Review

Weight Gain After Breast Cancer Diagnosis and All-Cause Mortality: Systematic Review and Meta-Analysis

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Abstract

Background: Overweight and obesity are associated with breast cancer mortality. However, the relationship between postdiagnosis weight gain and mortality is unclear. We conducted a systematic review and meta-analysis of weight gain after breast cancer diagnosis and breast cancer-specific, all-cause mortality and recurrence outcomes.

Methods: Electronic databases identified articles up through December 2014, including: PubMed (1966-present), EMBASE (1974-present), CINAHL (1982-present), and Web of Science. Language and publication status were unrestricted. Cohort studies and clinical trials measuring weight change after diagnosis and all-cause/breast cancer-specific mortality or recurrence were considered. Participants were women age 18 years or older with stage I-IIIC breast cancer. Fixed effects analysis summarized the association between weight gain (≥5.0% body weight) and all-cause mortality; all tests were two-sided.

Results: Twelve studies (n = 23,832) were included. Weight gain (≥5.0%) compared with maintenance (<±5.0%) was associated with increased all-cause mortality (hazard ratio [HR] = 1.12, 95% confidence interval [CI] = 1.03 to 1.22, P = .01, I² = 55.0%). Higher risk of mortality was apparent for weight gain ≥10.0% (HR = 1.23, 95% CI = 1.09 to 1.39, P < .001); 5% to 10.0% weight gain was not associated with all-cause mortality (P = .40). The association was not statistically significant for those with a prediagnosis body mass index (BMI) of less than 25 kg/m² (HR = 1.14, 95% CI = 0.99 to 1.31, P = .07) or with a BMI of 25 kg/m² or higher (HR = 1.00, 95% CI = 0.86 to 1.16, P = .19). Weight gain of 10.0% or more was not associated with hazard of breast cancer-specific mortality (HR = 1.17, 95% CI = 1.00 to 1.38, P = .05).

Conclusions: Weight gain after diagnosis of breast cancer is associated with higher all-cause mortality rates compared with maintaining body weight. Adverse effects are greater for weight gains of 10.0% or higher.

Breast cancer is the most common cancer in women in the United States besides nonmelanoma skin cancer and accounts for the majority of cancer deaths after lung and bronchial cancer (1,2). With earlier detection, more targeted treatment, and an aging population, the number of women living with a diagnosis of breast cancer continues to increase (3). Being overweight or obese, characterized by having a body mass index (BMI) at or above 25 kg/m² or a waist-hip ratio of 0.85 cm or higher for women is associated with an increased risk for postmenopausal breast cancer incidence and recurrence, breast cancer-specific and all-cause mortality in prospective, observational studies (4–10); the relationship with mortality differs by race/ethnicity (11,12). Weight gain throughout adult life is also associated with higher risk for developing breast cancer,
particularly estrogen and progesterone receptor (ER/PR)–positive cancer (13–17).

Evidence including a systematic review and meta-analysis of 82 studies suggests that obesity is also associated with breast cancer incidence and mortality in premenopausal women (18,19), even after adjustment for methodological biases and stratification by histological subtype (5,20,21). In a recent analysis of data from 80,000 women with early-stage breast cancer participating in 70 trials with average follow-up of eight years, obesity was strongly associated with breast cancer mortality, but only among premenopausal women with ER-positive disease (22). Collectively, these findings suggest that breast cancer survivors of all ages who are obese might be at higher risk of mortality, compared with women in the normal weight range, and highlights the importance of future randomized, controlled investigations of the effects of weight loss intervention on survival outcomes in this population.

During and after treatment for breast cancer the majority of women experience weight gain (23–27). However, the relationship between postdiagnosis weight gain and breast cancer mortality is unclear. Large observational studies show conflicting findings as a result of methodological limitations and differences in timing of exposure and other prognostic characteristics at baseline (28–34). Variation in magnitude of weight gain may be attributed to differences in treatment (35), physical activity (36), age, smoking status (37), and length of follow-up, which reflects different points in the cancer trajectory. Generally, there is a pattern of progressive weight gain over time among breast cancer survivors (26,38), and the prevalence increases longitudinally (39). The Behavioral Risk Factor Surveillance System (BRFSS) highlighted a statistically significant quadratic trend in increasing obesity prevalence in breast cancer survivors over time (40). Level of weight gain is greater than that observed in age-matched healthy women without breast cancer in some (26) but not all populations (41).

The objective of this systematic review and meta-analysis was to determine whether weight gain (≥5.0% body weight) compared with maintenance (<±5.0%) measured at least one year post–primary breast cancer diagnosis is associated with increased risk of all-cause mortality in women age 18 years or older diagnosed with stage I-IIIC breast cancer. We further explored the association between weight gain after diagnosis and all-cause mortality, stratifying by level of weight gain and BMI at diagnosis.

Methods

Selection Criteria

All prospective and historical cohort studies and clinical trials measuring weight gain after breast cancer diagnosis and all-cause/breast cancer–specific mortality or breast cancer recurrence were considered for inclusion. Selection criteria were: female, age 18 years or older, with previous diagnosis of stage I-IIIC breast cancer (all histological subtypes) (42).

