first cancer) diagnosed from late 1970s or between the 1980s and 1990s (Cook, 1996; Dignam, 2003; Dignam, 2006; Majed, 2011; Brooks, 2012). For Li et al. (2009), cancer diagnosis spanned from 1990 to 2005. Two studies included *in situ* and invasive breast cancers (Cook, 1996; Brooks, 2012). Five studies included invasive breast cancer only (Storm, 1992; Dignam, 2003; Dignam, 2006; Li, 2009; Majed, 2011). The studies by Dignam et al. were ancillary analyses using data from randomised controlled trials of adjuvant treatment, which consisted only of ER-negative and lymph node-negative breast cancer cases (Dignam et al. 2006) or ER-positive and lymph node-negative breast cancer cases (Dignam et al. 2003). Five studies were based on a case-control study (Horn, 1988; Storm, 1992; Cook, 1996; Li, 2009; Brooks, 2012). One study was a cohort of breast cancer survivors recruited in a cancer institute (Majed, 2011). Anthropometric data at-diagnosis were either taken

from medical records (Horn, 1988; Storm, 1992; Cook, 1996) or self-reported (Li, 2009, Brooks, 2012). Assessment was unclear in some (Dignam, 2003; Dignam, 2006; Majed, 2011). All studies involved women of all ages. Brooks et al. (2012) and Dignam et al. (2006) conducted analysis by menopausal data. All results were multivariate adjusted.

Published meta-analysis

Pecollo et al. (2012) recently published a meta-analysis on BMI and second primary breast cancer. A statistically significant 12% increased risk per 5 kg/m^2 increase in BMI (95% CI 1.06-1.20; I^2 = 10.6%; p = 0.35) was observed. The study of Li (2003) included by Pecollo et al. (2012) was included with before diagnosis BMI and second primary contralateral breast cancer in the present report.

Figure 129 Highest versus lowest forest plot of BMI less than 12 months after diagnosis and contralateral breast cancer

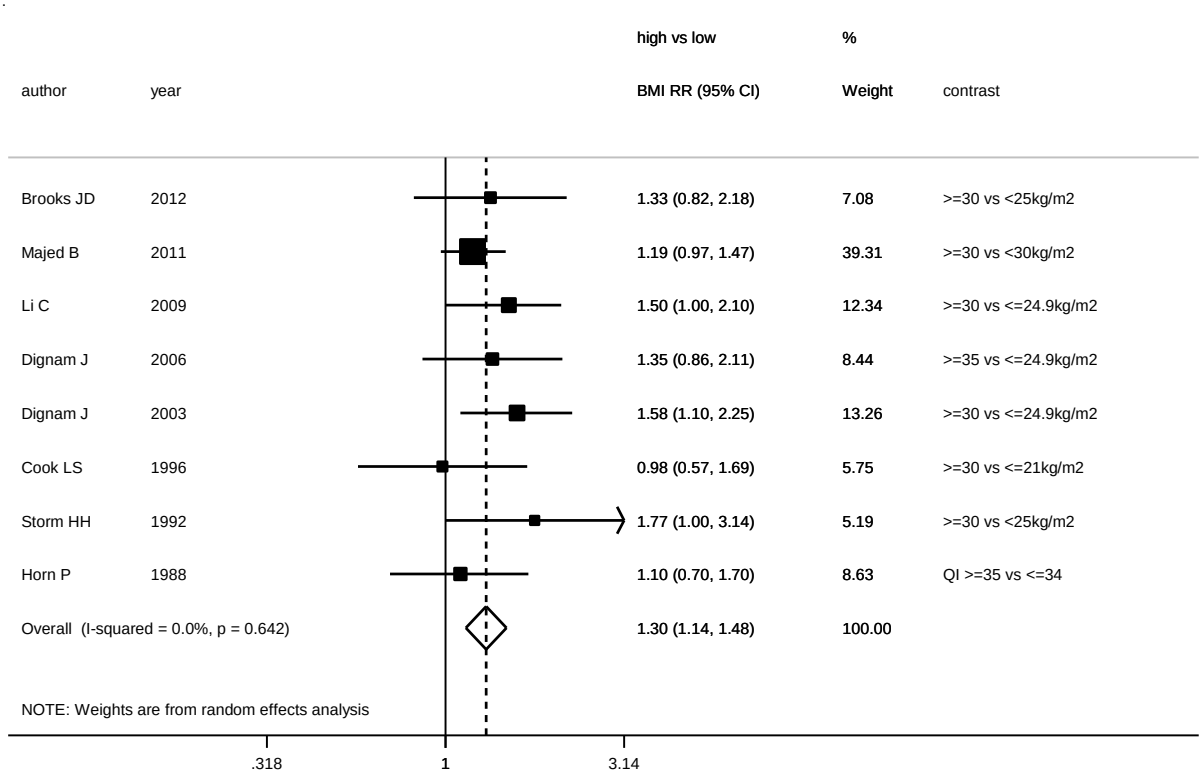


Figure 130 Linear dose-response meta-analysis of BMI less than 12 months after diagnosis and contralateral breast cancer

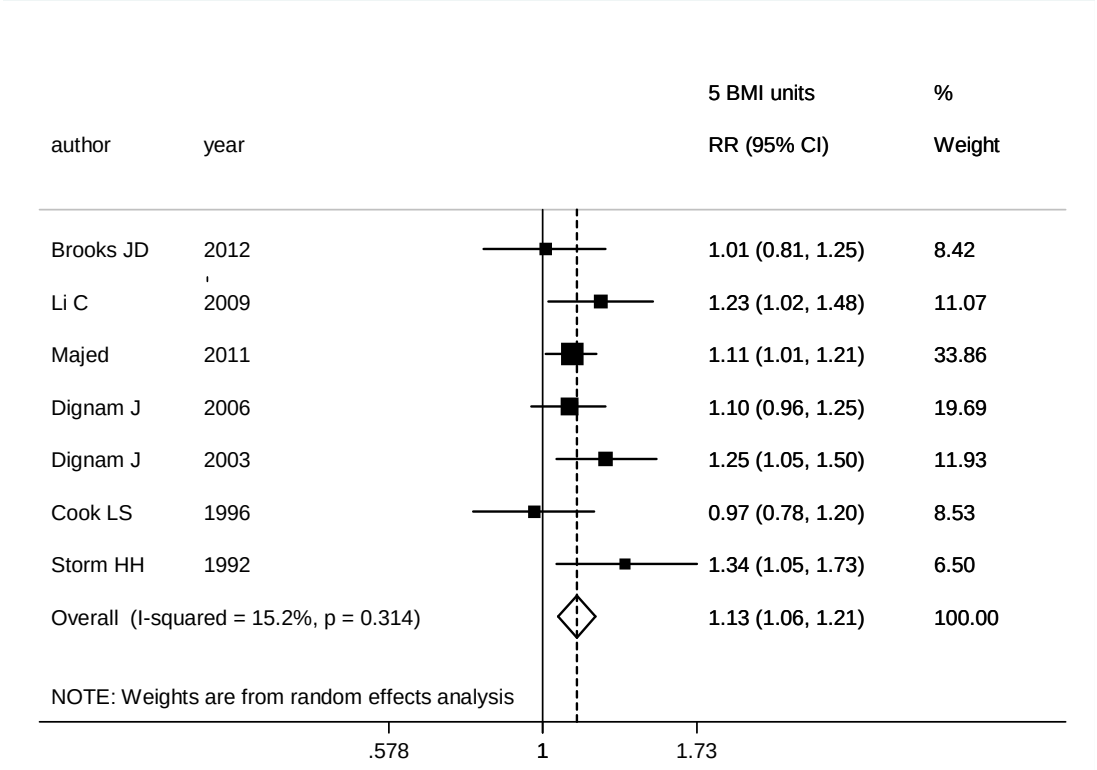


Figure 131 Individual dose-response curves of BMI less than 12 months after diagnosis and contralateral breast cancer

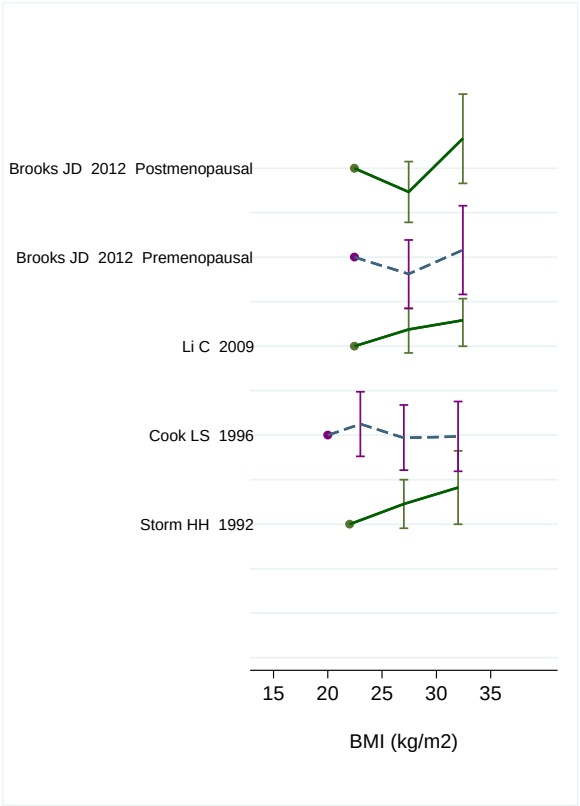


Table 97 Table of included studies on BMI less than 12 months after diagnosis and contralateral breast cancer

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Brooks JD (2012)	The Women's Environmental Cancer and Radiation Epidemiology Study USA and Denmark	Cancer diagnosis: 1985-2000 Study follow up started 1 year after the first diagnosis	Follow-up of cases of a case-control study	1510 participants 45 years (mean) 23 - 55 years 92% Caucasian 56.4% postmenopausal (1 year after diagnosis)	4 years	In situ or invasive breast cancer; 65.3% localized, 34.7% regional	49.8% ER+ve, 25.9% ER-ve, 24.2% other, 42% PR+ve, 23.3% PR-ve, 34.7% other	Chemotherapy: 44.3% yes, 55.7% no; Hormone treatment: 70.7% yes, 29.2% no; Radiation treatment: 70% ever, 30% never	71% in cases, 65% in controls	Self-reported at interview; height and weight at age 18 years, weight at first breast cancer diagnosis and at second breast cancer	1510 participants 511 contralateral breast cancer	Cancer registry	Premenopausal Postmenopausal >=30 vs. <25 Kg/m^2	1.12 (0.56-2.23) 1.59 (0.79-3.17)	Age at diagnosis, age of menarche, number of full-term pregnancies, family history, histology, tumor stage, chemotherapy, hormonal therapy, radiation therapy
Majed B (2011)	Curie Institute Breast Cancer Study France	Study recruitment: 1981-1999, Study follow-up: Until 2005 Recruited at diagnosis	Prospective cohort of breast cancer survivors	15116 participants 54 years (mean) 45% premenopausal, 47.1% postmenopausal, among those with data 20.2% cancers detected by mammography	10 years	Stages: 85% I and II; SBR grade: 8.7% non-gradable, 22.8% IIA, 19.3% IIB, 16.9% III, 10.2% unknown; Histology: 74.4% ductal, 8.4% lobular, 7.2% other, 10% unknown; Tumor size (cm): 12.1% 1, 23.5% 1-2, 43.6% 2-5, 13.2% >5, 7.6% unknown	50.1% ER+, 17% ER-, 32.9% unknown; 49.4% PR+, 23.8% PR-, 26.8% unknown Clinical nodes invasion: 68.7% N0, 29.8% N1, 1.1% N2-N3, 0.5% NX; Involved nodes after axillary dissection: 42% 0, 16.4% 1-3, 8.6% >3, 23.6% no dissection, 9.3% unknown	First treatment - mastectomy: 13.8% yes, lumpectomy: 52.6% yes, chemotherapy: 15.1% yes, radiotherapy: 18.5% yes; Adjuvant therapy - Chemo and hormone therapy 30.6% yes, hormone therapy alone: 17.4% yes, 52% none; Final surgical treatment: 29.1%		BMI assessed at diagnosis	15116 participants 1370 contralateral breast cancer	Cancer registry	>=30 vs. <30 Kg/m^2	1.19 (0.97-1.47)	Initial delivered treatment, tumor histology, hormonal receptor status, number of axillary invaded nodes, family history of breast cancer, age, menopausal status, period of recruitment
Li C (2009)	Seattle-Puget Sound Region Nested Case-Control Study United States	Cancer diagnosis: 1990-2005	Population-based nested case-control study	1091 participants 40 - 79 years HRT use: 19.6% current estrogen alone users, 17% current estrogen + progestin users, 10.2% former users, 47.1% never users, 6% missing	17 years	AJCC stages: 67.4% I, 32.6% II or III; Tumor size (cm): 33.4% <=1, 41.7% 1.1-2, 21.9% >2, 3% missing	23.8% +ve, 76.2% -ve	Chemotherapy: 26.1% yes, 73.9% no; Radiotherapy: 65.4% yes, 34.6% no, 0.1% missing; Adjuvant hormone therapy: 66.8% yes, 33.2% no	83% case, 75%controls	Self-reported at diagnosis	1091 participants 365 contralateral breast cancers	Cancer registry	>=30 vs. <=24.9 Kg/m^2 At first breast cancer diagnosis	1.50 (1.0 – 2.10)	Age, year of diagnosis, county, race, tumor stage, survival time, hormonal therapy, chemotherapy, BMI

Dignam J (2006)	National Surgical Adjuvant Breast and Bowel Project B-13, B-19, B-23 Trials United States	Study recruitment:1981-1988; Study follow up: until 2005	Follow up of cases of a randomised controlled trial of adjuvant treatment trial	4077 participants white: 81.7%, black: 12%, others/unknown: 6.3%, 54.5% pre/perimenopausal, 45.5% postmenopausal		Node-negative, ER-negative breast cancer; 54.9% tumour size<=2cm, 38.2% size 2.1-4cm, 6.9% size >=4.1cm	All ER-ve All node-ve	Participants of different adjuvant therapy trials		Measurement obtained only at baseline and during treatment; BMI at diagnosis was used	4077 participants 820 deaths, 624 deaths following a BC events, 196 other causes of death, 242 total second primary contralateral breast cancer	Medical records	Premenopausal Postmenopausal >=35 vs. <=24.9 Kg/m^2	0.98 (0.54-1.74) 2.13 (1.06-4.28)	Treatment, tumor size, age, ethnicity
Dignam J (2003)	National Surgical Adjuvant Breast and Bowel Project B-14 Trial United States	Study recruitment:1982-1988; Study follow up: until 2001	Randomised controlled trial of adjuvant treatment trial	3385 participants white: 91.1%, black: 4.3%, unknown: 4.6% 30.6% peri/premenopausal, 69.4% postmenopausal	166 months	Early stage breast cancer; 60.7% tumour size <= 2cm, 34.6% size 2.1-4 cm, 4.7% size >= 4 cm	All ER +ve All node-ve	64.9% tamoxifen, 35.1% placebo		From the records of original study	3385 participants 983 deaths, 595 deaths following a BC events, 388 other causes of death, 193 contralateral breast cancer, 232 other second primary cancers (plus 51 endometrium cancer)	trial medical staff (blinded)	>=30 vs. <=24.9 Kg/m^2	1.58 (1.10-2.25)	Age, menopausal status, ethnicity, tumor size, estrogen receptor level, progesterone receptor level, treatment
Cook LS (1996)	Washington SEER Nested Case-Control Study, three counties United States	Cancer diagnosis: 1978-1990; Study follow up: until 1992	Nested case-control study, within a population-based cohort of breast cancer survivor	640 participants <=85 years 33.4% premenopausal, 64.5% postmenopausal, 2% unknown	35 months	Primary in situ or invasive breast cancer; 90.2% stage I, 9.8% stage II	19.8% ER-ve, 51.8% ER+ve, 4.1% ER intermediate, 17.9% not done, 6.3% unknown, 19.8% PR-ve, 0.1% PR intermediate, 38.7% ER+ve, 26.1% not done, 15.1% unknown	Chemotherapy: 29.3% yes, 60.8% no, 9.9% unknown; Radiation therapy: 41.3% yes, 47.2% no, 11.5% unknown	9% lost	From hospital medical records; at initial diagnosis	640 participants 234 contralateral breast cancer	Cancer registry	>=30 vs. <=21 Kg/m^2	0.98 (0.57-1.69)	Age at diagnosis, stage, year of diagnosis, family history, tumor histology, menopausal status
Storm HH (1992)	Danish Cancer Registry Case-Control Study Denmark	Cancer diagnosis: 1943-1978 Recruited 8 years after the diagnosis of the first cancer	Nested case-control study, within a cohort of breast cancer survivor	1058 participants 38% premenopausal, 53% peri- & postmenopausal, 9% unknown	8 Years (min)	Primary invasive breast cancer; localized, regional, distant metastasis		> 90% mastectomy, 82% adjuvant radiotherapy		From hospital records; post diagnosis treatment	1058 participants 271 contralateral breast cancer	Hospital records	>=30 vs. <25 Kg/m^2	1.77 (1.0-3.14)	Radiotherapy, hormonal therapy, chemotherapy, menopausal status, family history, parity, age, year of diagnosis, survival time

Horn P (1988)	Connecticut Tumor Registry Case-Control Study United States	Cancer diagnosis: since 1935 for initial primary BC, 1975-1983 for contralateral BC	Follow-up of cases of a case-control study	556 participants 57 years (mean) 20 - 93 years Mostly white Among those with data: 32% pre/perimenopausal, 68% postmenopausal	8 Years (max)	First primary breast cancer		75% radical or modified radical mastectomy (both cases and controls)		From medical records post diagnosis / factors at initial diagnosis	556 participants 292 contralateral breast cancer, 264 unilateral breast cancer	Pathology	Quetelet Index I>=35 vs. <=34	1.10 (0.70-1.70)	Nulliparity, menopausal status, estrogen use, smoking, family history, histology ,chemotherapy, radiotherapy, time Since diagnosis, age, benign breast disease. Only 2 categories of BMI

Table 98 Table of excluded studies on BMI less than 12 months after diagnosis and contralateral breast cancer

Author Year	**Study name**	**Diagnosed / recruitment dates End of follow-up**	**Study type**	**Study characteristics**	**Follow-up time**	**Tumour characteristics**	**Hormone receptor status** / **Nodal status**	**Treatment info**	**Response rate** / **Loss to follow-up**	**Exposure assessment Timeframe**	**Outcome events Number in analysis**	**Outcome confirmation**	**Contrast**	**RR (95% CI)**	**Adjustments** / **Exclusion reason**
Majed B (2008)	Curie Institute Breast Cancer Study France	Breast cancer treatment: 1981-1999, Study follow-up: Until 2004	Prospective cohort of breast cancer survivors	14709 participants 44.8% premenopausal, 55.2% postmenopausal Obesity: 7.9% yes 20.2% cancers detected by mammography	8 years	Stages: 36.2% I, 51.1% II, 12.6% III; SBR grades: 22.9% I, 23% II weak, 18.8% II strong, 16.2% III, 9.4% non gradation, 9.7% NA; Tumor size (cm): 12% <=1, 23.9% 1-2, 44.4% 2-5, 13.5% >5, 6.2% NA; Tumor histology: 73.7% ductal, 8.5% lobular, 6.9	50.9% ER+, 17.4% ER-, 31.7% NA; 50.2% PR+, 24.2% PR-, 25.6% NA / Clinical node involvement: 82.1% N0-N1a, 17.9% N1b-N3	Conservative surgery: 57.2% yes; Non-conservative surgery: 29% yes; Non surgical local treatment: 13.8% yes; Hormonal therapy: 33.1% yes; Chemotherapy: 30.8%; Radiotherapy: 86.6% yes		Measured at diagnosis	14709 participants 1009 contralateral breast cancer	Cancer registry	>30 vs <=30kg/m^2	1.17 (0.93-1.48)	Age,tumor dimension,clinical node development,year of recruitment,year of diagnosis,tumor estrogen,progesterone receptor level,clinical tumor extension,number of axillary invaded nodes,Scarf-Bloom-Richardson grade / Superseded by Majed, 2011
Majed B (2009)	Curie Institute Breast Cancer Study France	Study recruitment: 1981-1999, Study follow-up: Until 2004	Prospective cohort of breast cancer survivors	14709 participants	8 years	First invasive unilateral breast cancer without distant dissemination				Measured at diagnosis	14709 participants 1009 contralateral breast cancer	Cancer registry	Training sub-cohort / Validation sub-cohort / <=24 vs >24 kg/m^2	1.33 (1.14-1.56) / 1.04 (0.82-1.32)	Age, menopausal status, tumor size, receptor status, nodal status, surgery type, hormonal therapy, chemotherapy, radiotherapy / Superseded by Majed, 2011

12 months or more after diagnosis BMI and second primary breast cancer/contralateral breast cancer

No study has reported data.

BMI and second primary endometrial cancer

BMI before diagnosis and second primary endometrial cancer

Only Trentham-Dietz et al. (2007) reported data. For the highest versus the lowest comparison, the RR for ≥ 28.9 vs. < 22.5 was 2.23, 95% CI 1.23-4.05, p_{trend} = < 0.0001.

BMI less than 12 months after diagnosis and second primary endometrial cancer

Methods

Four studies were identified. Dose-response meta-analysis was not conducted because only two studies (Ewertz, 1984; Bernstein, 1999) could be included. The other two studies provided results by two BMI categories only (Dignam, 2003; Pukkala, 2002). All four studies were included in a highest versus lowest meta-analysis. We included the BMI categories as defined by the studies. The reference category in most studies was the normal weight group, but may include underweight women. BMI could be assessed less than 12 months after, e.g. several months but less than a year after diagnosis or just before cancer treatment.

Main results and heterogeneity

In the highest versus lowest meta-analysis, the summary RR was 1.94 (95% CI 1.45-2.59; I^2 = 0%; p = 0.84; 4 studies).

Study quality

Number of second primary endometrial cancer cases ranged from 51 to 142 cases. The follow-up time ranged from an average of 3.9 years to a maximum of 15 years. The study by Dignam et al. (2003), originated from a randomised controlled trial of adjuvant treatment, examined pre-treatment BMI in lymph node negative and estrogen receptor positive breast cancer cases only. Bernstein et al. (1999) and Pukkala et al. (2002) identified cases via cancer registries. Ewertz et al. (1984) was originally a case-control study. Cases in the studies were diagnosed from 1943-1977 (Ewertz, 1984), from 1978-1992 (Bernstein, 1999), or in the 1980s (Pukkala, 2002; Dignam, 2003).

Two studies (Bernstein, 1999; Dignam, 2003) included women of all ages, while it was mostly postmenopausal women in the study by Pukkala et al. (2002). Results were

multivariate adjusted in three studies (Bernstein, 1999; Pukkala, 2002; Dignam, 2003). Adjustment was unclear in Ewertz et al. (1984), but the cases (with breast cancer patients with a second primary endometrial cancer) and controls (breast cancer patients) were matched by age and calender year of diagnosis, and length of survival with an intact uterus.

Published meta-analysis

The summary RR for obese compared with non-obese was 1.96 (95% CI 1.43-2.70; p = 0.80; 4 studies) in the meta-analysis conducted by Pecollo et al. (2012).

Figure 132 Highest versus lowest forest plot of BMI less than 12 months after diagnosis and second primary endometrial cancer

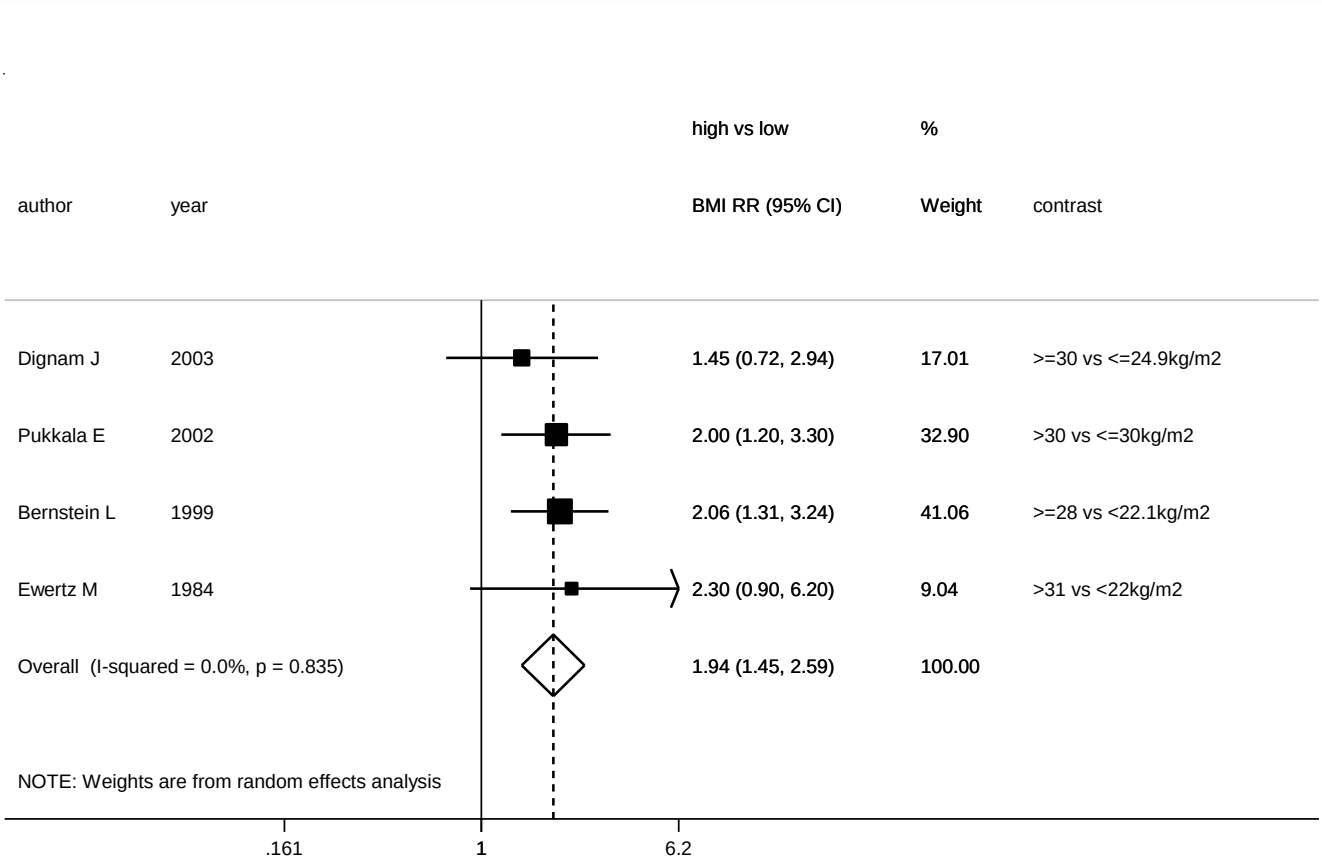


Table 99 Table of included studies on BMI less than 12 months after diagnosis and second primary endometrial cancer

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow -up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Dignam J (2003)	National Surgical Adjuvant Breast and Bowel Project B-14 Trial United States	Study recruitment:1982-1988; Study follow up: until 2001	Randomised controlled trial of adjuvant treatment trial	3385 participants white: 91.1%, black: 4.3%, unknown: 4.6% 30.6% peri/premenopausal, 69.4% postmenopausal	166 months	Early stage breast cancer; 60.7% tumour size <= 2cm, 34.6% size 2.1-4 cm, 4.7% size >= 4 cm	All ER +ve / All node -ve	64.9% tamoxifen, 35.1% placebo		From the records of original study	3385 participants 983 deaths, 595 deaths following a BC events, 388 other causes of death, 193 contralateral breast cancer, 232 other second primary cancers (plus 51 endometrium cancer)	trial medical staff (blinded)	>=30 vs. <=24.9 Kg/m^2	1.45 (0.72-2.94)	Age, menopausal status, ethnicity, tumor size, estrogen receptor level, progesterone receptor level, treatment
Pukkala E (2002)	Finnish Cancer Registry Case-Control Study Finland	Cancer diagnosis: since 1980, Study follow up: until 1995	Nested case-control study, within a population-based cohort of breast cancer survivor	512 participants Mostly white Mostly postmenopausal HRT use: 33.6% no use, 7.2% <5 yrs use, 6.2% >=5 yrs use, 52.9% unknown		60.5% localized, 30.1% regional, 3.5% distant breast cancer, 5.9% unknown	12.3% ER-ve/PR-ve, 40.6% ER+ve/PR+ve, 19.3% ER+ve/PR-ve or ER-ve/PR+ve, 27.7% unknown	Chemotherapy: 89.6% no, 7.6% yes, 2.7% unknown; Radiotherapy: 37.5% no, 59.8% yes, 2.7% unknown; 29% Tamoxifen, 1.8% toremifene		From hospital records post diagnosis; post diagnosis treatment	512 participants 144 endometrial cancers	Hospital records	>30 vs.<=30 Kg/m^2	2.0 (1.20-3.30)	Tamoxifen use, progesterone receptor level, parity, radiotherapy, chemotherapy, HRT
Bernstein L (1999)	Four US Regions Nested Case-Control Study United States	Cancer diagnosis: 1978-1992 (breast cancer), 1978-1993 (endometrial cancer)	Population-based nested case-control study	995 participants 38 - 94 years Mostly white HRT users: 314 estrogen users, 70 combined hormone users (40 of these previously used estrogen), 515 non-users, 136 unknown Comorbidities: History of diabetes: 11.8% yes, 88.2% no; History of hypertension: 47.7% yes, 52.3% no	3.9 years			Chemotherapy: 24.1% yes, 74.9% no; Radiotherapy: 29.3% yes, 69.1% no; Tamoxifen: 39.7% yes, 60.3% no		From medical records; weight and height at initial diagnosis	995 participants 324 second primary cancers (endometrial)	Medical records	>=28 vs. <22.1 Kg/m^2	2.06 (1.31-3.24)	Tamoxifen use, months of estrogen use, HRT, oral contraceptive use, smoking status at diagnosis, history of high blood pressure

Ewertz M (1984)	Danish Cancer Registry Case-Control Study	Cancer diagnosis: 1943-1977	Follow up of cases of a case-control study	350 participants 115 cases, 235 controls 59 years (mean) Comorbidities: Diabetes: 11 in cases and 22 in controls; Hypertension: 24 in cases and 50 in controls	10.8 years in cases, 12.1 years in controls	Primary breast cancer				From hospital records	350 participants 115 endometrial cancers		>31 vs. <22 kg/m^2	2.3 (0.9-6.2)	Matched by age at breast cancer diagnosis, length of survival with an intact uterus, calender year of breast cancer diagnosis

12 months or more after diagnosis BMI and second primary endometrial cancer

No study has reported data.

Before diagnosis BMI and second primary colorectal cancer

Only Trentham-Dietz et al. (2007) reported data. For the highest versus the lowest comparison, the RR for ≥ 28.9 vs. < 22.5 was 1.67 (95% CI 0.99-2.82; p = 0.07).

BMI less than 12 months after diagnosis and second primary colorectal cancer

Only Kmet et al. (2003) reported data. The OR for BMI ≥ 30 vs. < 30 kg/m^2 was 2.2 (95% CI 1.2-3.9).

12 months or more after diagnosis BMI and second primary colorectal cancer

No study has reported data.

Before diagnosis BMI and second primary ovarian cancer

Only Trentham-Dietz, 2007 had reported data. For the highest versus the lowest comparison, the RR for ≥ 28.9 vs. < 22.5 was 0.80 (95% CI 0.28-2.29, p_{trend} = 0.45).

BMI less than 12 months after diagnosis and second primary ovarian cancer

No study has reported data.

12 months or more after diagnosis BMI and second primary ovarian cancer

No study has reported data.

Table 100 Table of studies on BMI before diagnosis and second primary colorectal cancer

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Trentham-Dietz A (2007)	Wisconsin Follow-up Study of Women with Invasive Breast Cancer United States	Cancer diagnosis: 1987-2000, Study follow-up: Until 2002 Recruited approximately 1 year after diagnosis	Follow-up of cases of case-control studies	10953 participants 59.4 years (mean) 18 - 79 years	7.1 years	Stages: 63% local, 28.9% regional, 2.3% distant, 5.8% unknown			83.30%	Self-reported pre-diagnosis weight and height at interview approximately1year after diagnosis	10953 participants 1188 second cancers: 488 second breast cancers, 132 colorectal cancers, 113 endometrial cancers, 36 ovarian cancers In analysis: 8020 postmenopausal, 127 second primary colorectal cancer only	Cancer registry	>=28.9 vs. <=22.4 Kg/m^2	1.67 (0.99-2.82)	Age, year of diagnosis, tumor stage, family history, smoking, alcohol intake, parity, HRT, menopausal status

Table 101 Table of studies on BMI before diagnosis and second primary colorectal cancer

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Kmet L (2003)	Washington SEER Nested Case-Control Study United States	Cancer diagnosis: 1978-1992,	Nested case-control study within a retrospective cohort of breast cancer	470 participants 40.0 - 84.0 years 5.5% premenopausal, 94.5% postmenopausal HRT use: 32.2% estrogen only, 3.8% estrogen and progestin, 42.1% non-users, 21.9% unknown	47 months between 1st and 2nd cancer diagnosis	Stages I-III; 96% of cases, 94% of controls of stage I or II	66.1% ER+/PR+/ER+PR+, 11.5% ER-/PR-, 8.7% unknown, 13.7% not done			From hospital records	416 participants 146 colorectal cancer	Hospital records	>=30 vs. <30kg/m2	2.2 (1.2-3.9)	Cases and controls matched for calendar year, age, stage of disease; adjusted for family history of breast cancer

Table 102 Table of studies on BMI before diagnosis and second primary ovarian cancer

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow -up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Trentham-Dietz A (2007)	Wisconsin Follow-up Study of Women with Invasive Breast Cancer United States	Cancer diagnosis: 1987-2000, Study follow-up: Until 2002 Recruited approximately 1 year after diagnosis	Follow-up of cases of case-control studies	10953 participants 59.4 years (mean) 18 - 79 years	7.1 years	Stages: 63% local, 28.9% regional, 2.3% distant, 5.8% unknown			83.30%	Self-reported pre-diagnosis weight and height at interview approximately1year after diagnosis	10953 participants 1188 second cancers: 488 second breast cancers, 132 colorectal cancers, 113 endometrial cancers, 36 ovarian cancers In analysis: 8020 postmenopausal, 28 second primary ovarian cancer only	Cancer registry	>=28.9 vs. <=22.4 Kg/m^2	0.80 (0.28-2.29)	Age, year of diagnosis, tumor stage, family history, smoking, alcohol intake, parity, HRT, menopausal status

7.2 Other weight adjusted for height measures

Other weight adjusted for height measures before diagnosis and total mortality

No study has reported data.

Other weight adjusted for height measures less than 12 months after diagnosis and total mortality

Five studies reported results on other weight adjusted for height measures (relative weight, obesity index, and percentage of ideal weight) less than 12 months after diagnosis. Meta-analysis was not conducted because different measurements were used.

In general, studies showed that a higher measurement was associated with poorer survival. Kyogoku et al. (1990) showed that for the highest versus the lowest comparison, the RR for total mortality was 3.86 with relative weight, and 4.42 with obesity index (95% CIs not shown, both $p_{trend} < 0.01$). Majed et al. (2009) reported that for ≥ 20% versus < 20% over ideal weight, the RRs were respectively 1.11 (95% CI 1.02-1.21) and 1.10 (95% CI 0.96-1.25) for the training and validation samples in the study. Suissa et al. (1989) observed a significant non-linear increase in risk with each unit increase of ideal weight ratio (estimated coefficient = 0.133, p = 0.003). Abe et al. (1976) reported that obese subjects (≥ 20% over standard weight) had a worse survival than non-obese subjects (< 20% over standard weight). The survival rates were 55.6% and 79.9% respectively. However, a hospital-based study of 83 women reported that 5-year survival rates were not significantly lower for obese women (measured by an index of lb/in) compared to other women but the data was not available (Donegan, 1978).

Other weight adjusted for height measures 12 months or more after diagnosis and total mortality

No study has reported data.

Table 103 Table of studies on other weight adjusted for height measures less than 12 months after diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Majed B (2009)	Curie Institute Breast Cancer Study France	Study recruitment: 1981-1999, Study follow-up: Until 2004 Recruited at diagnosis	Prospective cohort of breast cancer survivors	14709 participants	8 years	First invasive unilateral breast cancer without distant dissemination				Measured at diagnosis	14709 participants 3693 deaths 1009 contralateral recurrences, 555 second primary cancers	Hospital records	Training sub-cohort Validation sub-cohort >=20 vs. <20 above ideal weight ratio – [(1-weight/(height-100)*0.9)*100]%	1.11 (1.02-1.21) 1.10 (0.96 - 1.25)	Age, menopausal status, tumor size, receptor status, nodal status, surgery type, hormonal therapy, chemotherapy, radiotherapy
Kyogoku S (1990)	Fukuoka Hospitals, Japan Follow-up Study Japan	Study recruitment:1975-1978; Study follow up: until 1987 Newly diagnosed patients recruited	Follow up of cases of a hospital-based case-control study	213 participants 55.5 years (mean) 32.3% pre-menopausal, 67.6% post-menopausal	12 years	80 patients had TNM Stage I, 102 Stage II, 13 Stage III	87 patients had N0, 91 had N1, 17 had N2, 17 had N3 and N4	16 patients had radiation therapy, 87 chemotherapy, 130 endocrine therapy	95.80% 9 patients lost	Assessed by an interview 1-3 after operation	213 participants 64 deaths, 47 breast cancer mortality, 6 second primary cancer mortality, 4 death from cardiac failures and 3 death from cerebro-vascular diseases and 4 other causes of death	Death certificate	Relative weight – weight/(height -100*0.9) >=1.2 vs. <1.0 Obesity index – weigh/(height$^{1.7499}$) >=8.0 vs. <6.0	3.86, p for trend<0.01 4.42, p for trend<0.01	Tumor stage, age of menarche, age at first birth, menopausal status, history of abortion, smoking, radiotherapy, chemotherapy, hormonal therapy, type of operative procedure, history of benign breast disease
Suissa S (1989)	National Surgical Adjuvant Breast project protocol B-04 Canada	Study recruitment: 1971-1973; Study follow up: until Jan 1986	Retrospective cohort study of cases of a randomised controlled trial	68 participants 52.7 years (mean) 29.0 - 72.0 years 38% premenopausal	13 years	31% stage II			1 patient lost	From the patients records; weight and height at the time of mastectomy	68 participants	Active follow-up and review	Per 1 WIR – 100 (weight/ideal weight)	Estimated coefficient 0.133, p-value=0.003	Age, tumor stage, menopausal status, treatment
Abe R (1976)	Breast Cancer Survivors Study, Sendai Japan Japan	Breast cancer treatment: within past 10 years, Study follow-up: minimum 5 years Post-treatment	Prospective cohort of breast cancer survivors	134.0 participants 47.0 years (mean) 59.7% premenopausal, 40.3% postmenopausal Obesity: 24.6%	At 5 years	Stages: 31.3% I, 42.5% II, 19.4% III, 6.7% IV; Tumor grades: 22.4% T1, 53% T2, 17.2% T3, 7.5% T4	65% +ve, 35.1% -ve		52 patients	At-diagnosis	82 participants, 21 deaths	Hospital records	Obese vs non-obese (>20% standard weight vs. <=20% standard weight) 5-year survival	55.6% vs 79.9%	
Donegan (1978)	Milwaukee hospital-based study United States		Hospital-based study	83 participants 56.4 years (mean)	At 5 years			Had mastectomy		At-diagnosis	83 participants	Hospital records	>2.45 <=2.45 lb/inch 5-year survival rates	Not signficaintly lower for obese women	Obesity index; 5-year survival rates only

Other weight adjusted for height measures before diagnosis and breast cancer mortality

Two studies reported results on other weight adjusted for height measures (obesity index and relative weight) at-diagnosis. Nomura et al. (1991) observed a statistically significant association between obesity index and breast cancer mortality in Japanese women and a non-significant association in Caucasian women (RR for high vs. low = 3.53; 95% CI 1.25-10.0, and 1.15; 95% CI 0.51-2.62, respectively). Jain et al. (1994b) reported a non-significant association with relative weight (RR for > 44.2% vs. < 35.9% = 0.96; 95% CI 0.58-1.60).

Other weight adjusted for height measures less than 12 months after diagnosis and breast cancer mortality

Bastarrachea et al. (1994) reported results on obesity, defined as weight > 20% over ideal weight. For obese versus non-obese, the RR was 1.36 (95% CI 1.06-1.76) in this study.

Other weight adjusted for height measures 12 months or more after diagnosis and breast cancer mortality

No study has reported data.