Primary Comparison

Weight maintenance was defined as fluctuations less than 5.0% above or below usual weight (<±5.0% change body weight) to account for baseline body size differences, usual weight variation, and measurement error and to provide a proportionate measure of weight change. A 5.0% weight change is considered clinically meaningful (43), and a cut point of 5.0% was consistent with previously reported data. Weight gain was calculated as the difference between postdiagnosis and usual body weight either: 1) recalled weight prior to diagnosis or 2) measured at diagnosis. A minimum timeframe of one year postdiagnosis for weight gain measurement was used to account for treatment-related weight fluctuation. The primary comparison was body weight gain (≥5.0%) vs weight maintenance (<±5.0% change).

Secondary Comparisons

Two secondary comparisons were conducted: 1) moderate weight gain (5%-10.0%) vs weight maintenance (<±5.0% change), and 2) high weight gain (>10.0%) vs weight maintenance (<±5.0% change). We were unable to conduct the following secondary comparisons because of insufficient data: progressive weight gain (increased weight ≥5.0% at each of at least 2 time points) vs weight maintenance (<±5.0% body weight change); body fat percentage gain (≥5.0%), vs maintenance (<±5.0% body fat percentage change).

Primary Outcome

The primary outcome was all-cause mortality, which is less prone to bias in classifying cause of death compared with disease-specific mortality (44). All-cause mortality was measured as crude mortality rate (total number of deaths/mid-interval population at follow-up), and all-cause mortality hazard defined as crude mortality rate at follow-up time conditional on survival to follow-up time.

Secondary Outcomes

Secondary outcomes were: 1) breast cancer–specific mortality rate (total number of deaths assigned to breast cancer/mid-interval population at follow-up) and breast cancer–specific hazard at follow-up; 2) breast cancer recurrence rate (total number of breast cancer recurrences/mid-interval population at least 1 year postdiagnosis) and breast cancer recurrence hazard.

Search Methods

Detailed MeSH terms used to develop the search strategy are presented in the Supplementary Materials (available online). Electronic databases were searched for identification of abstracts and articles meeting selection criteria, including PubMed (1966–present), EMBASE (1974 to present), CINAHL (1982 to present), and Web of Science. Language and publication status were not restricted. All original articles, previous reviews, and systematic reviews were evaluated for relevant references.

Data Collection and Analysis

A primary reviewer screened electronic databases for relevant titles in collaboration with a medical librarian. Abstracts were selected that met inclusion criteria and screened for selection of full text, original articles if relevant or where eligibility was unclear. All full-text articles that met selection criteria were included. Articles that were excluded were recorded in a table of characteristics of excluded studies, with justification. Full text articles were searched for relevant references to include as additional studies. Inclusion of potential studies was vetted by a second reviewer. Any disagreement was resolved by discussion among reviewers.
Study characteristics were tabulated using a data extraction form. Study protocol papers were obtained for clarification of exposure and outcome assessment in primary studies, as required. If a study reported multiple measures of body size, body weight change was prioritized. Outcome data were extracted from each included study for use in meta-analysis. If results of a study were reported in multiple publications, the most recent publication that included the relevant information was included. If a study reported on multiple outcomes (including multiple cancers), data were only included that met eligibility criteria. If outcomes were measured at multiple time points, the time point closest to average was used for assessment of the primary outcome.

Assessment of Risk of Bias

Methodological quality of each selected publication was evaluated to determine study validity. Studies were appraised for observing guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (45). Selection criteria and sampling fractions were used to assess sample representativeness. Bias was systematically evaluated and recorded in a risk of bias table based on the Cochrane Collaboration ‘Risk of bias’ tool (‘high risk of bias,’ ‘low risk of bias,’ or ‘unclear’) (46), and the Newcastle-Ottawa Scale (NOS) for assessing quality of nonrandomized studies in meta-analyses (47). Method of random assignment was not assessed because participants were not randomly assigned to weight change exposure groups. Criteria used to assess risk of bias are detailed in the Supplementary Materials (available online).

Measures of Exposure and Outcome

Studies were evaluated for clinical relevance including magnitude and precision of outcome estimates. Outcomes were assessed as dichotomous (died/alive; recurrence/no recurrence). Effect measures included hazard ratio (HR) or relative risk (RR) reported with 95% confidence intervals. Both median survival and survival curves were considered in assessment of survival.

Statistical Analysis

Summary hazard ratios (HRs) and 95% confidence intervals (CIs) were generated using fixed effects models with reference manager software (RevMan, version 5.2). Fixed effects meta-analysis was utilized because of the small number of studies included, making estimation of between-subject variance more likely to be imprecise (48); there was also some evidence that results for smaller studies were symmetrically different from larger studies (Supplementary Figure 1, available online), which can lead to exacerbation of biased estimates (46). We explored sources of heterogeneity using stratification and repeated the analysis using random effects as an additional sensitivity analysis (Table 2). All tests were two-sided, and a P value of less than .05 was considered statistically significant. Both methodological heterogeneity (similarity of study designs, participants, exposure, and outcome), and statistical heterogeneity (variability of reported outcomes) were assessed. The proportion of variability explained by heterogeneity rather than chance was quantified using Chi2 and I2 statistics. Meta-analysis was conducted for methodologically homogenous studies where participants, exposures, and outcomes were judged to be sufficiently similar. Heterogeneity was classified as low (0%-25.0%), medium (26%-75.0%), or high (>75.0%) (49). A qualitative analysis was conducted if high heterogeneity was present. Publication bias was not evaluated because of a total of fewer than 10 included studies for each outcome (recurrence, breast cancer-specific, and all-cause mortality). For descriptive purposes, a funnel plot is presented for studies contributing to the main comparison of interest in Supplementary Figure 1 (available online).

Subgroup Analysis

Subgroup analyses were defined a priori and tested effect modification with biological plausibility. We explored the effects of weight gain on all-cause mortality by level of weight gain (moderate or 5%-10.0%; high or >10.0%) and BMI at diagnosis (<25; ≥25 kg/m²). We were unable to conduct subgroup analyses by cancer treatment type, menopausal status, hormone receptor status, or follow-up duration because of insufficient data. As the comparison of interest was the effect of positive energy balance on cancer and mortality outcomes, we did not assess the effects of weight loss.

Sensitivity Analysis

Sensitivity analysis was performed to explore the variation between studies by including or excluding studies based on study methodological quality (high/low risk of bias). Summary statistics were presented for homogenous results. Data were presented by subgroup or individual trials if there was evidence for heterogeneity, with discussion of possible reasons for heterogeneity. We also explored heterogeneity by year of study entry to account for changes in breast cancer treatments over time, excluding studies 1) prior to 2000 and 2) after 2000.

Results

Included studies were identified up to December 2014 (Table 1). Twelve studies reported in nine publications (23 832 participants) met inclusion criteria for analysis of mortality or breast cancer recurrence outcomes. MeSH search terms identified 729 studies from four search databases. Following removal of duplicates, 424 studies were reviewed at title level, 261 at abstract level, and 70 at full text level. Two studies were identified after the initial search (50,51). Reasons for exclusion were: participants were not female, were younger than age 18 years, or had not been diagnosed with stage I-IIIC breast cancer; there was no measure of weight change at least six months postchemotherapy or one year postdiagnosis; there was no measure of body weight or BMI; the outcome was not all-cause or breast cancer mortality or breast cancer recurrence; the study was not a clinical or cohort study; and the study was not conducted in humans. Search results are summarized in Figure 1. All included studies were peer-reviewed and published in academic journals (28,31,33,50–55).

Study Design

Seven studies were prospective, including observational cohort designs (28,31,33,52,55); one study included data from two clinical trials (53). Two reports by Caan et al. (28,33) presented different outcomes from the same studies. The 2012 report presented mortality data and included a pooled analysis from four cohorts, whereas the 2006 report presented breast cancer recurrence data from two out of these four cohorts. For the remainder of this
Table 1. Characteristics of studies*  

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<th>First author, y</th>
<th>Study design</th>
<th>Participants</th>
<th>Exposure/covariates</th>
<th>Outcome</th>
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<td>Caan, 2006</td>
<td>Pooled data from a prospective cohort study (LACE study) and control group members of the WHEL study.</td>
<td>N = 3215. Women age 18–70 years diagnosed with stage I-IIIa breast cancer. Study inclusion criteria were identical between studies. Women were free of breast cancer on enrollment with no other cancers diagnosed within 5 years.</td>
<td>Weight maintenance: &lt;+5.0% body weight change. Weight gain: 5%-10.0%, &gt;10.0% body weight gain. Prediagnosis weight: 1 year prediagnosis; ascertained by self-report. Postdiagnosis weight: median time to follow-up weight measure 2 years; measured by trained assessors (WHEL) using balance beam and by self-report (LACE). Weight change: prediagnosis weight subtracted from postdiagnosis weight. Follow-up time for breast cancer recurrence outcomes was 3 years (LACE) to 5 years (WHEL) or 5–7 years from baseline. Covariates: stage, age, prediagnosis BMI, Tamoxifen use, treatment, number of positive nodes, ER/PR status.</td>
<td>Breast cancer recurrence (local/regional, distant, contralateral primary). Outcome measures obtained by telephone interview plus medical record review. Where clarity was required, a study pathologist confirmed breast cancer recurrence.</td>
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<td>Camoriano, 1990</td>
<td>Two concurrent, prospective clinical trials of adjuvant breast cancer therapy. Enrolment dates not reported.</td>
<td>N = 646. Pre- and postmenopausal women undergoing adjuvant therapy for node-positive breast cancer. Excluded participants that died within 60 weeks of randomization.</td>
<td>Comparison: weight gain &lt; median. Weight gain: &gt; median. Baseline weight: measured objectively at randomization (within 8 weeks of treatment). Post-treatment weight: measured objectively every 3 months for 2 years, every 6 months for years 2–4, and then annually. Weight change: calculated from 60 weeks postrandomization (post-treatment and resumption of normal weight; period considered at maximal weight gain). Follow-up time for breast cancer outcomes 6.6 years. Covariates: age, ER status, initial weight, Quetelet index.</td>
<td>Breast cancer progression and overall survival.</td>
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<tr>
<td>Goodwin, 1988</td>
<td>Retrospective cohort study. Enrollment dates: 1960–1984.</td>
<td>Three groups of women diagnosed with localized breast cancer: 1) (N = 637) Clinical or pathological node-negative breast cancer not receiving systemic adjuvant therapy (n = 307). 2) (N = 139) Clinical or pathological node-positive breast cancer not receiving systemic adjuvant therapy. 3) (N = 191) Pathological node-positive breast cancer receiving adjuvant therapy or ovarian ablation. Patients excluded where time between diagnosis and referral was &gt;3 months.</td>
<td>Baseline body weight: extracted from medical record. Weight measured within 1–2 months of breast cancer diagnosis. Follow-up body weight: measures at 6 and 12 months after initial diagnosis by medical record review. No explicit definition of weight gain vs weight maintenance. Weight change: weight gainers gained between 1.21–5.55 Kg over 1 year postinitial measurement. Covariates: age, menopausal status, axillary nodal status, adjuvant therapy use, height, initial weight.</td>
<td>Overall survival and relapse-free survival. Duration of survival determined from date of first hospital visit to last follow-up, death, or recurrence.</td>
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* ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; LACE = Life after Cancer Epidemiology study; NDI = National Death Index; PR = progesterone receptor; SBCSS = Shanghai Breast Cancer Survival Study; WHEL = Women’s Healthy Eating and Living Study.