Table 104 Table of studies on other weight adjusted for height measures before diagnosis and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Jain M (1994)b	National Breast Screening Study Canada	Study recruitment: 1980-1985; Cancer diagnosis:1981-1982; Study follow up: until 1988	Randomised controlled trial of mammography screening trial	1033 participants 52.2 years (mean) 40 - 66 years Trial group screened; 48% detected by screening	5.2 years	Invasive breast cancer; any stage	341 node+ve women			Measured during screening prior to diagnosis	1033 participants 133 breast cancer mortality	Death certificate	Weight/height >44.2% vs. <35.9%	0.96 (0.58-1.60)	Age at diagnosis, nodal Status (number of positive nodes)
Nomura AM (1991)	Hawaiian Caucasian, Japanese Follow-up Study, United States	Cancer diagnosis:1975-1980; Study follow up: until 1987	Follow-up of cases of a hospital-based case-control study	343.0 participants 45.0 - 74.0 years Japanese; Caucasian	12.5 years (max)	Japanese: 12% in situ, 63% localized, 24%regional, 1% distant; Caucasian: 5% in situ, 56% localized, 36% regional, 3% distant			82.70% 10% of the Caucasian cases and 3% of the Japanese	Interviewed after diagnosis in mean of 2.2 months;	161 Caucasian, 182 Japanese; 78.6% and 86.6% survival rate	Cancer registry	Obesity index – weight/height$^{1.5182}$ High vs low Caucasian Japanese	 1.15 (0.51-2.62) 3.53 (1.25-10.00)	Tumor stage,menopausal status,Hormonal therapy, total fat intake

Table 105 Table of studies on other weight adjusted for height measures less than 12 months after diagnosis and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Bastarrachea J (1994)	MD Anderson Cancer Center, Texas Review Study United States	Study recruitment: 1974-1982; Study follow up: 10.7 yrs (median)	Randomised controlled trial of adjuvant treatment trial; ancillary analysis	735.0 participants 47.7% premenopausal, 52.2% postmenopausal	10.7 years	Primary invasive breast cancer; 69.2% stage II, 30.7% stage III	All node +ve, 38.3% <= 3 nodes +ve, 37.8% 4-10 nodes +ve, 23.5% >10		1%	From medical records	735 participants, 298 breast cancer mortality	Hospital records	Obese vs non-obese (>20% ideal weight vs <=20% ideal weight)	1.36 (1.06-1.76)	Tumour stage, nodal status, menopausal status

7.3 Weight

Table 106 Summary results of meta-analysis on before and less than 12 months after diagnosis weight and total mortality and breast cancer mortality*

	Total mortality			Breast cancer mortality		
Comparison	**No. of studies**	**No. of events in studies**	**RR (95% CI) I^2, $P_{heterogeneity}$**	**No. of studies**	**No. of events in studies**	**RR (95% CI) I^2, $P_{heterogeneity}$**
Weight assessed before breast cancer diagnosis						
Highest vs. lowest	6	1908	1.33 (1.10-1.61) 49.2%, p = 0.08	3	511	1.11 (0.57-2.18) 77.7%, p = 0.01
Weight assessed less than 12 months after breast cancer diagnosis						
Highest vs. lowest	3	4117	1.16 (1.02-1.31) 27.1%, p = 0.25	3	576	1.38 (0.99-1.92) 58.9%, p = 0.09
Per 5 kg/day	3	424	1.05 (1.03-1.08) 18.2%, p = 0.30	3	289	1.04 (0.95-1.14) 73.7%, p = 0.02

*No studies on second cancers were included in the meta-analyses. Only studies on weight before and less than 12 months after diagnosis could be included in meta-analyses.

Weight and total mortality

Fifteen studies on total mortality were identified, with six studies from seven publications (Greenberg, 1985; Zhang, 1995; Ewertz, 1991; Kumar, 2000; Reeves, 2000; Bernstein, 2002; Cleveland, 2007) examined before diagnosis weight, nine studies (Heasman, 1985; Williams, 1988; Lees, 1989; Kyogoku, 1990; Haybittle, 1997; Saxe, 1999; Abrahamson, 2006b; Majed, 2009, Goodwin, 2012) examined weight less than 12 months after diagnosis, and one study (Ewertz, 1991) examined weight 12 months or more after diagnosis. Ewertz, et al (1991) reported on both before and 12 months or more after diagnosis weight.

Weight before diagnosis and total mortality

Methods

Six studies from seven publications were identified. The publication by Reeves et al. (2000) superseded the one by Greenberg et al. (1985) with more number of events. All six studies (Zhang, 1995; Ewertz, 1991; Kumar, 2000; Reeves, 2000; Bernstein, 2002; Cleveland, 2007) could be included in the highest versus lowest meta-analysis. Dose-response meta-analysis was not conducted becasuse only two studies (Zhang, 1995; Ewertz, 1991) could be included. The other studies either have results on two weight

categories only (Kumar, 2000; Cleveland, 2007) or of insufficient data (Reeves, 2000; Bernstein, 2002). Kumar et al. (2000) assessed weight at 30 years.

Main results and heterogeneity

For the highest compared to the lowest weight, the summary RR was 1.33 (95% CI 1.10-1.61; I^2 = 49.2%; p = 0.08; 6 studies).

Study quality

One study had 56 deaths after an average of 2.9 years of follow-up (Zhang, 1995). Another study had 83 deaths after a minimum of ten years (Kumar, 2000). All other studies had more than 100 deaths. Five studies (Ewertz, 1991; Kumar, 2000; Reeves, 2000; Bernstein, 2002; Cleveland, 2007) were follow-up of case-control studies, where cases were identified in hospitals or through cancer registries. One study (Zhang, 1995) was a population cohort. Cases in one study (Cleveland, 2007) were diagnosed between 1996 and 1997. Other studies had cancer diagnosis dated before this. Of those cases identified in the study by Cleveland et al., 410 cases were without follow-up data due to nonresponse, refusal, untraceability, or death without an identifiable, leaving 1508 participants in the study.

The study by Bernstein et al. (2002) involved women with a second primary breast cancer. Three studies (Zhang, 1995; Bernstein, 2002; Cleveland, 2007) included *in situ* and invasive breast cancers, while other studies (Ewertz, 1991; Kumar, 2000; Reeves, 2000) included invasive breast cancers at different stages. Five studies (Ewertz, 1991; Kumar, 2000; Reeves, 2000; Bernstein, 2002; Cleveland, 2007) retrospectively assessed pre-diagnosis anthropometry data at cancer diagnosis or within a year after diagnosis. One study collected the data before diagnosis (Zhang, 1995). All studies had pre- and postmenopausal women, except Zhang et al. (1995) with all postmenopausal women.

All studies provided results that were multivariate adjusted, including tumour stage, except Kumar et al. (2000) (tumour stage only) and Cleveland et al. (2007) (age and hypertension). Ewertz et al. (1991) performed stratified analysis by early or advance diseases. Analysis of the advance disease was multivariate adjusted, while the analysis of the early disease was age and area of residence adjusted only.

Figure 133 Highest versus lowest forest plot of weight before diagnosis and total mortality

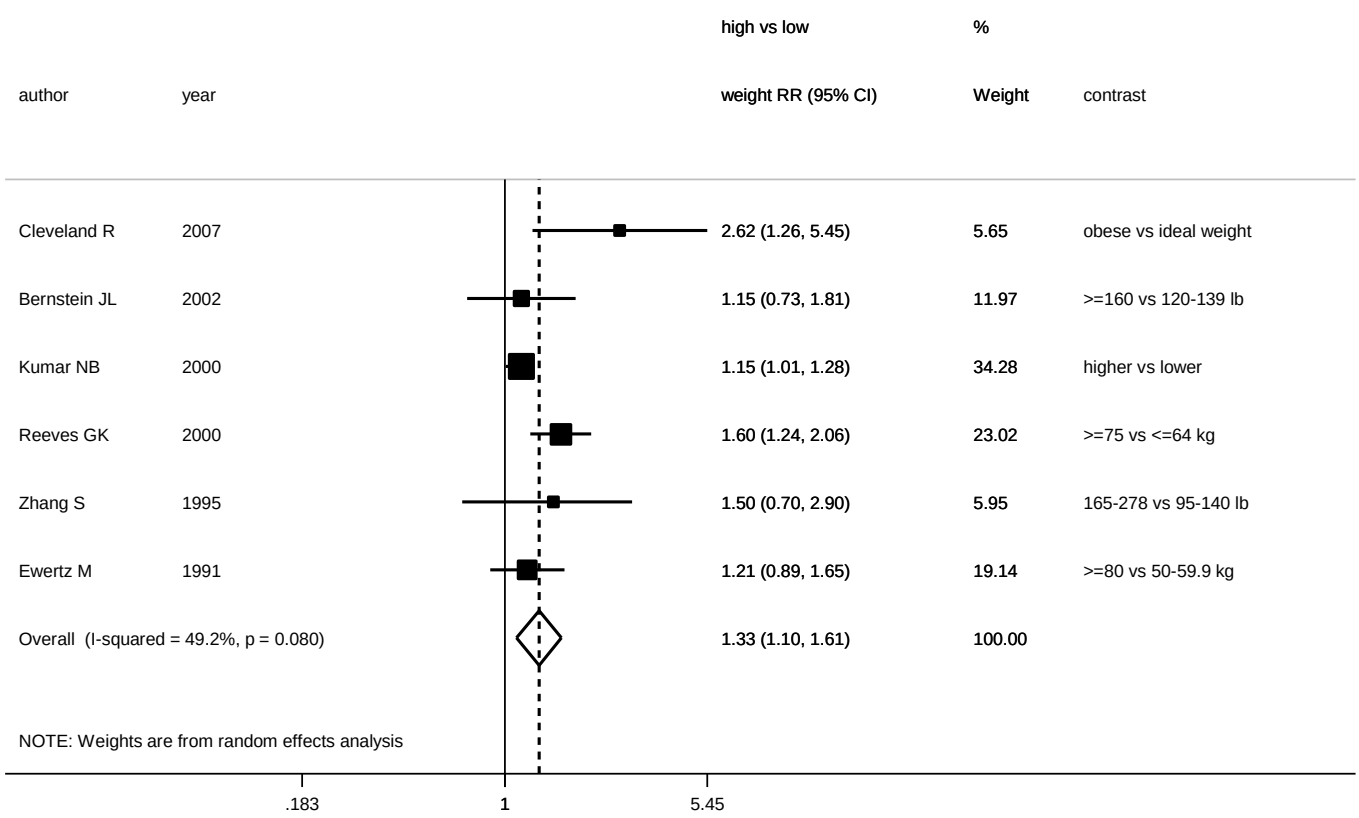


Table 107 Table of included studies on weight before diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Cleveland R (2007)	Long Island Breast Cancer Study Project United States	Cancer diagnosis:1996-1997; Study follow up: 2002- 2004	Follow up of cases of a case-control study	1508 participants 58.8 years (mean) 25 - 98 years Mostly white 32.2% premenopausal, 67.8% postmenopausal HRT use: 86.8% ever, 13.2% never	66.7 months	84.4% invasive and 15.6% In situ	26.7% ER-ve, 73.3% ER +ve, 35.8% PR-ve, 64.2% PR+ve 73.7% no nodes involved, 26.3% nodes involved	Radiation therapy, chemotherapy, hormone therapy	410 patients lost	Self-reported shortly after diagnosis; weight and height at each decade of life from age 20 years until 1 year before diagnosis	1508 participants 196 deaths (of which 21% from cardiovascular disease), 127 breast cancer mortality, 9 death from brain and lung metastases	National Death Index	Obese vs. ideal weight 1 year before diagnosis	2.62 (1.26-5.45)	Age at diagnosis, hypertension
Bernstein JL (2002)	Cancer and Steroid Hormone Study United States	Cancer diagnosis:1980-1982 (1st breast cancer) and before 1999 (2nd breast cancer); Study follow up: until 1998	Follow up of cases of a population-based case-control study	369 participants 20 - 54 years Multi-ethnic	18 years (max)	First primary breast cancer and a second primary in the contralateral breast; any stages including In situ breast cancer		81 and 71 patients had radiation treatment following first and second primary breast cancer respectively	28 patients lost	Interviewed within 6 months of diagnosis of primary cancer for data at age 18 years and adulthood	369 participants 160 deaths (90% death from cancer including 87% breast cancer mortality)	Cancer registry	>=160 vs. 120-139lb	1.15 (0.73-1.81)	Age at second diagnosis, education, tumor stage of both primary cancers, time between primary cancers
Kumar NB (2000)	H.Lee Moffitt Cancer Center and Research Institute Follow-up Study United States	Study follow-up: Until 1997 Diagnosed within 3 months of entry to the study	Follow-up of a cases of case-control study	166 participants white: 92%, black: 4%, others/Hispanic: 4% and other 17% premenopausal, 83% postmenopausal	10 years (min)	Stages: 33% I, 41% II, 9% III, 3% IV, 14% unknown	36% +ve, 64% -ve		100%	Measured within 3 months of diagnosis for exposures at diagnosis and self-reported prediagnosis from adolescence to adulthood/weight at 30 years	166 participants 83 deaths	Medical notes	Highest vs. Lowest	1.15 (1.01-1.28)	Tumor stage
Reeves GK (2000)	Six London Hospitals Follow-up Study UK	Study recruitment: 1968-1984; Cancer diagnosis: 1968-1980 for 1st study and 1980-1984 for 2nd study; Study follow up: until 1994 delete newly diagnosed	Follow-up of cases of case-control studies	1208 participants 24 - 59 years 74% premenopausal, 26% postmenopausal HRT use: Among those with data: 5% yes, 95% no use	25 Years (max)	TNM; 49.6% Stage I, 32% stage II, 17.2% stage III, 1.2% stage IV 36% node-ve, 47.8% node+ve, 16.2% unknown			39 women, 3% lost	From records of original studies	1208 participants 608 deaths	Medical records	>=75 vs. <=64 Kg	1.60 (1.24-2.06)	Age at diagnosis, year of diagnosis, hospital, stage, nodal status

Zhang S (1995)	Iowa Women's Health Study United States	Study recruitment:1986; Study follow up: until 1991	Cancer survivors of population-based prospective cohort study	698 participants 55 - 69 years Mostly white All postmenopausal	2.9 years	Unilateral breast cancer; 10% in situ, 58% local, 28% regional, 3%distant, and 1% unknown; 55% tumour size <2cm, 33% size >= 2cm and 11% unknown	Among those with data: 85% ER+ve and 72% PR+ve		42.60% < 1% migration rate	Self reported questionnaire within 6 years before diagnosis	698 participants 56 deaths, 40 breast cancer mortality (among the causes of death) and 2 death from coronary heart disease	Death certificates, National death index	165-278 vs. 95-140 lb	1.50 (0.70-2.90)	Age, smoking, education, tumor stage, ER status, tumor size
Ewertz M (1991)	Danish Breast Cancer Cooperative Group Denmark	Cancer diagnosis:1983-1984; Study follow up: until 1990	Follow up of cases of population-based case-control study	2445 participants <=70 years Among those with data, HRT use: 66.1% never usage, 33.8% ever usage	7 Years (max)	Primary Invasive breast cancer; 44.8%Grade I, 42.3% Grade II, 12.8% Grade III breast cancer	58.5% none node+ve, 28.6% 1-3 node+ve, 12.8% >4 node+ve		87%	Self-reported 1 year after diagnosis for weight 10 years prior to diagnosis	2445 participants 805 deaths	Cancer registry	Early diseases Advanced diseases >=80 vs. 50-59.9 kg	2.23 (0.87-5.61) 1.12 (0.81-1.56)	Age, area of residence Age, tumor size, nodal status, tumor grade, skin invasion, area of residence

Table 108 Table of excluded studies on weight before diagnosis and total mortality

Author Year	**Study name**	**Diagnosed / recruitment dates End of follow-up**	**Study type**	**Study characteristics**	**Follow-up time**	**Tumour characteristics**	**Hormone receptor status** **Nodal status**	**Treatment info**	**Response rate** **Loss to follow-up**	**Exposure assessment Timeframe**	**Outcome events Number in analysis**	**Outcome confirmation**	**Contrast**	**RR (95% CI)**	**Adjustments** **Exclusion reason**
Greenberg (1985)	Six London Hospitals Follow-up Study United Kingdom	Study recruitment:1968-1977; Study follow up: until December 1982	Follow up of cases of a hospital-based case-control study	582 participants 40.0 years (mean) 24.0 - 50.0 years All premenopausal	14 years	TNM; 62% Stage I, 20% Stage II, 19% Stage III+IV	40% node +ve		18 patients lost	Reported at the time of diagnosis	582 participants 228 deaths	Hospital records	>=155 vs. <=112 lb	1.7 P for trend=0.011	Tumor stage, age, social class, reproductive history, family history, smoking, oral contraceptive, year of diagnosis, hospital of diagnosis Superseded by Reeves, 2000

Weight less than 12 months after diagnosis and total mortality

Methods

Nine studies (Heasman, 1985; Williams, 1988; Lees, 1989; Kyogoku, 1990; Haybittle, 1997; Saxe, 1999; Abrahamson, 2006b; Majed, 2009; Goodwin, 2012) were identified. Three studies (Haybittle, 1997; Abrahamson, 2006b; Goodwin, 2012) could be included in the linear dose-response meta-analysis. Also, three studies (Abrahamson, 2006b; Majed, 2009; Goodwin, 2012) could be included in the highest versus lowest meta-analysis.

Saxe et al. (1999) reported unadjusted result and was not included in the analyses. No association was observed between body weight and total mortality in this study. The categorical result in Haybittle (1997) was also unadjusted (RR for > 60 vs. ≤ 60 kg = 1.20; 95% CI 1.08-1.33) and was excluded from the highest versus lowest meta-analysis. Four studes (Heasman, 1985; Williams, 1988; Lees, 1989; Kyogoku, 1990) did not have sufficient data to be included in the highest versus lowest and dose-response meta-analyses. Kyogoku et al. (1990) observed a 3.2-fold increased risk of total mortality, with a dose-response trend ($p < 0.02$), but did not present a 95% CI or p value for the association. Lees et al. (1989) also reported worsening survivalship with heavier participants ($p < 0.01$). Weight was not associated with survival in the remaining two studies (Heasman, 1985; Williams, 1988).

Goodwin et al. (2012) modelled weight as a quadratic term, with the second category being the reference group, to enhance the predictability of the relationship. For this study a linear relationship for the second to the highest category was estimated and included with other studies in the linear dose-response meta-analysis.

Main results and heterogeneity

The summary RR was 1.05 (95% 1.03-1.08; $I^2 = 18.2\%$; $p = 0.30$; 3 studies) per 5 kg increase in weight. In the influence analysis, the summary RR became statistically non-signficant when Haybittle et al. (1997) was omitted (RR 1.05; 95% CI 0.99-1.12). For the highest compared to the lowest weight, the summary RR was 1.16 (95% CI 1.02-1.31, $I^2 = 27.1\%$; $p = 0.25$; 3 studies).

Study quality

Numbers of events were 134 deaths after an average of 12.1 years of follow-up (Goodwin, 2012), 290 deaths after an average of 9.8 years of follow-up (Abrahamson, 2006b), and 3693 deaths after an average of 8 years of follow-up (Majed, 2009). In the study of Haybittle et al. (1997), 2455 stage I or II breast cancer cases were followed for 20 years, at which time 280 women remained at risk. The other studies included invasive breast cancer at different stages. Cases were either recruited in hospitals or through cancer registries (Abrahamson, 2006b; Majed, 2009; Goodwin, 2012), or orginated from a randomised controlled trial (RCT) of cancer treatment (Haybittle, 1997). Study recruitment was in 1970-1975 for the RCT, and between 1980s and 1990s for the other studies.

All studies included pre- and postmenopausal women, but Haybittle et al. (1997) analysed the association, adjusted for age, tumour size and stage, in postmenopausal women only. Abrahamson et al. (2006b) presented results adjusted for tumour stage and income. Other factors like age, race and menopausal status were not included in the final model in this study, as they did not make an appreciable change to the estimate. The other two studies (Goodwin, 2012; Majed, 2009) were adjusted for multiple risk factors, including age, tumour stage, hormone receptor status and treatment.

Figure 134 Highest versus lowest forest plot of weight less than 12 months after diagnosis and total mortality

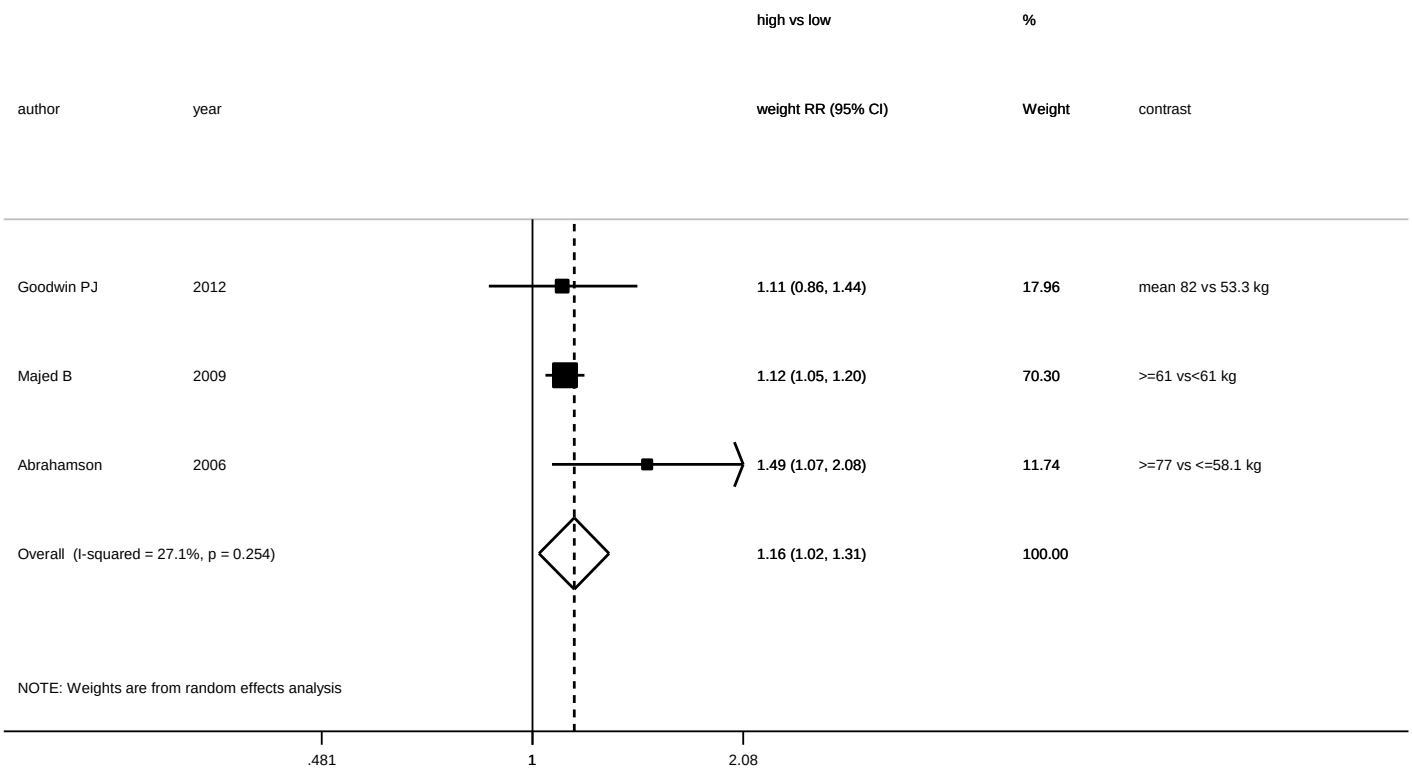


Figure 135 Linear dose-response meta-analysis of weight less than 12 months after diagnosis and total mortality

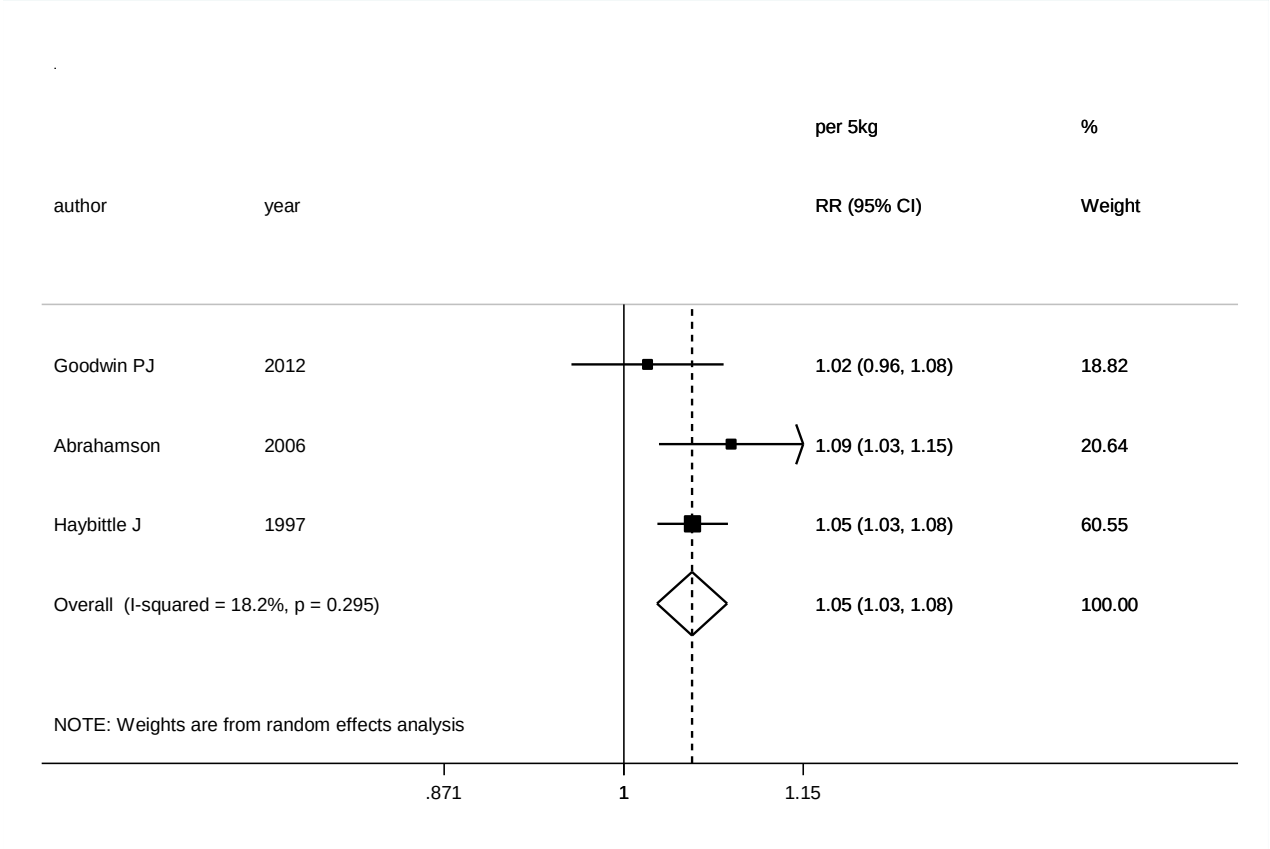


Figure 136 Individual dose-response graph of weight less than 12 months after diagnosis and total mortality

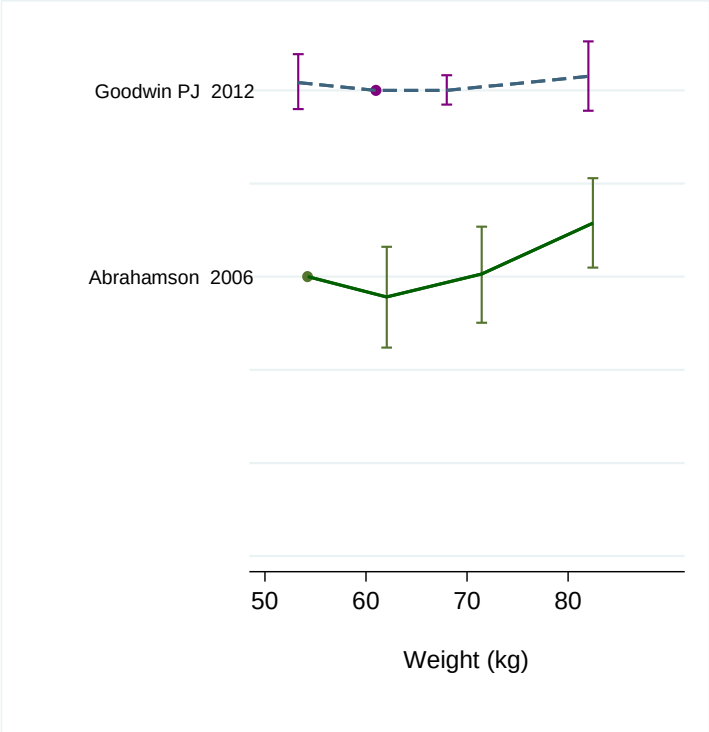


Table 109 Table of included studies on weight less than 12 months after diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments Remarks
Goodwin PJ (2012)	University of Toronto Hospitals Follow-up Study Canada	Cancer diagnosis:1989-1996; Study follow up: until 2007	Prospective cohort of breast cancer survivors	535 participants 50.3 years (mean) <=75 years Multi-ethnic 57.2% premenopausal, 4.9% perimenopausal, 37.9% postmenopausal	12.1 years	Early M0 invasive breast cancer; non-diabetic women; 55.5% T1, 32.5% T2, 5% T3, 6.9% Tx, N0-1,	67.7% ER+ve, 18.7% ER-ve, 13.6% unknown; 61.7% PR+ve, 23.4% PR-ve, 15% unknown 69.2% N0, 30.8% N1	22.8% mastectomy, 77.2% lumpectomy; adjuvant chemotherapy: 39.8% yes, 60.2% no; hormone therapy: 39.1% yes, 60.9% no	23 women, 4.3%	Measured post diagnosis; median, 7 weeks postoperatively	535 participants 134 deaths, 113 breast cancer mortality, 21 deaths from other causes	Hospital records	82 vs. 53.3 Kg	1.11 (0.86-1.44)	Age, tumor and nodal stage, tumor grade, hormone receptor status, adjuvant chemotherapy, hormonal therapy
Majed B (2009)	Curie Institute Breast Cancer Study France	Study recruitment: 1981-1999, Study follow-up: Until 2004 Recruited at diagnosis	Prospective cohort of breast cancer survivors	14709 participants	8 years	First invasive unilateral breast cancer without distant dissemination				Measured at diagnosis	14709 participants 3693 deaths 1009 contralateral recurrences, 555 second primary cancers	Hospital records	Training sub-cohort Validation sub-cohort >=61 vs. <61 Kg	1.12 (1.03-1.21) 1.12 (0.99-1.27)	Age, menopausal status, tumor size, receptor status, nodal status, surgery type, hormonal therapy, chemotherapy, radiotherapy Highest vs. lowest analysis only' two weight categories only
Abrahamson (2006)b	Atlanta, Seattle, New Jersey Follow-up Study United States	Cancer diagnosis:1990-1992; Study follow up: until 2000	Follow-up of cases of a population-based case-control study	1254 participants 20 - 54 years 78% premenopausal, 22% postmenopausal and unknown <1%	9.8 years	Invasive breast cancer; AJCC; any stage ; 57% local, 40% regional, 3% distant, <1% unknown	56% ER+ve, 35%ER-ve, 3% borderline, 6% unknown		86% <2% lost	Measured 4.2 months after diagnosis; weight and height at age 20 years and the year before diagnosis	1254 participants 290 deaths	Cancer registry + National Death Index	>=77 vs. <=58.1 Kg	1.49 (1.07-2.08)	Tumor stage, income (Result further adjusted for waist-hip-ratio was also provided in the article)
Haybittle J (1997)	Cancer Research Campaign Trial, UK	Study recruitment: 1970-1975, Study follow-up: Until 1991	Randomised controlled trial of primary treatment; ancillary analysis	2455 participants <=70 years 39.9% pre and perimenopausal, 60% postmenopausal	20 Years (max)	Stages I and II				BMI recorded at diagnosis; pre-treatment	1475 postmenopausal women		Per 1kg increase	β=0.0106, P-value=0.0003	Age, tumor size, tumor stage Dose-response analysis only; categorical result was unadjusted

Table 110 Table of excluded studies on weight less than 12 months after diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments Exclusion reason
Saxe GA (1999)	Medical Center, Michigan University Follow-up Study United States	Study recruitment: 1989-1991, Recruited during first medical center visit for suspected or newly diagnosed	Prospective cohort of breast cancer survivors	149 participants 57.8 years (mean) 26 - 95 years White: 90.6%, black:7.2% and other: 2.2%, 34.2% premenopausal, 65.8% postmenopausal	5 years (min)	Primary breast cancer, stages: 19.6% in situ, 34.5% I, 34.5% II, 8.8% III, 2.7% IV	73.4% ER+, 26.6% ER- 43% +ve, 57% -ve		0% lost	Measured close to time of diagnosis	149 participants 26 deaths	Hospital records	Per 10 kg increase	0.96 (0.76-1.21)	Unadjusted results
Kyogoku S (1990)	Fukuoka Hospitals, Japan Follow-up Study Japan	Study recruitment:1975-1978; Study follow up: until 1987 Newly diagnosed patients recruited	Follow up of cases of a hospital-based case-control study	213 participants 55.5 years (mean) 32.3% pre-menopausal, 67.6% post-menopausal	12 years	80 patients had TNM Stage I, 102 Stage II, 13 Stage III	87 patients had N0, 91 had N1, 17 had N2, 17 had N3 and N4	16 patients had radiation therapy, 87 chemotherapy, 130 endocrine therapy	95.80% 9 patients lost	Assessed by an interview 1-3 months after operation	213 participants 64 deaths, 47 breast cancer mortality, 6 second primary cancer mortality, 4 death from cardiac failures and 3 death from cerebro-vascular diseases and 4 other causes of death	Death certificate	>=60 vs. <=44.9 kg	3.2, p for trend <0.02	Tumor stage, age of menarche, age at first birth, menopausal status, history of abortion, smoking, radiotherapy, chemotherapy, hormonal therapy, type of operative procedure, history of benign breast disease Insufficient data – missing 95% CIs, missing numbers of events per category
Lees AW (1989)	Alberta Cancer Registry Follow-up Study Canada	Cancer diagnosis: 1971-1974	Retrospective cohort study	1121 participants 316 premenopausal, 60 perimenopausal, 709 postmenopausal	10 years (max)			Stage I and II were treated by either modified radical or total mastectomy, usually given with radiation therapy; Stage III patients were treated by radical radiation therapy, some had palliative radiation therapy and hormones	41 patients lost		1121 participants 369 breast cancer mortality, 122 other causes of deaths, 40 unknown causes of deaths	Cancer registry	Stratified by tumor stage Stratified by nodal status >=66 vs.<66kg 10- year survival	P-value<0.01 P-value<0.01	Unknown covariates in Cox's regression model Insufficient data – only P-value was provided for the comparison calculated in a Cox's regression model
Williams G (1988)	Christie Hospital and Holt Radium Institute Endocrine Therapy Study United Kingdom	Cancer treatment: 1975 - 1983	Prospective cohort of cancer survivors	227 participants 15% premenopausal, 4% perimenopausal, 74% postmenopausal	8 years (min)	59% operable disease 41% locally advanced tumours; 77% with one relapse, 19% two, and 4% three or more relapses	51% ER+ve, 23% ER-ve, 26% unknown; 37% PR+ve, 36% PR-ve, 27% unknown	Either received tamoxifen (88%) or orovarian ablation (12%) after relapse; Previous adjuvant chemotherapy: 85% no, 15% yes		Weight at start of endocrine therapy	227 participants		<64kg >=64kg Overall Within 133 operable cases	Log-rank test P=0.95 P=0.42	Log-rank test only; results in text – No significant difference in survival between patients above and below the median weight of 64kg. Results were not affected by menopausal

															status or hormone receptor status.
Heasman KZ (1985)	Princess Margaret Hospital Adjuvant Treatment Trial Canada	Cancer treatment: 1975 - 1981	Follow-up of a randomised controlled trial of adjuvant treatment	237 participants 25-70 years (mean 47.5 years) 80.2% premenopausal 18.1% postmenopausal 1.7% menopausal status unknown	12 months (min)	Breast cancer of all stages	Among those with ER assay: 38% ER+ve, 42% ER-ve, 20% ER status uncertain 44% 1-3 +ve nodes, 25% >=4 +ve nodes, 2% -ve node, 27% unknown, 2% unable to determine	Three arms: Melphalan or cyclophosphamide, methotrexate, and 5-fluorouracil with or without prednisone for various lengths of time		From medical records for weight before and after treatment	237 participants	Active follow-up	<=56.3kg 56.4-63.8kg 63.9-72.0kg >=72.1kg		 Results in text – No linear relationship existed between weight at entry of treatment and overall survival

Weight 12 months or more after diagnosis and total mortality

Only one study reported data (Ewertz, 1991). The RR for ≥ 80 kg versus < 50 kg was 1.02 (95% CI 0.77-1.37).

Weight and breast cancer mortality

Weight before diagnosis and breast cancer mortality

Methods

Four studies from five publications (Jain, 1994b; Zhang, 1995; Jain, 1997; Enger, 2004a; Cleveland, 2007) were identified. The two articles from Jain et al. were from the same study (Jain, 1994b; Jain, 1997). Overall results from Jain 1994b instead of the results subgrouped by tumour characteristics from Jain 1997 were reviewed here with other studies. Dose-response meta-analysis was not conducted because only two studies (Jain, 1994b; Enger, 2004a) could be included. Three studies (Jain, 1994b; Enger, 2004a; Cleveland, 2007) could be included in the highest versus lowest meta-analysis. Cleveland et al. (2007) only reported results by two weight categories and data in the remaining study (Zhang, 1995) was insufficient for the analyses. Zhang et al. (1995) reported a breast cancer mortality risk of 1.8 for the comparison of > 165-278 to 95-140 lb, with no 95% CI or p-value.

Main results and heterogeneity

For the highest compared to the lowest weight, the summary RR was 1.11 (95% CI 0.57-2.18; 3 studies), with high heterogeneity between studies (I^2 = 77.7%; p = 0.01).

Study quality

All studies had over 100 events - 127 breast cancer deaths after an average of 66.7 months of follow-up (Cleveland, 2007), 133 breast cancer deaths after an average of 5.2 years of follow-up (Jain, 1994b) and 251 breast cancer deaths after an average of 10.4 years of follow-up (Enger, 2004a). Two studies (Enger, 2004a; Cleveland, 2007) were follow-up of case-control studies and the remaining study (Jain, 1994b) was a follow-up of a breast cancer screening trial. Two studies (Enger, 2004a; Cleveland, 2007) included *in situ* and invasive breast cancers, while Jain et al. (1994b) included invasive breast cancer only. Cases in one study (Cleveland, 2007) were diagnosed between 1996 and 1997. Other studies had cancer diagnosis dated before this (1980-1989).

Of those cases identified in the study by Cleveland et al., 410 cases were without follow-up data due to nonresponse, refusal, untraceability, or death without an identifiable, leaving 1508 participants in the study. Anthropometric data referenced to times before diagnosis were collected prospectively in the study by Jain et al. (1994b), but retrospectively at or shortly after diagnosis in studies by Enger et al. (2004a) and Cleveland et al. (2007). Enger et al. (2004a) included premenopausal women only, while the other two studies

(Jain, 1994b; Cleveland, 2007) included women of all ages. Results were adjusted for age and hypertension only in Cleveland, 2007, age, tumour stage, physical activity and height in Enger, 2004a, and age, nodal status and skin-fold measurement in Jain, 1994b.