report, we refer to the number of independent studies as opposed to the number of publications that included meta-analyzed or pooled data. Three retrospective cohort studies were reviewed (50,51,54), however the results of two Cox proportional hazards analyses could not be included in meta-analysis because they did not report effect estimates for percent weight gain and all-cause mortality or breast cancer recurrence outcome (51,54).

Participants

All included studies enrolled women age 18 years or older diagnosed with stage I-IIIC breast cancer. In five studies, women were enrolled who were undergoing adjuvant chemotherapy for breast cancer (51,53-55). Women in all studies were both pre- and postmenopausal, with prediagnosis BMI varying from underweight to obese. Measurement of prediagnosis or adiagnosis body weight was at or within two months of breast cancer diagnosis. Three studies conducted stratified analysis by menopausal status (50,52,55) and six by baseline BMI (28,50,52), although one study was not included in subgroup analyses given that results were reported as ‘not significant’ (55).

Weight Gain Exposure Measurement

Exposure was defined as weight maintenance (≤±5.0% body weight) and weight gain (≥5.0% body weight) in six studies (28,33,50,52). Five studies further categorized weight gain into 5% to 10.0% and above 10.0% weight gain (28,33,52). The definition of weight gain in one study was unclear (55); weight gain was analyzed as a continuous variable in one study that was not included in the meta-analysis (54). One study reported tertiles of weight gain and a summary measure of at least 5 kg weight gain. For a mean BMI of 25 kg/m² reported in the study, 3 to 4 kg weight gain corresponds to approximately 5.0% body weight (31) based on average height of postmenopausal women (56). Weight maintenance was defined as ≤2 kg. We included tertiles of greater than 2 kg gain in calculation of weight gain (2-6 kg as moderate-level weight gain, and >6 kg as high-level weight gain). One study presenting data from two clinical trials defined weight gain as above vs below median weight change, which corresponded to an average 5.0% body weight change (53). Percentage BMI change was the unit of measurement for one study; although we were unable to convert these measures to percent weight change (51). The timing of exposure assessment varied between studies but all had initial weight measurements representing prediagnosis or usual weight (within a short period of diagnosis), with follow-up body weight measured at least one year postdiagnosis or six months postchemotherapy. The median follow-up time for measurement of weight gain exposure was 1.5 years. Where reported, the underlying time metric for Cox proportional hazards regression was time since diagnosis (28). Studies with multiple body weight change measures accounted for multiple measures using proportional hazards regression with time-varying covariates (52).

Exposure ascertainment was by self-report questionnaire in five studies (28,52), a combination of structured interview and
self-report questionnaire (31), objective measures and medical record review (51,55), retrospective self-report and objective measures (33), objective measures only (51,53), and medical record review only (50,54).

Outcomes

All-cause mortality was the primary outcome in nine studies (28,31,52–54). Nine studies included breast cancer–specific mortality as an outcome (28,31,52–54). Breast cancer recurrence was the primary outcome in five studies (33,50,51,55). Record linkage was used to ascertain outcomes in six studies (28,31,52), while medical record review was used for seven studies (28,33,50,54,55). Two studies validated self-report of breast cancer recurrence with confirmation by a study pathologist (33). Method of outcome assessment was unclear for three studies (51,53). Timing of outcome assessment from the second weight measurement varied from one to two (50), two (55), three to five (33), six (31,53), and eight years (28,52) and was not specified in one study (54).

Excluded Studies

Thirteen studies appeared to meet eligibility criteria but were excluded on detailed review. Two studies were excluded (29,34) as they described results from the same trials that were included in a subsequent pooled cohort study (28). A further four studies measured weight gain during chemotherapy (30,57–59). Three studies measured weight gain across the lifespan from the ages of 18 to 20 years until follow-up body weight measurement (60–62). One study did not measure all-cause mortality or BC recurrence (n=75). Outcome not all-cause/BC mortality or BC recurrence (n=22) - Not a clinical/cohort study (n=6) - Not human (n=2)

Figure 1. PRISMA flow diagram. BC = breast cancer; BMI = body mass index.
recurrence and overall survival outcomes. However, absolute weight and BMI changes were used as the exposure of interest, including both weight loss and weight gain. By combining weight loss/gain, overall relative weight change at five years was 3.5% gain, which was not associated with overall survival (P = .128) (64).

**Primary Outcome Measure**

**All-Cause Mortality**

Eight studies were included in a meta-analysis of the primary outcome, all-cause mortality (28,31,52,53) (Figure 2). Four studies reported on breast cancer recurrence and were not included (33,51,55). One study presented outcomes as P values only (P = 2 for a positive association with mortality) without any reporting of the number of events in each category, therefore we were unable to include the results (54). Of the included studies, all but two (53) presented effect estimates for categories of weight gain (5%-10.0%; ≥10.0%) or stratified by study in pooled analyses (28). Our first summary measure summarizes results from each of these analyses. The hazard of mortality for gaining 5.0% or higher body weight was 1.12 times the hazard of mortality for maintaining body weight (HR = 1.12, 95% CI = 1.03 to 1.22, P = .01). There was a moderate level of study heterogeneity (I^2 = 55.0%).

**Secondary Comparisons/Subgroup Analyses**

**All-Cause Mortality Stratified by Level of Weight Gain**

Six studies summarized the association between weight gain and all-cause mortality by level of weight gain (moderate [5%-10.0%], high [≥10.0%]) (28,31,52) (Figure 3). Compared with those who maintained weight, moderate-level weight gain was not associated with hazard of mortality (HR = 0.97, 95% CI = 0.86 to 1.11, P = .70). However, association with mortality was apparent for gaining 10.0% or higher body weight compared with maintenance (HR = 1.23, 95% CI = 1.09 to 1.39, P < .001). Study heterogeneity was low for the comparison of 5% to 10.0% weight gain (0.0%), and moderate for the analysis of 10.0% or higher weight gain and all-cause mortality (62.0%).

**All-Cause Mortality Stratified by Baseline Body Mass Index (BMI)**

Five studies were included in a subgroup analysis of weight gain of 5.0% or higher and all-cause mortality, stratified by baseline BMI (28,52) (Figure 4). For participants with baseline BMIs of less than 25 kg/m², the hazard of mortality for gaining weight was 1.14 times the hazard of maintaining weight (95% CI = 0.99 to 1.31, P = .07). For participants with BMIs of 25 kg/m² or higher, hazard of mortality for weight gainers was not different to maintainers (HR = 1.00, 95% CI = 0.86 to 1.16, P = .96). Heterogeneity was low for both the analysis of weight gain and all-cause mortality by overweight/obese baseline BMI (23.0%) compared with under/normal weight BMI (0.0%).

**Secondary Outcome Measures**

**Breast Cancer–Specific Mortality**

Six studies were included in the meta-analysis of body weight gain and breast cancer–specific mortality, stratified by level of weight gain (28,31,52) (Figure 5). Compared with weight maintainers, moderate weight gain (5%-10.0%) was not associated with breast cancer–specific mortality (HR = 0.98, 95% CI = 0.83 to 1.15, P = .77). Study heterogeneity was low (I^2 = 0.0%). However, for high-level weight gain of more than 10.0% there was suggestion of an association with breast cancer–specific mortality compared with weight maintenance, with moderate study heterogeneity (HR = 1.17, 95% CI = 1.00 to 1.38, P = .05, I^2 = 46.0%). Overall, the hazard of breast cancer mortality for weight gainers did not differ to weight maintainers (HR = 1.07, 95% CI = 0.96 to 1.20, P = .23).

**Breast Cancer Recurrence**

Different effect estimates were presented in the evaluation of weight gain and breast cancer recurrence (risk ratio or hazard ratio). Three studies, including one pooled analysis of two studies, that measured hazard of recurrence comparing less than ±5.0% and 5.0% or higher weight gain were meta-analyzed (33,50) (Figure 6). The summary hazard ratio showed no association between weight gain and breast cancer recurrence (HR = 0.93, 95% CI = 0.77 to 1.13, P = .46). However, there was moderate evidence for study heterogeneity (I^2 = 52.0%). Individual study data showed that weight gain 5.0% or more was not associated with breast cancer recurrence in the three studies reporting hazard of recurrence (HR = 0.80, 95% CI = 0.60 to 1.07, P = .13; HR = 1.00, 95% CI = 0.77 to 1.30, P = 1.00 [33]; and HR = 2.40, 95% CI = 0.80 to 7.20, P = .12 [50]) and risk ratio (RR = 1.36, 95% CI = 0.25 to 7.28 corresponding to HR = 2.4, 95% CI = 0.8 to 7.5 [55]). Weight change defined as percent

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Figure 2. Forrest plot: Fixed effects meta-analysis of the association between weight gain ≥ 5.0% and all-cause mortality. The black squares and horizontal lines represent study-specific hazard ratios (HR) and their 95% confidence intervals (CI). The P-values were calculated using Z score for overall effect and Chi^2 test for heterogeneity. All tests were two-sided (P < .05). KG = kilograms; LACED = Life After Cancer Epidemiology; NHS = Nurse’s Health Study; SBCSS = Shanghai Breast Cancer Survival Study; WG = Weight Gain; WHEL = Women’s Healthy Eating and Living.
BMI change 12 months postsurgery was reported in one study that was not included in the meta-analysis. Those that gained more than 5.71% BMI after treatment had suggestion of higher risk of mortality compared with those that gained less than 5.71% BMI (HR = 1.02, 95% CI = 1.00 to 1.03, \( P = 0.05 \)) (51).