Figure 137 Highest versus lowest forest plot of weight before diagnosis and breast cancer mortality

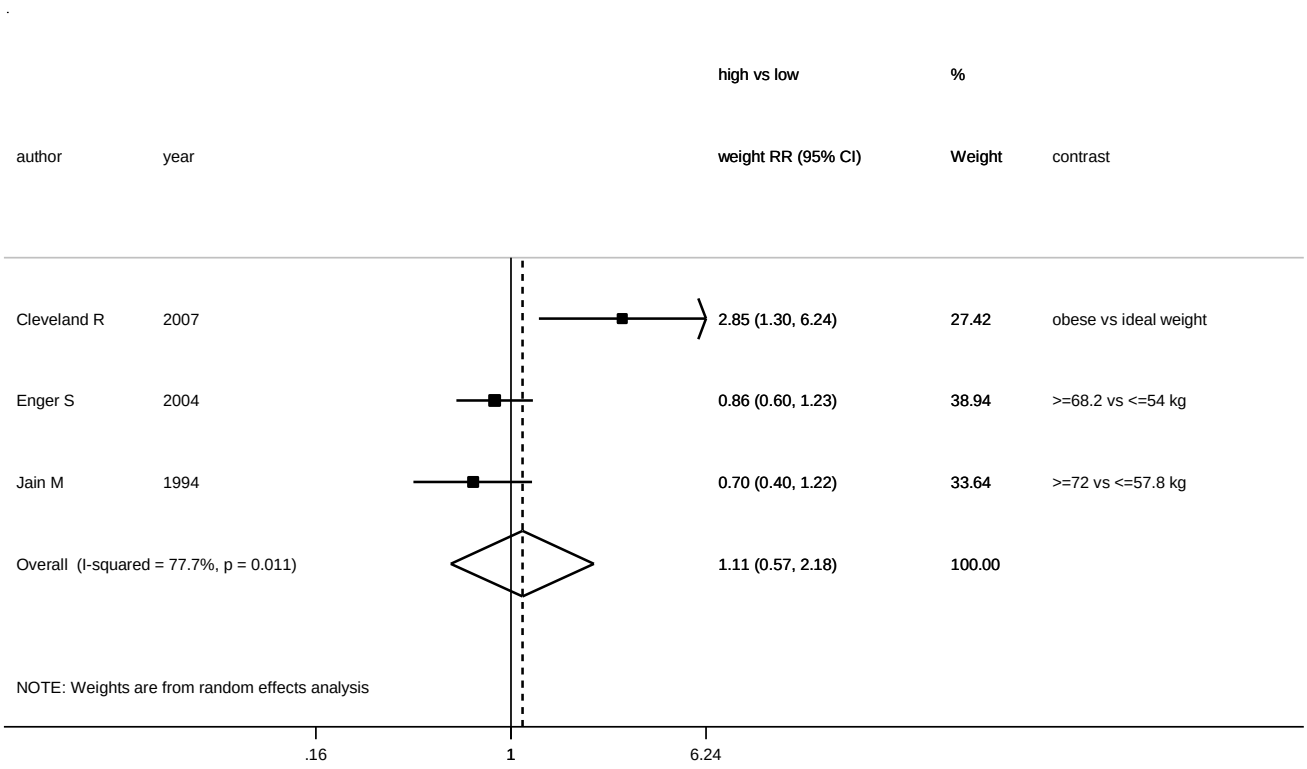


Table 111 Table of included studies on weight before diagnosis and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow -up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Cleveland R (2007)	Long Island Breast Cancer Study Project United States	Cancer diagnosis:1996-1997; Study follow up: 2002- 2004	Follow up of cases of a case-control study	1508 participants 58.8 years (mean) 25 - 98 years Mostly white 32.2% premenopausal, 67.8% postmenopausal HRT use: 86.8% ever, 13.2% never	66.7 months	84.4% invasive and 15.6% In situ	26.7% ER-ve, 73.3% ER +ve, 35.8% PR-ve, 64.2% PR+ve 73.7% no nodes involved, 26.3% nodes involved	Radiation therapy, chemotherapy, hormone therapy	410 patients lost	Self-reported shortly after diagnosis; weight and height at each decade of life from age 20 years until 1 year before diagnosis	1508 participants 196 deaths (of which 21% from cardiovascular disease), 127 breast cancer mortality, 9 death from brain and lung metastases	National Death Index	Obese vs. ideal weight 1 year before diagnosis	2.85 (1.30-6.24)	Age at diagnosis, hypertension
Enger S (2004)a	University of Southern California Cancer Surveillance Program United States	Cancer diagnosis: 1983-89, Study follow-up: Until 2000	Follow-up of cases of population-based case-control study	717 participants <=40 years Premenopausal	10.4 years	Stages: 9.9% in situ, 47.4% localized, 39.1% regional, 3.6% distant metastasis	41.1% +ve, 57.3% -ve, 1.5% unknown		76.80%	Self-reported a year prior to diagnosis in interview at study baseline	717 participants 251 breast cancer mortality, 2 deaths from coronary/CVD, 10 other causes of deaths	Death certificate	>=68.2 vs. <=54 Kg	0.86 (0.60-1.23)	Age, tumor stage, physical activity, height
Jain M (1994)b	National Breast Screening Study Canada	Study recruitment: 1980-1985; Cancer diagnosis:1981-1982; Study follow up: until 1988	Randomised controlled trial of mammography screening trial	1033 participants 52.2 years (mean) 40 - 66 years Trial group screened; 48% detected by screening	5.2 years	Invasive breast cancer; any stage	341 node+ve women			Measured during screening prior to diagnosis	1033 participants 133 breast cancer mortality	Death certificate	>=72 vs. <=57.8 Kg	0.70 (0.40-1.22)	Age at diagnosis, nodal status, anthropometry (skin-fold)

Table 112 Table of excluded studies on weight before diagnosis and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments Exclusion reason
Jain M (1997)	National Breast Screening Study Canada	Cancer diagnosis: 1982-1985, Study follow-up: Until 1992 Recruited between1980-1985 and diagnosed after July 1982	Randomised controlled trial of mammography screening trial; ancillary analysis	676 participants 49.9 years (mean) 40 - 59 years 90% Caucasian 57% postmenopausal (at enrollment) 48.4% cases detected through mammography	7.7 years	Invasive breast cancer; any stage				Measured at enrollment in screening center	83 deaths, 76 breast cancer mortality, 7 other causes of deaths	Death certificate	With ER status With PR status With nodal status With tumour size Per 5/kg increase	1.01 (0.89-1.15) 1.07 (0.93-1.23) 0.92 (0.82-1.03) 0.89 (0.78-1.00)	Age at diagnosis, weight, smoking, energy intake, when appropriate ER status, PR status, nodal status, tumour size Superseded by Jain, 1994b
Zhang S (1995)	Iowa Women's Health Study United States	Study recruitment:1986; Study follow up: until 1991	Cancer survivors of population-based prospective cohort study	698 participants 55 - 69 years Mostly white All postmenopausal	2.9 years	Unilateral breast cancer; 10% in situ, 58% local, 28% regional, 3%distant, and 1% unknown; 55% tumour size <2cm, 33% size >= 2cm and 11% unknown	Among those with data: 85% ER+ve and 72% PR+ve		42.60% <1% migration rate	Self reported questionnaire within 6 years before diagnosis	698 participants 56 deaths, 40 breast cancer mortality and 2 death from coronary heart disease	Death certificates, National death index	>165-278 vs. 95-140 lb	1.8	Age,smoking,education,Tumor stage,ER status,Tumor size Insufficient data – T3 vs. T1 only, missing 95% CI, missing numbers of events and non-events per tertile

Weight less than 12 months after diagnosis and breast cancer mortality

Methods

Six studies (Newman, 1986; Mohle-Boetani, 1988; Rohan, 1993; Hoe, 1993; Haybittle, 1997; Enger, 2004a) were identified. Three studies (Hoe, 1993; Haybittle, 1997; Enger, 2004a) could be included in the linear dose-response meta-analysis. Also, three studies (Newman, 1986; Mohle-Boetani, 1988; Enger, 2004a) could be included in the highest versus lowest meta-analysis.

Rohan et al. (1993) reported unadjusted results and was not included in the highest versus lowest and dose-response meta-analyses. A statistical significant increased risk in dying of breast cancer was reported in this study (RR for ≥ 76 vs. ≤ 57 kg = 2.06; 95% CI 1.11-3.82). Two studies were not in the highest versus lowest meta-analysis because one (Haybittle, 1997) reported unadjusted categorical results and the other reported a dose-response result (Hoe, 1993). Also two studies (Newman, 1986; Mohle-Boetani, 1988) only reported results by two weight categories and were not in the dose-response meta-analysis.

Main results and heterogeneity

The summary RR per 5 kg was 1.04 (95% CI 0.95-1.14; 3 studies), with high heterogeneity between studies (I^2 = 73.7%; p = 0.02). In the influence analysis, the summary RRs ranged from 0.99 (95% CI 0.86-1.13) when Haybittle et al. (1997) was omitted to 1.08 (95% CI 1.01-1.16) when Hoe et al. (1993) was omitted. For the highest compared to the lowest weight, the summary RR was 1.38 (95% CI 0.99-1.92; I^2 = 58.9%; p = 0.09; 3 studies).

Study quality

Hoe et al. (1993) had 43 breast cancer deaths after an average of 5.2 years follow-up. Newman et al. (1986) had 73 breast cancer deaths after a maximum of 7 years of follow-up. In the analysis by Haybittle et al. (1997), 1005 postmenopausal women were followed for 20 years, by which time 123 women remained at risk. The remaining two studies (Mohle-Boetani, 1988; Enger, 2004a) had approximately 250 breast cancer deaths after an average of 6 years or a maximum of 6.8 years of follow-up.

All studies identified participants in hospitals and/or through cancer registries, or from a randomised controlled trial (RCT) of cancer treatment (Haybittle, 1997). In this RCT, only stage I or II breast cancer cases were included. Other studies had invasive cases at different stages. Cases were diagnosed in 1970s in two studies (Newman, 1986; Haybittle, 1997), and in 1970s through to 1980s (Mohle-Boetani,1988). For the cases in Enger et al. (2004a), diagnosis dated between 1988 and 1995, and in Hoe et al. (1993), treatment dated between 1984 and 1985.

Anthropometric data were assessed at or shortly after diagnosis. All studies included pre- and postmenopausal women, but the analysis performed by Haybittle et al. (1997)

included postmenopausal women only. One result was adjusted for surgery only (Newman, 1986), or age, tumour size and stage only (Haybittle, 1997).

Figure 138 Highest versus lowest forest plot of weight less than 12 months after diagnosis and breast cancer mortality

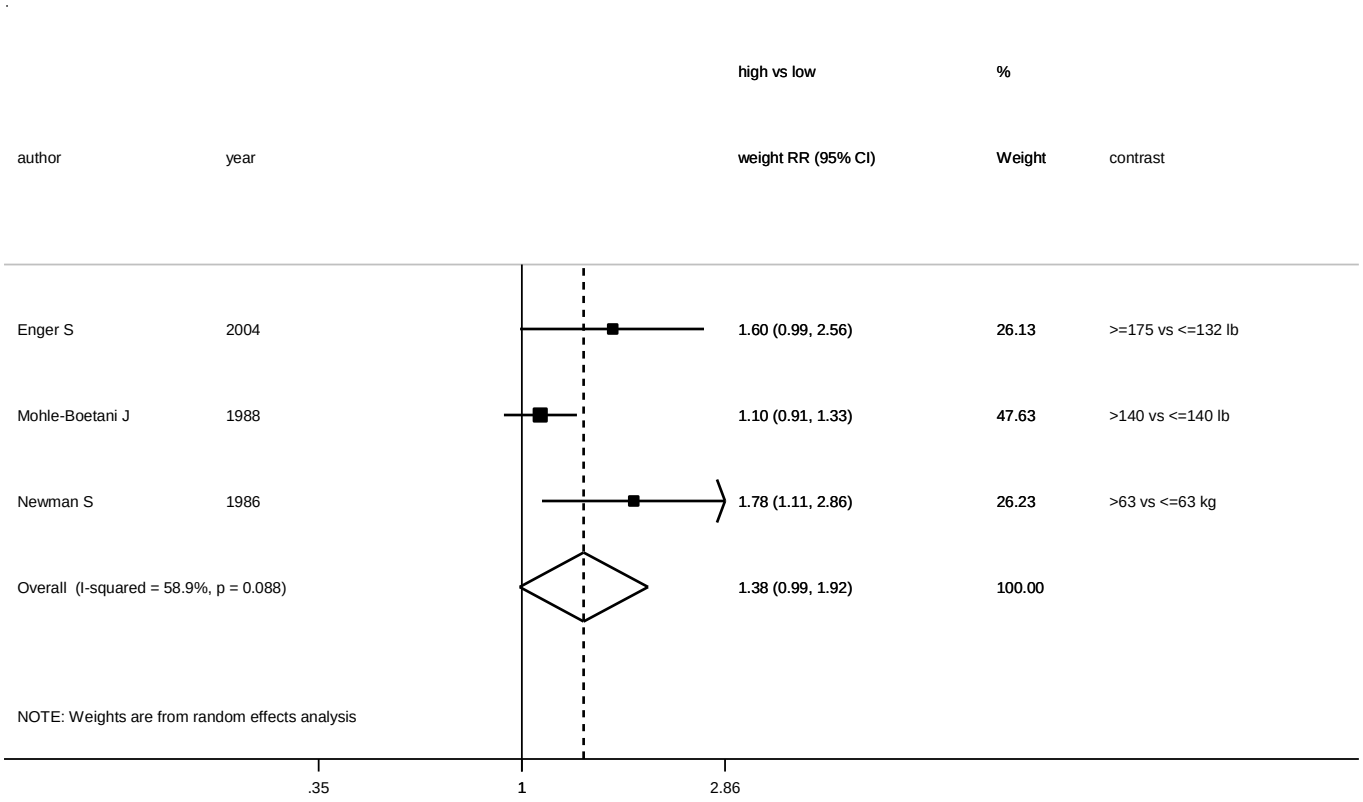
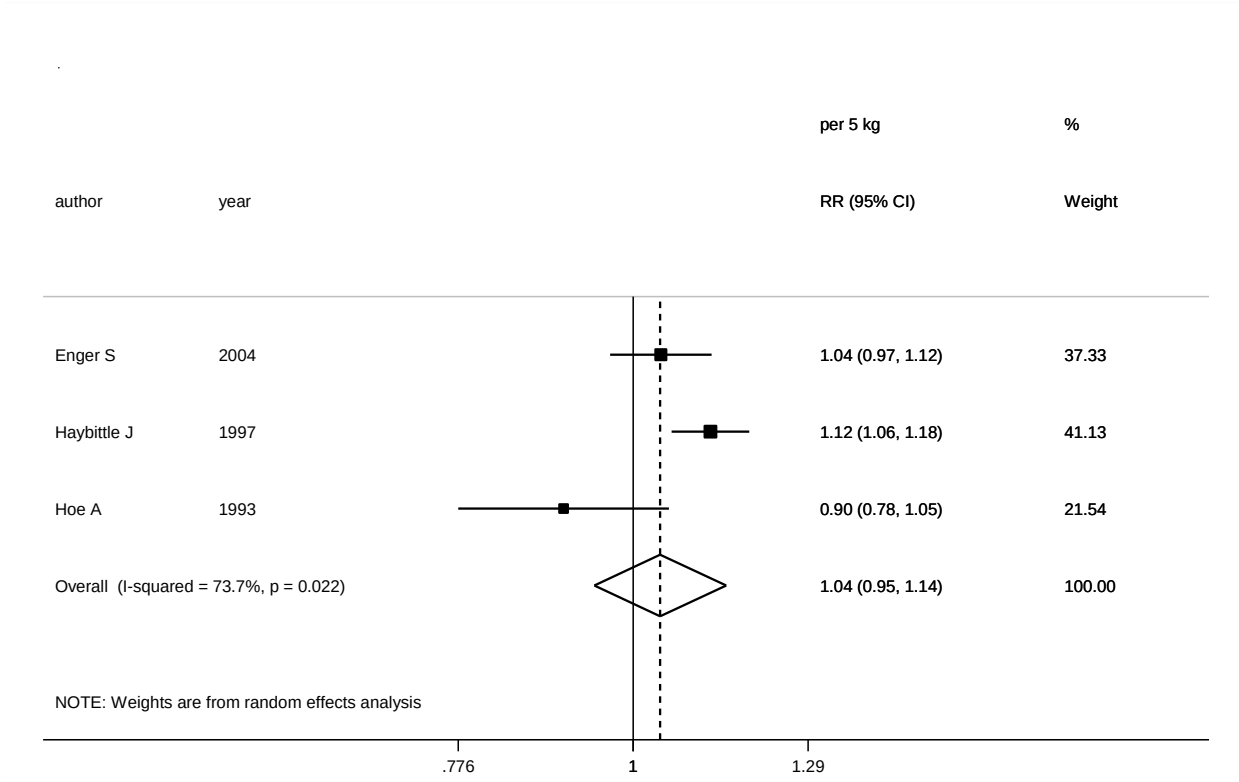


Figure 139 Linear dose-response meta-analysis of weight less than 12 months after diagnosis and breast cancer mortality



Note: A dose-response curve for individual studies was not produced as only Enger, 2004 reported categorical results (categorical results from Haybittle, 1997 was not adjusted). HRs were 1.78 (95% CI 1.09-2.89), 1.41 (95% CI 0.86-2.29), and 1.60 (95% CI 0.99-2.56) for the categories of 133-150 lb, 151-174 lb, and ≥ 175 lb compared with < 133 lb in Enger, 2004.

Table 113 Table of included studies on weight less than 12 months after diagnosis and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments / Remarks
Enger S (2004)a	The Kaiser Permanente Medical Center Follow-up Study United States	Cancer diagnosis:1988-1995;	Hospital-based retrospective cohort study	1376 participants 24 - 81 years 80.5% white	6.8 years (max)	Invasive breast cancer; TNM; 50.3% stage I, 0.3% stage II, 25.9% stage IIA, 13.4% stage IIB, 2.3% stage IIIA, 3.2% stage IIIB, 4.6% stage IV	61.6% node-ve, 38% node+ve, 0.4% unknown			From medical records; at diagnosis	1376 participants 246 breast cancer mortality	Cancer registry + death certificate	>=175 vs. <=132 lb	1.60 (0.99-2.56)	Age, tumor stage, tumor grade, tumor size, nodal status, ER status
Mohle-Boetani J (1988)	San Francisco-Oakland Bay Area Follow-up Study United States	Cancer diagnosis: 1973-1982	Follow-up of cases of case-control study	838 participants 56 years (mean) 22 - 74 years White 27.2% premenopausal, 71.7% postmenopausal, 1.1% unknown	6 years	AJCC Stages: 24% I, 32% II, 34% II or IIIA, 5% IIIA, 4% IIIB, 2% IV				Self-reported BMI obtained at diagnosis	838 participants 257 breast cancer mortality	SEER record	>140 vs. <=140 lb	1.1, p-value=0.32	Age at diagnosis, tumor stage, follow up time Highest vs. lowest analysis only; two weight categories only
Newman S (1986)	Study of Diet and Health Canada	Cancer diagnosis: 1973-1975, Study follow-up: Until 1980	Follow-up of cases of multicenter case-control study	300 participants 35 - 74 years	7 years (max)					Self-reported at interview near to time of diagnosis (3-5 months after surgery)	300 participants 87 deaths, 73 breast cancer mortality	Death certificate	>63 vs. <=63Kg	1.78, p-value=0.017	Surgery Highest vs. lowest analysis only; two weight categories only
Haybittle J (1997)	Cancer Research Campaign Trial, UK	Study recruitment: 1970-1975, Study follow-up: Until 1991	Randomised controlled trial of primary treatment; ancillary analysis	2455 participants <=70 years 39.9% pre and perimenopausal, 60% postmenopausal	20 years (max)	Stages I and II				BMI recorded at diagnosis; pre-treatment	1005 postmenopausal women followed for more than 5 years		Per 1 Kg increase	β=0.0225, P-value<0.0001	Age, tumor size, tumor stage Dose-response analysis only; categorical result was unadjusted
Hoe A (1993)	Southampton General Hospital, UK Follow-up Study UK	Breast cancer treatment: 1984-1985, Study follow-up: Until 1990 Recruited at diagnosis	Prospective cohort of breast cancer survivors	196 participants 30.6% premenopausal, 69.4% postmenopausal All had mammogram at initial presentation	5.2 years	84.7% infiltrative duct, 9.2% infiltrative lobular, 6.1% in situ; 43.9% T1 tumor, 56.1% T2 tumor	67.5% ER+, 32.5% ER-; 57.1% PR+, 42.9% PR-, among those with data 62.8% no nodes, 37.2% mobile nodes	Mastectomy: 74% yes; Wide local excision: 26% yes		Measured at diagnosis	181 participants 43 breast cancer mortality, 13 other causes of deaths	Hospital records	Per 1 Kg increase	0.98 (0.95-1.01)	Age, menopausal status, tumour stage, nodal stage, breast size Dose-response analysis only; continuous results only

Table 114 Table of excluded studies on weight less than 12 months after diagnosis and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments / Exclusion reason
			Randomised												
Rohan T (1993)	Diet and Breast Cancer in Australia Follow-up Study Australia	Cancer diagnosis: 1982-1984, Study follow-up: Until 1989	Follow-up of cases of population-based case-control study	412 participants 55.1 years (mean) 20 - 74 years 30.7% premenopausal, 5.4% perimenopausal, 64% postmenopausal, among those with data	5.5 years	Primary breast cancer, any stages			80.70% / 39 patients lost	Interval between diagnosis and interview was 4.8months	412 participants 112 breast cancer mortality, 11 other causes of deaths	Cancer registry + death certificate	>=76 vs. <=57 kg	2.06 (1.11-3.82)	Unadjusted results

Weight 12 months or more after diagnosis and breast cancer mortality

No study has reported data.

Weight and second primary breast cancer/contralateral breast cancer

Four studies were identified (Kato, 1986; Cook, 1996; Li, 2003; Majed, 2009). One study (Li, 2003) examined weight before diagnosis. Three studies examined weight less than 12 months after diagnosis (Kato, 1986; Cook, 1996; Majed, 2009). No study reported on weight 12 months or more after diagnosis.

Weight before diagnosis and second primary breast cancer/contralateral breast cancer

Only one study reported data (Li, 2003). The RR for ≥ 156 lb vs. ≤ 123 lb was 2.2 (95% CI 1.1-4.4).

Weight less than 12 months after diagnosis and second primary breast cancer/contralateral breast cancer

Three studies (Kato, 1986; Cook, 1996; Majed, 2009) were identified. Dose-response and highest versus lowest meta-anaylses were not conducted due to insufficient data. Kato et al. (1986) found a statistically significant 3-fold increase in risk ($RR_{for \geq 60 \text{ vs. } < 60} = 3.01$; $p < 0.05$). Cook et al. (1996) reported no association ($RR_{for \geq 80 \text{ vs. } < 60} = 0.97$; 95 % CI 0.55-1.69). Majed et al. (2009) observed a significant 26% (95% CI 1.08-1.47) increase in risk for ≥ 64 vs. < 64 kg but the result was not repeated in a validation sub-sample of the study population (RR 1.13; 95% CI 0.89-1.43).

7.4 Weight gain

Table 115 Summary results of meta-analysis on weight gain and total mortality and breast cancer mortality*

	Total mortality			Breast cancer mortality		
Comparison	**No. of studies**	**No. of events in studies**	**RR (95% CI) I^2, $P_{heterogeneity}$**	**No. of studies**	**No. of events in studies**	**RR (95% CI) I^2, $P_{heterogeneity}$**
Weight gain during adulthood						
Highest vs. lowest	4	1664	1.27 (1.10-1.46) 0%, p = 0.39	4	2123	1.19 (0.92-1.53) 53.2%, p = 0.09
Per 5kg gain	-	-	-	3	1725	1.05 (0.95-1.16) 64.8%, p = 0.06
Weight gain before and 12 months or more after diagnosis/treatment						
Highest vs. lowest	6	2467	1.43 (1.10-1.87) 60.9%, p = 0.03	3	810	1.59 (1.05-2.41) 47.1%, p = 0.15
Weight gain during treatment						
Highest vs. lowest	3	347	1.38 (0.79-2.44) 79.7%, p = 0.01	-	-	-

*No studies on second cancers were included in the meta-analyses.

Weight gain and total mortality

Weight gain during adulthood and total mortality

Methods

Four studies were identified. All studies could be included in the highest versus lowest meta-analysis (Ewertz, 1991; Bernstein, 2002; Cleveland, 2007; Dal Maso, 2008). Since that weight gain was quantified differently in the studies (by kg or percentage change in weight or by kg/m^2 change in BMI), dose-response meta-analysis could not be conducted. In the studies, weight gain during various periods in adulthood were measured – from age 18 or 20 years to a year prior to diagnosis, 10 years before diagnosis, or from age 30 years to diagnosis. The comparisons between the weight change categories used in our analyses are taken as reported in the studies. The reference group was those of stable weight or lowest category of weight change.

Main results and heterogeneity

For the highest compared with the lowest weight gain/stable weight during adulthood, the summary RR was 1.27 (95% CI 1.10-1.46; I^2 = 0%; p = 0.39; 4 studies). Elevated risks were also reported in postmenopausal women for weight gain between age 20 and 50 years (HR for >14.1 kg vs. ± 3 kg = 1.83; 95 % CI 0.65-5.14), and between 50 years and one year before diagnosis (HR for > 12.7 kg vs. ± 3 kg = 2.77; 95% CI 1.67-4.61) (Cleveland, 2007).

Study quality

Number of events ranged from 160 events (Bernstein, 2002) to 485 events (Dal Maso, 2008). Average time of follow-up was 66.7 months (Cleveland, 2007) or 12.6 years (Dal Maso, 2008) or of a maximum of 7 years (Ewertz, 1991) or 18 years (Bernstein, 2002). Loss to follow-up was minimal, with 2.7% lost (Dal Maso, 2008) or 28 patients lost (Bernstein, 2002) when reported. Also, Cleveland et al. (2007) reported that 410 cases (1508 participants in study) were without follow-up data due to nonresponse, refusal, untraceability, or death without an identifiable proxy.

Two studies (Dal Maso, 2008; Ewertz, 1991) included women with invasive breast cancer only. Cleveland et al. (2007) included in situ breast cancer, while all participants in Bernstein et al. (2002) had a second primary breast cancer. Cases were diagnosed no longer than a year before the study interview for anthropometric data at various time points in life in the study by Dal Maso et al. (2008). Other studies (Cleveland, 2007; Bernstein, 2002; Ewertz, 1991) also collected the data retrospectively after cancer diagnosis. All studies adjusted for multiple confounders. Tumor stage was adjusted in all but one study (Cleveland, 2007).

Figure 140 Forest plot of the highest weight gain versus lowest weight gain/stable weight during adulthood and total mortality

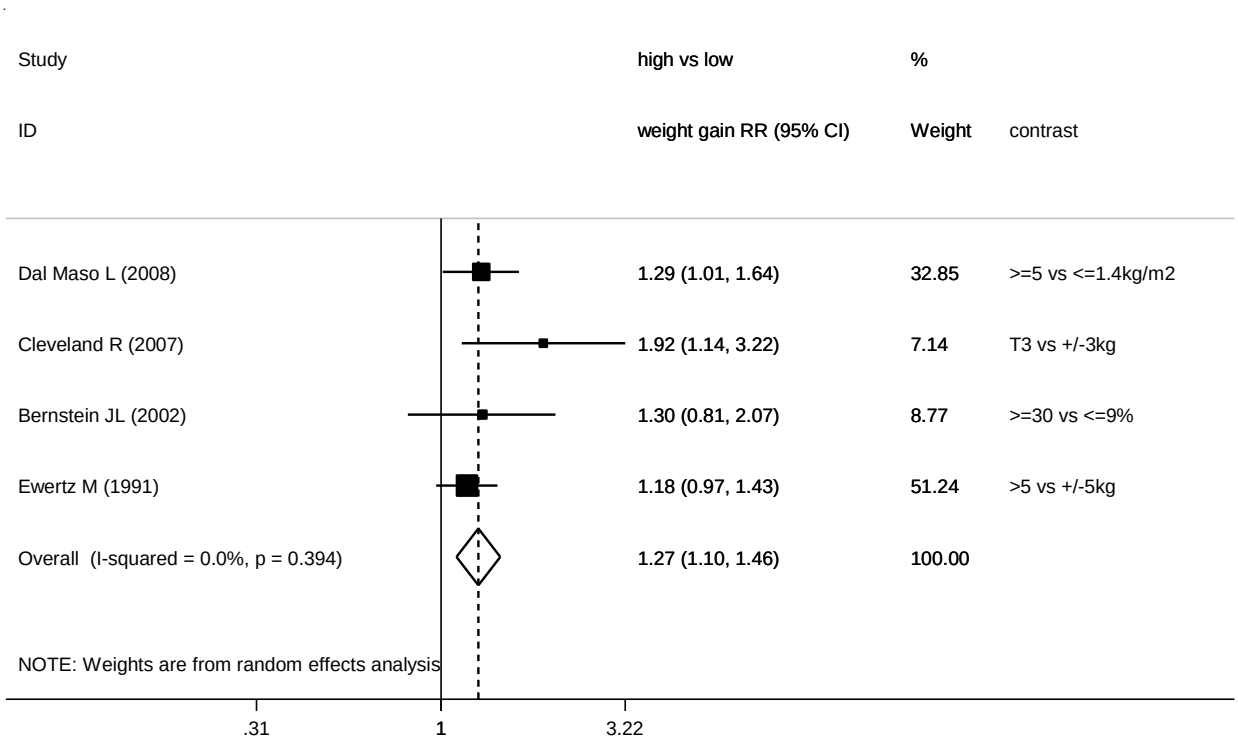


Table 116 Table of included studies on weight gain during adulthood and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Dal Maso L (2008)	Six Italian Regions Follow-up Study Italy	Cancer diagnosis: 1991-1994; Study follow up: until 2005-2006 diagnosed no longer than 1 year before the interview	Follow-up of cases of a case-control study	1453 participants 55 years (mean) 23 - 74 years Among those with data (pre diagnosis): 45.5 % peri/pre menopausal, 54.9% postmenopausal HRT use: 91.3% never, 8.6% ever	12.6 years	Invasive breast cancer; TNM; 32.7% Stage I, 44.1% stage II, 13.2% stage III-IV, 9.8% unknown	41.5% ER+ve/PR+ve, 3.5% ER-ve/PR+ve, 6.3% ER+ve/PR-ve, 10.1% ER-ve/ PR-ve 45.6% no node+ve, 44.2% node+ve, 10.1%		2.70% lost	Self-reported at study baseline; height, weight 1 year before cancer diagnosis and at different ages; hip and waist measured at interview	1453 participants 503 deaths, 398 breast cancer mortality, 6.2% death from other cancers, 7.4% from cardiovascular disease; 485 deaths from 1415 participants in analysis	Cancer registry	>=5 vs. <1.4 kg/m2 from age 30 years to diagnosis	1.29 (1.01-1.64)	Region, age at diagnosis, year of diagnosis, TNM stage, Receptor status
Cleveland R (2007)	Long Island Breast Cancer Study Project United States	Cancer diagnosis:1996-1997; Study follow up: 2002-2004	Follow up of cases of a case-control study	1508 participants 58.8 years (mean) 25 - 98 years Mostly white 32.2% premenopausal, 67.8% postmenopausal HRT use: 86.8% ever, 13.2% never	66.7 months	84.4% invasive and 15.6% In situ	26.7% ER-ve, 73.3% ER +ve, 35.8% PR-ve, 64.2% PR+ve 73.7% no nodes involved, 26.3% nodes involved	Radiation therapy, chemotherapy, hormone therapy	410 patients lost	Self-reported shortly after diagnosis; weight and height at each decade of life from age 20 years until 1 year before diagnosis	1508 participants 196 deaths (of which 21% from cardiovascular disease), 127 breast cancer mortality, 9 death from brain and lung metastases	National Death Index	Premenopausal >=16 vs. ±3Kg gain Postmenopausal >=22.3 vs. ±3Kg gain Between age 20 years and 1 year before diagnosis	2.45 (0.96-6.27) 1.72 (0.92-3.21)	Age at diagnosis, hypertension, weight at age 20y
Bernstein JL (2002)	Cancer and Steroid Hormone Study United States	Cancer diagnosis:1980-1982 (1st breast cancer) and before 1999 (2nd breast cancer); Study follow up: until 1998	Follow up of cases of a population-based case-control study	369 participants 20 - 54 years Multi-ethnic	18 Years (max)	First primary breast cancer and a second primary in the contralateral breast; any stages including In situ breast cancer		81 and 71 patients had radiation treatment following first and second primary breast cancer respectively	28 patients lost	Interviewed within 6 months of diagnosis of primary cancer for data at age 18 years and adulthood	369 participants 160 deaths (90% death from cancer including 87% breast cancer mortality)	Cancer registry	>=30 vs. <=9% gain in Quetelet's index from age 18 to adult	1.30 (0.81-2.07)	Age at second diagnosis, education, tumor stage of both primary cancers, time between primary cancers
Ewertz M (1991)	Danish Breast Cancer Cooperative Group Denmark	Cancer diagnosis:1983-1984; Study follow up: until 1990	Follow up of cases of population-based case-control study	2445 participants <=70 years Among those with data, HRT use: 66.1% never usage, 33.8% ever usage	7 years (max)	Primary Invasive breast cancer; 44.8%Grade I, 42.3% Grade II, 12.8% Grade III breast cancer	58.5% none node+ve, 28.6% 1-3 node+ve, 12.8% >4 node+ve		87%	Self-reported 1 year after diagnosis for weight 10 years prior to diagnosis	2445 participants 805 deaths	Cancer registry	>5 vs. ±5kg gain 10 years prior to diagnosis	1.18 (0.97-1.43)	Age, tumor size, nodal status, tumor grade, skin invasion, area of residence

Weight gain before and 12 months or more after diagnosis/treatment and total mortality

Methods

Seven studies from eight publications were identified. The publication by Bradshaw et al. in 2012 superseded the one in 2010. All but one study (Kroenke, 2005; Abrahamson, 2006b; Caan, 2008; Nichols, 2009; Chen, 2010; Bradshaw, 2012) could be included in the highest versus lowest meta-analysis. The excluded study provided a p-value for the weight change groups from a log-rank test (Makari-Judson, 2007). Weight change > 2.5 kg at year 1 (measured from diagnosis) was not associated with overall survival (p = 0.58) in this study. Weight gain was quantified differently in the studies (by kg or percentage change in weight or by kg/m^2 change in BMI). Three studies (Bradshaw, 2012; Abrahamson, 2006b; Caan, 2008) measured weight gain by percentage weight change but one study (Bradshaw, 2012) was missing numbers of events/non-events per weight change category, thus a dose-response meta-analysis was not conducted with the remaining two studies.

In the studies, weight gain was measured in different time periods from before to after cancer diagnosis/treatment – from age 20 years to several months after diagnosis, from before diagnosis to within or more than a year after diagnosis, or from before to after diagnosis. The comparisons between the weight change categories used in our analyses are taken as reported in the studies. The reference group was those of stable weight or lowest category of weight change.

Main results and heterogeneity

For the highest compared with the lowest weight gain/stable weight from before to after diagnosis/treatment, the summary RR was 1.43 (95% CI 1.10-1.87; I^2 = 60.9%; p = 0.03; 6 studies).

Chen et al. also reported results on weight gain during other time periods in addition to from before diagnosis to 18 months after diagnosis as used in the meta-analysis (Chen, 2010). A HR of 1.11 (95% CI 0.80-1.53) for ≥ 5 kg gain compared to stable weight (+/-1 kg) between pre-diagnosis to 6 months post-diagnosis was observed, and a HR of 1.54 (95% CI 1.03-2.29) was reported for at-diagnosis to 18 months post-diagnosis.

Study quality

Number of events ranged from 152 events (Caan, 2008) to 860 events (Kroenke, 2005). Average time of follow-up was from 46 months (Chen, 2010) to 9 years (Kroenke, 2005), or of a maximum of 9.8 years (Abrahamson, 2006b). Loss to follow-up was < 2% (Abrahamson, 2006b) or 55 patients lost (Bradshaw, 2012) when reported. Two studies (Chen, 2010; Bradshaw, 2012) included women with *in situ* and invasive breast cancers. Other studies (Abrahamson, 2006b; Nichols, 2009; Caan, 2008; Kroenke, 2005) included

invasive breast cancer only. Participants in Kroenke, et al. (2005) originated from a prospective cohort, while other studies either recruited at-diagnosis, or several months after diagnosis.

Cancer diagnosis dates varied between studies. One spanned from 1976 to 2000 (Kroenke, 2005), another from 1988 to 1999 (Nichols, 2009). Three studies recruited cancer diagnosed in the 1990s, or until 2000 (Abrahamson, 2006b; Caan, 2008; Bradshaw, 2012). Study recruitment in Chen et al. was between 2002 and 2006, which took place approximately six months after diagnosis. All studies included pre- and postmenopausal women. All results were adjusted for multiple confounders, including tumour stage. The result of Abrahamson et al. (2006b) was adjusted for tumour stage, income and BMI at interview. Other factors like age, race and menopausal status were not included in the final model in this study, as they did not make an appreciable change to the estimate.

Published pooled analysis

The After Breast Cancer Pooling Project (ABCPP) published results on weight change before and after breast cancer diagnosis and total, breast cancer, and non-breast cancer mortality risks (Caan, 2012).

Data from four prospective studies of breast cancer survivors (Shanghai Breast Cancer Survival Study, Life After Cancer Epidemiology, Women's Healthy Eating and Living, and Nurses' Health Study) were available in the project. After a mean follow-up of 8.1 years, 1603 deaths (1040 breast cancer mortality) from 12915 participants with stage I-III invasive breast cancer were accrued. Analyses were conducted using data from the US studies and the Chinese study separately.

Compared with stable weight (weight change within 5%), the HRs for weight gain $\geq$ 10% for total mortality risk was 1.15 (95% CI 0.98-1.35) for the U.S. sites, and 1.16 (95% CI 0.84-1.62) for China. There were no significant interactions on the effects of weight gain on overall mortality by before diagnosis BMI, comorbid status, ER status, and smoking status.

The highest vs. lowest meta-analysis in this report included results from the Shanghai Breast Cancer Survival Study (Chen, 2010), Life After Cancer Epidemiology (Caan, 2008), and the Nurses' Health Study (Kroenke, 2005), but not the Women's Healthy Eating and Living RCT as in the ABCPP.