**Sensitivity Analysis**

We conducted sensitivity analysis for the primary outcome, all-cause mortality, by excluding studies with high/unclear risk of bias (Supplementary Table 1, available online). After removing studies with high/unclear risk of selection bias (28,31,53), the hazard of mortality for weight gain higher than 5.0% compared with weight maintenance as well as study heterogeneity were increased (HR = 1.81, 95% CI = 1.10 to 2.98, \( P = 69.0\% \) vs HR = 1.12, 95% CI = 1.03 to 1.22, \( I^2 = 55.0\% \)). Results were not materially modified after removing one study with high/unclear risk for performance, detection, attrition and reporting bias (HR = 1.10, 95% CI = 1.01 to 1.21, \( I^2 = 54.0\% \)) (53). All other studies had low risk of these biases. The study removed was also the only study conducted prior to 2000, and thus this analysis reflects the distinct period when there was a shift in breast cancer chemotherapy regimens to include doxorubicin/cyclophosphamide, which corresponded to improved treatment efficacy for early-stage breast cancer (65). Table 2 presents the results of the sensitivity analysis comparing fixed and random effects meta-analysis.
Study Heterogeneity

Moderate heterogeneity (Chi² P < .1) was evident for the primary comparison of any weight gain of 5.0% or higher and all-cause mortality (Chi² = 19.9, P = .02, I² = 55.0%) and for studies of high-level weight gain of more than 10.0% and all-cause mortality (Chi² = 10.5, P = .03, I² = 62.0%).

Risk of Bias

Overall, seven studies met criteria for low risk of bias for five out of six categories (28, 31, 33, 50, 52). Justifications for risk of bias judgments are presented in Supplementary Table 2 (available online). Six studies were classified as low risk for selection bias (33, 50-52), one study was high risk (31), and level of selection bias was unclear for seven studies (28, 53, 55).

Seven studies were classified as low risk for performance bias (28, 31, 33, 50, 52) and six at low risk for detection bias (28, 31, 52). One study demonstrated high risk for performance bias (55), while four were high risk for detection bias (51, 53, 55).

Discussion

The results of the current systematic review and meta-analysis highlight that weight gain after a diagnosis of breast cancer and following completion of treatment is an important prognostic factor, particularly for those who gain more than 10.0% body weight, on average 1.5 years postdiagnosis. In this meta-analysis of twelve studies with a total of 23,832 women (2769 overall deaths excluding those used to calculate HR in [53]) age 18 years and older diagnosed with stage I-IIIC breast cancer, weight gain of 5.0% or higher was associated with increased hazard of all-cause mortality compared with weight maintenance after breast cancer diagnosis. Weight gain of more than 10.0% after breast cancer diagnosis was associated with increased hazard...
of all-cause mortality, whereas weight gain of between 5% and 10.0% was not associated with all-cause mortality. Stratified by prediagnosis BMI, there was a suggestion of an association between weight gain (>5%) and mortality for those with an initial BMI measurement of less than 25 kg/m² but no association for those with a baseline BMI of 25 kg/m² or higher. Analysis of secondary outcomes showed that weight gain of 5% to 10.0% was not associated with hazard of breast cancer–specific mortality, whereas there was a suggestive association for weight gain of more than 10.0%. Overall, heterogeneity was low to moderate. Sensitivity analyses removing studies with high/unclear risk of selection bias increased hazard of all-cause mortality with weight gain of 5% and more than 5% as well as study heterogeneity; removing studies with high/unclear risk of other potential biases slightly attenuated the main effect of weight gain on all-cause mortality, but the association remained statistically significant and level of study heterogeneity was not substantially altered. To date, the literature has been mixed with regards to whether weight gain after diagnosis of breast cancer is associated with increased risk of mortality (24). If weight gain after breast cancer diagnosis confers a survival disadvantage, there are major implications for clinical recommendations for women during and after treatment, including targeted recommendations for weight management and intervention to prevent weight gain as part of the survivorship care plan (SCP).

Findings supporting the current review were presented at the 2014 American Association for Cancer Research Annual Meeting. Weight gain of more than 5.0% at one year post breast cancer surgery was statistically significantly associated with earlier breast cancer events in a population-based cohort of 849 breast cancer patients (66). The fact that mortality risk with weight gain depends on the magnitude of weight change was also observed in a large prospective cohort study of 14,823 healthy adults, where large weight gain was associated with increased mortality for those with a class II BMI (>35 kg/m²), whereas smaller gains were not associated with increased mortality at any baseline BMI (67).

In a population of breast cancer survivors, greater weight gain has previously been associated with younger age, premenopausal status, ER/PR receptor status, more advanced disease stage, prediagnosis weight loss, lower BMI at diagnosis, and cigarette smoking (28,68,69). The majority of studies included in this review controlled for these covariates in multivariable analyses. The lack of control for important confounders (eg, type of cancer treatment) in some of the included studies may have confounded results either towards or away from the null. Other treatment-related and genetic risk factors that were not controlled for include use of systemic and multi-agent treatments, longer treatment duration (23,70–72), and fat mass and obesity-associated protein (FTO) and adiponectin pathway genes (ADIPQ and ADIPOR1) that may increase risk for weight gain postdiagnosis (69). Other drivers of energy imbalance include lifestyle change in response to treatment-related side effects (24), such as aromatase inhibitor–induced arthralgia and concomitant reduction in physical activity (73,74), and changes in dietary energy intake (75–77).

Obesity-related mechanisms associated with mortality include prolonged hyperinsulinemia and reduced production of insulin-like growth factor binding proteins (IGFBP-3), resulting in elevated circulating insulin-like growth factors (IGF-1). Additionally, obesity is associated with reduced sex hormone binding globulin (SHBG) and elevated circulating sex hormones, including estrogen. Weight gain alters energy-sensing, metabolically active hormones such as leptin and adiponectin and elevates inflammatory cytokine production. Collectively, these mechanisms create an environment that promotes cell growth and angiogenesis and inhibits apoptosis, triggering tumor initiation and promoting cancer progression (78–80). Recent clinical trials have also highlighted that excess adiposity reduces the effectiveness of aromatase inhibitor treatment for hormone receptor–positive breast cancer (10).

We found that weight gainers with a prediagnosis BMI of less than 25 kg/m² had a suggestion of a higher risk for all-cause mortality compared with weight maintainers, while no association was evident for those with a prediagnosis BMI above 25 kg/m². Of the analyses that stratified by baseline BMI, those in the normal weight range gained more weight than those with higher baseline BMI in some (28) but not all studies (31,52). The studies included in this subgroup analysis stratified by collapsing overweight and normal weight BMI. For consistency, this category was included in the current analysis. It is possible that participants that were underweight at diagnosis may have differed to those with a normal weight on variables, such as other pre-existing conditions that were not controlled for in the original multivariable analyses, influencing the magnitude and statistical significance of the observed associations.
Additionally, women that were included were either pre- or postmenopausal. Obesity in premenopausal women has been associated with reduced breast cancer incidence in contrast to higher risk for postmenopausal women; emerging hypotheses suggest negative feedback on the hypothalamic pituitary-controlled release of gonadotropins with subsequent reduction in the cell proliferation promoter progesterone (81). Large cohort studies, including the Million Women Study, have demonstrated that increasing BMI was associated with breast cancer mortality in postmenopausal but not premenopausal women, where there was a suggestion of a protective effect for being overweight (82). In the current analysis, the proportion of premenopausal women that were in each BMI subgroup is unclear and not all studies controlled for menopausal status in statistical analyses. Additionally, we were unable to further stratify by finer levels of prediagnosis adiposity (ie, prediagnosis BMI being overweight vs obese or severely obese), which may have altered the findings.

Most studies defined weight gain according to percentage weight change. However, no studies assessed the effects of changes in body composition, including body fat percentage or waist-to-hip ratio (WHR). The literature is limited with respect to the use of validated measures of body composition to assess adiposity in studies of breast cancer prognosis (83). Many studies in the current review enrolled large numbers of participants where gold standard measures of body composition such as Dual X-ray Absorptiometry (DXA) may not be feasible. It is possible that subjects categorized as weight maintainers experienced muscle loss and/or gains in body fat or lean tissue that may play an important prognostic role in this population and may have attenuated weight gain–mortality associations. The process of aging is associated with increases in trunk fat mass (84), with loss of lean mass evident even with weight stability (85). Additionally, chemotherapy is associated with sarcopenic obesity (lean mass lower than expected for a given amount of fat mass (86)) and menopause-induced changes in body composition favoring increased body fat percentage and decreased lean muscle mass (75,87), promoting weight gain. The Health, Eating, Activity, and Lifestyle (HEAL) study showed that waist circumference measured 30 months postdiagnosis was statistically significantly associated with all-cause mortality but not breast cancer–specific mortality; WHR was statistically significantly associated with both all-cause and breast cancer mortality in 621 women diagnosed with local or regional disease. Adjustment for homeostatic model assessment (HOMA) score and C-reactive protein attenuated results, suggesting mediation by these factors (88).

We found a suggestion of an association between high-level weight gain (>10.0%) and breast cancer–specific mortality (P = .05). Measurement of cancer-specific mortality is prone to outcome misclassification that could bias results if levels of misclassification differ between exposure groups (89). For weight gain, misclassification would likely be nondifferential, thus attenuating our results. Our findings suggest that weight gain after diagnosis plays a role in overall (both breast cancer-specific and non-breast cancer), mortality. A recent analysis of 63,566 older women from the Surveillance, Epidemiology, and End Results Medicare (SEER-Medicare) database found that cardiovascular disease was the leading cause of mortality in women diagnosed with breast cancer, with breast cancer–specific mortality the second leading cause (90), although the proportion of deaths attributable to breast cancer is substantially higher for women younger than age 45 years (91). The contribution of weight gain to cardiovascular risk in breast cancer survivors is therefore an important area for future research.