Figure 141 Forest plot of the highest weight gain versus lowest weight gain/stable weight before and 12 months or more after diagnosis/treatment and total mortality

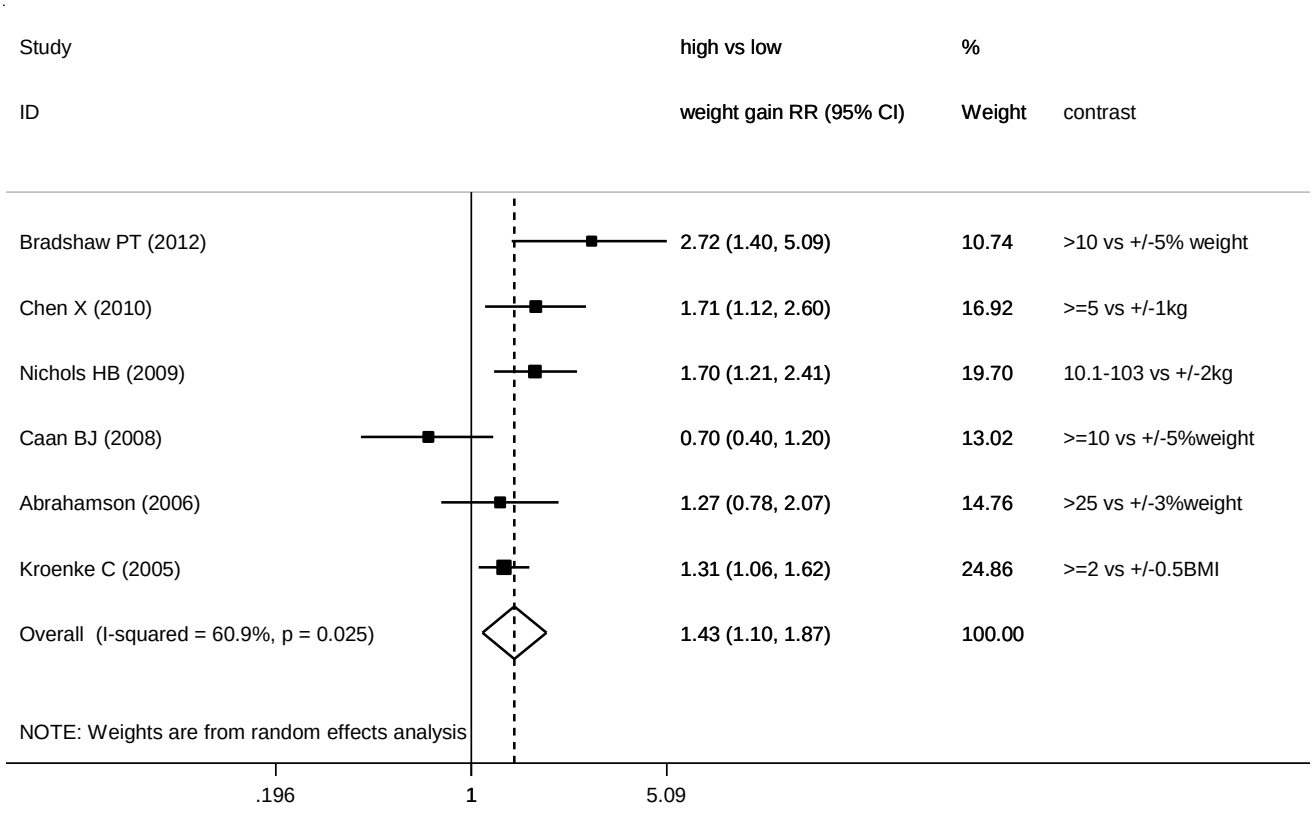


Table 117 Table of included studies on weight gain before and 12 months or more after diagnosis/treatment and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Abrahamson (2006)b	Atlanta, Seattle, New Jersey Follow-up Study United States	Cancer diagnosis:1990-1992; Study follow up: until 2000	Follow-up of cases of a population-based case-control study	1254 participants 20 - 54 years 75% white 25% nonwhite 78% premenopausal, 22% postmenopausal and unknown <1%	9.8 Years (max)	Invasive breast cancer; AJCC; any stage ; 57% local, 40% regional, 3% distant, <1% unknown	56% ER+ve, 35%ER-ve, 3% borderline, 6% unknown		86% <2% lost	Measured 4.2 months after diagnosis; self-reported weight and height at age 20 years and the year before diagnosis	1217 participants 290 deaths, 275 deaths included in analysis	Cancer registry + National Death Index	>25 vs. ±3% weight gain From age 20 to interview ~4.2 months after diagnosis	1.27 (0.78-2.07)	Tumor stage, income, BMI at interview (Result not adjusted for BMI at interview was also provided in the article)
Chen X (2010)	Shanghai Breast Cancer Survival Study China	Study recruitment: 2002-2006; Recruited approximately 6 months after diagnosis	Prospective cohort of breast cancer survivors	5042 participants 53.5 years (mean) 20 - 75 years 51.1% postmenopausal	46 months	TNM; 36.4% stage 0-I, 32.6% IIA, 16.6% IIB, 9.8% IIIIV, 4.6% unknown	49.9% ER+ve/PR+ve, 27.6% ER-ve/PR-ve, 20.4% mixed (ER+ve PR-ve/ER-ve PR+ve), 2.1% unknown	Mastectomy:93.9% ; Chemotherapy: 91.2%; Radiotherapy: 32.1% ; Tamoxifen usage: 52%	80%	Self-reported weight 1 year prior to diagnosis and at diagnosis, measured at baseline interview approximately 6 months after diagnosis	5042 participants 442 deaths	Cancer register	>=5 vs. ±1Kg gain From before diagnosis to 18 months after diagnosis	1.71 (1.12, 2.60)	Age at diagnosis, pre-diagnosis BMI, education, Income, marital status, meat intake, cruciferous vegetables, soy protein, time from diagnosis to study enrollment, menopausal status, menopausal symptoms, chemotherapy, surgery type, radiotherapy, tamoxifen use, nodal status, immunotherapy, TNM stage, comorbidity, exercise, hormone receptor status
Nichols HB (2009)	Collaborative Women's Longevity Study United States	Study recruitment: 1988-2001; Cancer diagnosis: 1988-1999; Study follow up: until 2005 Recruited 5.8 years after breast cancer diagnosis	Follow-up of cases of case-control studies	3993 participants 58.4 years (mean) 20 - 79 years Mostly white: 98%, 28.1% premenopausal; 71.9% postmenopausal HRT use: 38.9% (postmenopausal hormone use)	6.3 years	Invasive nonmetastatic breast cancer; 64.1% local, 24.7% regional, 0.6% distant, 10.6% unknown			40%	Self-reported body weight 1-5 years before diagnosis and at study baseline	3993 participants 421 deaths, 121 breast cancer mortality, 95 deaths from cardiovascular disease	Death record	10.1-103 vs. ±2Kg gain From 1-5 years before diagnosis to within a year after diagnosis	1.70 (1.21-2.41)	Age, tumor stage, time from diagnosis to exposure assessment, family history, smoking, physical activity, menopausal status, pre-diagnosis weight
Caan BJ (2008)	LACE United States	Cancer diagnosis:1997-2000; Study follow up: until 2007 Diagnosed 11–39 months before study enrolment	Prospective cohort study of breast cancer survivors	1692 participants 58.3 years (mean) 18 - 70 years 22.8% premenopausal, 63.8% postmenopausal	83.9 months	Early stage invasive breast cancer; AJCC; 46.7% Stage I, 50.2% Stage II, 3.1% Stage IIIA	69.2% ER+/PR+, 13.6% ER+/PR-, 1.7% ER-/PR+, 15.5% ER-/PR- 63.2% o node+ve, 26.3% 1-3 nodes+ve, 5.7% 4-6 nodes+ve, 1.7% 7-9 nodes+ve, 3.1% >=10	19% chemotherapy; 24.8% radiotherapy; 38.4% chemo- and radiotherapy; 49.2% mastectomy; 50.8% breast-conserving surgery; 70.9% current tamoxifen users, 6.7% past tamoxifen	46%	Self-reported at baseline; one year pre-diagnosis and also after diagnosis at baseline	1689 participants 162 deaths, 152 deaths included in the analysis, 99 breast cancer mortality	Medical records	>=10 vs. ±5% weight gain From before diagnosis to study entry ~22.7 months after diagnosis	0.70 (0.40-1.20)	Tumor stage, age at diagnosis, tamoxifen use, treatment, nodal status, estrogen receptor level, progesterone receptor level, smoking, physical activity

							nodes+ve	users							
Kroenke C (2005)	Nurses' Health Study United States	Cancer diagnosis: 1976 - 2000, Study follow-up: Until 2002	Cancer survivors of population-based prospective cohort study	5204 participants 30 - 55 years	9 years	Invasive non metastatic breast cancer, any stages; 86.9% tumor size >2cm	73.2% ER+ 85.2% node +ve	Chemotherapy: 63.9% yes; Tamoxifen: 64.8% yes		Self-reported at cohort baseline; pre and post-diagnosis weight	5204 participants 860 deaths, 533 breast cancer mortality	Family+ National Death Index	Never smoker >=2 vs. ±0.5BMI gain Past/Current smoker >=2 vs. ±0.5BMI gain From before diagnosis to >=12 months after diagnosis	1.59 (1.12-2.27) 1.18 (0.91-1.54)	Age, oral contraceptive, birth index, menopausal status, age at menopause, hormonal therapy, smoking, tumor size, nodal status, chemotherapy, tamoxifen use, protein intake, BMI prior to diagnosis
Bradshaw PT (2012)	Long Island Breast Cancer Study United States	Cancer diagnosis: 1996-1997, Study follow-up: until 2005 Recruited on average 3 months after diagnosis	Follow up of cases of a population-based case-control study	1436 participants 59 years (mean) 25-98 years 32% premenopausal, 68% postmenopausal	8.8 years	Primary in situ or invasive breast cancer; 76% tumour size <2cm , 24% >=2 cm, 453 unknown	26% ER-ve, 74% ER+ve, 483 missing; 36% PR -ve, 64% PR +ve, 487 missing	Chemotherapy: 41% yes, 59% no, 459 unknown	82% 55 patients lost	Self-reported at baseline and during follow up; height and weight 1 yr prior to diagnosis, at diagnosis and post diagnosis weight change	1436 participants 292 deaths, 156 breast cancer mortality	Death record	>10 vs. ±5% weight gain From diagnosis to post-diagnosis	2.72 (1.40-5.09)	Age, chemotherapy, ER status, PR status, tumor size (result further adjusted for BMI 1 year before diagnosis and weight change from 20 years to 1 year before diagnosis was also provided in the article)

Table 118 Table of excluded studies on weight gain before and 12 months or more after diagnosis/treatment and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments Exclusion reason
Bradshaw PT (2010)	Long Island Breast Cancer Study Project United States	Cancer diagnosis: 1996-1997	Follow-up of cases of population-based case-control study	1436 participants 58.79 years (mean) 32.2% premenopausal, 67.8% postmenopausal	8.8 years	Tumor size >2cm: 16.3% yes, 52.2% no, 31.5% missing	35.5% ER+, 22.1% ER-, 42.4% missing among those with data; 42.4% PR+, 23.7% PR-, 33.9% missing	Chemotherapy: 28.1% yes, 39.9% no, 32% missing	68.5%	Self-reported at baseline and during follow up; height and weight 1 yr prior to diagnosis, at diagnosis and post diagnosis weight change	1436 participants 292 deaths, 156 breast cancer mortality	Death record	>10% gain vs. +/-5% From data not missing in random model	2.72 (1.40-5.10) Corresponded to log-HR of 1.00 (0.34-1.63) reported in article	Age, chemotherapy, ER status, PR status, tumour size Superseded by Bradshaw 2012

Makari-Judson G (2007)	Review of a Oncology Practise and Clinical Trials Participants, United States	Cancer diagnosis: 1997-2002	Prospective cohort of breast cancer survivors	185 participants 50.8 years (mean) 20-91 years 50% pre-treatment postmenopausal, 24% treatment-associated menopause, 26% post-treatment premenopausal	38 months (max)	Invasive breast cancer; AJCC; 34% Stage I, 34% Stage IIA, 23% Stage IIB, 6% Stage IIIA, 3% Stage IIIB		60% breast-conserving therapy, 40% mastectomy; systemic adjuvant therapy: 4% none, 27% hormonal therapy, 30% chemotherapy, 39% both hormonal and chemotherapy	12 patients lost	From chart review data after diagnosis; data at diagnosis and at 1 yrs, 2 yrs, and 3 yrs after diagnosis	185 participants	Hospital records	<=2.5kg gain vs. >2.5kg gain At 1 year after diagnosis	P-value=0.58	Insuficcient data – weight change groups were compared by a log-rank test

Weight gain less than 12 months after diagnosis and total mortality

Methods

Six studies were identified. Three studies (Camoriano, 1990; Abrahamson, 2006b; Thivat, 2010) could be included in the highest versus lowest meta-analysis. Three studies could not be included reported weight gain during treatment was not associated with survival (Heasman, 1985; Chlebowski, 1986; Kumar 1997). Weight gain was quantified differently in the studies (by kg or percentage change in weight), thus a dose-response meta-analysis could not be conducted.

In the studies, weight gain was measured in different time periods from before to after cancer treatment – from the beginning to the last cycle of treatment, or from diagnosis to several months after diagnosis. The comparisons between the weight change categories used in our analyses are taken as reported in the studies. The reference group was those of stable weight or lowest category of weight change.

Main results and heterogeneity

A statistically non-significant 38% increased risk (95% CI 0.79-2.44) was observed. There was evidence of high heterogeneity between studies (I^2 = 79.7%; p = 0.01; 3 studies).

Study quality

Thivat et al. (2010) accured 57 deaths from 111 participants after an average of 20.4 years follow-up. Camoriano et al. (1990) (545 participants, mean 6.6 years of follow-up) did not report an outcome number. All cases were of lymph-node positive breast cancer in this study. Abrahamson et al. (2006b) accured 290 deaths within 1254 participants in a maximum of 9.8 years of follow-up, with minimal lost to follow-up (< 2%). Thivat et al. (2010) and Abrahamson et al. (2006b) included invasive breast cancer cases only. Two studies were clinical series with cases identified during 1976-1989 or 1990-1992 in hospitals or through cancer registries. Camorian et al. (1990) was originally a randomised controlled trial of adjuvant treatment in lymph-node positive breast cancer patients.

Weight change was measured before and after treatment in all studies. All results were adjusted for multiple confounders including tumor stage. The result of Abrahamson et al. (2006b) was adjusted for tumour stage, income and BMI at interview. Other factors like age, race and menopausal status were not included in the final model in this study, as they did not make an appreciable change to the estimate.

Figure 142 Forest plot of the highest weight gain versus lowest gain/stable weight less than 12 months after diagnosis and total mortality

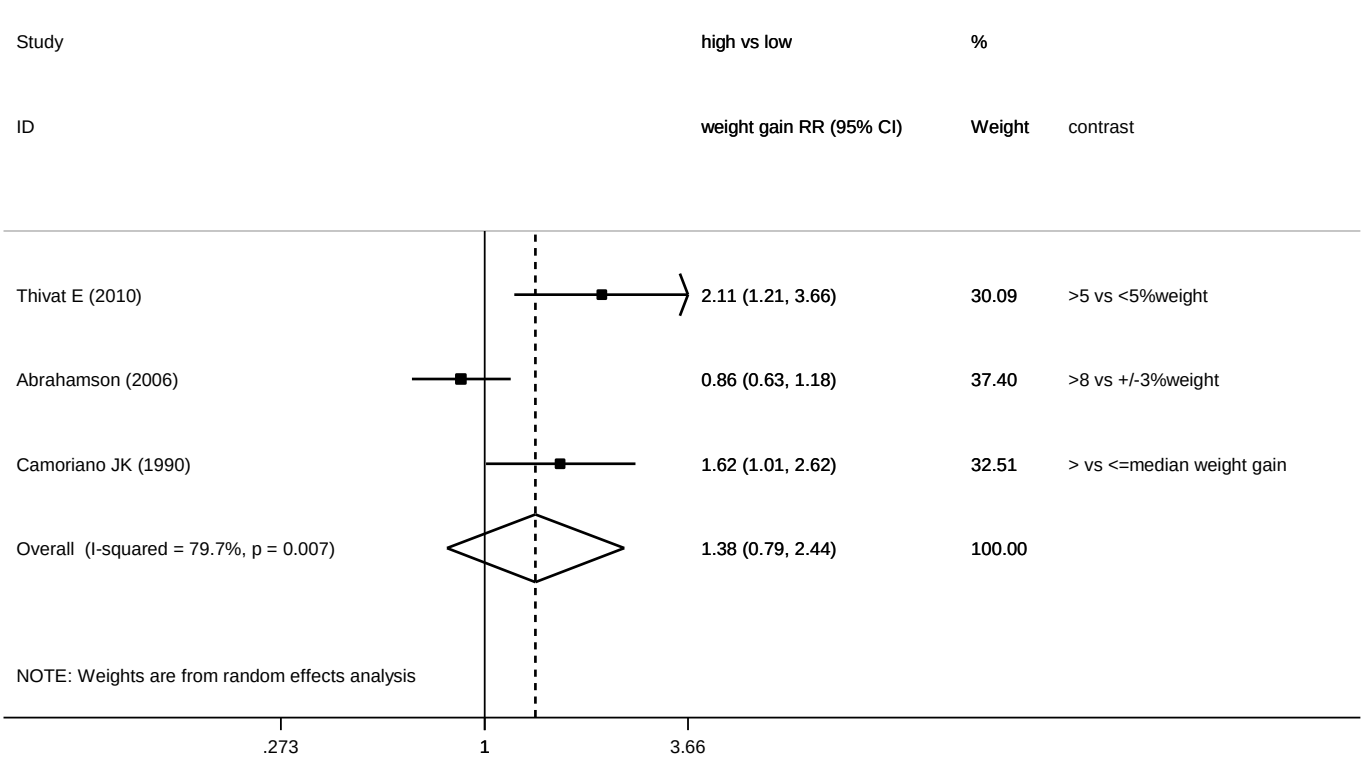


Table 119 Table of included studies on weight gain less than 12 months after diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Thivat E (2010)	Jean Perrin Center, Clermont-Ferrand Review Study France	Cancer treatment:1976-1989; Study follow up: until 2009	Hospital-based retrospective cohort study of cancer survivors	111 participants 54 years (mean) 32 - 74 years 45% premenopausal, 55% post-menopausal	20.4 years	Early stage and locally advanced breast cancer; 19% T1, 44% T2, 15% T3, 22% T4; 8% patients had Scarff-Bloom-Richardson Grade I, 55% II, 20% III	42% ER+ve, 44% ER-ve, 35% PR+ve, 47% PR-ve / 50% N0, 44% N1, 5% N2, 1% N3	Anthracycline-based chemotherapy: all patients; Tumourectomy: 66 patients; Mastectomy: 44 patients; Radiation: 97% (after chemotherapy); Hormonal therapy: 44% (90% with tamoxifen)	0% lost	Measured at the beginning of treatment and in the last chemotherapy cycle	111 participants 57 deaths	Hospital records	>5 vs. <5% weight gain before and after treatment	2.11 (1.21-3.66)	Nodal status, tumor stage, menopausal status, hormonal therapy, initial BMI
Abrahamson (2006)b	Atlanta, Seattle, New Jersey Follow-up Study United States	Cancer diagnosis:1990-1992; Study follow up: until 2000	Follow-up of cases of a population-based case-control study	1254 participants 20 - 54 years 75% white 25% nonwhite 78% premenopausal, 22% postmenopausal and unknown <1%	9.8 Years (max)	Invasive breast cancer; AJCC; any stage ; 57% local, 40% regional, 3% distant, <1% unknown	56% ER+ve, 35%ER-ve, 3% borderline, 6% unknown		86% / <2% lost	Measured 4.2 months after diagnosis; self-reported weight and height at age 20 years and the year before diagnosis	1254 participants 290 deaths	Cancer registry + National Death Index	>8 vs. ±3% weight gain From diagnosis to interview ~4.2 months after diagnosis	0.86 (0.63-1.18)	Tumor stage, income, BMI at interview Result not adjusted for BMI at interview was also provided in the article)
Camoriano JK (1990)	Review of Adjuvant Chemotherapy Trials of Node-Positive Breast Cancer United States		Randomised controlled trial of adjuvant treatment trial; ancillary analysis	545 participants 20 - 75 years 60.5% premenopausal, 39.5% postmenopausal	6.6 years	Node-positive breast cancer; mastectomy; any stages				BMI measured at randomisation, within 8 weeks of primary breast surgery, at follow-ups	330 premenopausal women in the analysis	Active follow-up and review	> vs. <= median weight gain From randomization to after 60 weeks, end of treatment	1.62 (1.01-2.62)	Age, nodal status, estrogen receptor level, tumor size, BMI (initial Quetelet Index), nuclear grade

Table 120 Table of excluded studies on weight gain less than 12 months after diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments / Exclusion reason
Chlebowski RT (1986)	Western Cancer Study Group Adjuvant Treatment Trial United States	Cancer treatment: 1974 - Recruited no more than 6 weeks after mastectomy	Follow-up of a randomised controlled trial of adjuvant treatment	62 participants Pre and postmenopausal	112 months	Invasive breast cancer	All >=4 nodes +ve	Two arms: 5-FU or CMF for 12 months after mastectomy	Zero lost	Weight recorded weekly during period of adjuvant therapy	62 participants – 32 in 5-FU arm; 30 in CMF arm	Active follow-up	Mean (median) weight gain before and after treatment: 5-FU – 2kg (1.3kg) CMF – 3.7kg (2.4kg)	Overall survival 51% 31%	Results in text – The amount of weight increase was not directly correlated with survival in either arm. None of the five women who gained more than 10kg survived

Heasman KZ (1985)	Princess Margaret Hospital Adjuvant Treatment Trial Canada	Cancer treatment: 1975 - 1981	Follow-up of a randomised controlled trial of adjuvant treatment	237 participants 25-70 years (mean 47.5 years) 80.2% premenopausal 18.1% postmenopausal 1.7% menopausal status unknown	12 months (min)	Breast cancer of all stages	Among those with ER assay: 38% ER+ve, 42% ER-ve, 20% ER status uncertain 44% 1-3 +ve nodes, 25% >=4 +ve nodes, 2% -ve node, 27% unknown, 2% unable to determine	Three arms: Melphalan or cyclophosphamide, methotrexate, and 5-fluorouracil with or without prednisone for various lengths of time		From medical records for weight before and after treatment	237 participants	Active follow-up	Mean (median) weight gain before and after treatment: 4.3kg; 0-1.5kg gained - 60 participants, 1.6-3.4kg gained - 57 participants, 3.5-6.4kg gained – 61 participants, 6.5-18.9kg gained – 59 participants		Results in text – No statistically significant differences in overall survival between the weight groups
Kumar NB (1997)	H.Lee Moffitt Cancer Center and Research Institute Follow-up Study, United States	Breast surgery: 1986-1997	Prospective cohort of breast cancer survivors	200 participants 25-85 years Multi-ethnic	40 months (max)	Stages IA-IIB		All had surgery with or without radiotherapy and tamoxifen, not receiving systemic chemotherapy		From medical records; weight at diagnosis, during treatment and follow-up period		Medical records			Results in text only - Weight gain during treatment was not related with survival

Weight gain and breast cancer mortality

Weight gain during adulthood and breast cancer mortality

Methods

Four studies were identified. All studies (Enger, 2004b; Whiteman, 2005; Cleveland, 2007; Dal Maso, 2008) could be included in the highest versus lowest meta-analysis. Weight gain was quantified differently in the studies (by kg change in weight or kg/m^2 change in BMI). A dose-response meta-analysis was conducted with the three studies (Cleveland, 2007; Whiteman, 2005; Enger, 2004b) that measured the change in weight.

In the studies, weight gain during various periods in adulthood were measured – from age 18 or 20 years to a year prior to diagnosis or to the usual adult weight just before diagnosis. The comparisons between the weight change categories used in our analyses are taken as reported in the studies. The reference group was those of stable weight or lowest category of weight change.

Main results and heterogeneity

The summary RR was 1.05 (95% CI 0.95-1.16; I^2 = 64.8%; p = 0.06; 3 studies) per 5 kg gain in weight during adulthood. In the influence analysis, the summary RR changed from 1.02 (95% CI 0.97-1.07) when Cleveland et al. (2007) was omitted to 1.09 (95% CI 0.96-1.24) when Enger et al. (2004b) was omitted. For the highest compared to the lowest weight gain/stable weight, the summary RR was 1.19 (95% CI 0.92-1.53; I^2=53.2%; p = 0.09; 4 studies).

Cleveland et al. (2007) reported results on weight gain during other time periods in addition to from age 20 years to a year before diagnosis as used in the meta-analysis. Elevated risks were reported in postmenopausal women for weight gain between age 20 and 50 years (HR for > 14.1 kg vs. ± 3 kg = 1.66, 95% CI 0.40-6.84), and between 50 years and a year before diagnosis (HR for > 12.7 kg vs. ± 3 kg = 3.00, 95% CI 1.37-6.56).

Study quality

Number of events ranged from 127 to 383 breast cancer deaths. Mean study follow-up ranged from 66.7 months to 14.6 years. Of those cases identified in the study by Cleveland et al., 410 cases were without follow-up data due to nonresponse, refusal, untraceability, or death without an identifiable, leaving 1508 participants in the study. Other studies had minimal lost to follow-up. All were follow-up of case-control studies. Two studies (Enger, 2004b; Cleveland, 2007) included *in situ* and invasive breast cancers. Two studies (Whiteman, 2005; Dal Maso, 2008) included invasive breast cancer only. Weight at various time points were self-reported. Enger, et al. (2004b) included premenopausal women only. Other studies included women of all ages. Most results were multivariate

adjusted, including tumour stage, except Cleveland et al. (2007) that adjusted for age, hypertension and weight at age 20 years only.

Figure 143 Forest plot of the highest weight gain versus lowest weight gain/stable weight during adulthood and breast cancer mortality

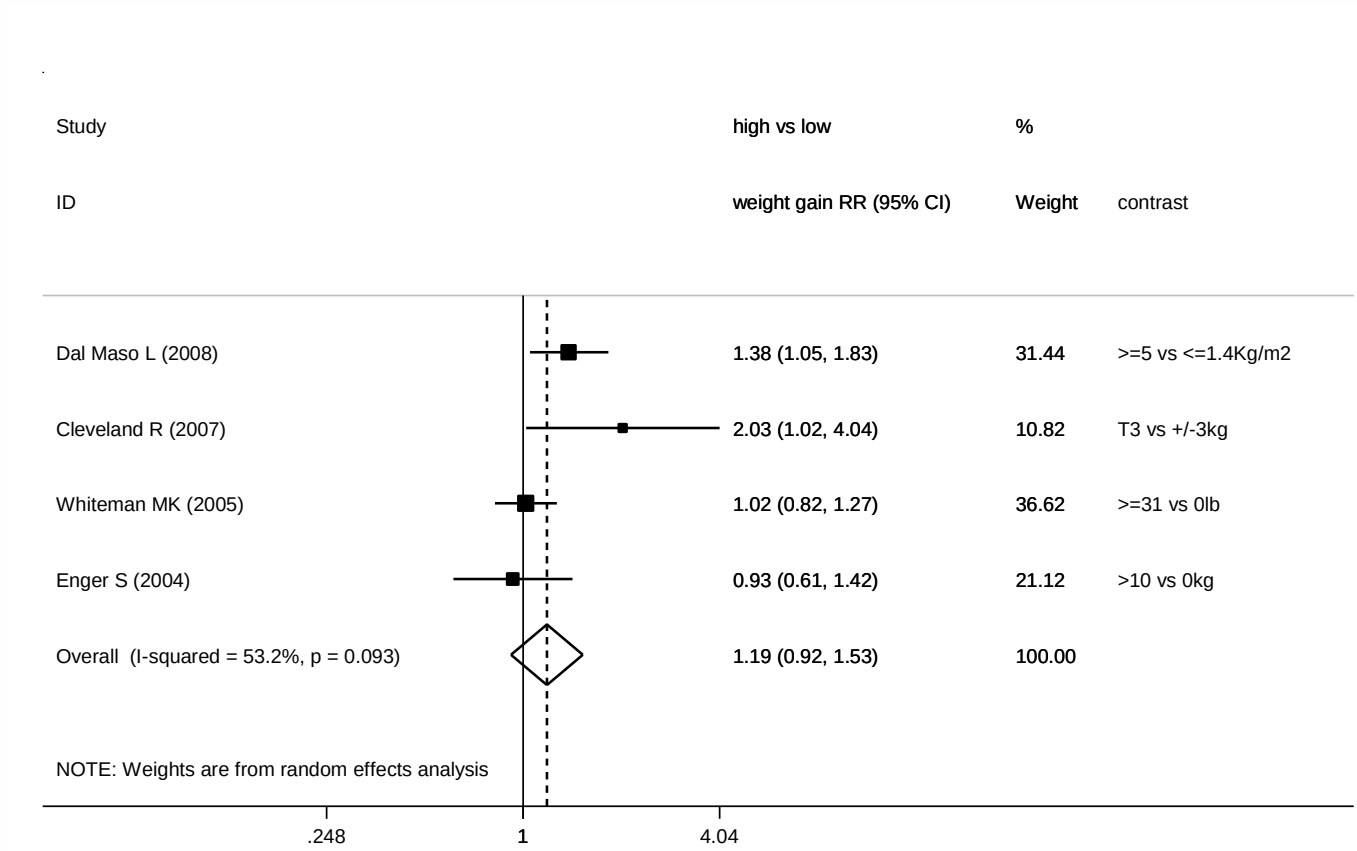


Figure 144 Dose-response meta-analysis of weight gain during adulthood and breast cancer mortality

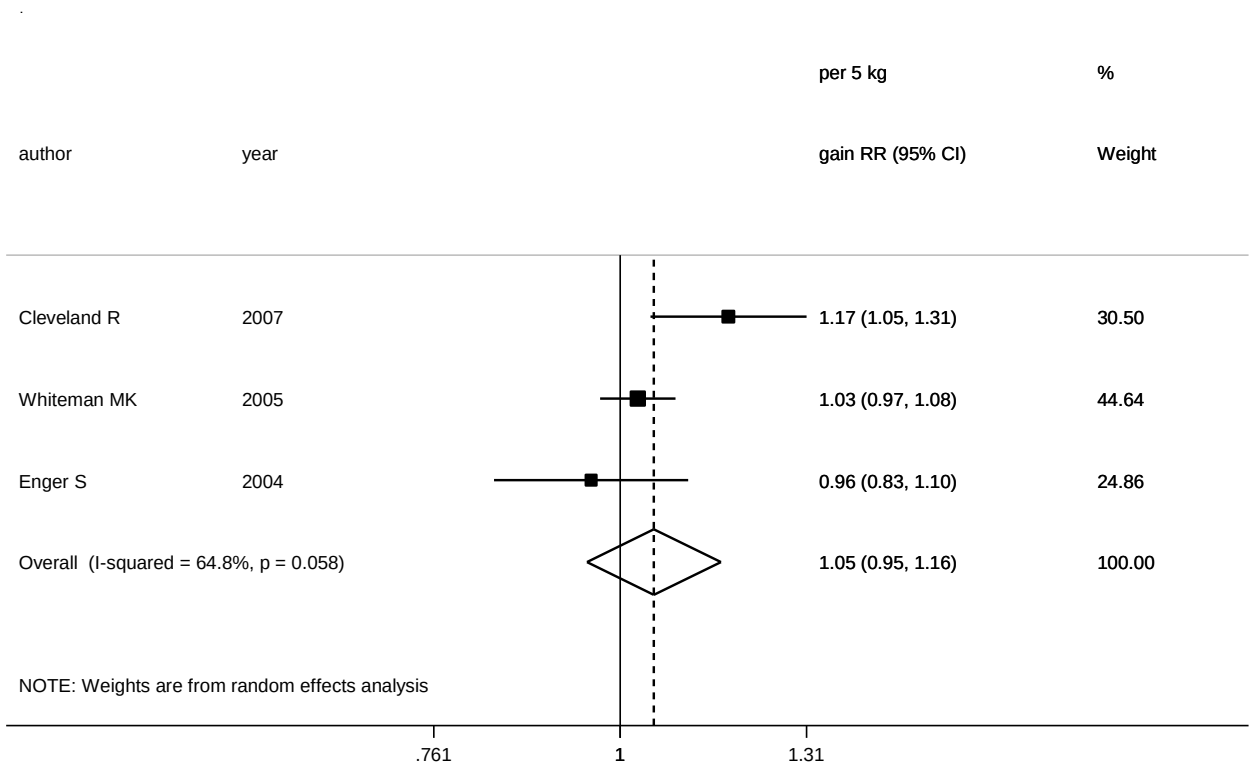


Figure 145 Individual dose-response graph of weight gain during adulthood and breast cancer mortality

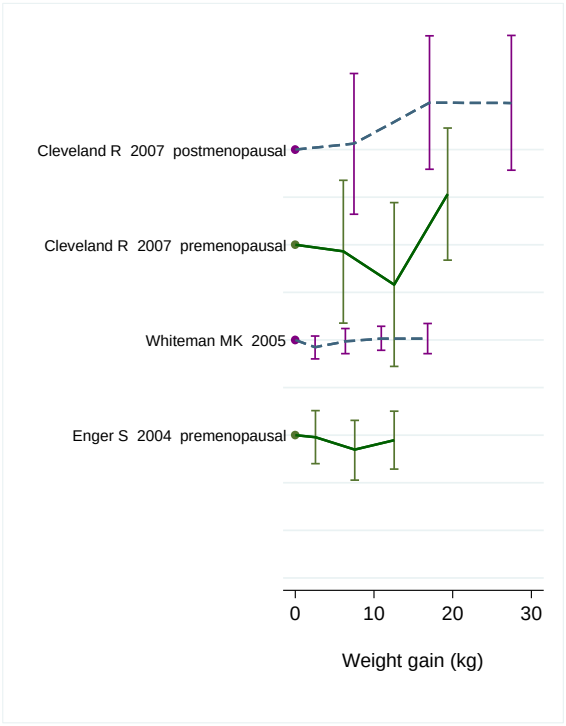


Table 121 Table of included studies on weight gain during adulthood and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments Remarks
Dal Maso L (2008)	Six Italian Regions Follow-up Study Italy	Cancer diagnosis: 1991-1994; Study follow up: until 2005-2006 diagnosed no longer than 1 year before the interview	Follow-up of cases of a case-control study	1453 participants 55 years (mean) 23 - 74 years Among those with data (pre diagnosis): 45.5 % peri/pre menopausal, 54.9% postmenopausal HRT use: 91.3% never, 8.6% ever	12.6 years	Invasive breast cancer; TNM; 32.7% Stage I, 44.1% stage II, 13.2% stage III-IV, 9.8% unknown	41.5% ER+ve/PR+ve, 3.5% ER-ve/PR+ve, 6.3% ER+ve/PR-ve, 10.1% ER-ve/ PR-ve 45.6% no node+ve, 44.2% node+ve, 10.1%		2.70% lost	Self-reported at study baseline; height, weight 1 year before cancer diagnosis and at different ages; hip and waist measured at interview	1453 participants 503 deaths, 398 breast cancer mortality, 6.2% death from other cancers, 7.4% from cardiovascular disease; 383breast cancer deaths from 1415 participants in analysis	Cancer registry	>=5 vs. <1.4 kg/m2 from age 30 years to diagnosis	1.38 (1.05-1.83)	Region, age at diagnosis, year of diagnosis, TNM stage, Receptor status Highest vs. lowest analysis only; measured change in BMI unlike the other studies in weight
Cleveland R (2007)	Long Island Breast Cancer Study Project United States	Cancer diagnosis:1996-1997; Study follow up: 2002-2004	Follow up of cases of a case-control study	1508 participants 58.8 years (mean) 25 - 98 years Mostly white:93.7%, 32.2% premenopausal, 67.8% postmenopausal HRT use: 86.8% ever, 13.2% never	66.7 months	84.4% invasive and 15.6% In situ	26.7% ER-ve, 73.3% ER +ve, 35.8% PR-ve, 64.2% PR+ve 73.7% no nodes involved, 26.3% nodes involved	Radiation therapy, chemotherapy, hormone therapy	410 patients lost	Self-reported shortly after diagnosis; weight and height at each decade of life from age 20 years until 1 year before diagnosis	1508 participants 196 deaths (of which 21% from cardiovascular disease), 127 breast cancer mortality, 9 death from brain and lung metastases	National Death Index	Premenopausal >=16 vs. ±3Kg gain Postmenopausal >=22.3 vs. ±3Kg gain Between age 20 and 1 year before diagnosis	2.09 (0.80-5.48) 1.97 (0.74-5.27)	Age at diagnosis, hypertension, weight at age 20y
Whiteman MK (2005)	Cancer and Steroid Hormone Study United States	Cancer diagnosis:1980-1982; Study follow up: until 1997	Follow-up of cases of a population-based case-control study	3924 participants 20 - 54 years White: 87.5%, black: 12.5% and other 47% premenopausal, 18% postmenopausal Comorbidities: 37.2% due to diabetes, high blood pressure, blood clots, kidney disease, gallbladder disease, heart attack, paralysis, rheumatoid arthritis, stroke, other cancer	14.6 years	Primary invasive incident breast cancer; 51.4% local, 45.4% regional, 3.2% distant		22.4% radiation therapy; info on adjuvant treatment not available	80.40% 4.10% lost	Self-reported at interview on average 2.5 months of diagnosis; BMI at age 18 years and after diagnosis	3924 participants 1,671 deaths, 1, 347 breast cancer mortality	SEER record	>=31 vs. 0 lb gain From age 18 to usual adult weight	1.02 (0.82-1.27)	Age at diagnosis, race, radiotherapy, history of benign breast disease, education, menopausal status, tumor stage,adult BMI
Enger S (2004)b	University of Southern California Cancer	Cancer diagnosis: 1983-89, Study follow-up: Until	Follow-up of cases of population-based	717 participants <=40 years White or Hispanic Premenopausal	10.4 years	Stages: 9.9% in situ, 47.4% localized, 39.1%			76.80%	Self-reported data for age 18, a year prior to	717 participants 251 breast cancer	Death certificate	>10 vs. 0 Kg gain From age	0.93 (0.61-1.42)	Age, tumor stage, BMI, physical activity

	Surveillance Program United States	2000	case-control study			regional, 3.6% distant metastasis	41.1% +ve, 57.3% -ve, 1.5% unknown			diagnosis in interview at study baseline	mortality, 2 deaths from coronary/CVD, 10 other causes of deaths		18 to a year before diagnosis		

Weight gain before and 12 months or more after diagnosis/treatment and breast cancer mortality

Methods

Three studies from four publications were identified. The publication by Bradshaw et al. in 2012 superseded the one in 2010. All studies (Kroenke, 2005; Nichols, 2009; Bradshaw, 2012) could be included in the highest versus lowest meta-analysis. Weight gain was quantified differently in the studies (by kg or percentage change in weight or by kg/m^2 change in BMI), thus a dose-response meta-analysis was not conducted. In the studies, weight gain was measured in different time periods from before to 12 months or more after cancer diagnosis/treatment. The comparisons between the weight change categories used in our analyses are taken as reported in the studies. The reference group was those of stable weight.

Main results and heterogeneity

For the highest compared with the lowest weight gain/stable weight from before to 12 months or more after diagnosis/treatment, the summary RR was 1.59 (95% CI 1.05-2.41; $I^2 = 47.1\%$; p = 0.15; 3 studies).

Study quality

Number of events ranged from 121 to 533 breast cancer deaths. Mean follow-up ranged from 6.3 to 9 years. Two studies were follow-up of case-control studies (Nichols, 2009; Bradshaw, 2012) and one study was a population cohort (Kroenke, 2005). Cases were diagnosed from 1976 to 2000 (Kroenke, 2005), from 1988 to 1999 (Nichols, 2009) and from 1996 to 1997 (Bradshaw, 2012). Bradshaw et al. (2012) included *in situ* and invasive breast cancers, while the other two studies (Kroenke, 2005; Nichols, 2009) included invasive breast cancer only. Weight at various time points were self-reported. All studies included women of all ages. All results were adjusted for multiple confounders, including tumour stage or size.

Published pooled analysis

The After Breast Cancer Pooling Project (ABCPP) published results on weight change before and 12 months or more after breast cancer diagnosis and total, breast cancer, and non-breast cancer mortality risks (Caan, 2012).

Data from four prospective studies of breast cancer survivors (Shanghai Breast Cancer Survival Study, Life After Cancer Epidemiology, Women's Healthy Eating and Living, and Nurses' Health Study) were available in the project. After a mean follow-up of 8.1 years, 1603 deaths (1040 breast cancer mortality) from 12915 participants with stage I-III invasive breast cancer were accrued. Analyses were conducted using data from the US

studies and the Chinese study separately.

Compared with stable weight (weight change within 5%), the HRs for weight gain ≥10% for the risk of dying of breast cancer was 1.03 (95% CI 0.84-1.26) for the U.S. sites, and 1.25 (95% CI 0.88-1.77) for China.

The highest vs. lowest meta-analysis in this report included results from the Nurses' Health Study (Kroenke, 2005) only.

Figure 146 Forest plot of the highest weight gain versus lowest weight gain/stable weight before and 12 months or more after diagnosis/treatment and breast cancer mortality

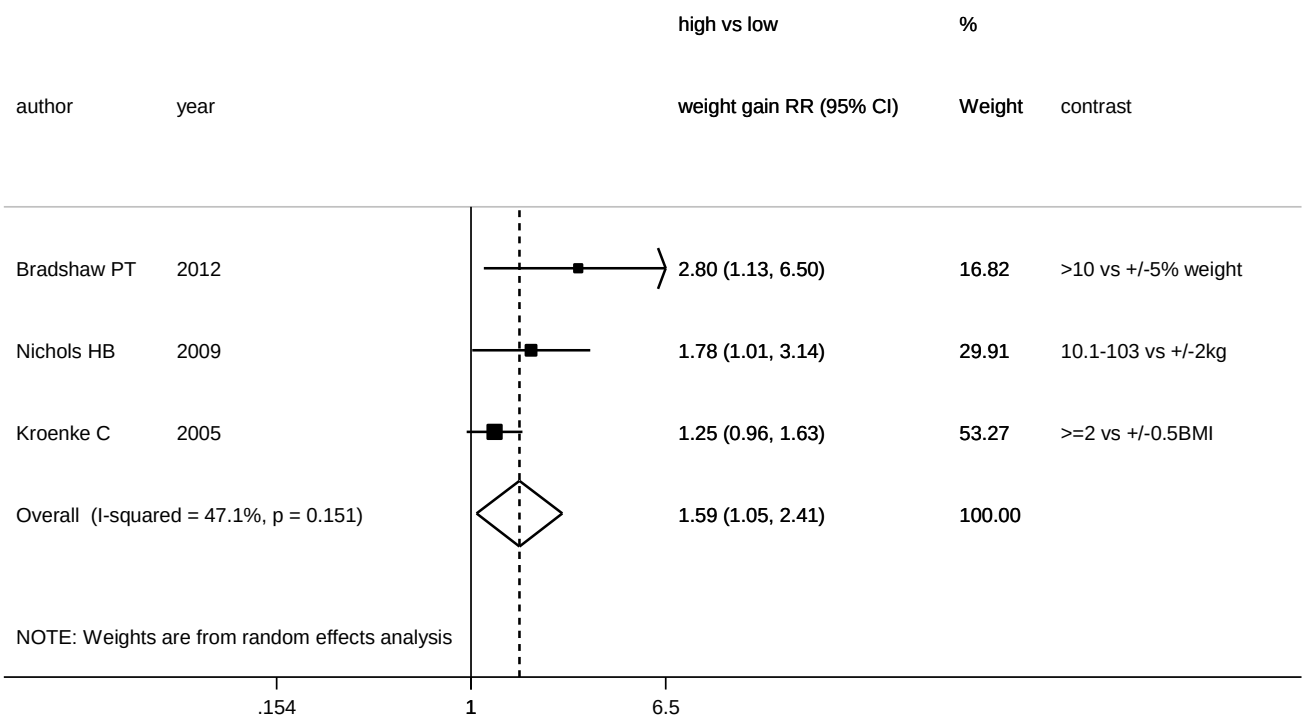


Table 122 Table of included studies on weight gain before and 12 months or more after diagnosis/treatment and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Nichols HB (2009)	Collaborative Women's Longevity Study United States	Study recruitment: 1988-2001; Cancer diagnosis: 1988-1999; Study follow up: until 2005 Recruited 5.8 years after breast cancer diagnosis	Follow-up of cases of case-control studies	3993 participants 58.4 years (mean) 20 - 79 years Mostly white: 98%, 28.1% premenopausal; 71.9% postmenopausal HRT use: 38.9% (postmenopausal hormone use)	6.3 years	Invasive nonmetastatic breast cancer; 64.1% local, 24.7% regional, 0.6% distant, 10.6% unknown			40%	Self-reported body weight 1-5 years before diagnosis and at study baseline	3993 participants 421 deaths, 121 breast cancer mortality, 95 deaths from cardiovascular disease	Death record	10.1-103 vs. ±2Kg gain From 1-5 years before diagnosis to within a year after diagnosis	1.78 (1.01-3.14)	Age, tumor stage, time from diagnosis to exposure assessment, family history, smoking, physical activity, menopausal status, pre-diagnosis weight
Kroenke C (2005)	Nurses' Health Study United States	Cancer diagnosis: 1976 - 2000, Study follow-up: Until 2002	Cancer survivors of population-based prospective cohort study	5204 participants 30 - 55 years	9 years	Invasive non metastatic breast cancer, any stages; 86.9% tumor size >2cm	73.2% ER+ 85.2 % node+ve	Chemotherapy: 63.9% yes; Tamoxifen: 64.8% yes		Self-reported at cohort baseline; pre and post-diagnosis weight	5204 participants 860 deaths, 533 breast cancer mortality	Family+ National Death Index	Never smoker >=2 vs. ±0.5BMI gain Past/Current smoker >=2 vs. ±0.5BMI gain From before diagnosis to >=12 months after diagnosis	1.64 (1.07-2.51) 1.05 (0.74-1.47)	Age, oral contraceptive, birth index, menopausal status, age at menopause, hormonal therapy, smoking, tumor size, nodal status, chemotherapy, tamoxifen use, protein intake, BMI prior to diagnosis
Bradshaw PT (2012)	Long Island Breast Cancer Study United States	Cancer diagnosis: 1996-1997, Study follow-up: until 2005 Recruited on average 3 months after diagnosis	Follow up of cases of a population-based case-control study	1436 participants 59 years (mean) 25-98 years 32% premenopausal, 68% postmenopausal	8.8 years	Primary in situ or invasive breast cancer; 76% tumour size <2cm , 24% >=2 cm, 453 unknown	26% ER-ve, 74% ER+ve, 483 missing; 36% PR -ve, 64% PR +ve, 487 missing	Chemotherapy: 41% yes, 59% no, 459 unknown	82% 55 patients lost	Self-reported at baseline and during follow up; height and weight 1 yr prior to diagnosis, at diagnosis and post diagnosis weight change	1436 participants 292 deaths, 156 breast cancer mortality	Death record	>10 vs. ±5% weight gain From diagnosis to after diagnosis	2.80 (1.13-6.50)	Age, chemotherapy, ER status, PR status, tumor size (result further adjusted for BMI 1 year before diagnosis and weight change from 20 years to 1 year before diagnosis was also provided in the article)

Table 123 Table of excluded studies on weight gain before and 12 months or more after diagnosis/treatment and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments Exclusion reason
Bradshaw PT (2010)	Long Island Breast Cancer Study Project United States	Cancer diagnosis: 1996-1997	Follow-up of cases of population-based case-control study	1436 participants 58.79 years (mean) 32.2% premenopausal, 67.8% postmenopausal	8.8 years	Tumor size >2cm: 16.3% yes, 52.2% no, 31.5% missing	35.5% ER+, 22.1% ER-, 42.4% missing among those with data; 42.4% PR+, 23.7% PR-, 33.9% missing	Chemotherapy: 28.1% yes, 39.9% no, 32% missing	68.5%	Self-reported at baseline and during follow up; height and weight 1 yr prior to diagnosis, at diagnosis and post diagnosis weight change	1436 participants 292 deaths, 156 breast cancer mortality	Death record	>10% gain vs +/-5% From "data not missing in random model"	2.80 (1.13-6.49) Corresponded to log-HR of 1.03 (0.12-1.87) reported in article	Age, chemotherapy, ER status, PR status, tumour size Superseded by Bradshaw 2012

Weight gain less than 12 months after diagnosis and breast cancer mortality

No study has reported data.

7.5 Weight loss

Table 124 Summary results of meta-analysis on weight loss and total mortality and breast cancer mortality*

	Total mortality			Breast cancer mortality		
Comparison	**No. of studies**	**No. of events in studies**	**RR (95% CI) I^2, $P_{heterogeneity}$**	**No. of studies**	**No. of events in studies**	**RR (95% CI) I^2, $P_{heterogeneity}$**
Weight loss before and 12 months or more after diagnosis/treatment						
Highest vs. lowest	6	2467	2.33 (1.42-3.83) 89.7%, p<0.0001	3	810	1.86 (0.43-7.98) 93.9%, p<0.0001

*No studies on second cancers were included in the meta-analyses. Only studies on weight loss before and after diagnosis could be included in meta-analyses.

Weight loss and total mortality

Weight loss during adulthood and total mortality

Three studies with results on weight loss during various pre-diagnosis/treatment periods in relation to total mortality were identified. Meta-analysis was not conducted as only two studies (Cleveland, 2007; Ewertz, 1991) have sufficient data; the third study (Swenerton, 1979) provided a p-value for the weight change groups. Intent of weight loss was not assessed in the studies.

One study observed a statistically non-significant increased risk for weight loss more than 3kg compared to stable weight, between age 20 years and one year before diagnosis in postmenopausal women (HR 1.99; 95% CI 0.83-4.73), and in premenopausal women (HR 1.07; 95% CI 0.26-4.50) (Cleveland, 2007). A non-significant increased risk was also reported in postmenopausal women for weight loss between age 20 and 50 years (HR 2.06; 95% CI 0.69-6.14). For weight loss between age 50 years and one year before diagnosis, a significant increased risk (HR 3.04; 95% CI 1.70-5.46) was observed in this study. The other study reported a statistically significant increased risk for weight loss ten years before diagnosis (HR > 5 vs. +/- 5 kg = 1.59; 95% CI 1.23-2.05) (Ewertz, 1991). In addition, pre-treatment weight loss of <5% was reported to relate to a longer survival when compared to 5-10% and > 10% loss (p < 0.01) (Swenerton, 1979).

Weight loss before and 12 months or more after diagnosis/treatment and total mortality

Methods

Six studies from seven publications were identified. The publication by Bradshaw et al. in 2012 superseded the one in 2010. All studies could be included in a highest versus lowest meta-analysis (Bradshaw, 2012; Chen, 2010; Nichols, 2009; Caan, 2008; Abrahamson, 2006b; Kroenke, 2005). Weight loss was quantified differently in the studies (by kg or percentage change in weight or by kg/m^2 change in BMI). Three studies (Bradshaw, 2012; Abrahamson, 2006b; Caan, 2008) measured weight loss by percentage weight change but one study (Bradshaw, 2012) was missing numbers of events/non-events per weight change category, thus a dose-response meta-analysis was not conducted with the remaining two studies.

In the studies, weight loss was measured in different time periods from before to after cancer diagnosis/treatment – from age 20 years to several months after diagnosis, from before diagnosis to within or more than a year after diagnosis, or from before to after diagnosis. Intent of weight loss was only assessed in one study. Nichols et al. (2009) excluded women with unintentional weight loss of > 5% body weight. Caan et al. (2008) also examined the association by excluding women who died within a year of study entry.The comparisons between the weight change categories used in our analyses are taken as reported in the studies. The reference group was those of stable weight.

Main results and heterogeneity

The summary RR for weight loss versus stable weight was 2.33 (95% CI 1.42-3.83). There was evidence of a high heterogeneity between studies (I^2 = 89.7%; p < 0.0001; 6 studies).

Chen et al. (2010) also reported results on weight loss during other time periods. A HR of 1.21 (95% CI 0.92-1.60) for > 1 kg loss compared to stable weight (+/- 1kg) between pre-diagnosis to 6 months post-diagnosis was observed, and a HR of 2.16 (95% CI 1.48-3.16) was reported for diagnosis to 18 months post-diagnosis.

Study quality

Number of events ranged from 138 to 860 deaths. Average time of follow-up was from 46 months to a maximum of 9.8 years. Loss to follow-up was < 2% (Abrahamson, 2006b) or 55 patients lost (Bradshaw, 2012) when reported. Two studies (Chen, 2010; Bradshaw, 2012) included women with *in situ* and invasive breast cancers. Other studies (Abrahamson, 2006b; Nichols, 2009; Caan, 2008; Kroenke, 2005) included invasive breast cancer only. Participants in Kroenke, et al. (2005) originated from a prospective cohort, while other studies either recruited at-diagnosis, or several months after diagnosis.

Cancer diagnosis dates varied between studies. One spanned from 1976 to 2000 (Kroenke, 2005), another from 1988 to 1999 (Nichols, 2009). Three studies recruited cancer diagnosed in the 1990s, or until 2000 (Abrahamson, 2006b; Caan, 2008; Bradshaw, 2012). Study recruitment in Chen et al. was between 2002 and 2006, which took place approximately six months after diagnosis. All studies included pre- and

postmenopausal women. All results were adjusted for multiple confounders, including tumour stage. The result of Abrahamson et al. (2006b) was adjusted for tumour stage, income and BMI at interview. Other factors like age, race and menopausal status were not included in the final model in this study, as they did not make an appreciable change to the estimate.

Published pooled analysis

The After Breast Cancer Pooling Project (ABCPP) published results on weight change before and 12 months or more after breast cancer diagnosis and total, breast cancer, and non-breast cancer mortality risks (Caan, 2012).

Data from four prospective studies of breast cancer survivors (Shanghai Breast Cancer Survival Study, Life After Cancer Epidemiology, Women's Healthy Eating and Living, and Nurses' Health Study) were available in the project. After a mean follow-up of 8.1 years, 1603 deaths (1040 breast cancer mortality) from 12915 participants with stage I-III invasive breast cancer were accrued. Analyses were conducted using data from the US studies and the Chinese study separately.

Compared with stable weight (weight change within 5%), the HRs for weight loss $\geq$ 10% was 1.41 (95% CI 1.14-1.75) for total mortality risk for the US sites and 3.25 (95% CI 2.24-4.73) for China. In the US, women who lost ≥10% weight and had comorbidities were associated with a lower survival. The HRs were 1.70 (95% CI 1.29-2.23) and 1.13 (95% CI 0.77-1.65), respectively, for those with and without comorbidity at diagnosis ($p_{contrast}$ = 0.05).

The highest vs. lowest meta-analysis in this report included results from the Shanghai Breast Cancer Survival Study (Chen, 2010), Life After Cancer Epidemiology (Caan, 2008), and the Nurses' Health Study (Kroenke, 2005), but not the Women's Healthy Eating and Living RCT as in the ABCPP.

Figure 147 Forest plot of weight loss versus stable weight before and 12 months or more after diagnosis/treatment and total mortality

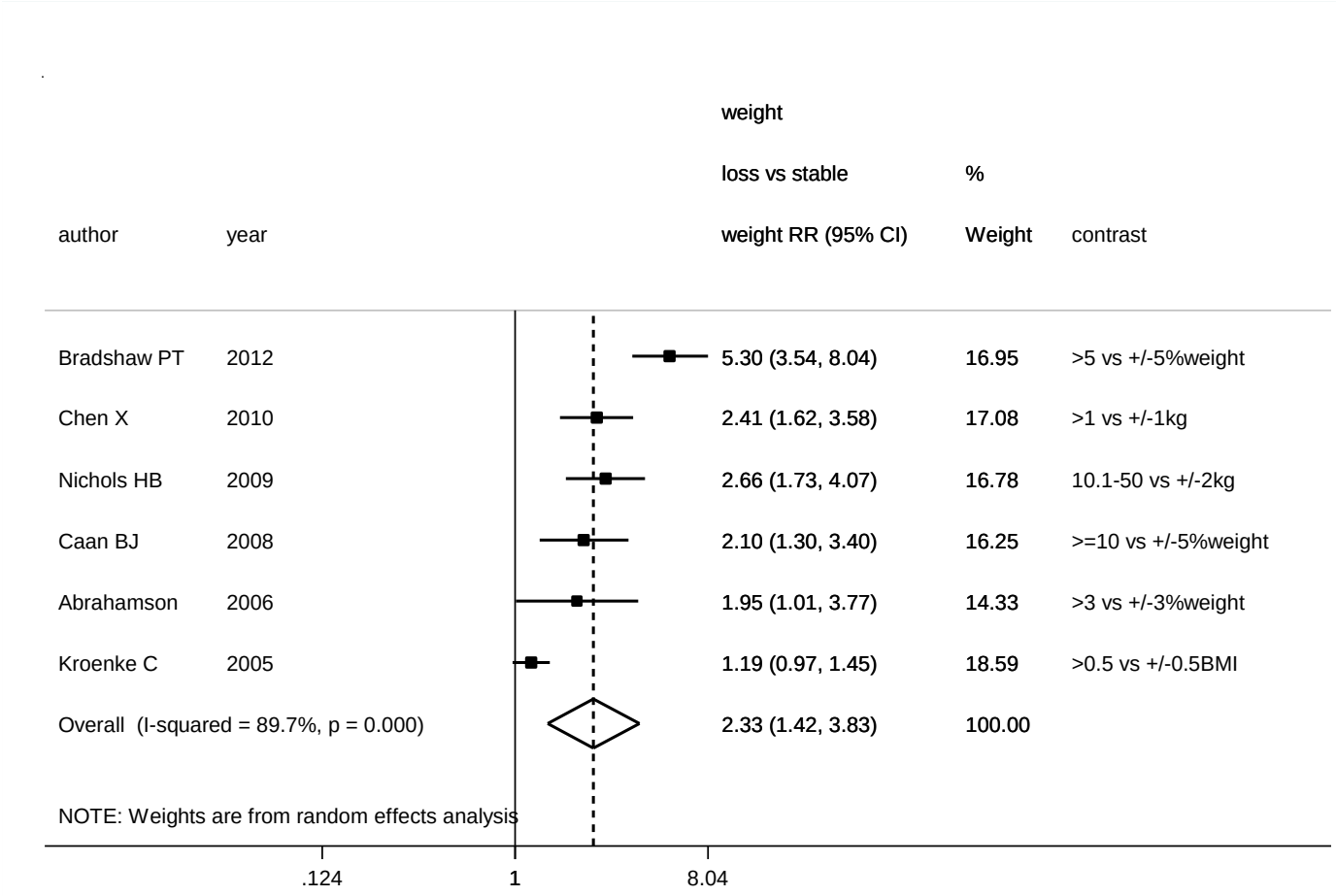


Table 125 Table of included studies on weight loss before and 12 months or more after diagnosis/treatment and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Bradshaw PT (2012)	Long Island Breast Cancer Study United States	Cancer diagnosis: 1996-1997, Study follow-up: until 2005 Recruited on average 3 months after diagnosis	Follow up of cases of a population-based case-control study	1436 participants 59 years (mean) 25-98 years 32% premenopausal, 68% postmenopausal	8.8 years	Primary in situ or invasive breast cancer; 76% tumour size <2cm , 24% >=2 cm, 453 unknown	26% ER-ve, 74% ER+ve, 483 missing; 36% PR -ve, 64% PR +ve, 487 missing	Chemotherapy: 41% yes, 59% no, 459 unknown	82% / 55 patients lost	Self-reported at baseline and during follow up; height and weight 1 yr prior to diagnosis, at diagnosis and post diagnosis weight change	1436 participants 292 deaths, 156 breast cancer mortality	Death record	>5vs. ±5% weight lost From diagnosis to after diagnosis	5.30 (3.54-8.04)	Age, chemotherapy, ER status, PR status, tumor size (result further adjusted for BMI 1 year before diagnosis and weight change from 20 years to 1 year before diagnosis was also provided in the article)
Chen X (2010)	Shanghai Breast Cancer Survival Study China	Study recruitment: 2002-2006;	Prospective cohort of breast cancer survivors	5042 participants 53.5 years (mean) 20 - 75 years 51.1% postmenopausal	46 months	TNM; 36.4% stage 0-I, 32.6% IIA, 16.6% IIB, 9.8% IIIIV, 4.6% unknown	49.9% ER+ve/PR+ve, 27.6% ER-ve/PR-ve, 20.4% mixed (ER+ve PR-ve/ER-ve PR+ve), 2.1% unknown	Mastectomy:93.9% ; Chemotherapy: 91.2%; Radiotherapy: 32.1% ; Tamoxifen usage: 52%	80%	Self-reported weight 1 year prior to diagnosis and at diagnosis, measured at baseline interview approximately 6 months after diagnosis	5042 participants 442 deaths	Cancer register	>1 vs. ±1Kg lost From before diagnosis to 18 months after diagnosis	2.41 (1.62, 3.58)	Age at diagnosis, pre-diagnosis BMI, education, Income, marital status, meat intake, cruciferous vegetables, soy protein, time from diagnosis to study enrollment, menopausal status, menopausal symptoms, chemotherapy, surgery type, radiotherapy, tamoxifen use, nodal status, immunotherapy, TNM stage, comorbidity, exercise, hormone receptor status
Nichols HB (2009)	Collaborative Women's Longevity Study United States	Study recruitment: 1988-2001; Cancer diagnosis: 1988-1999; Study follow up: until 2005 Recruited 5.8 years after breast cancer diagnosis	Follow-up of cases of case-control studies	3993 participants 58.4 years (mean) 20 - 79 years Mostly white: 98%, 28.1% premenopausal; 71.9% postmenopausal HRT use: 38.9% (postmenopausal hormone use)	6.3 years	Invasive nonmetastatic breast cancer; 64.1% local, 24.7% regional, 0.6% distant, 10.6% unknown			40%	Self-reported body weight 1-5 years before diagnosis and at study baseline; excluded unintentional weight loss of >5% body weight (n=262)	3993 participants 421 deaths, 121 breast cancer mortality, 95 deaths from cardiovascular disease	Death record	10.1-50 vs. ±2Kg lost From 1-5 years before diagnosis to within a year after diagnosis	2.66 (1.73-4.07)	Age, tumor stage, time from diagnosis to exposure assessment, family history, smoking, physical activity, menopausal status, pre-diagnosis weight
Caan BJ (2008)	LACE United States	Cancer diagnosis:1997-2000; Study follow up: until 2007 Diagnosed 11–39 months before study enrolment	Prospective cohort study of breast cancer survivors	1692 participants 58.3 years (mean) 18 - 70 years 22.8% premenopausal, 63.8% postmenopausal	83.9 months	Early stage invasive breast cancer; AJCC; 46.7% Stage I, 50.2% Stage II, 3.1% Stage IIIA	69.2% ER+/PR+, 13.6% ER+/PR-, 1.7% ER-/ PR+, 15.5% ER-/PR- / 63.2% o node+ve, 26.3% 1-3 nodes+ve, 5.7% 4-6 nodes+ve, 1.7% 7-9	19% chemotherapy; 24.8% radiotherapy; 38.4% chemo- and radiotherapy; 49.2% mastectomy; 50.8% breast-conserving surgery; 70.9% current tamoxifen	46%	Self-reported at baseline; one year pre-diagnosis and also after diagnosis at baseline	1692 participants 162 deaths, 99 breast cancer mortality, 138 deaths, 1689 participants included in the analysis	Medical records	>=10 vs. ±5% weight lost From before diagnosis to study entry ~22.7 months after diagnosis Excluding deaths occurred	2.10 (1.30-3.40) Association remained	Tumor stage, age at diagnosis, tamoxifen use, treatment, nodal status, estrogen receptor level, progesterone receptor level, smoking, physical activity

							nodes+ve, 3.1% >=10 nodes+ve	users, 6.7% past tamoxifen users					within a year to study entry	unchanged	
Abrahamson (2006)b	Atlanta, Seattle, New Jersey Follow-up Study United States	Cancer diagnosis:1990-1992; Study follow up: until 2000	Follow-up of cases of a population-based case-control study	1254 participants 20 - 54 years 75% white 25% non-white, 78% premenopausal, 22% postmenopausal and unknown <1%	9.8 Years (max)	Invasive breast cancer; AJCC; any stage ; 57% local, 40% regional, 3% distant, <1% unknown	56% ER+ve, 35%ER-ve, 3% borderline, 6% unknown		86% <2% lost	Measured 4.2 months after diagnosis; self-reported weight and height at age 20 years and the year before diagnosis	1254 participants 290 deaths	Cancer registry + National Death Index	>3 vs. ±3% weight lost From age 20 to interview ~4.2 months after diagnosis	1.95 (1.01-3.77)	Tumor stage, income, BMI at interview Result not adjusted for BMI at interview was also provided in the article)
Kroenke C (2005)	Nurses' Health Study United States	Cancer diagnosis: 1976 - 2000, Study follow-up: Until 2002	Cancer survivors of population-based prospective cohort study	5204 participants 30 - 55 years	9 years	Invasive non metastatic breast cancer, any stages; 86.9% tumor size >2cm	73.2% ER+ 85.2% node+ve	Chemotherapy: 63.9% yes; Tamoxifen: 64.8% yes		Self-reported at cohort baseline; pre and post-diagnosis weight	5204 participants 860 deaths, 533 breast cancer mortality	Family+ National Death Index	Never smoker >0.5 vs. ±0.5BMI lost Past/Current smoker >0.5 vs. ±0.5BMI lost From before diagnosis to >=12 months after diagnosis	1.23 (0.96-1.57) 1.11 (0.78-1.56)	Age, oral contraceptive, birth index, menopausal status, age at menopause, hormonal therapy, smoking, tumor size, nodal status, chemotherapy, tamoxifen use, protein intake, BMI prior to diagnosis

Table 126 Table of excluded studies on weight loss before and 12 months or more after diagnosis/treatment and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments Exclusion reason
Bradshaw PT (2010)	Long Island Breast Cancer Study Project United States	Cancer diagnosis: 1996-1997	Follow-up of cases of population-based case-control study	1436 participants 58.79 years (mean) 32.2% premenopausal, 67.8% postmenopausal	8.8 years	Tumor size >2cm: 16.3% yes, 52.2% no, 31.5% missing	35.5% ER+, 22.1% ER-, 42.4% missing among those with data; 42.4% PR+, 23.7% PR-, 33.9% missing	Chemotherapy: 28.1% yes, 39.9% no, 32% missing	68.5%	Self-reported at baseline and during follow up; height and weight 1 yr prior to diagnosis, at diagnosis and post diagnosis weight change	1436 participants 292 deaths, 156 breast cancer mortality	Death record	>5% loss vs. +/-5% From data not missing in random model	5.31 (3.56-8.00) Corresponded to log-HR of 1.67 (1.27-2.08) reported in article	Age, chemotherapy, ER status, PR status, tumour size Superseded by Bradshaw, 2012

Weight loss less than 12 months after diagnosis and total mortality

Two studies reported results on weight loss less than 12 months after diagnosis were identified. A statistically non-significant increased risk was observed in one study (HR > 3 vs. +/-3% weight change = 1.27, 95% CI 0.93-1.74) (Abrahamson, 2006b), but no association was reported in the other (log-rank test for ≥ 0% vs. <0% weight loss, p = 0.12) (Costa, 2002). Intent of weight loss was not assessed in the studies.

Weight loss and breast cancer mortality

Weight loss during adulthood and breast cancer mortality

One study was identified. Cleveland et al. (2007) reported a HR of 0.72 (95% CI 0.14-3.73) for breast cancer mortality for comparing more than 3 kg weight loss to stable weight (+/- 3 kg) during early adulthood (age 20 years to one year before diagnosis) in premenopausal women. In postmenopausal women, the HRs were 2.56 (95% CI 0.67-9.76) during the same time period, 3.42 (95% CI 0.75-15.6) during 20 to 50 years, and 4.55 (95% CI 1.98-10.5) during age 50 years to one year before diagnosis. There were only 8-26 breast cancer deaths in these analyses. Intent of weight loss was not assessed in the study.

Weight loss before and 12 months or more after diagnosis/treatment and breast cancer mortality

Methods

Three studies from four publications were identified. The publication by Bradshaw et al. in 2012 superseded the one in 2010. All studies (Kroenke, 2005; Nichols, 2008; Bradshaw, 2012) could be included in a highest versus lowest meta-analyis. Weight loss was quantified differently in the studies (by kg or percentage change in weight or by kg/m^2 change in BMI), thus a dose-response meta-analysis could not be conducted. Weight loss was observed in different time periods before and after diagnosis/treatment – from 1-5 years before diagnosis or at-diagnosis to within or more than a year after diagnosis. Intent of weight loss was only assessed in one study. Nichols et al. (2009) excluded women with unintentional weight loss of > 5% body weight.

Main results and heterogeneity

The summary RR for weight loss versus stable weight was 1.86 (95% CI 0.43-7.98; I^2 = 93.9%; p < 0.0001; 3 studies).

Study quality

Number of events ranged from 121 to 533 breast cancer deaths. Mean follow-up ranged from 6.3 to 9 years. Two studies were follow-up of case-control studies (Nichols, 2009; Bradshaw, 2012) and one study was a population cohort (Kroenke, 2005). Cases were diagnosed from 1976 to 2000 (Kroenke, 2005), from 1988 to 1999 (Nichols, 2009) and from 1996 to 1997 (Bradshaw, 2012). Bradshaw et al. (2012) included *in situ* and invasive breast cancers, while the other two studies (Kroenke, 2005; Nichols, 2009) included invasive breast cancer only. Weight at various time points were self-reported. All studies included women of all ages. All results were adjusted for multiple confounders, including tumour stage or size.

Published pooled analysis

The After Breast Cancer Pooling Project (ABCPP) published results on weight change before and 12 months or more after breast cancer diagnosis and total, breast cancer, and non-breast cancer mortality risks (Caan, 2012).

Data from four prospective studies of breast cancer survivors (Shanghai Breast Cancer Survival Study, Life After Cancer Epidemiology, Women's Healthy Eating and Living, and Nurses' Health Study) were available in the project. After a mean follow-up of 8.1 years, 1603 deaths (1040 breast cancer mortality) from 12915 participants with stage I-III invasive breast cancer were accrued. Analyses were conducted using data from the US studies and the Chinese study separately.

Compared with stable weight (weight change within 5%), the HRs for weight loss ≥ 10% was 1.13 (95% CI 0.83-1.56) for the risk of dying of breast cancer for the U.S. sites and 3.60 (95% CI 2.39-5.42) for China.

The highest vs. lowest meta-analysis in this report included results from the Nurses' Health Study only (Kroenke, 2005).

Figure 148 Forest plot of weight loss versus stable weight before and 12 months or more after diagnosis/treatment and breast cancer mortality

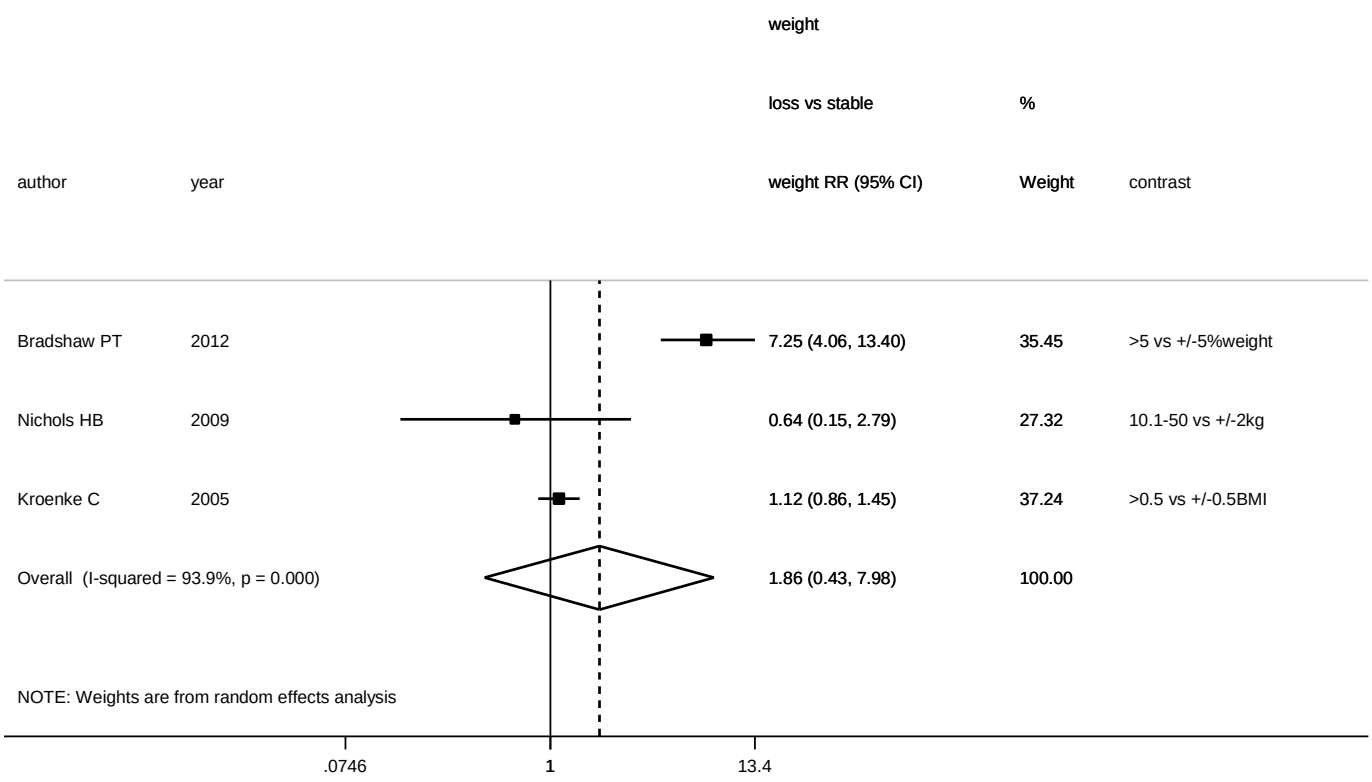


Table 127 Table of included studies on weight loss before and 12 months or more after diagnosis/treatment and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Nichols HB (2009)	Collaborative Women's Longevity Study United States	Study recruitment: 1988-2001; Cancer diagnosis: 1988-1999; Study follow up: until 2005 Recruited 5.8 years after breast cancer diagnosis	Follow-up of cases of case-control studies	3993 participants 58.4 years (mean) 20 - 79 years Mostly white 28.1% premenopausal; 71.9% postmenopausal HRT use: 38.9% (postmenopausal hormone use)	6.3 years	Invasive nonmetastatic breast cancer; 64.1% local, 24.7% regional, 0.6% distant, 10.6% unknown			40%	Self-reported body weight 1-5 years before diagnosis and at study baseline excluded; unintentional weight loss of >5% body weight (n=262)	3993 participants 421 deaths, 121 breast cancer mortality, 95 deaths from cardiovascular disease	Death record	10-1-50 vs. ±2Kg lost From 1-5 years before diagnosis to within a year after diagnosis	0.64 (0.15-2.79)	Age, tumor stage, time from diagnosis to exposure assessment, family history, smoking, physical activity, menopausal status, pre-diagnosis weight
Kroenke C (2005)	Nurses' Health Study United States	Cancer diagnosis: 1976 - 2000, Study follow-up: Until 2002	Cancer survivors of population-based prospective cohort study	5204 participants 30 - 55 years	9 years	Invasive non metastatic breast cancer, any stages; 86.9% tumor size >2cm	73.2% ER+ 85.2 % node+ve	Chemotherapy: 63.9% yes; Tamoxifen: 64.8% yes		Self-reported at cohort baseline; pre and post-diagnosis weight	5204 participants 860 deaths, 533 breast cancer mortality	Family+ National Death Index	Never smoker >0.5 vs. ±0.5BMI lost Past/Current smoker >0.5 vs. ±0.5BMI lost From before diagnosis to >=12 months after diagnosis	1.01 (0.65-1.58) 1.18 (0.85-1.63)	Age, oral contraceptive, birth index, menopausal status, age at menopause, hormonal therapy, smoking, tumor size, nodal status, chemotherapy, tamoxifen use, protein intake, BMI prior to diagnosis
Bradshaw PT (2012)	Long Island Breast Cancer Study United States	Cancer diagnosis: 1996-1997, Study follow-up: until 2005 Recruited on average 3 months after diagnosis	Follow up of cases of a population-based case-control study	1436 participants 59 years (mean) 25-98 years 32% premenopausal, 68% postmenopausal	8.8 years	Primary in situ or invasive breast cancer; 76% tumour size <2cm , 24% >=2 cm, 453 unknown	26% ER-ve, 74% ER+ve, 483 missing; 36% PR -ve, 64% PR +ve, 487 missing	Chemotherapy: 41% yes, 59% no, 459 unknown	82% 55 patients lost	Self-reported at baseline and during follow up; height and weight 1 yr prior to diagnosis, at diagnosis and post diagnosis weight change	1436 participants 292 deaths, 156 breast cancer mortality	Death record	>5vs. ±5% weight lost From diagnosis to after diagnosis	7.25 (4.06-13.40)	Age, chemotherapy, ER status, PR status, tumor size (result further adjusted for BMI 1 year before diagnosis and weight change from 20 years to 1 year before diagnosis was also provided in the article)

Table 128 Table of excluded studies on weight loss before and 12 months or more after diagnosis/treatment and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments Exclusion reason
Bradshaw PT (2010)	Long Island Breast Cancer Study Project United States	Cancer diagnosis: 1996-1997	Follow-up of cases of population-based case-control study	1436 participants 58.79 years (mean) 32.2% premenopausal, 67.8% postmenopausal	8.8 years	Tumor size >2cm: 16.3% yes, 52.2% no, 31.5% missing	35.5% ER+, 22.1% ER-, 42.4% missing among those with data; 42.4% PR+, 23.7% PR-, 33.9% missing	Chemotherapy: 28.1% yes, 39.9% no, 32% missing	68.5%	Self-reported at baseline and during follow up; height and weight 1 yr prior to diagnosis, at diagnosis and post diagnosis weight change	1436 participants 292 deaths, 156 breast cancer mortality	Death record	>5% loss vs. +/-5% From data not missing in random model	7.24 (4.05-13.33) Corresponded to log-HR of 1.98 (1.40-2.59) reported in article	Age, chemotherapy, ER status, PR status, tumour size Superseded by Bradshaw, 2012

Weight loss less than 12 months after diagnosis and breast cancer mortality

No study has reported data.

7.6 Waist circumference

Table 129 Summary results of meta-analysis on waist circumference less than 12 months after diagnosis and total mortality*

Comparison	No. of studies	No. of events in studies	RR (95% CI)	I^2, $P_{heterogeneity}$
Highest vs. lowest	3	664	1.38 (0.99-1.93)	66.2%, p = 0.05
Per 10 cm	3	664	1.21 (0.97-1.49)	75.4%, p = 0.02

*No studies on breast cancer mortality and second cancers were included in the meta-analyses. Only studies on waist circumference at diagnosis could be included in meta-analyses.

Waist circumference and total mortality

Four studies on total mortality were identified. One study (Zhang, 1995) examined waist circumference before diagnosis, three studies examined waist circumference less than 12 months after diagnosis, and no study examined waist circumference 12 months or more after diagnosis.

Waist circumference before diagnosis and total mortality

Only one study reported data (Zhang, 1995). In this study, the RR for 36.6-56 inches vs. 23-32 inches waist circumference was 1.1 (95% CI 0.6-2.1, p_{trend} = 0.77) (Zhang, 1995).

Waist circumference less than 12 months after diagnosis and total mortality

Methods

All three studies identified could be included in the dose-response and highest versus lowest meta-analyses (Abrahamson, 2006b; Tao, 2006; Goodwin, 2012). Goodwin et al. (2012) modelled waist circumference as a quadratic term, with the second category being the reference group, to enhance the predictability of the relationship. For this study a linear relationship for the second to the highest category was estimated and included with other studies in the linear dose-response meta-analysis.

Main results and heterogeneity

The summary RR per 10 cm was 1.21 (95% CI 0.97-1.49; 3 studies). There is evidence of high heterogeneity between studies (I^2 = 75.4%; p = 0.02). In the influence analysis, the summary RRs ranged from 1.08 (95% CI 0.95-1.23) when Abrahamson et al. (2006b) was omitted to 1.30 (95% CI 1.02-1.67) when Goodwin et al. (2012) was omitted. For the highest compared to the lowest waist circumference, the summary RR was 1.38 (95% CI 0.99-1.93; I^2 = 66.2%; p = 0.05; 3 studies).

Study quality

Number of events ranged from 134 to 290 deaths. Follow-up time ranged from 5.1 years to 12.1 years. All studies included breast cancer cases at different stages. Tao et al. (2006) included TNM stage 0 cases and the other two studies (Goodwin, 2012; Abrahamson, 2006b) included invasive breast cancer cases only. All studies included both pre- and postmenopausal women. All studies used measured anthropometric data. All models were adjusted for multiple confounders, including tumour stage. The result of Abrahamson et al. (2006b) was adjusted for tumour stage and income. Other factors like age, race and menopausal status were not included in the final model in this study, as they did not make an appreciable change to the estimate.

Figure 149 Highest versus lowest forest plot of waist circumference less than 12 months after diagnosis and total mortality

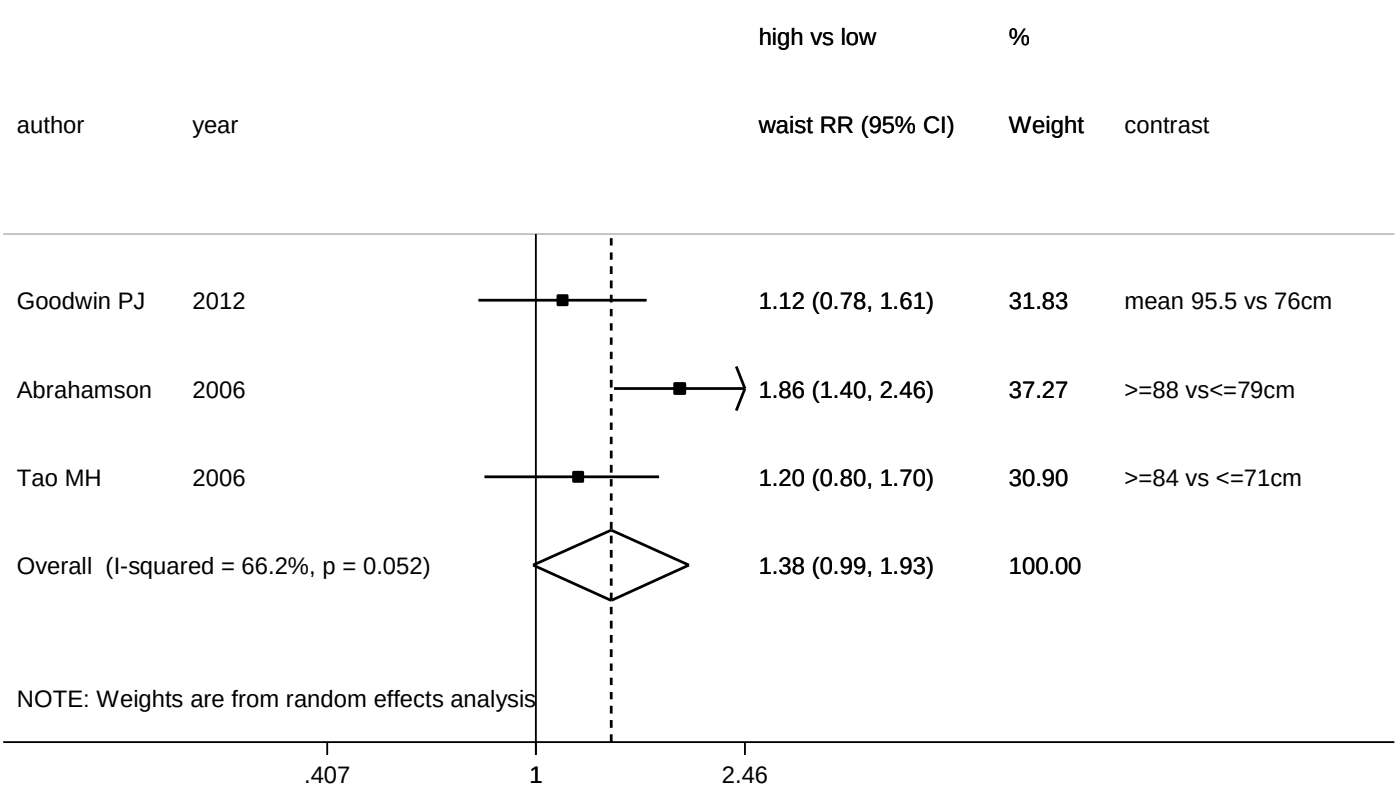


Figure 150 Linear dose-response meta-analysis of waist circumference less than 12 months after diagnosis and total mortality

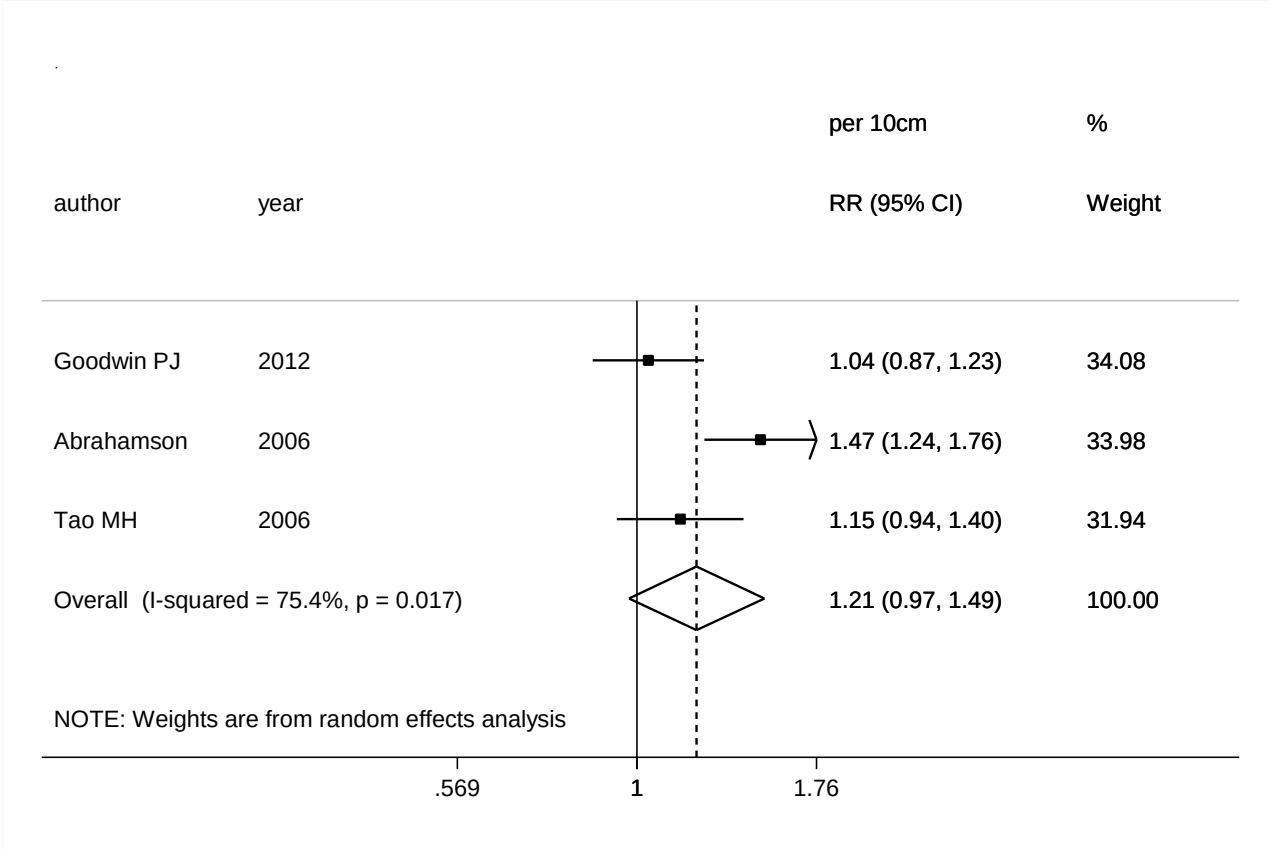


Figure 151 Individual dose-response graph of waist circumference less than 12 months after diagnosis and total mortality

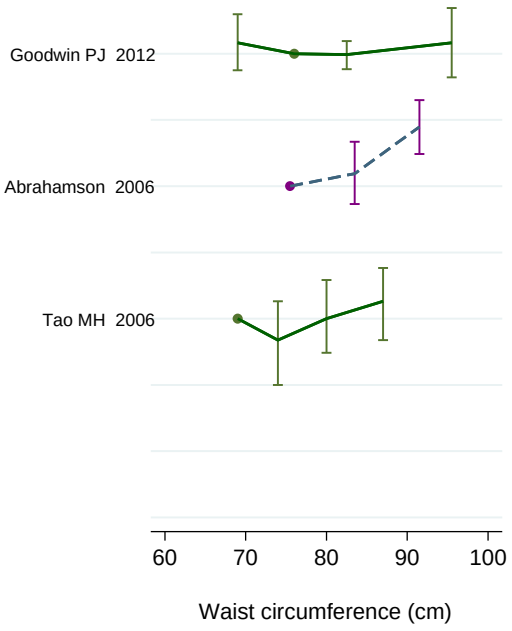


Table 130 Table of included studies on waist circumference less than 12 months after diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Goodwin PJ (2012)	University of Toronto Hospitals Follow-up Study Canada	Cancer diagnosis:1989-1996; Study follow up: until 2007	Prospective cohort of breast cancer survivors	535 participants 50.3 years (mean) <=75 years Multi-ethnic 57.2% premenopausal, 4.9% perimenopausal, 37.9% postmenopausal	12.1 years	Early M0 invasive breast cancer; non-diabetic women; 55.5% T1, 32.5% T2, 5% T3, 6.9% Tx, N0-1,	67.7% ER+ve, 18.7% ER-ve, 13.6% unknown; 61.7% PR+ve, 23.4% PR-ve, 15% unknown 69.2% N0, 30.8% N1	22.8% mastectomy, 77.2% lumpectomy; adjuvant chemotherapy: 39.8% yes, 60.2% no; hormone therapy: 39.1% yes, 60.9% no	23 women, 4.3%	Measured post diagnosis; median, 7 weeks postoperatively	535 participants 134 deaths, 113 breast cancer mortality, 21 deaths from other causes	Hospital records	95.5 vs. 76 cm	1.12 (0.78-1.61)	Age, tumor and nodal stage, tumor grade, hormone receptor status, adjuvant chemotherapy, hormonal therapy
Abrahamson (2006)b	Atlanta, Seattle, New Jersey Follow-up Study United States	Cancer diagnosis:1990-1992; Study follow up: until 2000	Follow-up of cases of a population-based case-control study	1254 participants 20 - 54 years 78% premenopausal, 22% postmenopausal and unknown <1%	9.8 years	Invasive breast cancer; AJCC; any stage ; 57% local, 40% regional, 3% distant, <1% unknown	56% ER+ve, 35%ER-ve, 3% borderline, 6% unknown		86% < 2%lost	Measured 4.2 months after diagnosis; weight and height at age 20 years and the year before diagnosis	1254 participants 290 deaths	Cancer registry + National Death Index	>=88 vs. <=79 cm	1.86 (1.40-2.46)	Tumor stage, income (Results further adjusted for BMI at interview was also provided in the article)
Tao MH (2006)	Shanghai Breast Cancer Study China	Cancer diagnosis: 1996-1998; Study follow up: until 2002 Recruited/interview on average 67 days after diagnosis	Follow-up of cases of a population-based case-control study	1455 participants 25 - 64 years	5.1 years	Primary breast cancer; TNM; 24.6% Stage 0-I, 34.9% stage IIA, 21.9% stage IIB, 11.3% stage III-IV, 7.1% unknown	44.4% ER+ve, 25.5% ER-ve, 30% unknown; 43.5% PR+ve, 25.2% PR-ve, 31.1% unknown	Surgery: 99%; Adjuvant chemotherapy: 94% ; adjuvant chemotherapy and traditional Chinese medicine: 63%; radiotherapy: 38.9% yes, 47.4% no, 13.6% unknown; tamoxifen use: 63.2% yes, 18 no, 18.6% unknown	91% 126 patients lost (assumed to be still living)	Measured at or soon after diagnosis at study baseline	1455 participants 240 deaths	Death certificate	>=84 vs. <=71 cm	1.20 (0.80-1.70)	Age at diagnosis, education, menopausal status, tumor Stage (TNM), chemotherapy, tamoxifen use, radiotherapy, estrogen receptor level, progesterone receptor level

Waist circumference 12 months or more after diagnosis and total mortality

No study has reported data.