A number of factors may have contributed to the moderate study heterogeneity observed for the primary comparison. All studies followed up to at least nine years, but the range of follow-up differed, including between 0.2 and 9.4 years (52), over 10 years (28), and between three and nine years (31). Studies controlled for different covariates, and levels of covariates (eg, any as opposed to type of chemotherapy treatment, menopausal status, prediagnosis BMI) that may have impacted the results. One study categorized weight gain by kilograms of gain (31). We estimated percentage weight gain based on population-based estimates of average height for postmenopausal women. It is possible that these categories may have been misclassified, depending on the height distribution of the study population. The Shanghai Breast Cancer Survival Study (SBCSS) included only women from China. Asian populations have different body composition profiles compared with Caucasian populations, and it has been reported that breast cancer survival rates are better compared with other populations (92). The SBCSS contributed substantially to the overall power of these analyses (N = 4441), although effect estimates were similar compared with the pooled US populations reported in the same publication (28). All studies measured weight exposure by self-report, and ascertained outcomes by record linkage.

To date, a limited number of studies have explored weight change after breast cancer diagnosis and breast cancer outcomes, whereas obesity and breast cancer survival has been more extensively investigated (8). The current review searched four up-to-date databases for relevant studies. Reference checks were conducted for all included and excluded studies to ensure completeness. It is possible that relevant publications were missed, although our search strategy yielded studies that were cited in the most recent publications on this topic. Although a limited quantity of studies comprised this review, included studies summarized results from multiple clinical trials and prospective cohort studies. In total, data were presented for twelve studies (reported within nine manuscripts) measuring weight gain and mortality or recurrence outcomes in breast cancer survivors. In particular, the After Breast Cancer Pooling Project (ABCPP), which was judged to have a low risk of bias, contributed substantially to the power of the current meta-analysis, providing data from four large prospective cohorts.

We were unable to stratify by cancer treatment type, menopausal status, hormone receptor type, or progressive weight gain over time because of limited data availability, although the majority of studies controlled for age at initial weight measurement, which is correlated with menopausal status. It is possible that these factors may modify the relationship between weight gain and breast cancer outcomes (29,31,34,35). The current review did not include studies that measured weight gain during chemotherapy and less than six months postdiagnosis. Recently, 5.0% or higher weight gain during chemotherapy for breast cancer was found to be associated with statistically significantly worse survival and increased recurrence with a follow-up of more than 20 years (30). Similar results were observed for weight increases above 10 kg during chemotherapy (57). Additionally, the association between weight gain across the lifespan prior to diagnosis and breast cancer recurrence and survival has been explored in a number of studies, with mixed results (52,60–62).

Overall, the quality of the evidence for the current review was judged to be high. The majority of studies met criteria for low risk of bias and high study heterogeneity was not observed, supporting the validity of our findings. A strength of the systematic review was the measurement of all-cause mortality.
outcomes, where outcome ascertainment by record linkage is less subject to biased estimates (93).

However, there were several limitations in the available data. Older studies tended to be of poorer methodological quality, although removal during sensitivity analyses did not substantially alter findings. Studies that measured breast cancer recurrence outcomes presented different effect estimates. Additionally, one study reported only P values. The differential effect of study cohort characteristics on the association between weight gain and mortality was highlighted in the ABCPP pooled analysis, where participants from China differed to those from the United States on a number of covariates and a variable magnitude of effect for the same level of weight gain was observed (28).

Differences in prognostic and patient characteristics may have contributed to the moderate study heterogeneity given that control for confounders and prognostic variables differed between studies and populations of mixed race/ethnicity were included in the meta-analysis. We were also unable to assess whether the associations between weight gain and mortality were comparable with age-matched women without breast cancer, as the included studies did not report results for control groups of healthy women. The majority of studies measured weight gain at a single time point as opposed to longitudinal analysis of weight change over time, which would have strengthened criteria for causation. We were unable to explore publication bias because of the limited number of studies included in the review. Publication bias may contribute to overestimation of effect sizes with positive trials favored for publication. Finally, it is possible that the results for the primary and subgroup analyses may be because of chance. Controlling for multiple comparisons for the primary outcome would result in a Bonferroni-corrected alpha of 0.01, making the comparison of weight gain of greater than 10.0% and all-cause mortality statistically significant (P < .001).

In summary, weight gain following breast cancer diagnosis is associated with mortality. Patients that gain 10.0% or more body weight after diagnosis may be at higher risk for mortality compared with those that gain only moderate amounts of weight (<10.0%). These findings have implications for clinical practice, where traditionally weight management has focused on targeting patients that are overweight or obese. Prevention of weight gain during and after treatment for breast cancer has the potential to have an impact on mortality rates. This review could be strengthened by inclusion of additional large studies of high methodological quality that measure the effect of weight gain on breast cancer recurrence. The current review supports future interventions of prevention of weight gain after a diagnosis of breast cancer.

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Contributions of authors: MCP conducted the following: drafted the protocol, study selection, extracted data from studies, entered data into RevMan, carried out the analysis, interpreted the analysis, drafted the final review, updated the review. MLI conducted the following: study selection, study review, reviewed the paper. MBB conducted the following: study review, reviewed the paper. TBS, JAL, MH conducted the following: reviewed the paper.

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References

Tom SE, Cooper R, Patel KV, et al. Menopausal characteristics and physical functioning in older adulthood in the National Health and Nutrition Examination Survey III.

Levine E, Raczynski, JM, Carpenter, JT. Weight Gain With Breast Cancer Adjuvant Treatment.