Waist circumference and breast cancer mortality

No study has reported data.

7.7 Hip circumference

Hip circumference and total mortality

Three studies on total mortality were identified. One study (Zhang, 1995) examined hip circumference before diagnosis and two studies (Abrahamson, 2006b; Goodwin, 2012) examined hip circumference less than 12 months after diagnosis. No study examined 12 months or more after diagnosis data.

Hip circumference before diagnosis and total mortality

Only one study reported data (Zhang, 1995). In this study, the RR for 42.5-59.8 inches vs. 21-39.1 inches hip circumference was 1.8 (95% CI 0.8-3.8; p_{trend} = 0.15) (Zhang, 1995).

Hip circumference less than 12 months after diagnosis and total mortality

Two studies reported data (Abrahamson, 2006b; Goodwin, 2012). Abrahamson et al. (2006b) observed a statistically non-signficant increased risk for the comparison of the highest to lowest hip circumference (HR for 109.9-223.0 vs. 50.7-96.0 cm = 1.21, 95% CI 0.88-1.66, p_{trend} = 0.04). The association was attenuated after adjustment for BMI (HR 0.80; 95% CI 0.49-1.3; p_{trend} = 0.54). Goodwin et al. (2012) modelled the association with a quardratic model to improved predictability. The HR was 1.12 (95% CI 0.80-1.55; p_{trend} = 0.71) for 107-166 vs. 96-101 cm.

Hip circumference 12 months or more after diagnosis and total mortality

No study has reported data.

Hip circumference and breast cancer mortality

One study on hip circumference before diagnosis and breast cancer mortality was identified (Zhang, 1995).

Hip circumference before diagnosis and breast cancer mortality

Only one study reported data, in which a 2.1-fold increased risk for 42.5-59.8 inches versus 21.0-39.1 inches hip circumference was observed (Zhang, 1995). 95% CI and P-value was not provided.

Hip circumference less than 12 months after diagnosis and breast cancer mortality

No study has reported data.

Hip circumference 12 months or more after diagnosis and breast cancer mortality

No study has reported data.

7.8 Waist-hip ratio

Table 131 Summary results of meta-analysis on waist-hip ratio less than 12 months after diagnosis and total mortality*

Comparison	No. of studies	No. of events in studies	RR (95% CI)	I^2, $P_{heterogeneity}$
Highest vs. lowest	4	1475	1.31 (1.11-1.55)	20.7%, p = 0.29
Per 0.1 unit	4	1475	1.31 (1.17-1.48)	0%, p = 0.73

*No studies on breast cancer mortality and second cancers were included in the meta-analyses. Only studies on waist-hip ratio assessed at diagnosis could be included in meta-analyses.

Waist-hip ratio and total mortality

Five studies on total mortality were identified. One study (Zhang, 1995) examined waist-hip ratio before diagnosis and four studies (Abrahamson, 2006b; Tao, 2006; Dal Maso, 2008; Chen 2010) examined waist-hip ratio less than 12 months after diagnosis. No study examined 12 months or more after diagnosis data.

Waist-hip ratio before diagnosis and total mortality

Only one study reported data (Zhang, 1995). Zhang et al. (1995) found no significant association for the highest compared with the lowest waist-to-hip ratio (RR for 0.89-1.62 vs. 0.58-0.80 = 1.1; 95% CI 0.6-2.2; p_{trend} = 0.69).

Waist-hip ratio less than 12 months after diagnosis and total mortality

Methods

All four studies identified could be included in the dose-response and the highest versus lowest meta-analyses (Abrahamson, 2006b; Tao, 2006; Dal Maso, 2008; Chen, 2010).

Main results and heterogeneity

The summary RR per 0.1 unit was 1.31 (95% CI 1.17-1.48; I^2 = 0%, p = 0.73; 4 studies). There is no evidence of strong influence from any individual study on the summary estimate, which remained statistically significant when each study was omitted in turn in the influence analysis, ranging from 1.26 (95% CI 1.09 -1.46) when Abrahamson et al. (2006) was omitted to 1.34 (95% CI 1.18-1.52) when Tao et al. (2006) was omitted. For the highest compared with the lowest waist-to-hip ratio, the summary RR was 1.31 (95% CI 1.11-1.55; I^2 = 20.7%; p = 0.29; 4 studies).

Study quality

Number of events ranged from 240 events (Abrahamson, 2006b) to 503 events (Dal Maso, 2008). Follow-up time ranged from 46 months (Chen, 2010) to 12.6 years (Dal Maso, 2008). All studies included breast cancer cases at different stages. Two studies (Tao, 2006; Chen, 2010) included TNM stage 0 cases and the other two studies (Abrahamson, 2006b; Dal Maso, 2008) involved invasive breast cancer cases only. All studies included both pre- and postmenopausal women.

Chen et al. (2010) and Dal Maso et al. (2008) used self-reported anthropometric data, while Tao et al. (2006) and Abrahamson et al. (2006b) used measured data. Two studies were from China (Tao, 2006; Chen, 2010), one study from Italy (Dal Maso, 2008) and the other from America (Abrahamson, 2006b). All models were adjusted for multiple confounders, including tumour stage. The result of Abrahamson et al. (2006b) was adjusted for tumour stage and income. Other factors like age, race and menopausal status were not included in the final model in this study, as they did not make an appreciable change to the estimate.

Published meta-analysis

Protani et al. (2010) observed a statistically significant increased risk for total mortality when comparing high WHR to low WHR, (RR 1.31; 95% CI 1.14-1.50; I^2 = 0%; 4 studies; 6 estimates).

Figure 152 Highest versus lowest forest plot of waist-hip ratio less than 12 months after diagnosis and total mortality

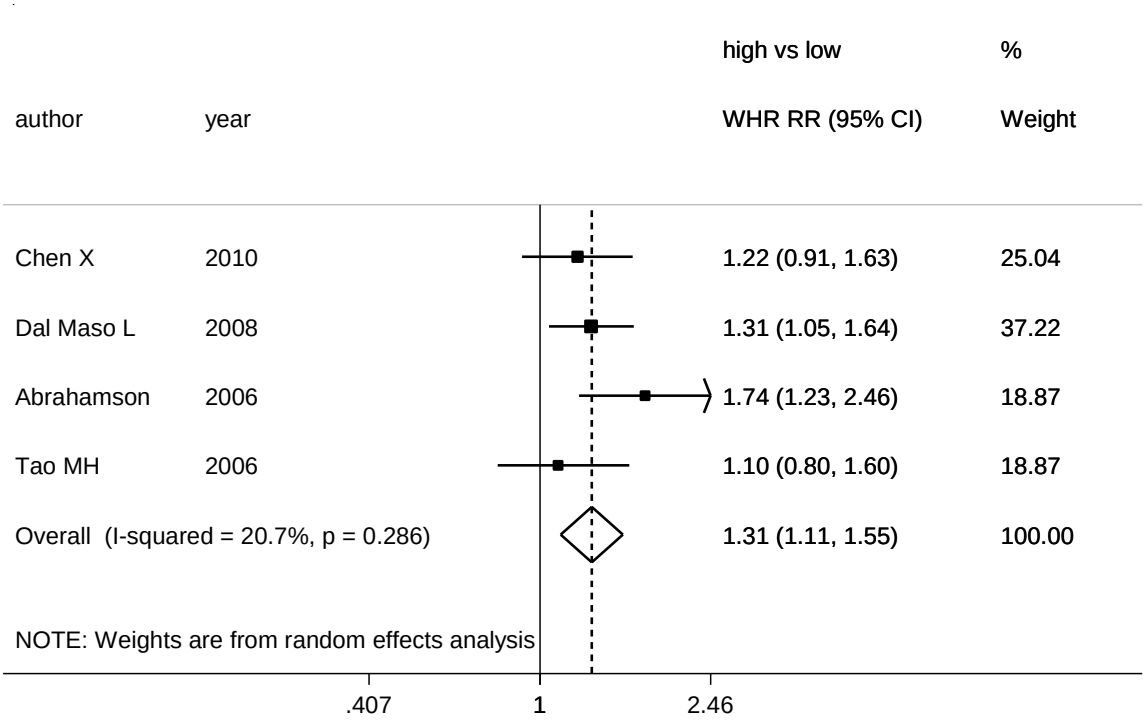


Figure 153 Linear dose-response meta-analysis of waist-hip ratio less than 12 months after diagnosis and total mortality

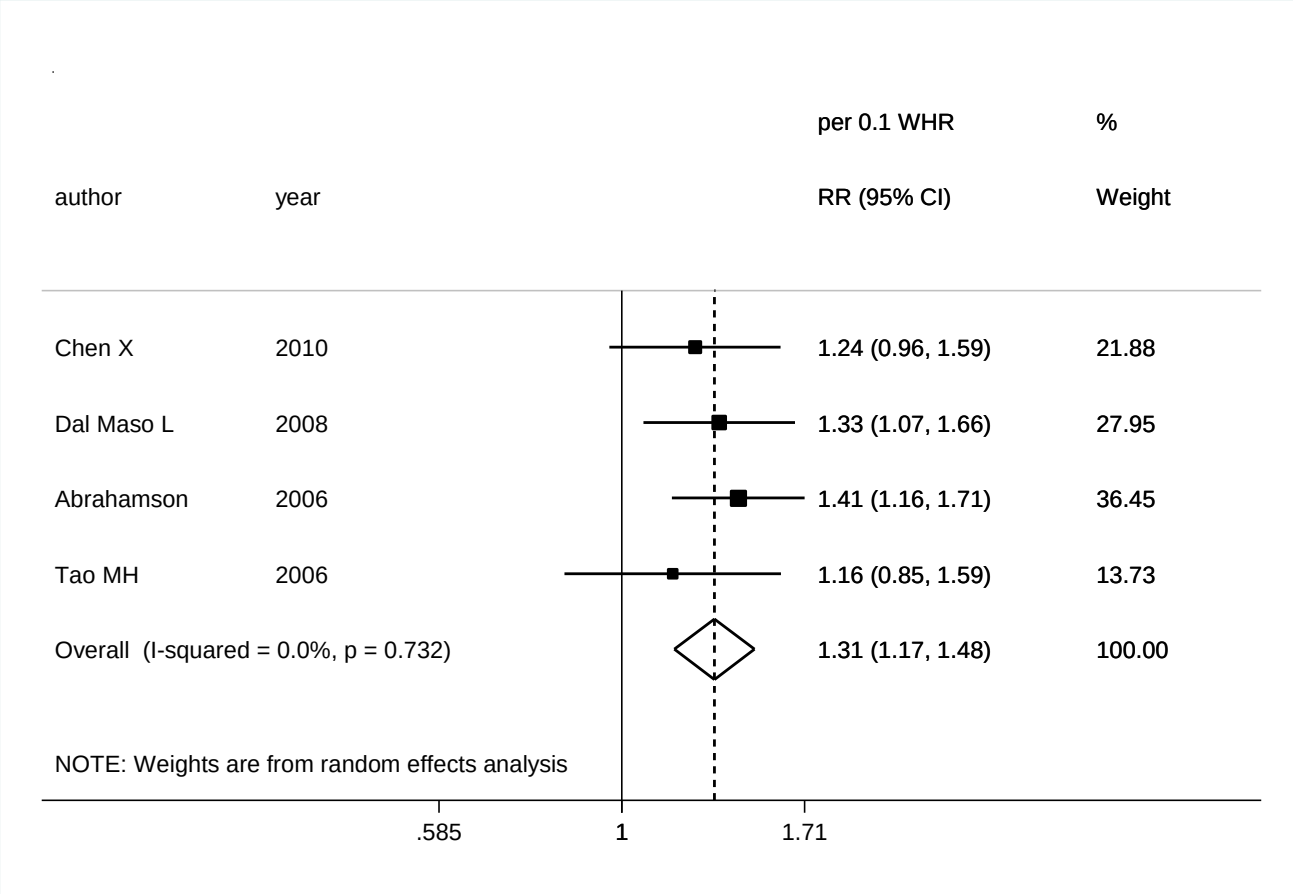


Figure 154 Individual dose-response graph of waist-hip ratio less than 12 months after diagnosis and total mortality

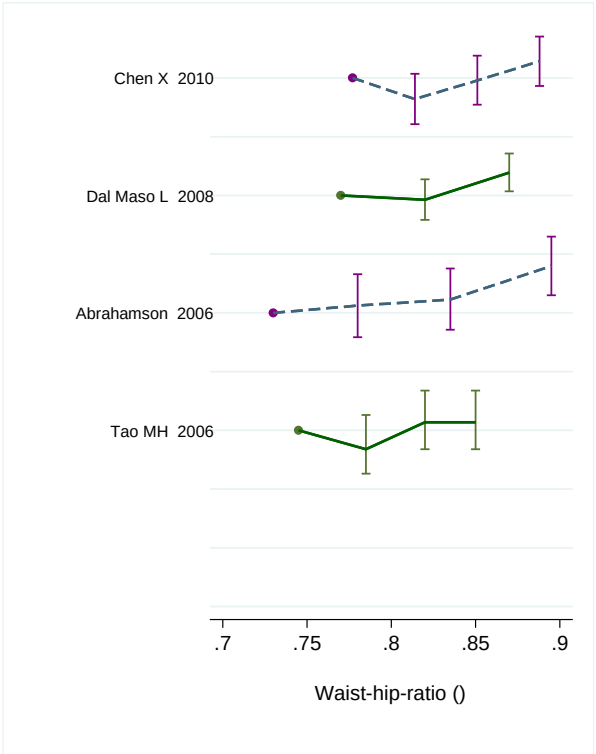


Table 132 Table of included studies on waist-hip ratio less than 12 months after diagnosis and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status Nodal status	Treatment info	Response rate Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Chen X (2010)	Shanghai Breast Cancer Survival Study China	Study recruitment: 2002-2006;	Prospective cohort of breast cancer survivors	5042 participants 53.5 years (mean) 20 - 75 years 51.1% postmenopausal	46 months	TNM; 36.4% stage 0-I, 32.6% IIA, 16.6% IIB, 9.8% IIIIV, 4.6% unknown	49.9% ER+ve/PR+ve, 27.6% ER-ve/PR-ve, 20.4% mixed (ER+ve PR-ve/ER-ve PR+ve), 2.1% unknown	Mastectomy:93.9% ; Chemotherapy: 91.2%; Radiotherapy: 32.1% ; Tamoxifen usage: 52%	80%	Self-reported 1 year prior to diagnosis at baseline interview approximately 6 months after diagnosis	5042 participants 442 deaths	Cancer register	>=0.87 vs. <=0.795	1.22 (0.91, 1.63)	Age at diagnosis, education, income, marital status, exercise, meat intake, cruciferous vegetables, soy protein, time from diagnosis to study enrollment, menopausal status, menopausal symptoms, chemotherapy, surgery type, radiotherapy, tamoxifen use, nodal status, immunotherapy, TNM stage, comorbidity, estrogen/progesterone receptor status, BMI at 6 months post-diagnosis
Dal Maso L (2008)	Six Italian Regions Follow-up Study Italy	Cancer diagnosis: 1991-1994; Study follow up: until 2005-2006 diagnosed no longer than 1 year before the interview	Follow-up of cases of a case-control study	1453 participants 55 years (mean) 23 - 74 years Among those with data (pre diagnosis): 45.5 % peri/pre menopausal, 54.9% postmenopausal HRT use: 91.3% never, 8.6% ever	12.6 years	Invasive breast cancer; TNM; 32.7% Stage I, 44.1% stage II, 13.2% stage III-IV, 9.8% unknown	41.5% ER+ve/PR+ve, 3.5% ER-ve/PR+ve, 6.3% ER+ve/PR-ve, 10.1% ER-ve/ PR-ve 45.6% no node+ve, 44.2% node+ve, 10.1%		2.70% lost	Self-reported at study baseline; height, weight 1 year before cancer diagnosis and at different ages; hip and waist measured at interview	1453 participants 503 deaths, 398 breast cancer mortality, 6.2% death from other cancers, 7.4% from cardiovascular disease	Cancer registry	>=0.85 vs. <=0.79	1.31 (1.05–1.64)	Region, age at diagnosis, year of diagnosis, TNM stage, Receptor status
Abrahamson (2006)b	Atlanta, Seattle, New Jersey Follow-up Study United States	Cancer diagnosis:1990-1992; Study follow up: until 2000	Follow-up of cases of a population-based case-control study	1254 participants 20 - 54 years 78% premenopausal, 22% postmenopausal and unknown <1%	9.8 years	Invasive breast cancer; AJCC; any stage ; 57% local, 40% regional, 3% distant, <1% unknown	56% ER+ve, 35%ER-ve, 3% borderline, 6% unknown		86% < 2%lost	Measured 4.2 months after diagnosis; weight and height at age 20 years and the year before diagnosis	1254 participants 290 deaths	Cancer registry + National Death Index	>=0.87 vs. <=0.75	1.74 (1.23-2.46)	Tumor stage, income (Results further adjusted for BMI at interview was also provided in the article
Tao MH (2006)	Shanghai Breast Cancer Study China	Cancer diagnosis: 1996-1998; Study follow up: until 2002 Recruited/interv	Follow-up of cases of a population-based case-control study	1455 participants 25 - 64 years	5.1 years	Primary breast cancer; TNM; 24.6% Stage 0-I, 34.9% stage IIA, 21.9% stage IIB, 11.3% stage III-	44.4% ER+ve, 25.5% ER-ve, 30% unknown; 43.5% PR+ve,	Surgery: 99%; Adjuvant chemotherapy: 94% ; adjuvant chemotherapy and traditional Chinese	91%	Measured at or soon after diagnosis at study baseline	1455 participants 240 deaths	Death certificate	>=0.84 vs. <=0.76	1.10 (0.80-1.60)	Age at diagnosis, education, menopausal status, tumor Stage (TNM), chemotherapy, tamoxifen use, radiotherapy, estrogen receptor level,

		iew on average 67 days after diagnosis				IV, 7.1% unknown	25.2% PR-ve, 31.1% unknown	medicine: 63%; radiotherapy: 38.9% yes, 47.4% no, 13.6% unknown; tamoxifen use: 63.2% yes, 18 no, 18.6% unknown	126 patients lost (assumed to be still living)						progesterone receptor level

Waist-hip ratio 12 months or more after diagnosis and total mortality

No study has reported data.

Waist-hip ratio and breast cancer mortality

Waist-hip ratio before diagnosis and breast cancer mortality

No study has reported data.

Waist-hip ratio less than 12 months after diagnosis and breast cancer mortality

Only two studies reported data (Dal Maso, 2008; Borugian, 2003). Dal Maso et al. (2008) observed a statistically non-significant positive association for the highest compared with the lowest waist-hip-ratio (HR for ≥ 0.85 vs. ≤ 0.79 = 1.27; 95% CI 0.98-1.64; p_{trend} = 0.06). Borugian et al. (2003) reported a significant increased risk in postmenopausal women, but not in premenopausal women (RR for >0.848 vs. < 0.756 = 3.3; 95% CI 1.1-10.4, and RR 1.2; 95% CI 0.4-3.4, respectively).

Waist-hip ratio 12 months or more after diagnosis and breast cancer mortality

No study has reported data.

7.9 Height

Table 133 Summary results of meta-analysis on height and breast cancer mortality and second primary breast cancer*

	Breast cancer mortality			Second primary breast cancer		
Comparison	**No. of studies**	**No. of events in studies**	**RR (95% CI) I^2, $P_{heterogeneity}$**	**No. of studies**	**No. of events in studies**	**RR (95% CI) I^2, $P_{heterogeneity}$**
Height assessed before, less than 12 months after or 12 months or more after breast cancer diagnosis						
Highest vs. lowest	4	2801	1.03 (0.92-1.16) 0%, p = 0.80	3	783	0.85 (0.56-1.29) 48.3%, p = 0.15
Per 5 cm	3	418	1.00 (0.91-1.10) 0%, p = 0.67	-	-	-

*No studies on total mortality were included in the meta-analyses.

Height and total mortality

Six studies from seven publications on total mortality were identified. Three studies (four publications) examined height before diagnosis (Greenberg, 1985; Zhang, 1995; Vatten, 1991; Reeves, 2000), two studies examined height less than 12 months after diagnosis (Kyogoku; 1990; Menon, 1999) and one study (Barnett, 2008) examined height 12 months or more after diagnosis. Since attained adult height remains reasonably unchanged in time relative to periods of cancer diagnosis/treatment, all results on total mortality were reviewed together.

No meta-analysis was conducted. Two studies from three publications did not have sufficient data to be included in the highest versus lowest meta-analysis (Greenberg 1985, Kyogoku 1990) or dose-response meta-analysis (Reeves, 2000). Two studies (Menon 1999; Barnett, 2008) reported unadjusted results. Vatten et al. (1991) conducted a log-rank test on survival with height. Three of the six studies reported an inverse association, of which one was statistically significant; two studies reported no association, and one study observed a non-significant positive association.

Barnett et al. (2008) reported a significant inverse association with height 12 months or more after diagnosis (unadjusted HR for ≥ 1.68 vs. < 1.57 m = 0.73; 95% CI 0.57-0.95; p_{trend} = 0.04). Zhang et al. (1995) and Kyogoku et al. (1990) reported a non-significant inverse association (RR for 66-79 vs. 48-63 inches before diagnosis = 0.9; 95% CI 0.5-1.7; p_{trend} = 0.80, and RR for ≥ 156 vs. < 146 cm up to 12 months after diagnosis = 0.49; no 95% CI; p_{trend} = 0.49, respectively). Vatten et al. (1991) and Menon et al. (1999) reported no relationship with survival (log-rank test for before diagnosis height, p = 0.29 and unadjusted HR per 1 m at-diagnosis = 0.137, 95% CI 0.012-1.514 respectively). A statistically non-significant increased risk was observed by Reeves et al. (2000) (RR for ≥ 170 vs. ≤ 159 cm before diagnosis = 1.17; 95% CI 0.91-1.51; p_{trend} = 0.25). An earlier publication on premenopausal women in the same study as Reeves, 2000 observed the same trend (≥ 68 vs. < 62 inches = 1.8; no 95% CI; p_{trend} = 0.28) (Greenberg, 1985).

Table 134 Table of studies on height and total mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Barnett GC (2008)	Studies of Epidemiology and Risk Factors in Cancer Heredity Breast Cancer Study UK	Cancer diagnosis: 1991-2005	Prospective cohort study of breast cancer survivors	4560 participants 51.5 years (mean) 23 - 69 years 98% white Among those with data: 55.2% pre-menopausal, 44.7% postmenopausal HRT use: 62 % never usage, 37.9% ever usage	6.82 years	Invasive breast cancer; 73% incident and 27% prevalent; among those with data: 49.7% stage I, 45.8% stage II, 3.3% stage III, 1.1% stage IV; 24.1% grade 1, 47.2% grade 2, 28.6% grade 3	18.7% ERve, 81.2% ER+ve		67%	Self-reported at study baseline	4346 participants, 586 deaths included in analysis	Cancer registry + death certificate	>=1.68 vs <=1.57m	0.73 (0.57-0.95)	
Reeves GK (2000)	Six London Hospitals Follow-up Study UK	Study recruitment: 1968-1984; Cancer diagnosis: 1968-1980 for 1st study and 1980-1984 for 2nd study; Study follow up: until 1994 delete newly diagnosed	Follow-up of cases of case-control studies	1208 participants 24 - 59 years 74% premenopausal, 26% postmenopausal HRT use: Among those with data: 5% yes, 95% no use	25 Years (max)	TNM; 49.6% Stage I, 32% stage II, 17.2% stage III, 1.2% stage IV	36% node-ve, 47.8% node+ve, 16.2% unknown		39 women, 3% lost	From records of original studies	1208 participants 608 deaths	Medical records	>170 vs <=159 cm	1.17 (0.91-1.51)	Age at diagnosis, year of diagnosis, hospital, stage, nodal status
Menon KV (1999)	William Harvey Hospital, Kent Follow-up Study UK	From cancer diagnosis until 1997	Randomised controlled trial of adjuvant treatment trials; ancillary analysis	448 participants 7% premenopausal, 93% postmenopausal	6 years	Invasive primary breast cancer; any stages				Self-reported height; BMI calculated at the time of diagnosis	448 participants 162 deaths	Hospital records	Per 1 m increase	0.137 (0.012-1.514)	
Zhang S (1995)	Iowa Women's Health Study United States	Study recruitment:1986; Study follow up: until 1991	Cancer survivors of population-based prospective cohort study	698 participants 55 - 69 years Mostly white: 98%, Postmenopausal	2.9 years	Unilateral breast cancer; 10% in situ, 58% local, 28% regional, 3%distant, and 1% unknown; 55% tumour size <2cm, 33% size >= 2cm and 11% unknown	Among those with data: 85% ER+ve and 72% PR+ve		42.60% / < 1% migration rate	Self reported questionnaire within 6 years before diagnosis semi-quantitative FFQ	698 participants 56 deaths, 40 breast cancer mortality (among the causes of death) and 2 death from coronary heart disease	Death Certificates + National Death Index	66-79 vs 48-63 inches	0.9 (0.5-1.7)	Age, smoking, education, tumor stage, ER status, tumor size
Vatten LJ (1991)	Norwegian Health Screening Examination Cohort Study	Study recruitment:1974-1978; Study follow up: until 1989	Cancer survivors of population-based prospective cohort	242 participants 50.0 years (mean) 36.0 - 63.0 years White 93.8%	5 years	40% stage I, 33% stage II, 7.5% stage III or IV, 20% unspecified stage					242 participants 61 deaths	Death certificate	<159, 159-162, 163-166, >=167cm	Log-rank test =0.29	

	Norway		study	participated in health screening											
Kyogoku S (1990)	Fukuoka Hospitals, Japan Follow-up Study Japan	Study recruitment:1975-1978; Study follow up: until 1987 Newly diagnosed patients recruited	Follow up of cases of a hospital-based case-control study	213 participants 55.5 years (mean) 32.3% pre-menopausal, 67.6% post-menopausal	12 years	80 patients had TNM Stage I, 102 Stage II, 13 Stage III	87 patients had N0, 91 had N1, 17 had N2, 17 had N3 and N4	16 patients had radiation therapy, 87 chemotherapy, 130 endocrine therapy	95.80% 9 patients lost	Assessed by an interview 1-3 after operation	213 participants 64 deaths, 47 breast cancer mortality, 6 second primary cancer mortality, 4 death from cardiac failures and 3 death from cerebro-vascular diseases and 4 other causes of death	Death certificate	>=156 vs <=145.9cm	0.49 p for trend=0.49	Tumor stage, age of menarche, age at first birth, menopausal status, history of abortion, smoking, radiotherapy, chemotherapy, hormonal therapy, type of operative procedure, history of benign breast disease
Greenberg (1985)	Six London Hospitals Follow-up Study United Kingdom	Study recruitment:1968-1977; Study follow up: until December 1982	Follow up of cases of a hospital-based case-control study	582 participants 40.0 years (mean) 24.0 - 50.0 years All premenopausal	14 years	TNM; 62% Stage I, 20% Stage II, 19% Stage III+IV	40% node +ve		18 patients lost	Reported at the time of diagnosis	582 participants 228 deaths	Hospital records	>=68 vs <62 inches	1.8 p for trend=0.278	Tumor stage, age, social class, reproductive history, family history, smoking, oral contraceptive, year of diagnosis, hospital of diagnosis

Height and breast cancer mortality

Five studies from six publications on breast cancer mortality were identified. Four studies, five publications (Galanis, 1998; Jain, 1994b; Tretli, 1990; Enger, 2004b; Jain, 1997) examined height before diagnosis, one study (Rohan, 1993) examined height less than 12 months after diagnosis, and no study examined height 12 months or more after diagnosis.

Methods

Since attained adult height remains reasonably unchanged in time relative to periods of cancer diagnosis/treatment, all results on breast cancer mortality were reviewed together. The two articles by Jain et al. were from the same study (Jain 1994b, Jain 1997). Overall results from Jain 1994b instead of the results subgrouped by tumour charactersitics from Jain 1997 were reviewed here with other studies. Three (Jain, 1994b; Galanis, 1998; Enger, 2004b) and four (Tretli, 1990; Jain, 1994b; Galanis, 1998; Enger, 2004b) of the five studies identified had sufficient format of data to be included in the dose-response and highest versus lowest meta-analysis respectively. All these studies assessed height before cancer diagnosis. The study not included in the analyses reported unadjusted results assessed at diagnosis (Rohan, 1993). A statistically non-signficant decreased risk in dying of breast cancer was observed in this study (RR for ≥ 170 vs. < 160 cm = 0.71; 95% CI 0.38-1.34).

Main results and heterogeneity

The summary RR per 5 cm was 1.00 (95% CI 0.91-1.10; 3 studies), which ranged from 0.96 (95% CI 0.84-1.10) when Enger et al. (2004b) was omitted to 1.04 (95% CI 0.92-1.17) when Jain et al. (1994b) was omitted in an influence analysis. For the highest compared with the lowest height, the summary RR was 1.03 (95% CI 0.92-1.16; 4 studies). There is no evidence of heterogeneity between studies in both analyses (I^2 = 0%; p = 0.67; and p = 0.80 respectively).

Study quality

One study (Galanis, 1998) had only 34 events among 378 participants after an average of 14.9 years of follow-up. Other studies had more events, ranging from 133 (Jain, 1994b) to 2383 (Tretli, 1990) events. The follow-up time ranged from an average of 4.3 years (Tretli, 1990) to 14.9 years (Galanis, 1998). Enger, et al. (2004b) included breast cancer in situ (9.9%) and other cancer stages, among a study population of only premenopausal women. All other studies involved both pre- and postmenopausal women. Two studies used measured anthropometric data (Tretli, 1990; Jain, 1994b), while the other two studies (Enger, 2004b, Galanis, 1998) used self-reported data. Tretli et al. (1990) was an European study, and all others were North American studies. All models were adjusted for age, tumour stage and other risk factors, except Tretli et al. (1990) which was unadjusted but stratified by tumour stage.

Figure 155 Highest versus lowest forest plot of height before diagnosis and breast cancer mortality

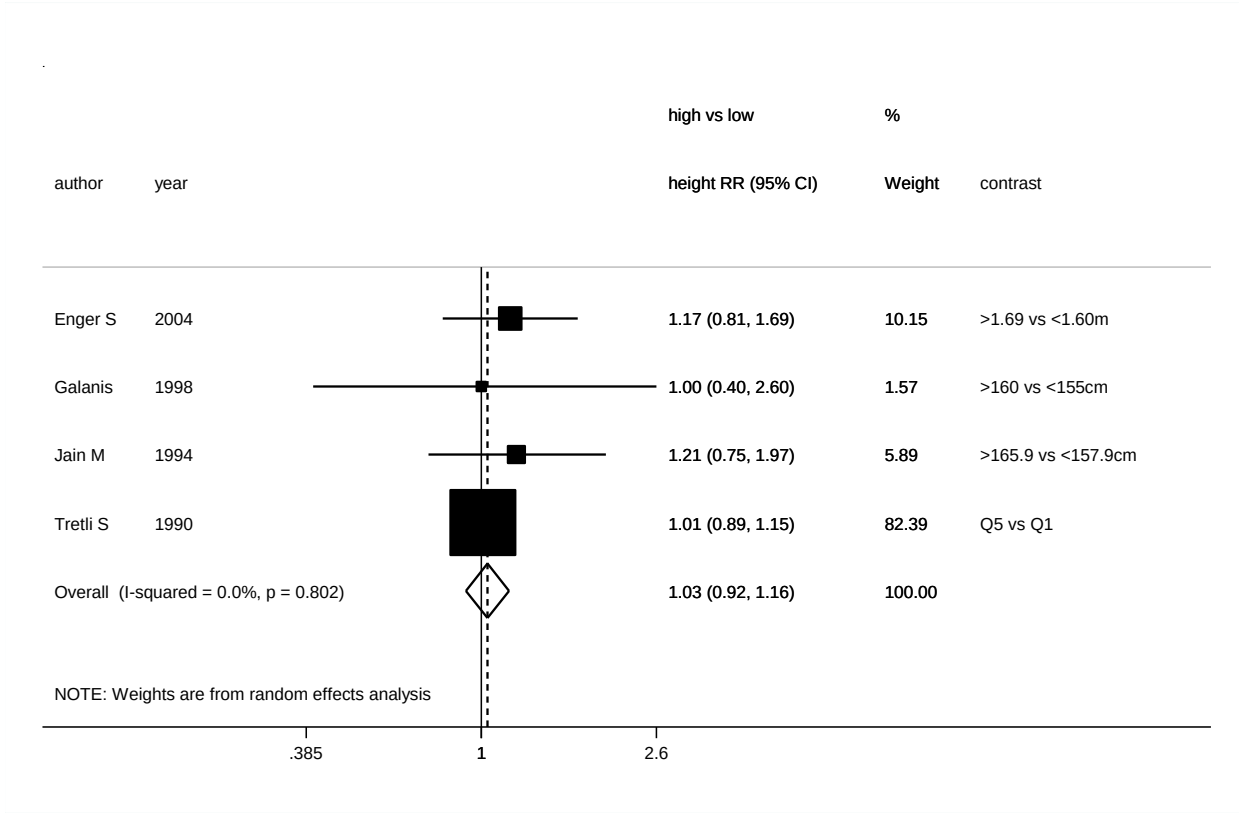


Figure 156 Linear dose-response meta-analysis of height before diagnosis and breast cancer mortality

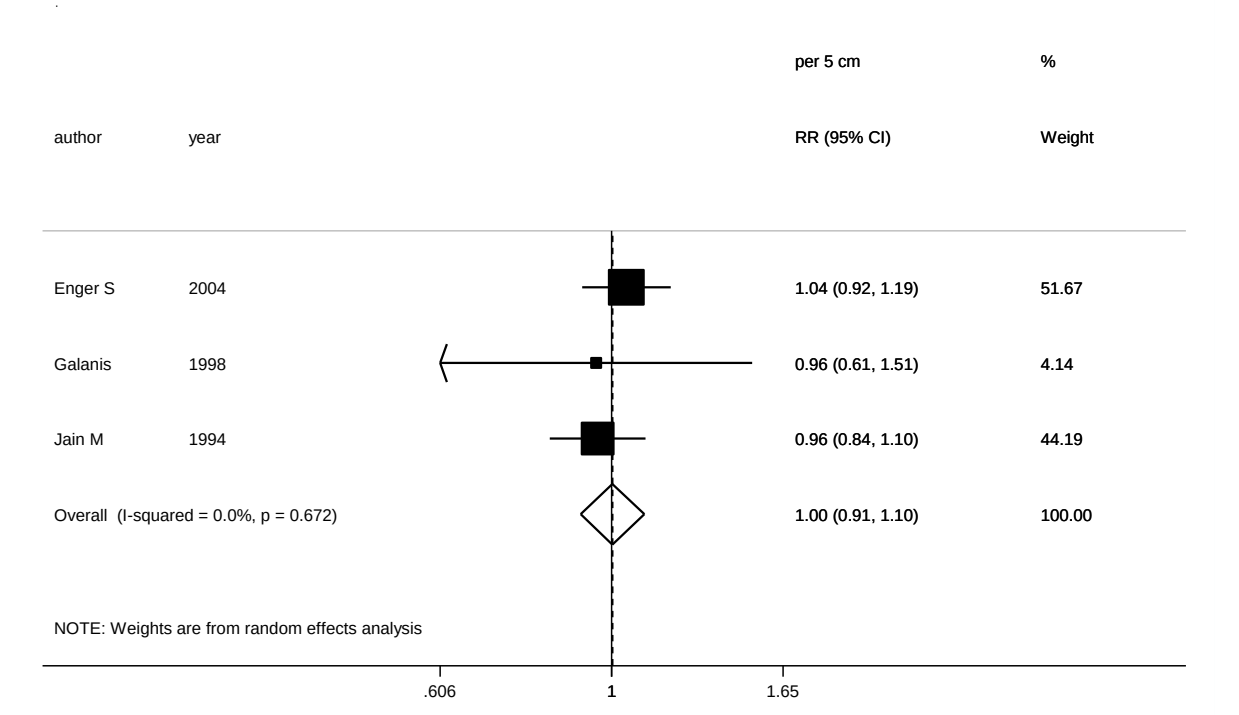


Figure 157 Individual dose-response graph of height before diagnosis and breast cancer mortality

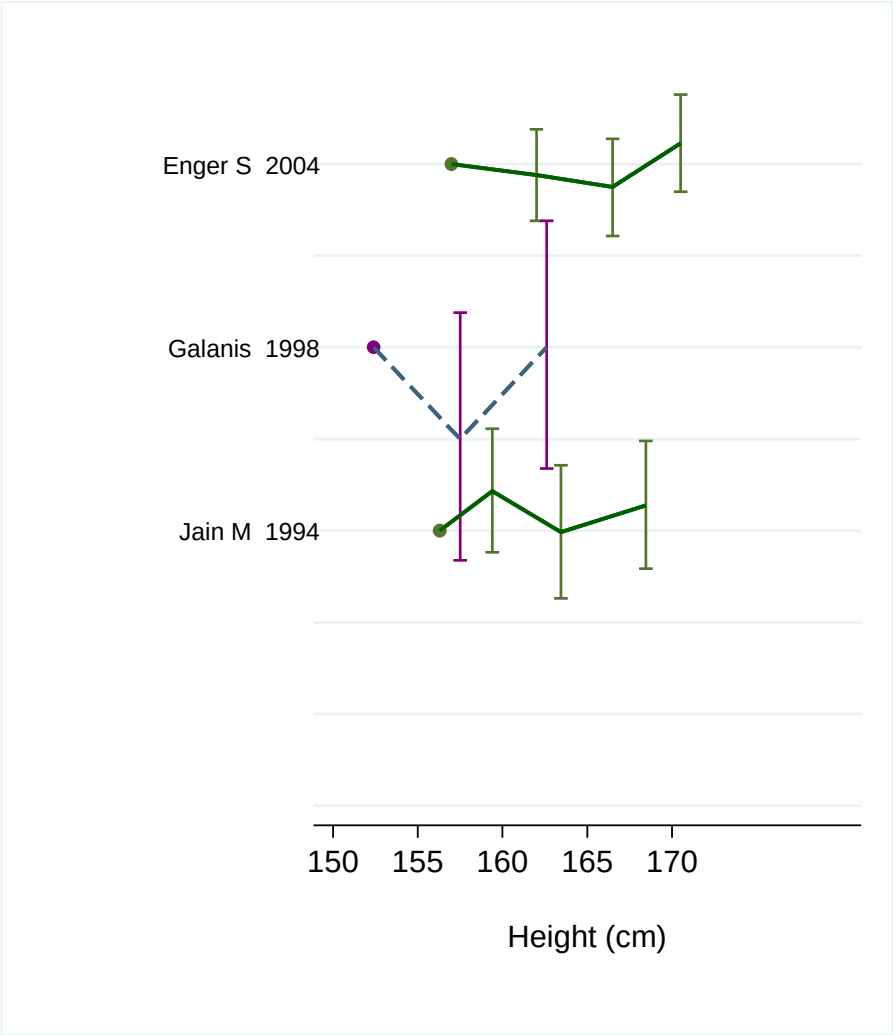


Table 135 Table of included studies on height before diagnosis and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments / Remarks
Enger S (2004)b	University of Southern California Cancer Surveillance Program United States	Cancer diagnosis: 1983-89, Study follow-up: Until 2000	Follow-up of cases of population-based case-control study	717 participants <=40 years White or Hispanic Premenopausal	10.4 years	Stages: 9.9% in situ, 47.4% localized, 39.1% regional, 3.6% distant metastasis	41.1% +ve, 57.3% -ve, 1.5% unknown		76.80%	Self-reported a year prior to diagnosis in interview at study baseline	717 participants 251 breast cancer mortality, 2 deaths from coronary/CVD, 10 other causes of deaths	Death certificate	>1.69 vs. <1.60m	1.17 (0.81-1.69)	Age, tumor stage, physical activity, weight
Galanis (1998)	The Multiethnic Cohort Study Hawai	Study recruitment: 1975-1980; Study follow up: until 1994	Prospective cohort study of cancer survivors	378 participants 43 years (mean) 86 (22.75%) premenopausal cases, 292 (77.25%) postmenopausal cases	14.9 years					Self-reported; height and weight before diagnosis	378 participants 34 breast cancer mortality	Cancer registry	>160 vs. <155 cm	1.0 (0.40-2.60)	Age, ethnicity, tumor stage, education, alcohol intake
Jain M (1994)b	National Breast Screening Study Canada	Study recruitment: 1980-1985; Cancer diagnosis:1981-1982; Study follow up: until 1988	Randomised controlled trial of mammography screening trial	1033 participants 52.2 years (mean) 40 - 66 years Trial group screened; 48% detected by screening	5.2 years	Invasive breast cancer; any stage	341 node+ve women			Measured during screening prior to diagnosis	1033 participants 133 breast cancer mortality	Death certificate	>165.9 vs. <157.9 cm	1.21 (0.75-1.97)	Age at diagnosis, nodal Status (number of positive nodes)
Tretli S (1990)	Norwegian Health Surveys Follow-up Study Norway	Cancer diagnosis: 1963-1975; Study follow up: until 1981	Cancer survivors of a population-based prospective cohort study	8427 participants 30 - 69 years, participants of a health screening cohort	4.3 years	Any TNM stages IIV; 47.7% stage I, 33.3% stage II, 5.5% stage III, 7.5% stage IV			85%	Measured during screening	8427 participants 2383 breast cancer mortality, 430 death from other causes	Death certificate	Stage I Q5 vs. Q1 Stage II Q5 vs. Q1 Stage III Q5 vs. Q1 Stage IV Q5 vs. Q1	1.29 (0.99-1.68) 0.93 (0.77-1.13) 0.96 (0.62-1.49) 0.93 (0.71-1.23)	Highest vs. lowest analysis only; missing exposure values

Table 136 Table of excluded studies on height before diagnosis and breast cancer mortality

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments / Exclusion reason
Jain M (1997)	National Breast Screening Study Canada	Cancer diagnosis: 1982-1985, Study follow-up: Until 1992 Recruited between1980-1985 and diagnosed after July 1982	Randomised controlled trial of mammography screening trial; ancillary analysis	676 participants 49.9 years (mean) 40 - 59 years 90% Caucasian 57% postmenopausal (at enrollment) 48.4% cases detected through mammography	7.7 years	Invasive breast cancer; any stage				Pre-diagnosis; diet history completed at enrollment	83 deaths, 76 breast cancer mortality, 7 other causes of deaths	Death certificate	With ER status With PR status With nodal status With tumour size Per 5cm increase	0.79 (0.63-0.97) 0.82 (0.64-1.06) 0.89 (0.74-1.08) 0.87 (0.71-1.06)	Age at diagnosis, weight, smoking, energy intake, when appropriate ER status, PR status, nodal status, tumour size Used overall results from Jain 1994b
Rohan T (1993)	Diet and Breast Cancer in Australia Follow-up Study Australia	Cancer diagnosis: 1982-1984, Study follow-up: Until 1989	Follow-up of cases of population-based case-control study	412 participants 55.1 years (mean) 20 - 74 years 30.7% premenopausal, 5.4% perimenopausal, 64% postmenopausal, among those with data	5.5 years	Primary breast cancer, any stages			80.70% 39 patients lost	Interval between diagnosis and interview was 4.8months	412 participants 112 breast cancer mortality, 11 other causes of deaths	Cancer registry + death certificate	>=170 vs. <160 cm	0.71 (0.38-1.34)	Unadjusted results

Height and second primary breast cancer/contralateral breast cancer

Three studies on second primary breast cancer/contralateral breast cancer were identified. One study (Trentham-Dietz, 2007) examined height before diagnosis, two studies (Cook, 1996; Kato, 1986) examined height less than 12 months after diagnosis, and no study examined height 12 months or more after diagnosis. Cook et al. (1996) reported results for contralateral breast cancer, while the other two studies (Kato, 1986; Trentham-Dietz, 2007) were on primary breast cancer.

Methods

Since attained adult height remains reasonably unchanged in time relative to periods of cancer diagnosis/treatment, all results on second primary breast cancer/contralateral breast cancer were reviewed together. All three studies (Trentham-Dietz, 2007; Cook, 1996; Kato, 1986) identified could be included in the highest versus lowest meta-analysis. Only two studies could be included in a dose-response meta-analysis (Trentham-Dietz, 2007; Cook, 1996), which was not conducted. Kato et al. (1986) reported results by two height categories only.

Main results and heterogeneity

The summary RR for the highest compared with the lowest height was 0.85 (95% CI 0.56-1.29; 3 studies). There is evidence of low to moderate heterogeneity between studies (I^2 = 48.3%; p = 0.15).

Study quality

All studies were either a case-control or nested case-control studies. Number of events ranged from 61 events (Kato, 1986) to 488 events (Trentham-Dietz, 2007). Follow-up time of the original cohorts ranged from 35 months (Cook, 1996) to 7.1 years (Trentham-Dietz, 2007). Cook et al. (1996) included breast cancer in situ among cases at other stages. All studies involved both pre- and postmenopausal women. Trentham-Dietz et al. (2007) used self-reported anthropometric data and the other two studies (Cook, 1996; Kato, 1986) took data from medical charts. Kato et al. (1986) was a Japanese study, while the other two were American studies. All models were adjusted for multiple confounders.

Figure 158 Highest versus lowest forest plot of height and second primary breast cancer

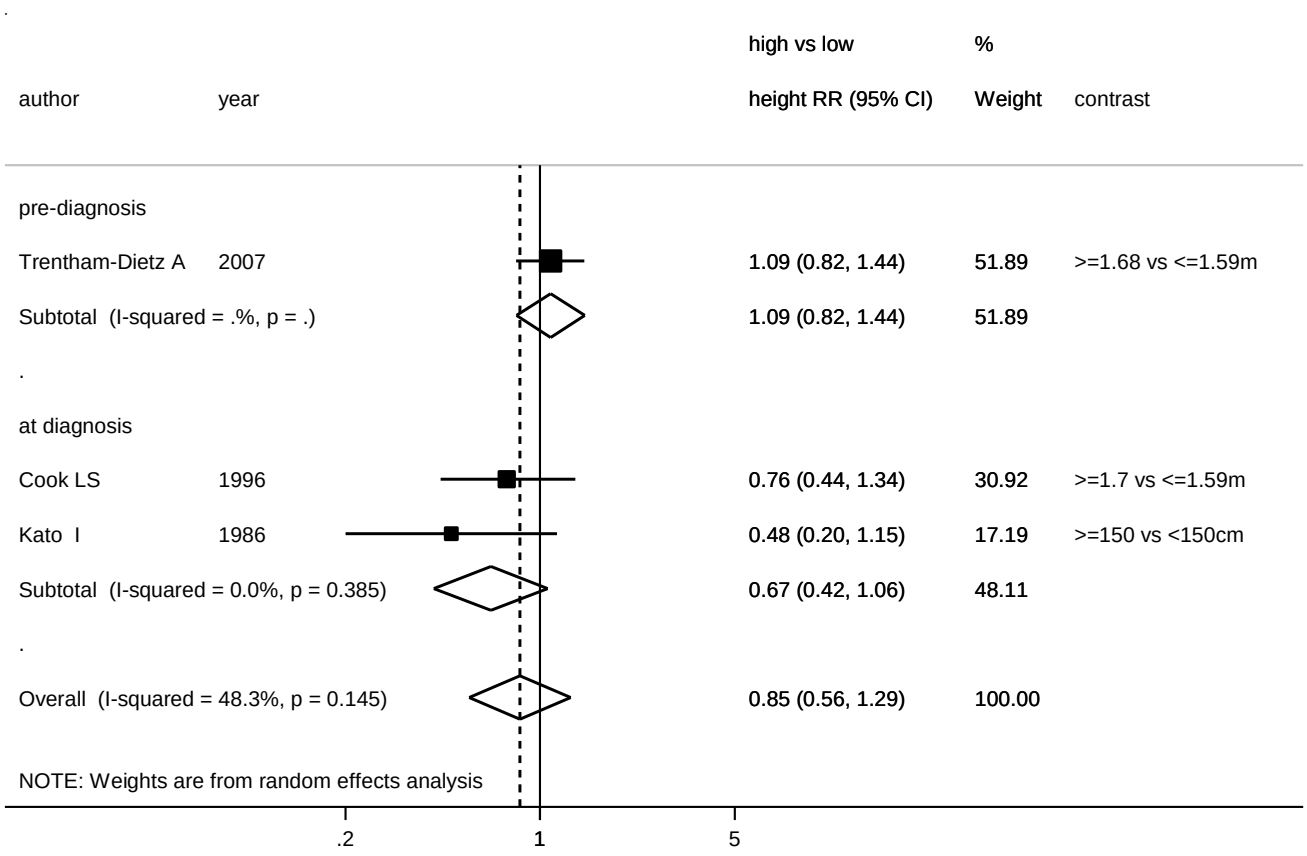


Table 137 Table of included studies on height and second primary breast cancer

Author Year	Study name	Diagnosed / recruitment dates End of follow-up	Study type	Study characteristics	Follow-up time	Tumour characteristics	Hormone receptor status / Nodal status	Treatment info	Response rate / Loss to follow-up	Exposure assessment Timeframe	Outcome events Number in analysis	Outcome confirmation	Contrast	RR (95% CI)	Adjustments
Trentham-Dietz A (2007)	Wisconsin Follow-up Study of Women with Invasive Breast Cancer United States	Cancer diagnosis: 1987-2000, Study follow-up: Until 2002 Recruited approximately 1 year after diagnosis	Follow-up of cases of case-control studies	10953 participants 59.4 years (mean) 18 - 79 years	7.1 years	Stages: 63% local, 28.9% regional, 2.3% distant, 5.8% unknown			83.30%	Self-reported pre-diagnosis weight and height at interview approximately1year after diagnosis	10953 participants 1188 second cancers: 488 second breast cancers, 132 colorectal cancers, 113 endometrial cancers, 36 ovarian cancers	Cancer registry	>=1.68 vs. <=1.59 m	1.09 (0.82-1.44)	Age, year of diagnosis, tumor stage, family history, smoking, alcohol intake, parity, HRT, menopausal status, weight
Cook LS (1996)	Washington SEER Nested Case-Control Study, three counties United States	Cancer diagnosis: 1978-1990; Study follow up: until 1992	Nested case-control study, within a population-based cohort of breast cancer survivor	640 participants <85 years 33.4% premenopausal, 64.5% postmenopausal, 2% unknown	35 months	Primary in situ or invasive breast cancer; 90.2% stage I, 9.8% stage II	19.8% ER-ve, 51.8% ER+ve, 4.1% ER intermediate, 17.9% not done, 6.3% unknown, 19.8% PR-ve, 0.1% PR intermediate, 38.7% PR+ve, 26.1% not done, 15.1% unknown	Chemotherapy: 29.3% yes, 60.8% no, 9.9% unknown; Radiation therapy: 41.3% yes, 47.2% no, 11.5% unknown	9% lost	From hospital medical records; at initial diagnosis	640 participants 234 contralateral breast cancer	Cancer registry	>=1.70 vs. <=1.59 m	0.76 (0.44-1.34)	Age at diagnosis, stage, year of diagnosis, family history, tumor histology, menopausal status
Kato I (1986)	Aichi Cancer Center Hospital Case-Control Study Japan	Cancer surgery: 1964-1984	Nested case-control study, within a hospital based cohort of breast cancer survivors	345 participants About 49 years (mean) 59.6% premenopausal in cases and 59% in controls Comorbidities: 6.1% 9 diabetes, 24.3% cardiovascular disease, in both cases and controls		Multiple primary cancers		All had surgery		From medical records post diagnosis	345 participants 61 bilateral breast cancer and 156 other multiple primary cancers	Medical records	>=150 vs. <150 cm	0.48, P-value between 0.05 and 0.1	Smoking, wine or whisky, family history (siblings' cancer history), weight

Reference list

1. Abe R, Kumagai N, Kimura M, Hirosaki A, Nakamura T. Biological characteristics of breast cancer in obesity. Tohoku Journal of Experimental Medicine 1976;120:351-9.

2. Abrahamson PE, Gammon MD, Lund MJ et al. Recreational physical activity and survival among young women with breast cancer. Cancer 2006;107:1777-85.

3. Abrahamson PE, Gammon MD, Lund MJ et al. General and abdominal obesity and survival among young women with breast cancer. Cancer Epidemiology, Biomarkers & Prevention 2006;15:1871-7.

4. Ademuyiwa FO, Groman A, O'Connor T, Ambrosone C, Watroba N, Edge SB. Impact of body mass index on clinical outcomes in triple-negative breast cancer. Cancer 2011;117:4132-40.

5. Albain KS, Green S, LeBlanc M, Rivkin S, O'Sullivan J, Osborne CK. Proportional hazards and recursive partitioning and amalgamation analyses of the Southwest Oncology Group node-positive adjuvant CMFVP breast cancer data base: a pilot study. Breast Cancer Research & Treatment 1992;22:273-84.

6. Allemani C, Berrino F, Krogh V et al. Do pre-diagnostic drinking habits influence breast cancer survival? Tumori 2011;97:142-8.

7. Allin KH, Nordestgaard BG, Flyger H, Bojesen SE. Elevated pre-treatment levels of plasma C-reactive protein are associated with poor prognosis after breast cancer: a cohort study. Breast Cancer Res 2011;13:R55.

8. Alsaker MDK, Opdahl S, Asvold BO, Romundstad PR, Vatten LJ. The association of reproductive factors and breastfeeding with long term survival from breast cancer. Breast Cancer Res Treat 2011;130:175-82.

9. Anderson SJ, Wapnir I, Dignam JJ et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in patients treated by breast-conserving therapy in five National Surgical Adjuvant Breast and Bowel Project protocols of node-negative breast cancer. Journal of Clinical Oncology 2009;27:2466-73.

10. Azambuja E, McCaskill-Stevens W, Francis P et al. The effect of body mass index on overall and disease-free survival in node-positive breast cancer patients treated with docetaxel and doxorubicin-containing adjuvant chemotherapy: the experience of the BIG 02-98 trial. Breast Cancer Res Treat 2010;119:145-53.

11. Barnett GC, Shah M, Redman K, Easton DF, Ponder BA, Pharoah PD. Risk factors for the incidence of breast cancer: do they affect survival from the disease? Journal of Clinical Oncology 2008;26:3310-6.

12. Bastarrachea J, Hortobagyi GN, Smith TL, Kau SW, Buzdar AU. Obesity as an adverse prognostic factor for patients receiving adjuvant chemotherapy for breast cancer. Annals of Internal Medicine 1994;120:18-25.

13. Baumgartner AK, Hausler A, Seifert-Klauss V, Schuster T, Schwarz-Boeger U, Kiechle M. Breast cancer after hormone replacement therapy - does prognosis differ in perimenopausal and postmenopausal women? Breast 2011;20:448-54.

14. Bayraktar S, Hernadez-Aya LF, Lei X et al. Effect of metformin on survival outcomes in diabetic patients with triple receptor-negative breast cancer. Cancer 2012;118:1202-11.

15. Beasley JM, Newcomb PA, Trentham-Dietz A et al. Post-diagnosis dietary factors and survival after invasive breast cancer. Breast Cancer Res Treat 2011;128:229-36.

16. Beasley JM, Kwan ML, Chen WY et al. Meeting the physical activity guidelines and survival after breast cancer: Findings from the after breast cancer pooling project. Breast Cancer Res Treat 2012;131:637-43.

17. Belle FN, Kampman E, McTiernan A et al. Dietary fiber, carbohydrates, glycemic index, and glycemic load in relation to breast cancer prognosis in the HEAL cohort. Cancer Epidemiol Biomarkers Prev 2011;20:890-9.

18. Berclaz G, Li S, Price KN et al. Body mass index as a prognostic feature in operable breast cancer: the International Breast Cancer Study Group experience. Ann Oncol 2004;15:875-84.

19. Bernstein JL, Thompson WD, Risch N, Holford TR. Risk factors predicting the incidence of second primary breast cancer among women diagnosed with a first primary breast cancer. Am J Epidemiol 1992;136:925-36.

20. Bernstein JL, Lapinski R, Lynch C, Holford T, Thompson WD. Factors influencing mortality among young women with second primary breast carcinoma. Cancer 2002;95:2051-8.

21. Bernstein L, Deapen D, Cerhan JR et al. Tamoxifen therapy for breast cancer and endometrial cancer risk. J Natl Cancer Inst 1999;91:1654-62.

22. Bertram LAC, Stefanick ML, Saquib N et al. Physical activity, additional breast cancer events, and mortality among early-stage breast cancer survivors: Findings from the WHEL Study. Cancer Causes and Control 2011;22:427-35.

23. Borugian MJ, Sheps SB, Kim-Sing C et al. Waist-to-hip ratio and breast cancer mortality. Am J Epidemiol 2003;158:963-8.

24. Borugian MJ, Sheps SB, Kim-Sing C et al. Insulin, macronutrient intake, and physical activity: are potential indicators of insulin resistance associated with mortality from breast cancer? Cancer Epidemiology, Biomarkers & Prevention 2004;13:1163-72.

25. Boyapati SM, Shu XO, Ruan ZX et al. Soyfood intake and breast cancer survival: a followup of the Shanghai Breast Cancer Study. Breast Cancer Research & Treatment 2005;92:11-7.

26. Bradshaw PT, Ibrahim JG, Gammon MD. A Bayesian proportional hazards regression model with non-ignorably missing time-varying covariates. Stat Med 2010;29:3017-29.

27. Bradshaw PT, Ibrahim JG, Stevens J et al. Postdiagnosis change in bodyweight and survival after breast cancer diagnosis. Epidemiology 2012;23:320-7.

28. Brooks JD, John EM, Mellemkjaer L et al. Body mass index and risk of second primary breast cancer: The WECARE Study. Breast Cancer Res Treat 2012;131:571-80.

29. Buck K, Vrieling A, Zaineddin AK et al. Serum enterolactone and prognosis of postmenopausal breast cancer. Journal of Clinical Oncology 2011;29:3730-8.

30. Buck K, Zaineddin AK, Vrieling A et al. Estimated enterolignans, lignan-rich foods, and fibre in relation to survival after postmenopausal breast cancer. Br J Cancer 2011;105:1151-7.

31. Caan BJ, Kwan ML, Hartzell G et al. Pre-diagnosis body mass index, post-diagnosis weight change, and prognosis among women with early stage breast cancer. Cancer Causes & Control 2008;19:1319-28.

32. Caan BJ, Natarajan L, Parker B et al. Soy food consumption and breast cancer prognosis. Cancer Epidemiol Biomarkers Prev 2011;20:854-8.

33. Camoriano JK, Loprinzi CL, Ingle JN, Therneau TM, Krook JE, Veeder MH. Weight change in women treated with adjuvant therapy or observed following mastectomy for node-positive breast cancer. Journal of Clinical Oncology 1990;8:1327-34.

34. Carmichael AR, Bendall S, Lockerbie L, Prescott RJ, Bates T. Does obesity compromise survival in women with breast cancer? Breast 2004;13:93-6.

35. Chang S, Alderfer JR, Asmar L, Buzdar AU. Inflammatory breast cancer survival: the role of obesity and menopausal status at diagnosis. Breast Cancer Research & Treatment 2000;64:157-63.

36. Chen X, Lu W, Zheng W et al. Obesity and weight change in relation to breast cancer survival. Breast Cancer Research & Treatment 2010;122:823-33.

37. Chen X, Lu W, Zheng W et al. Exercise after diagnosis of breast cancer in association with survival. Cancer Prev Res 2011;4:1409-18.

38. Chlebowski RT, Weiner JM, Reynolds R, Luce J, Bulcavage L, Bateman JR. Long-term survival following relapse after 5-FU but not CMF adjuvant breast cancer therapy. Breast Cancer Res Treat 1986;7:23-30.

39. Chlebowski RT, Blackburn GL, Thomson CA et al. Dietary fat reduction and breast cancer outcome: interim efficacy results from the Women's Intervention Nutrition Study. J Natl Cancer Inst 2006;98:1767-76.

40. Cleveland RJ, Eng SM, Abrahamson PE et al. Weight gain prior to diagnosis and survival from breast cancer. Cancer Epidemiology, Biomarkers & Prevention 2007;16:1803-11.

41. Cleveland RJ, Eng SM, Stevens J et al. Influence of prediagnostic recreational physical activity on survival from breast cancer. Eur J Cancer Prev 2012;21:46-54.

42. Clough-Gorr KM, Ganz PA, Silliman RA. Older breast cancer survivors: factors associated with self-reported symptoms of persistent lymphedema over 7 years of follow-up. Breast Journal 2010;16:147-55.

43. Coates RJ, Clark WS, Eley JW, Greenberg RS, Huguley CM, Jr., Brown RL. Race, nutritional status, and survival from breast cancer. J Natl Cancer Inst 1990;82:1684-92.

44. Conroy SM, Maskarinec G, Wilkens LR, White KK, Henderson BE, Kolonel LN. Obesity and breast cancer survival in ethnically diverse postmenopausal women: The Multiethnic Cohort Study. Breast Cancer Res Treat 2011;129:565-74.

45. Cook LS, White E, Schwartz SM, McKnight B, Daling JR, Weiss NS. A population-based study of contralateral breast cancer following a first primary breast cancer (Washington, United States). Cancer Causes Control 1996;7:382-90.

46. Costa LJ, Varella PC, del GA. Weight changes during chemotherapy for breast cancer. Sao Paulo Medical Journal = Revista Paulista de Medicina 2002;120:113-7.

47. Dal Maso L, Zucchetto A, Talamini R et al. Effect of obesity and other lifestyle factors on mortality in women with breast cancer. Int J Cancer 2008;123:2188-94.

48. Daling JR, Malone KE, Doody DR, Johnson LG, Gralow JR, Porter PL. Relation of body mass index to tumor markers and survival among young women with invasive ductal breast carcinoma. Cancer 2001;92:720-9.

49. Davidson NE, O'Neill AM, Vukov AM et al. Chemoendocrine therapy for premenopausal women with axillary lymph node-positive, steroid hormone receptor-positive breast cancer: results from INT 0101 (E5188). J Clin Oncol 2005;23:5973-82.

50. Dawood S, Broglio K, Gonzalez-Angulo AM et al. Prognostic value of body mass index in locally advanced breast cancer. Clinical Cancer Research 2008;14:1718-25.

51. den Tonkelaar I, de Waard F, Seidell JC, Fracheboud J. Obesity and subcutaneous fat patterning in relation to survival of postmenopausal breast cancer patients participating in the DOM-project. Breast Cancer Research & Treatment 1995;34:129-37.

52. Dignam JJ, Wieand K, Johnson KA, Fisher B, Xu L, Mamounas EP. Obesity, tamoxifen use, and outcomes in women with estrogen receptor-positive early-stage breast cancer. J Natl Cancer Inst 2003;95:1467-76.

53. Dignam JJ, Wieand K, Johnson KA et al. Effects of obesity and race on prognosis in lymph node-negative, estrogen receptor-negative breast cancer. Breast Cancer Research & Treatment 2006;97:245-54.

54. Donegan WL, Jayich S, Koehler MR. The prognostic implications of obesity for the surgical cure of breast cancer. Breast Dis Breast 1978;4:14-7.

55. Druesne-Pecollo N, Touvier M, Barrandon E et al. Excess body weight and second primary cancer risk after breast cancer: a systematic review and meta-analysis of prospective studies. Breast Cancer Res Treat 2012;135:647-54.

56. Eley JW, Hill HA, Chen VW et al. Racial differences in survival from breast cancer. Results of the National Cancer Institute Black/White Cancer Survival Study. JAMA 1994;272:947-54.

57. Emaus A, Veierod MB, Tretli S et al. Metabolic profile, physical activity, and mortality in breast cancer patients. Breast Cancer Research & Treatment 2010;121:651-60.

58. Enger SM, Greif JM, Polikoff J, Press M. Body weight correlates with mortality in early-stage breast cancer. Archives of Surgery 2004;139:954-8.

59. Enger SM, Bernstein L. Exercise activity, body size and premenopausal breast cancer survival. Br J Cancer 2004;90:2138-41.

60. Eralp Y, Smith TL, Altundag K et al. Clinical features associated with a favorable outcome following neoadjuvant chemotherapy in women with localized breast cancer aged 35 years or younger. Journal of Cancer Research & Clinical Oncology 2009;135:141-8.

61. Ewertz M, Gillanders S, Meyer L, Zedeler K. Survival of breast cancer patients in relation to factors which affect the risk of developing breast cancer. Int J Cancer 1991;49:526-30.

62. Ewertz M. Breast cancer in Denmark - Incidence, risk factors, and characteristics of survival. Acta Oncologica 1993;32:595-615.

63. Ewertz M, Jensen MB, Gunnarsdottir KA et al. Effect of obesity on prognosis after early-stage breast cancer. Journal of Clinical Oncology 2011;29:25-31.

64. Fetting JH, Gray R, Fairclough DL et al. Sixteen-week multidrug regimen versus cyclophosphamide, doxorubicin, and fluorouracil as adjuvant therapy for node-positive, receptor-negative breast cancer: an Intergroup study. J Clin Oncol 1998;16:2382-91.

65. Fink BN, Gaudet MM, Britton JA et al. Fruits, vegetables, and micronutrient intake in relation to breast cancer survival. Breast Cancer Research & Treatment 2006;98:199-208.

66. Fink BN, Steck SE, Wolff MS et al. Dietary flavonoid intake and breast cancer survival among women on Long Island. Cancer Epidemiology, Biomarkers & Prevention 2007;16:2285-92.

67. Flatt SW, Thomson CA, Gold EB et al. Low to moderate alcohol intake is not associated with increased mortality after breast cancer. Cancer Epidemiology, Biomarkers & Prevention 2010;19:681-8.

68. Fleischauer AT, Simonsen N, Arab L. Antioxidant supplements and risk of breast cancer recurrence and breast cancer-related mortality among postmenopausal women. Nutrition & Cancer 2003;46:15-22.

69. Franceschi S, Dal ML, Zucchetto A, Talamini R, Prospective Analysis of Case-control studies on Environmental factors and health (PACE) study group. Alcohol consumption and survival after breast cancer. Cancer Epidemiology, Biomarkers & Prevention 2009;18:1011-2.

70. Friedenreich CM, Gregory J, Kopciuk KA, Mackey JR, Courneya KS. Prospective cohort study of lifetime physical activity and breast cancer survival. Int J Cancer 2009;124:1954-62.

71. Galanis DJ, Kolonel LN, Lee J, Le ML. Anthropometric predictors of breast cancer incidence and survival in a multi-ethnic cohort of female residents of Hawaii, United States. Cancer Causes & Control 1998;9:217-24.

72. George SM, Irwin ML, Smith AW et al. Postdiagnosis diet quality, the combination of diet quality and recreational physical activity, and prognosis after early-stage breast cancer. Cancer Causes and Control 2011;22:589-98.

73. Gonzalez-Angulo AM, Broglio K, Kau SW et al. Women age < or = 35 years with primary breast carcinoma: disease features at presentation. Cancer 2005;103:2466-72.

74. Goodwin PJ, Ennis M, Pritchard KI et al. Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. Journal of Clinical Oncology 2002;20:42-51.

75. Goodwin PJ, Ennis M, Pritchard KI, Koo J, Trudeau ME, Hood N. Diet and breast cancer: evidence that extremes in diet are associated with poor survival. Journal of Clinical Oncology 2003;21:2500-7.

76. Goodwin PJ, Ennis M, Pritchard KI et al. Insulin- and obesity-related variables in early-stage breast cancer: Correlations and time course of prognostic associations. Journal of Clinical Oncology 2012;30:164-71.

77. Gordon NH, Crowe JP, Brumberg DJ, Berger NA. Socioeconomic factors and race in breast cancer recurrence and survival. Am J Epidemiol 1992;135:609-18.

78. Greenberg ER, Vessey MP, McPherson K, Doll R, Yeates D. Body size and survival in premenopausal breast cancer. Br J Cancer 1985;51:691-7.

79. Gregorio DI, Emrich LJ, Graham S, Marshall JR, Nemoto T. Dietary fat consumption and survival among women with breast cancer. J Natl Cancer Inst 1985;75:37-41.

80. Habel LA, Daling JR, Newcomb PA et al. Risk of recurrence after ductal carcinoma in situ of the breast. Cancer Epidemiology, Biomarkers & Prevention 1998;7:689-96.

81. Harris HR, Bergkvist L, Wolk A. Alcohol intake and mortality among women with invasive breast cancer. Br J Cancer 2012;106:592-5.

82. Harris HR, Bergkvist L, Wolk A. Folate intake and breast cancer mortality in a cohort of Swedish women. Breast Cancer Res Treat 2012;132:243-50.

83. Haybittle J, Houghton J, Baum M. Social class and weight as prognostic factors in early breast cancer. Br J Cancer 1997;75:729-33.

84. Heasman KZ, Sutherland HJ, Campbell JA, Elhakim T, Boyd NF. Weight gain during adjuvant chemotherapy for breast cancer. Breast Cancer Research & Treatment 1985;5:195-200.

85. Hebert JR, Hurley TG, Ma Y. The effect of dietary exposures on recurrence and mortality in early stage breast cancer. Breast Cancer Research & Treatment 1998;51:17-28.

86. Hellmann SS, Thygesen LC, Tolstrup JS, Gronbaek M. Modifiable risk factors and survival in women diagnosed with primary breast cancer: results from a prospective cohort study. Eur J Cancer Prev 2010;19:366-73.

87. Hoe AL, Mullee MA, Royle GT, Guyer PB, Taylor I. Breast size and prognosis in early breast cancer. Annals of the Royal College of Surgeons of England 1993;75:18-22.

88. Holick CN, Newcomb PA, Trentham-Dietz A et al. Physical activity and survival after diagnosis of invasive breast cancer. Cancer Epidemiology, Biomarkers & Prevention 2008;17:379-86.

89. Holmberg L, Lund E, Bergstrom R, Adami HO, Meirik O. Oral contraceptives and prognosis in breast cancer: effects of duration, latency, recency, age at first use and relation to parity and body mass index in young women with breast cancer. European Journal of Cancer 1994;30A:351-4.

90. Holmes MD, Stampfer MJ, Colditz GA, Rosner B, Hunter DJ, Willett WC. Dietary factors and the survival of women with breast carcinoma.[Erratum appears in Cancer 1999 Dec 15;86(12):2707-8]. Cancer 1999;86:826-35.

91. Holmes MD, Stampfer MJ, Colditz GA, Rosner B, Hunter DJ, Willett WC. Dietary factors and the survival of women with breast carcinoma. Cancer 1999;86:826-35.

92. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. JAMA 2005;293:2479-86.

93. Holmes MD, Chen WY, Hankinson SE, Willett WC. Physical activity's impact on the association of fat and fiber intake with survival after breast cancer. Am J Epidemiol 2009;170:1250-6.

94. Horn PL, Thompson WD. Risk of contralateral breast cancer: associations with factors related to initial breast cancer. Am J Epidemiol 1988;128:309-23.

95. Ingram D. Diet and subsequent survival in women with breast cancer. Br J Cancer 1994;69:592-5.

96. Irwin ML, Smith AW, McTiernan A et al. Influence of pre- and postdiagnosis physical activity on mortality in breast cancer survivors: the health, eating, activity, and lifestyle study. Journal of Clinical Oncology 2008;26:3958-64.

97. Irwin ML, McTiernan A, Manson JE et al. Physical activity and survival in postmenopausal women with breast cancer: Results from the women's health initiative. Cancer Prev Res 2011;4:522-9.

98. Jain M, Miller AB, To T. Premorbid diet and the prognosis of women with breast cancer. J Natl Cancer Inst 1994;86:1390-7.

99. Jain M, Miller AB. Pre-morbid body size and the prognosis of women with breast cancer. Int J Cancer 1994;59:363-8.

100. Jain M, Miller AB. Tumor characteristics and survival of breast cancer patients in relation to premorbid diet and body size. Breast Cancer Research & Treatment 1997;42:43-55.

101. Jung SY, Sereika SM, Linkov F, Brufsky A, Weissfeld JL, Rosenzweig M. The effect of delays in treatment for breast cancer metastasis on survival. Breast Cancer Res Treat 2011;130:953-64.

102. Jung SY, Rosenzweig M, Sereika SM, Linkov F, Brufsky A, Weissfeld JL. Factors associated with mortality after breast cancer metastasis. Cancer Causes and Control 2012;23:103-12.

103. Kang X, Zhang Q, Wang S, Huang X, Jin S. Effect of soy isoflavones on breast cancer recurrence and death for patients receiving adjuvant endocrine therapy. CMAJ Canadian Medical Association Journal 2010;182:1857-62.

104. Kato I, Miura S, Yoshida M, Tominaga S. Risk factors of multiple primary cancers in breast cancer patients. Japanese Journal of Cancer Research 1986;77:296-304.

105. Katoh A, Watzlaf VJ, D'Amico F. An examination of obesity and breast cancer survival in post-menopausal women. Br J Cancer 1994;70:928-33.

106. Keegan TH, Milne RL, Andrulis IL et al. Past recreational physical activity, body size, and all-cause mortality following breast cancer diagnosis: results from the Breast Cancer Family Registry. Breast Cancer Res Treat 2010;123:531-42.

107. Kim EHJ, Willett WC, Fung T, Rosner B, Holmes MD. Diet quality indices and postmenopausal breast cancer survival. Nutr Cancer 2011;63:381-8.

108. Kimura M. Obesity as prognostic factors in breast cancer. Diabetes Research and Clinical Practice 1990;10:S247-S251.

109. Kmet LM, Cook LS, Weiss NS, Schwartz SM, White E. Risk factors for colorectal cancer following breast cancer. Breast Cancer Research & Treatment 2003;79:143-7.

110. Knight JA, Bernstein L, Largent J et al. Alcohol intake and cigarette smoking and risk of a contralateral breast cancer: The Women's Environmental Cancer and Radiation Epidemiology Study. Am J Epidemiol 2009;169:962-8.

111. Kroenke CH, Chen WY, Rosner B, Holmes MD. Weight, weight gain, and survival after breast cancer diagnosis. Journal of Clinical Oncology 2005;23:1370-8.

112. Kroenke CH, Fung TT, Hu FB, Holmes MD. Dietary patterns and survival after breast cancer diagnosis. Journal of Clinical Oncology 2005;23:9295-303.

113. Kumar NB, Allen K, Cantor A et al. Weight gain associated with adjuvant tamoxifen therapy in stage I and II breast cancer: fact or artifact? Breast Cancer Research & Treatment 1997;44:135-43.

114. Kumar NB, Cantor A, Allen K, Cox CE. Android obesity at diagnosis and breast carcinoma survival: Evaluation of the effects of anthropometric variables at diagnosis, including body composition and body fat distribution and weight gain during life span,and survival from breast carcinoma. Cancer 2000;88:2751-7.

115. Kwan ML, Weltzien E, Kushi LH, Castillo A, Slattery ML, Caan BJ. Dietary patterns and breast cancer recurrence and survival among women with early-stage breast cancer. Journal of Clinical Oncology 2009;27:919-26.

116. Kwan ML, Kushi LH, Weltzien E et al. Alcohol consumption and breast cancer recurrence and survival among women with early-stage breast cancer: the life after cancer epidemiology study. Journal of Clinical Oncology 2010;28:4410-6.

117. Kwan ML, Chen WY, Kroenke CH et al. Pre-diagnosis body mass index and survival after breast cancer in the After Breast Cancer Pooling Project. Breast Cancer Res Treat 2012;132:729-39.

118. Kwan ML, Chen WY, Flatt SW et al. Postdiagnosis alcohol consumption and breast cancer prognosis in the after breast cancer pooling project. Cancer Epidemiol Biomarkers Prev 2013;22:32-41.

119. Kyogoku S, Hirohata T, Takeshita S, Nomura Y, Shigematsu T, Horie A. Survival of breast-cancer patients and body size indicators. Int J Cancer 1990;46:824-31.

120. Kyogoku S, Hirohata T, Nomura Y, Shigematsu T, Takeshita S, Hirohata I. Diet and prognosis of breast cancer. Nutrition & Cancer 1992;17:271-7.

121. Labidi SI, Mrad K, Mezlini A et al. Inflammatory breast cancer in Tunisia in the era of multimodality therapy. Ann Oncol 2008;19:473-80.

122. Lara-Medina F, Perez-Sanchez V, Saavedra-Perez D et al. Triple-negative breast cancer in Hispanic patients: High prevalence, poor prognosis, and association with menopausal status, body mass index, and parity. Cancer 2011;117:3658-69.

123. Lees AW, Jenkins HJ, May CL, Cherian G, Lam EW, Hanson J. Risk factors and 10-year breast cancer survival in northern Alberta. Breast Cancer Research & Treatment 1989;13:143-51.

124. Lethaby AE, Mason BH, Harvey VJ, Holdaway IM. Survival of women with node negative breast cancer in the Auckland region. New Zealand Medical Journal 1996;109:330-3.

125. Li CI, Malone KE, Porter PL, Daling JR. Epidemiologic and molecular risk factors for contralateral breast cancer among young women. Br J Cancer 2003;89:513-8.

126. Li CI, Daling JR, Porter PL, Tang MT, Malone KE. Relationship between potentially modifiable lifestyle factors and risk of second primary contralateral breast cancer among women diagnosed with estrogen receptor-positive invasive breast cancer. Journal of Clinical Oncology 2009;27:5312-8.

127. Litton JK, Gonzalez-Angulo AM, Warneke CL et al. Relationship between obesity and pathologic response to neoadjuvant chemotherapy among women with operable breast cancer. Journal of Clinical Oncology 2008;26:4072-7.

128. Loi S, Milne RL, Friedlander ML et al. Obesity and outcomes in premenopausal and postmenopausal breast cancer. Cancer Epidemiology, Biomarkers & Prevention 2005;14:1686-91.

129. Lu Y, Ma H, Malone KE et al. Obesity and survival among black women and white women 35 to 64 years of age at diagnosis with invasive breast cancer. Journal of Clinical Oncology 2011;29:3358-65.

130. Maehle BO, Tretli S. Pre-morbid body-mass-index in breast cancer: reversed effect on survival in hormone receptor negative patients. Breast Cancer Research & Treatment 1996;41:123-30.

131. Maehle BO, Tretli S, Thorsen T. The associations of obesity, lymph node status and prognosis in breast cancer patients: dependence on estrogen and progesterone receptor status. APMIS 2004;112:349-57.

132. Majed B, Moreau T, Senouci K, Salmon RJ, Fourquet A, Asselain B. Is obesity an independent prognosis factor in woman breast cancer? Breast Cancer Research & Treatment 2008;111:329-42.

133. Majed B, Moreau T, Senouci K et al. [Stoutness and prognosis of female non-metastatic breast cancer: results from a French observational cohort study]. [French]. Bulletin du Cancer 2009;96:531-41.

134. Majed B, Dozol A, Ribassin-Majed L, Senouci K, Asselain B. Increased risk of contralateral breast cancers among overweight and obese women: a time-dependent association. Breast Cancer Research & Treatment 2011;126:729-38.

135. Makari-Judson G, Judson CH, Mertens WC. Longitudinal patterns of weight gain after breast cancer diagnosis: observations beyond the first year. Breast J 2007;13:258-65.

136. Maskarinec G, Pagano I, Lurie G, Bantum E, Gotay CC, Issell BF. Factors affecting survival among women with breast cancer in Hawaii. Journal of Women's Health 2011;20:231-7.

137. Mason BH, Holdaway IM, Stewart AW, Neave LM, Kay RG. Season of tumour detection influences factors predicting survival of patients with breast cancer. Breast Cancer Research & Treatment 1990;15:27-37.

138. McCann SE, Thompson LU, Nie J et al. Dietary lignan intakes in relation to survival among women with breast cancer: the Western New York Exposures and Breast Cancer (WEB) Study. Breast Cancer Research & Treatment 2010;122:229-35.

139. McDonald PA, Williams R, Dawkins F, ms-Campbell LL. Breast cancer survival in African American women: is alcohol consumption a prognostic indicator? Cancer Causes & Control 2002;13:543-9.

140. McEligot AJ, Largent J, Ziogas A, Peel D, nton-Culver H. Dietary fat, fiber, vegetable, and micronutrients are associated with overall survival in postmenopausal women diagnosed with breast cancer. Nutrition & Cancer 2006;55:132-40.

141. Menon KV, Hodge A, Houghton J, Bates T. Body mass index, height and cumulative menstrual cycles at the time of diagnosis are not risk factors for poor outcome in breast cancer. Breast 1999;8:328-33.

142. Mohle-Boetani JC, Grosser S, Whittemore AS, Malec M, Kampert JB, Paffenbarger RS, Jr. Body size, reproductive factors, and breast cancer survival. Preventive Medicine 1988;17:634-42.

143. Moon HG, Han W, Noh DY. Underweight and breast cancer recurrence and death: a report from the Korean Breast Cancer Society. Journal of Clinical Oncology 2009;27:5899-905.

144. Nechuta SJ, Caan BJ, Chen WY et al. Soy food intake after diagnosis of breast cancer and survival: an in-depth analysis of combined evidence from cohort studies of US and Chinese women. Am J Clin Nutr 2012;96:123-32.

145. Newman SC, Miller AB, Howe GR. A study of the effect of weight and dietary fat on breast cancer survival time. Am J Epidemiol 1986;123:767-74.

146. Newman SC, Lees AW, Jenkins HJ. The effect of body mass index and oestrogen receptor level on survival of breast cancer patients. International Journal of Epidemiology 1997;26:484-90.

147. Nichols HB, Trentham-Dietz A, Egan KM et al. Body mass index before and after breast cancer diagnosis: associations with all-cause, breast cancer, and cardiovascular disease mortality. Cancer Epidemiology, Biomarkers & Prevention 2009;18:1403-9.

148. Niraula S, Ocana A, Ennis M, Goodwin PJ. Body size and breast cancer prognosis in relation to hormone receptor and menopausal status: a meta-analysis. Breast Cancer Res Treat 2012;134:769-81.

149. Nomura AM, Marchand LL, Kolonel LN, Hankin JH. The effect of dietary fat on breast cancer survival among Caucasian and japanese women in Hawaii. Breast Cancer Research & Treatment 1991;18:Suppl-41.

150. Olsson A, Garne JP, Tengrup I, Zackrisson S, Manjer J. Body mass index and breast cancer survival in relation to the introduction of mammographic screening. European Journal of Surgical Oncology 2009;35:1261-7.

151. Petrelli JM, Calle EE, Rodriguez C, Thun MJ. Body mass index, height, and postmenopausal breast cancer mortality in a prospective cohort of US women. Cancer Causes Control 2002;13:325-32.

152. Pierce JP, Stefanick ML, Flatt SW et al. Greater survival after breast cancer in physically active women with high vegetable-fruit intake regardless of obesity. Journal of Clinical Oncology 2007;25:2345-51.

153. Pierce JP, Natarajan L, Caan BJ et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. JAMA 2007;298:289-98.

154. Protani M, Coory M, Martin JH. Effect of obesity on survival of women with breast cancer: systematic review and meta-analysis. Breast Cancer Res Treat 2010;123:627-35.

155. Pukkala E, Kyyronen P, Sankila R, Holli K. Tamoxifen and toremifene treatment of breast cancer and risk of subsequent endometrial cancer: a population-based case-control study. Int J Cancer 2002;100:337-41.

156. Reding KW, Daling JR, Doody DR, O'Brien CA, Porter PL, Malone KE. Effect of prediagnostic alcohol consumption on survival after breast cancer in young women. Cancer Epidemiology, Biomarkers & Prevention 2008;17:1988-96.

157. Reeves GK, Patterson J, Vessey MP, Yeates D, Jones L. Hormonal and other factors in relation to survival among breast cancer patients. Int J Cancer 2000;89:293-9.

158. Reeves KW, Faulkner K, Modugno F et al. Body mass index and mortality among older breast cancer survivors in the Study of Osteoporotic Fractures. Cancer Epidemiology, Biomarkers & Prevention 2007;16:1468-73.

159. Rohan TE, Hiller JE, McMichael AJ. Dietary factors and survival from breast cancer. Nutrition & Cancer 1993;20:167-77.

160. Rohan TE, Fu W, Hiller JE. Physical activity and survival from breast cancer. Eur J Cancer Prev 1995;4:419-24.

161. Rosenberg L, Czene K, Hall P. Obesity and poor breast cancer prognosis: an illusion because of hormone replacement therapy? Br J Cancer 2009;100:1486-91.

162. Sanchez L, Lana A, Hidalgo A et al. Risk factors for second primary tumours in breast cancer survivors. Eur J Cancer Prev 2008;17:406-13.

163. Saquib J, Rock CL, Natarajan L et al. Dietary intake, supplement use, and survival among women diagnosed with early-stage breast cancer. Nutr Cancer 2011;63:327-33.

164. Saxe GA, Rock CL, Wicha MS, Schottenfeld D. Diet and risk for breast cancer recurrence and survival. Breast Cancer Research & Treatment 1999;53:241-53.

165. Schairer C, Gail M, Byrne C et al. Estrogen replacement therapy and breast cancer survival in a large screening study. J Natl Cancer Inst 1999;91:264-70.

166. Schuetz F, Diel IJ, Pueschel M et al. Reduced incidence of distant metastases and lower mortality in 1072 patients with breast cancer with a history of hormone replacement therapy. American Journal of Obstetrics & Gynecology 2007;196:342-9.

167. Sellers TA, Alberts SR, Vierkant RA et al. High-folate diets and breast cancer survival in a prospective cohort study. Nutrition & Cancer 2002;44:139-44.

168. Sestak I, Distler W, Forbes JF, Dowsett M, Howell A, Cuzick J. Effect of body mass index on recurrences in tamoxifen and anastrozole treated women: an exploratory analysis from the ATAC trial. Journal of Clinical Oncology 2010;28:3411-5.

169. Shu XO, Zheng Y, Cai H et al. Soy food intake and breast cancer survival. JAMA 2009;302:2437-43.

170. Singh AK, Pandey A, Tewari M et al. Obesity augmented breast cancer risk: a potential risk factor for Indian women. Journal of Surgical Oncology 2011;103:217-22.

171. Sparano JA, Wang M, Zhao F et al. Race and hormone receptor-positive breast cancer outcomes in a randomized chemotherapy trial. J Natl Cancer Inst 2012;104:406-14.

172. Sternfeld B, Weltzien E, Quesenberry CP, Jr. et al. Physical activity and risk of recurrence and mortality in breast cancer survivors: findings from the LACE study. Cancer Epidemiology, Biomarkers & Prevention 2009;18:87-95.

173. Storm HH, Andersson M, Boice JD, Jr. et al. Adjuvant radiotherapy and risk of contralateral breast cancer. J Natl Cancer Inst 1992;84:1245-50.

174. Suissa S, Pollak M, Spitzer WO, Margolese R. Body size and breast cancer prognosis: a statistical explanation of the discrepancies. Cancer Res 1989;49:3113-6.

175. Swenerton KD, Legha SS, Smith T et al. Prognostic factors in metastatic breast cancer treated with combination chemotherapy. Cancer Res 1979;39:1552-62.

176. Tammemagi CM, Nerenz D, Neslund-Dudas C, Feldkamp C, Nathanson D. Comorbidity and survival disparities among black and white patients with breast cancer. JAMA 2005;294:1765-72.

177. Tao MH, Shu XO, Ruan ZX, Gao YT, Zheng W. Association of overweight with breast cancer survival. Am J Epidemiol 2006;163:101-7.

178. Taylor SG, Knuiman MW, Sleeper LA et al. Six-year results of the Eastern Cooperative Oncology Group trial of observation versus CMFP versus CMFPT in postmenopausal patients with node-positive breast cancer. Journal of Clinical Oncology 1989;7:879-89.

179. Thivat E, Therondel S, Lapirot O et al. Weight change during chemotherapy changes the prognosis in non metastatic breast cancer for the worse. BMC Cancer 2010;10:648.

180. Tominaga K, Andow J, Koyama Y et al. Family environment, hobbies and habits as psychosocial predictors of survival for surgically treated patients with breast cancer. Japanese Journal of Clinical Oncology 1998;28:36-41.

181. Tornberg S, Carstensen J. Serum beta-lipoprotein, serum cholesterol and Quetelet's index as predictors for survival of breast cancer patients. European Journal of Cancer 1993;29A:2025-30.

182. Trentham-Dietz A, Newcomb PA, Nichols HB, Hampton JM. Breast cancer risk factors and second primary malignancies among women with breast cancer. Breast Cancer Research & Treatment 2007;105:195-207.

183. Tretli S, Haldorsen T, Ottestad L. The effect of pre-morbid height and weight on the survival of breast cancer patients. Br J Cancer 1990;62:299-303.

184. Vatten LJ, Foss OP, Kvinnsland S. Overall survival of breast cancer patients in relation to preclinically determined total serum cholesterol, body mass index, height and cigarette smoking: a population-based study. European Journal of Cancer 1991;27:641-6.

185. Vitolins MZ, Kimmick GG, Case LD. BMI influences prognosis following surgery and adjuvant chemotherapy for lymph node positive breast cancer. Breast Journal 2008;14:357-65.

186. Von Drygalski A, Tran TB, Messer K et al. Obesity is an independent predictor of poor survival in metastatic breast cancer: Retrospective analysis of a patient cohort whose treatment included high-dose chemotherapy and autologous stem cell support. Int J Breast Cancer 2011;1.

187. West-Wright CN, Henderson KD, Sullivan-Halley J et al. Long-term and recent recreational physical activity and survival after breast cancer: the California Teachers Study. Cancer Epidemiology, Biomarkers & Prevention 2009;18:2851-9.

188. Whiteman MK, Hillis SD, Curtis KM, McDonald JA, Wingo PA, Marchbanks PA. Body mass and mortality after breast cancer diagnosis. Cancer Epidemiology, Biomarkers & Prevention 2005;14:2009-14.

189. Williams G, Howell A, Jones M. The relationship of body weight to response to endocrine therapy, steroid hormone receptors and survival of patients with advanced cancer of the breast. Br J Cancer 1988;58:631-4.

190. Xu X, Gammon MD, Wetmur JG et al. B-vitamin intake, one-carbon metabolism, and survival in a population-based study of women with breast cancer. Cancer Epidemiology, Biomarkers & Prevention 2008;17:2109-16.

191. Yu GP, Ostroff JS, Zhang ZF, Tang J, Schantz SP. Smoking history and cancer patient survival: a hospital cancer registry study. Cancer Detection & Prevention 1997;21:497-509.

192. Zhang S, Folsom AR, Sellers TA, Kushi LH, Potter JD. Better breast cancer survival for postmenopausal women who are less overweight and eat less fat: The Iowa women's health study. Cancer 1995;76:275-83.

193. Zhang YF, Kang HB, Li BL, Zhang RM. Positive effects of soy isoflavone food on survival of breast cancer patients in China. Asian Pac J Cancer Prev 2012;13:479-82.

Annex 1. Protocol for systematic review on nutrition, physical activity and health outcomes in breast cancer survivors

Continuous update literature review on diet and cancer

Protocol for systematic review on nutrition, physical activity and health outcomes in breast cancer survivors.

Version 2. October 2010

The Continuous Update Project on breast cancer survivors is an extension of the Continuous Update Project (CUP) on diet, nutrition, physical activity, and cancer prevention.

The current protocol for the Continuous Update on breast cancer survivors should ensure consistency of approach to the evidence used in the literature reviews for the WCRF/AICR Second Expert Report for cancer incidence and in the CUP.

The starting points for this protocol are:

- The convention for conducting systematic reviews developed by WCRF International for the Second Expert Report.[1]
- The recommendations of the Cancer Survivors Protocol Development Committee (Appendix 1)
- The protocol developed by the SLR group on cancer survivors for the Second Expert Report (SLR centre: University of Bristol) (Appendix 2)

The peer-reviewed protocol will represent the agreed plan for the Continuous Update on breast cancer survivors. Should departure from the agreed plan be considered necessary at a later stage, this must be agreed by the WCRF/AICR Secretariat and the reasons documented.

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BACKGROUND

The Panel of Experts for the 2007 WCRF/AICR report concluded that the available evidence from clinical trials on nutrition and physical activity and cancer prognosis was limited, and did not support specific recommendations for cancer survivors[1,2]. The Panel recommended that all cancer survivors should receive nutritional care from an appropriately trained professional and if able to do so, and unless otherwise advised, cancer survivors should aim to follow the recommendations for diet, healthy weight and physical activity for cancer prevention.

Advances in early detection and treatment have increased breast cancer survival considerably. With the increasing numbers of long-term survivors, research specific to cancer prognosis, new breast cancer events, quality of life and mortality is of considerable public health importance. In Europe, the five-year relative survival of women diagnosed with breast cancer in 1995–1999 is estimated to be above 82% in Northern Europe, France, Italy and Switzerland, and around 77% in the United Kingdom. In Eastern European countries, five-year relative survival is around 73% or lower[3]. In United States, the overall five-year relative survival for 1999-2006 has been estimated as 89% and for localized disease, the estimated five-year relative survival is 98% [4].

Recent studies suggest that diet and exercise interventions may be of benefit in ameliorating adverse sequelae of cancer and its treatment, as well as cancer-specific survival and overall survival after breast cancer. [5-7]

The objective of this project is to identify and summarize the available information from published epidemiologic research on lifestyle and several health outcomes among women with a history of breast cancer. This review differs to the Systematic Literature Review for the 2007 WCRF/AICR report in two main aspects: it will be focused on studies in breast cancer survivors and it will include not only clinical trials but also follow-up studies in breast cancer survivors.

RESEARCH QUESTION.

The research topic is:

The associations between food, nutrition, dietary patterns, weight control, nutrition-related complementary medicine and physical activity with mortality, breast cancer recurrence, second cancers, long-term treatment side effects and quality of life in breast cancer survivors.

1. REVIEW TEAM

REVIEW TEAM, IMPERIAL COLLEGE LONDON

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2. TIMELINE.

Task	Deadline
Preparation and approval of the protocol	November 2010
Changes to the structure of the database†	June-December 2010
Start Medline search of relevant articles	November 2010
Review abstracts and citations identified in initial electronic search. Select papers for complete review	30 January 2011
Report to WCRF number of papers by study type for establishing priorities¶	28 February 2011
Select papers for data extraction¶	30 May 2011
Data extraction	30 June 2011
Data analysis	30 August 2011
Preparation of report for Panel of experts¶	30 October 2011
Send report to WCRF	30 October 2011
Transfer Endnote files to WCRF	30 October 2011

† Changes to the database will continue through all the review process
¶ Deliveries will depend of priorities.

3. SEARCH STRATEGY

The search strategy will be:

a) Search for all studies relating to breast cancer prognosis (mortality, breast cancer recurrence, second cancers, long-term treatment side effects and quality of life):

b) Search for all studies relating to food, nutrition, body fatness, complementary medicine, dietary supplements and physical activity:

The CUP review team will use the search strategy developed by medical librarians and tested during the SLR for the WCRF/AICR 2nd Expert Report. The search was additionally reviewed and implemented for Medline and EMBASE using OVID as platform by a librarian at Imperial College (Appendix 3). The search strategy retrieves foods, macronutrients, micronutrients from diet and supplements, dietary supplements, herbs, breast feeding, anthropometric characteristics and physical activity.

4. SELECTION OF ARTICLES

Only articles that match the inclusion criteria will be updated in the database.

4.1 Inclusion criteria

The articles that will be included in the systematic review:

- Investigate the associations between food, nutrition, weight control, nutrition-related complementary medicine, physical activity and mortality, breast cancer recurrence, second cancers, long-term treatment side effects and quality of life in survivors of primary breast cancer.

- The study population are pre- or post-menopausal women with diagnosis of in situ or invasive breast cancer.

- Present results of primary analysis, secondary analysis or ancillary analyses of randomised controlled trials, or follow-up studies in breast cancer survivors. If the study is a randomised clinical trial, length of follow-up should be at least six months.

- Report a measure of the effect/association of the intervention/exposure on the outcomes relevant to this review.

- The intervention/exposures investigated are those relevant to the WCRF/AICR 2nd Expert Report (food, nutrition, weight control, physical activity) and nutrition-related complementary medicine.

- Present results for any of the following outcomes:
    - Breast cancer mortality
    - Overall mortality
    - Any other mortality cause
    - Disease free survival (as defined by the authors in the identified articles)
    - Cancer recurrence
    - Second primary breast cancer
    - Other second primary cancer
    - Weight change
    - Quality of life (if the study is a randomised clinical trial, length of follow-up should be at least six months)
    - Development of comorbidities (e.g. fractures, cardiovascular disease, diabetes)
    - Long-term treatment related effects (e.g. lymphoedema, fatigue, osteoporosis).
    - Side-effect of diet-related modifications, physical activity interventions, nutrition-related complementary medicine, micronutrient supplementation or other dietary supplementation.
- Are original articles published in peer-reviewed journals.
- Are published in English language*

** The search in this review will not be restricted by language. However, for feasibility reasons, only articles in English language will be included. Approximately 9% of clinical trials indexed in EMBASE are in languages other than English and from these about 2% are in Chinese language.*

Articles in non-English language relevant to this review can be identified when the title and abstract are translated to English, and when the translation provides enough information to decide if the article is relevant or not to the review. The references and abstracts of relevant studies published in languages other than English will be stored in a Reference Manager database.

The WCRF Secretariat and the Expert Panel will decide what articles published in non-English language should be translated to English.

4.2 Exclusion criteria

The articles to be excluded from the review are:

- Pooled analysis and meta-analysis (these will be used as support for interpretation, but the data will not be included in the database.)
- Comments, reviews, conference abstracts.

5. EXPOSURES/INTERVENTIONS.

The methods of exposure assessment will be extracted and whether the method has been validated, the number of items in the questionnaires and the number of assessments.

The duration of the exposure/intervention will be recorded as well as the time between exposure assessment/intervention and outcome assessment.

5.1 Labels of exposure/interventions.

During data extraction, interventions/exposures will be labelled using the exposure codes listed in the Guidelines for the systematic literature reviews of the 2007 WCRF/AICR expert Report[1]. The interventions/exposures are allocated under the main headings and subheadings listed in Appendix 4. For example, diet modifications –e.g. diets rich in fruit and vegetables and low in fats- will be coded under “Dietary patterns” and combinations of micronutrients in supplements will be coded under “Dietary Constituents”.

An additional main heading for “Nutrition-related complementary and alternative Medicine” has been added for this review (**code 9** in Appendix 4) with the following subheadings: Traditional medicine, Naturopathy, Phytotherapy, Homeopathy. Biomarkers of exposure will be extracted under the heading of the corresponding exposure, Biomarkers for which there is no evidence on appropriate validity and repeatability will not be included in the review (List of biomarkers is in Appendix 5).

5.2 Timeframe of exposure assessment.

The timeframe of exposure assessment in observational studies will be recorded as follows:

-Exposure assessment refers to a period **before** primary breast cancer diagnosis (childhood, adolescence, adulthood).

-Exposure assessment refers to the period **during therapy** for primary breast cancer.

-Exposure assessment refers to a period **after** primary breast cancer diagnosis.

6. OUTCOME

The outcomes relevant to this review are:

- Mortality
  - All cause mortality
  - Breast cancer mortality
  - Other causes of deaths
- Disease free survival (as defined by the authors in the identified articles)
- Cancer recurrence
- Second primary breast cancer
- Other second primary cancer
- Weight change
- Quality of life [psychological well being (e.g. fatigue, depression) and function (including performance status) but not spirituality].
- Treatment side effects such as lymphoedema, fatigue.
- Development of comorbidities. This includes bone health (e.g. fractures, cardiovascular disease, diabetes).
- Side-effect of diet-related modifications, physical activity interventions, nutrition-related complementary medicine, micronutrient supplementation or other dietary supplementation.

There will not be specific search for markers of tumor biology (e.g. proliferation rate, apoptosis, circulating cancer cells) because they are not relevant outcomes of the review. Results on markers of tumor biology will be extracted under “Notes” only from articles that provide results on the relevant outcomes.

7. DATABASES

The databases to be searched are:

a) Medline.

b) The Cochrane Library:

- CDSR (Cochrane Database of Systematic Reviews): includes all Cochrane Reviews (and protocols) prepared by Cochrane Review Groups in The Cochrane Collaboration.

- CENTRAL (The Cochrane Central Register of Controlled Trials): is comprised of a merge of relevant records retrieved from MEDLINE, relevant records retrieved from EMBASE, all Review Groups' Specialised Registers and the hand search results register.

c) EMBASE

8. HAND SEARCHING FOR CITED REFERENCES

For feasibility reasons, journals will not be hand searched.

The CUP team will review the references of meta-analyses, reviews and pooling projects identified during the search.

9 . REFERENCE MANAGER FILES

Reference Manager files are generated in the continuous update containing the references of the initial searches in all databases.

1) One of the customized fields (User Def 1) is named ‘inclusion’ and this field is marked ‘included’, ‘excluded’ for each paper, thereby indicating which papers are deemed potentially relevant based on an assessment of the title and abstract.

2) One of the customized fields (User Def 2) is named ‘reasons’ and this field should include the reason for exclusion for each paper.

3) The study identifier should be entered under the field titled ‘label’.

4) One of the customized fields (User Def 3) is named “study design”. This field indicates the study design of each paper:

- Randomised controlled trials excluding interventions during cancer treatment.
- Randomised controlled trials during cancer treatment.
- Group Intervention trials
- Observational studies where exposure refers to the period before breast cancer diagnosis
- Observational studies where exposure refers to the period from diagnosis through adjuvant treatment.
- Observational studies where exposure refers to the period after breast cancer diagnosis after adjuvant treatment.

The Reference Management databases will be converted to EndNote and sent to WCRF Secretariat as part of the report.

9. RETRIEVING ARTICLES

The references of articles retrieved in the searches in the different databases will be merged by the database manager into a Reference Manager (RefMan) database.

Animal and in vitro studies will be excluded with the following stop terms: transgenic, mice, hamster, rat, dog, cat, in vitro. *(This procedure was tested by the SLR team Leeds during the SLR for the 2007 WCRF/AICR expert report.)*

Non-relevant exposures under the Mesh term “Complementary medicine” will be excluded using the following stop terms: Acupuncture Therapy, Anthroposophy , Auriculotherapy, Holistic Health, Mind-Body Therapies, Musculoskeletal Manipulations, Organotherapy, Reflexotherapy, Rejuvenation, Sensory Art Therapies, Speleotherapy, Spiritual Therapies, Shamanism, Aromatherapy , Eclecticism, Historical.

The database manager will identify and eliminate duplicates in the RefMan database using as key terms the first author name, publication year, journal name, volume, starting page number of the article. Automatic searches for duplicates in Ref Man are not recommended because the references retrieved in each database may be exported differently.

The reviewer will assess relevant articles on the Reference Manager database upon reading of titles and abstracts. The complete papers of relevant and potentially relevant references and of references that cannot be excluded upon reading the title and abstracts will be reviewed. A second assessment will be done after review of the complete papers.

The assessments of inclusion of articles will be done in duplicate by two independent reviewers for articles published in 2009 and 2010. If there is full agreement in the selection, 10% of the remaining articles will be double assessed for inclusion. This decision is based on feasibility of the project with the existing resources. The WCRF secretariat and the Expert Panel will be consulted on this before changes to the protocol are implemented.

11. LABELLING OF ARTICLES

For consistency with the previous data collected during the SLR process for the Second Expert Report, the CUP review team will use the same labelling of articles: the unique identifier for a particular reference will be constructed using S to indicate “survivors” and a 2-letter code to represent the cancer site (e.g. BR for breast cancer), followed by a 5-digit number that will be allocated in sequence.

12. DATA EXTRACTION

Data extraction will be performed by the reviewer using a screen extraction form designed by the database manager of the CUP. Extractions will be double checked by a second reviewer for 10% of the extracted articles by the first reviewer.

The data will be extracted to the WCRF database located in a protected server at Imperial College London. The structure of the existing database will be adapted to the scope of the search on breast cancer survivors before the start of the search. Further modifications of the database structure may be needed during the search.

12. 1. Information to be extracted.

The list of study variables for observational and intervention studies in the CUP database is in Appendix 6.

For this review, new variables will be added:

-Study type:

- Intervention study
- Follow-up study on breast cancer survivors

-Characteristics of primary breast cancer:

- Distribution of “in situ” and invasive breast cancer in the study population
- Proportion of cases in which primary breast cancer was detected by screening.
- Distribution of the study population by stage at diagnosis
- Distribution by estrogen receptor (ER), progesterone receptor (PR), human epithelial growth factor receptor 2 (Her2) status
- Distribution by cancer subtype defined by immunohistochemical analysis or gene expression profiling (e.g. Luminal A, Luminal B, etc as given in the manuscript)
- Distribution of the study population by treatment for primary breast cancer (surgery, chemotherapy, radiotherapy, hormonal therapy specifying if tamoxifen, aromatase inhibitors, monoclonal antibodies such as herceptin, other treatments, unknown).

12.2 Choice of Result

The results for all relevant exposures and outcomes will be extracted. In epidemiologic studies, authors often present a series of models, e.g. unadjusted, age-adjusted, multivariable adjusted models. Sometimes authors do additional adjustments for factors likely to be in the causal pathway (“mechanistic models”). The extracted results will be labeled depending on the model as: not adjusted, intermediately adjusted, “fully” adjusted, or mechanistic model. “Fully” adjusted models and “mechanistic” models will be extracted in this review. A “fully” adjusted model will be considered the most adjusted model in the

paper that is not a “mechanistic model”. If only an unadjusted or an age-adjusted model is given in the paper, this should be extracted.

The reviewer should indicate a “best model” for inclusion in reports and meta-analyses. Usually, the “fully” adjusted model will be considered the “best model”. In there is a “mechanistic model”, the “best model” for analysis will be the “fully” adjusted and not the “mechanistic” model.

The results for subgroup and stratified analyses will be extracted and the models labelled as indicated before. The “best model” for analysis will be indicated by the reviewer.

The authors of the papers will not be contacted during the process of data extraction. Only the data provided in the article will be extracted to the database.

12.3 Multiple articles

Data should be extracted for each individual article, even if there is more than one article from any one study, unless the information is identical. The most appropriate set of data on a particular exposure will be selected among the articles published on a study to ensure there is no duplication of data from the same study in an analysis.

12.4 Quality control

Inclusion assessment will be done in duplicate for articles published in 2009 and 2010. If there is concordance in the selection between the two reviewers, the quality control of the selection procedure will be done by a second reviewer on only 10% of the papers excluded by the first reviewer. This is due to limited resources (section 9 “ Retrieving Articles”). Any disagreement between reviewers will be solved with the principal investigator at Imperial College. In case of doubt about the study selection, the WCRF Secretariat will be contacted for advice. When discrepancies are detected, the protocol will be revised to add more clarifications.

Data extraction will be checked by a second reviewer. Only 10% of the data extraction will be reviewed. If there are discrepancies, another 10% of the extracted information will be checked.

12.5 Gene-nutrient interaction

No attempt was made to critically appraise or analyse the studies that reported gene-nutrient interactions in the 2007 WCRF/AICR second expert report[1]. The results of relevant studies on gene-environment interactions will be described in a narrative review

13. ASSESSMENT OF STUDY QUALITY AND SUSCEPTIBILITY TO BIAS.

The evaluation of randomised controlled trials will be based in the checklist proposed by the Cochrane Collaboration (http://www.cochrane-handbook.org/).
The dimensions of quality and susceptibility to bias in the check lists are:

- Selection bias: Systematic differences between baseline characteristics of the groups that are compared.
- Performance bias: Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest.
- Attrition bias: Systematic differences between groups in withdrawals from a study.
- Detection bias: Systematic differences between groups in how outcomes are determined.
- Reporting bias: Systematic differences between reported and unreported findings.

The items will receive score 1 point if susceptibility to bias is low and 0 if susceptibility to bias is considered high. The total score of the article will be the sum of the item scores (details in Appendix 7).

Numerous tools have been proposed for evaluation of methodological quality of observational epidemiological studies but there is no agreed "gold standard" [8]. We will assess the quality of observational studies using the Newcastle-Ottawa quality assessment scale, which is simpler to use and has been used in recently published meta-analysis (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

The dimensions included are:

- Selection of study population (ascertainment of exposure is included in this dimension).
- Comparability: control for confounding
- Outcome: ascertainment and follow-up

We will exclude the item "representativeness of the study population" as criteria of study quality, because it does not affect the study internal validity [8]. The characteristic of the study population will be extracted and could be use for further analysis.
Studies will not be excluded on the basis of study quality. The assessment of study quality will be used to inform narrative reviews and for sensitivity and meta-regression analyses. Scores of study quality or susceptibility to bias will be included in tables of study characteristics in the reports.

15. DATA ANALYSIS

Meta-analyses and narrative reviews will complement each other.

15.1 When to do a meta-analysis

A meta-analysis for a particular exposure/intervention and outcome will be conducted when three or more trials or observational studies that can be combined have been published. If meta-analyses are not possible, the results will be summarised in a narrative review.

Special care will be taken to avoid including more than once the results of the same study (e.g. previous analyses and re-analyses after a longer follow-up).

15. 2 Methods

The methods that will be used to do meta-analyses will be the same methods used for the Second Expert Report[1].

Meta-analyses will be conducted separately by study type, outcome and timeframe of exposure (before diagnosis, during treatment, after treatment). The best model (most often the “fully” adjusted measure of association or effect) from each analysis will be used.

In trials with multiple intervention arms and intervention of different types (e.g. one multivitamin supplement and one dietary counselling intervention), each arm will be compared with the usual treatment group (or specific placebo group) and analysed separately. Consequently, some studies may contribute data to more than one analysis.

When multiple interventions in a trial are of the same type, the results of each arm will be compared first with the results of the control data arm separately. If the results of each arm are consistent in size and direction of effect, the data from the interventions arms will be treated as one group. This method will avoid the control groups being included twice in the same meta-analysis[2]. Factorial trials will be analyzed by assuming no interaction between interventions.

In meta-analysis of two categories (or ‘‘high-low’’ comparisons), summary RR estimates with their corresponding 95% CIs will be derived using fixed and random effect models [9]. A difference in the point estimate in fixed and random effect analysis must indicate that results from smaller studies differ from those of larger studies.

To estimate the dose-response relationship, category-specific risk estimates will be transformed into estimates of the relative risk (RR) associated with a unit of increase in exposure by use of the method of generalised least-squares for trend estimation[10]. When exposure levels are reported as means or medians for each category of exposure, these values will be used directly in the dose-response meta-analyses. If the exposure is given as an interval, the mid-point of the interval will be assigned to each closed-ended category of exposure. The median will be assigned to each open-ended category. The median will be calculated assuming a normal distribution for exposure[11]. When categorical and continuous results are provided, the continuous results will be used in the dose-response meta-analysis. The relative risk estimates for each unit of increase of the exposure from each study will be combined by use of fixed and random-effect meta-analysis[9].

Forest plots will be examined as usual method of assessing and displaying heterogeneity between studies. Heterogeneity will be tested using the Q statistic. The amount of heterogeneity in each meta-analysis will be quantified with the I^2 statisticc[12]. Influence-analyses to assess the effect of each study on the summary size effect estimates[13]. Publication and small study bias will be examined in funnel plots.

If the number of studies allows it, the sources of heterogeneity will be explored with the use of meta-regression. Possible variables to be examined are breast cancer subtype, geographic area where the study was conducted, publication year, stage of disease, duration of follow-up, timeframe of exposure assessment. Other variables that may be considered as source of heterogeneity are characterisation of the exposure (FFQ, recall, diary, self-reported or measured anthropometry etc.) and adjustment for confounders. In clinical trials, variables to be considered are whether the outcome was the primary or secondary outcome or an ancillary analysis. The interpretation of these analyses should be cautious. If a considerable number of study characteristics are considered as possible explanations for heterogeneity in a meta-analysis containing only a small number of studies, then there is a high probability that one or more will be found to explain heterogeneity, even in the absence of real associations.

The analysis will be done using STATA version 9.2 (College Station, TX, USA).

15.3 Missing values

Failure to include all available evidence in the meta-analyses will reduce precision of summary estimates and may also lead to bias if propensity to report results in sufficient

detail is associated with the magnitude and/or direction of associations. Published standard procedures [14] will be used to calculate missing information (Appendix 8).

15. REPORTS

Content of the report:

1. Changes to the agreed protocol

2. Narrative summary of the results of the search and the data analysis

3. Results of the search.

- Flow chart showing number of records downloaded, number of papers thought potentially relevant after reading titles and abstracts and number of included relevant papers. The reasons for excluding papers should also be described.
- For each intervention, number of trials by outcome.
- For each exposure, number of studies by study type and outcome.

4. Tabulation of study characteristics

> Information on the characteristics (e.g. population, exposure/intervention, outcome, study design) and results of the study (e.g. direction and magnitude) of the new studies should be summarised in tables using the same format as for the SLR for the Second Expert Report[1]. The tables will include the scores of study quality.

The tables for randomisation controlled trials will be ordered by exposure as follows:

- Food-related interventions
- Micronutrient supplementation
- Physical activity-related interventions
- Nutrition-related complementary medicine.
- Combination of interventions

The tables of study characteristic of clinical trials will include the following information:

- Trial reference, year
- Characteristics of study population (age, race/ethnicity, BMI, menopausal status, BRCA1-2 carrier)
- Characteristics of the tumour (stage, subtype, hormone receptor status)
- Treatment at time of intervention (after, during, unclear)
- Randomization, blinding
- Intervention, duration
- Follow-up time

- Number of events and total number of participants in intervention and control arms
- Percentage of missing outcome data
- Outcome
- Results and whether these are primary endpoints or secondary endpoints; final or interim analysis; ad-hoc analysis; based on intention-to treat analysis or treated;
- Matching criteria, adjustment factors in the analysis
- Quality score

The tables for observational studies will be ordered by exposure and exposure assessment timeframe (before breast cancer diagnosis, during treatment or after treatment). The tables will contain the following information:

- Study reference, year
- Study design
- Characteristics of study population (age, ethnicity, BMI, menopausal status, use of HRT before cancer diagnosis)
- Number of cases and study size
- Whether exposure from foods or supplements, levels or increment
- Outcome
- Results
- Adjustment factors in the analysis
- Quality score

5. Description of results of assessment of quality and risk of bias of included studies

Tabulation of results for individual items of the check lists.

6. Results of meta-analysis

The results of meta-analysis will be displayed in tables and forest plots. The characteristic of excluded studies and reasons for exclusions will be tabulated.

Funnel plots for examining publication and small study bias will be included.

6. Reference list.

List of all relevant studies identified in the review.

References

1. World Cancer Research Fund/ American Institute for Cancer Research. Systematic Literature Review – Support Resource. In : Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective.Washington DC: AICR , 2007

2. Davies AA, Davey Smith G, Harbord R, Bekkering GE, Sterne JA, Beynon R, Thomas S. Nutritional interventions and outcome in patients with cancer or preinvasive lesions: systematic review. J Natl Cancer Inst. 2006 Jul 19;98(14):961-73.

3. Sant M, Allemani C, Santaquilani M, Knijn A, Marchesi F, Capocaccia R; EUROCARE Working Group. EUROCARE-4. Survival of cancer patients diagnosed in 1995-1999. Results and commentary. Eur J Cancer. 2009 Apr;45(6):931-91 .

4. American Cancer Society. *Breast Cancer Facts & Figures 2009-2010*. Atlanta: American Cancer Society, Inc. (http://www.cancer.org/downloads/STT/F861009_final%209-08-09.pdf)

5. Demark-Wahnefried W, Morey MC, Sloane R, Snyder DC, Cohen HJ. Promoting healthy lifestyles in older cancer survivors to improve health and preserve function. J Am Geriatr Soc. 2009 Nov;57 Suppl 2:S262-4.

6. Kushi LH, Kwan ML, Lee MM, Ambrosone CB. Lifestyle factors and survival in women with breast cancer. J Nutr. 2007 Jan;137(1 Suppl):236S-242S

7. Patterson RE, Cadmus LA, Emond JA, Pierce JP. Physical activity, diet,adiposity and female breast cancer prognosis: a review of the epidemiologic literature. Maturitas. 2010;66(1):5-15

8. Sanderson S, Tatt ID, Higgins JP. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. Int J Epidemiol. 2007 Jun;36(3):666-76.

9. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188

10. N Orsini, R Bellocco and S Greenland, Generalized least squares for trend estimation of summarized dose-response data, Stata *J* 6 (2006), pp. 40–57

11. Chêne G, Thompson SG. Methods for summarizing the risk associations of quantitative variables in epidemiologic studies in a consistent form.Am J Epidemiol. 1996;144(6):610-21.

12. JP Higgins and SG Thompson, Quantifying heterogeneity in a meta-analysis, Stat Med 21 (2002), pp. 1539–1558.

13. A Tobias, Assessing the influence of a single study in meta-analysis, Stata Tech Bull 47 (1999), pp. 15–17.

14. Bekkering GE et al. How much of the data published in observational studies of the association between diet and colorectal or bladder cancer is usable for meta-analysis? Am J Epidemiol (2008);167(9):1017-26.

Annex 2 List of abbreviations

5-FU – fluorouracil
BMI - body mass index
CHO - carbohydrate
CI - confidence interval
cm – centimetres
CMF – cyclophosphamide, methotrexate, and fluorouracil
CMFVP - cyclophosphamide, methotrexate, fluorouracil, vincristine, prednisone
CUP - Continuous Update Project
d - day
DIS - distal colon cancer
E – energy
ER+ - estrogen receptor positive
ER- - estrogen receptor negative
F – female
FFQ – Food Frequency Questionnaire
g – grams
h - hour
HR - hazards ratio
HRT - hormone replacement therapy
I – incidence
IDR - incident density ratio
IU - International unit
ICL - Imperial College London
KBCR - Korean Breast Cancer Registry
Kcal – kilocalorie
Kg - kilogram
Kg/m^2 - kilogram/$metre^2$
L – liter
lb - pound
LCI - lower confidence interval
m – metre
MET - metabolic equivalent of task or metabolic equivalent
mcg - microgram
mg - milligram
ng – nanogram
OI - obesity index
OR - odds ratio
PA - physical activity
PR+ - progesterone receptor positive
PR- - progesterone receptor negative
QI – Quetelet Index
RCT - randomised controlled trial
RR - relative risk
SEER - Surveillance, Epidemiology, and End Results
SLR - systematic literature review
SNUHBCC - Seoul National University Hospital Breast Care Center

UCI - upper confidence interval
WC - waist circumference
WHR - waist-hip-ratio
vs. - versus
+ve – node positive
-ve – node negative