Research Article

Cancer Epidemiology, Biomarkers & Prevention

Weight Change and Survival after Breast Cancer in the After Breast Cancer Pooling Project

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Abstract

Background: Weight change after a breast cancer diagnosis has been linked to lower survival. To further understand effects of postdiagnostic weight variation on survival, we examined the relationship by comorbid status and initial body mass index (BMI).

Methods: The current analysis included 12,915 patients with breast cancer diagnosed between 1990 and 2006 with stage I–III tumors from four prospective cohorts in the United States and China. HRs and 95% confidence intervals (CI) representing the associations of five weight change categories [within <5% (reference); 5%–<10% and ≥10% loss and gain] with mortality were estimated using Cox proportional hazards models.

Results: Mean weight change was 1.6 kg. About 14.7% women lost and 34.7% gained weight. Weight stability in the early years postdiagnosis was associated with the lowest overall mortality risk. Weight loss ≥10% was related to a 40% increased risk of death (HR, 1.41; 95% CI, 1.14–1.75) in the United States and over three times the risk of death (HR, 3.25; 95% CI: 2.24, 4.73) in Shanghai. This association varied by prediagnosis BMI, and in the United States, lower survival was seen for women who lost weight and had comorbid conditions. Weight gain ≥10% was associated with a nonsignificant increased risk of death.

Conclusions: Prevention of excessive weight gain is a valid public health goal for breast cancer survivors. Although intentionality of weight loss could not be determined, women with comorbid conditions may be particularly at risk of weight loss and mortality.

Impact: Weight control strategies for breast cancer survivors should be personalized to the individual's medical history. *Cancer Epidemiol Biomarkers Prev; 21(8); 1260–71. ©2012 AACR.*

Introduction

Current data indicate that a body mass index (BMI) of 30 kg/m^2 or more at the time of breast cancer diagnosis is linked to poorer prognosis (1–7). However, effects of weight change on survival after a breast cancer diagnosis are less consistent (1, 8–12) with some studies suggesting a U-shaped relationship with increasing risk for both weight gain and loss. Furthermore, among those studies that have found adverse relationships between weight gain and survival (1, 8, 11), it is unclear what degree of weight gain poses an increased risk. In addition, none of the studies were able to distinguish whether the weight loss associated with worse survival was intentional or unintentional and whether it was related to more advanced disease. Women most likely to lose weight after a breast cancer diagnosis may be those who were already at higher risk of poor outcomes: those who are obese (1, 10, 13) and/or have serious comorbid conditions (1, 14).

Using the resources of the After Breast Cancer Pooling Project (ABCCP) that includes follow-up of more than 18,000 patients with breast cancer, we conducted a comprehensive evaluation of the association of weight changes with mortality. The purpose of our study was to examine the effects of postdiagnostic weight change on survival by comorbid status and initial weight status.

Materials and Methods

The After Breast Cancer Pooling Project

The ABCPP is an international collaboration of prospective studies of breast cancer survivors established to examine the role of physical activity, adiposity, dietary factors, supplement use, and quality of life in breast cancer prognosis (15). Briefly, the ABCPP includes data on 18,333 breast cancer survivors from 4 population-based prospective cohort studies recruited from multiple U.S. sites and

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Shanghai, China. Three of the cohorts specifically recruited patients with breast cancer: the Shanghai Breast Cancer Survival Study (SBCSS; ref. 16), the Life after Cancer Epidemiology (LACE) Study (17), and the Women's Healthy Eating and Living (WHEL) Study (18). The fourth cohort included patients with breast cancer diagnosed in the Nurses' Health Study (NHS), a large prospective cohort study of female nurses (19).

ABCPP participants were diagnosed with invasive breast cancer [American Joint Committee on Cancer (AJCC) version 6 stages I–IV] between ages 20 and 83 years. Each cohort collected data on clinical factors (tumor characteristics, treatment status), reproductive factors, family history of breast cancer, quality of life, and medical history including comorbidities, anthropometry, smoking history, alcohol intake, supplement use, physical activity, and diet. As part of the ABCPP, these data have been harmonized into a common data set. Investigators of each individual cohort received Institutional Review Board approval from their respective institution(s) to participate in this collaboration.

Ascertainment of weight change and covariates

Weight change. Prediagnosis weight was collected from self-report from all studies and was defined as weight around 1 year before diagnosis. Postdiagnosis weight was assessed from self-report (SBCSS, LACE, NHS) and measurement (WHEL) between 18 and 48 months (mean, 2.1 years) after diagnosis depending on the study. The rationale for this postdiagnosis assessment window was to allow sufficient time after completion of treatment for women to return to their usual weight Change in weight from pre- to postdiagnosis was calculated by subtracting the weight measure prediagnosis from the weight measure postdiagnosis; a positive and negative value were indicative of weight gain and loss, respectively.

Sociodemographic and lifestyle factors. Data assessed at baseline/first postdiagnosis survey included race/ethnicity (non-Hispanic white, non-Hispanic black, Asian, Hispanic, other), education (<college graduate vs. college graduate or higher), menopausal status at diagnosis (premenopausal, postmenopausal, unknown), and smoking history (never vs. ever). Pre-diagnosis BMI was categorized as normal weight (<20.0 kg/m^2), normal weight (>20.0–25.0 kg/m^2), or overweight (>25 kg/m^2). Exercise participation in metabolic equivalents (MET-h/wk) was determined from semiquantitative questionnaires.

Clinical characteristics. Data included age at diagnosis (years), AJCC stage (I, II, III, IV), joint estrogen receptor (ER)/progesterone receptor (PR) status (ER+/PR+, ER+/PR–, ER–/PR+, ER–/PR–), surgery (none, lumpectomy, mastectomy, unknown), joint adjuvant therapy (none, chemotherapy only, radiation therapy only, both), hormonal therapy (no, yes), and any comorbidity (diabetes, hypertension, myocardial infarction, stroke). However, WHEL did not collect information on myocardial infarction and stroke. For all studies, clinical data and tumor characteristics were collected by medical record review or by self-report and verified by medical record.

Ascertainment of breast cancer outcomes

Outcomes were death due to breast cancer and all-cause mortality. All studies ascertained outcome events by self-report and regular linkage to electronic medical records and vital statistics registries. Reported events were verified by medical record review except for self-report of recurrences in the NHS. Cause of death was determined from death certificates and supplemented with medical records if necessary. Details of outcome ascertainment have been published (15).

Statistical analysis

A 5-level weight change variable of weight stable, weight loss (moderate, large), and weight gain (moderate, large) was created. Weight loss/weight gain was defined as 5% to <10% change for moderate and ≥10% change for large relative to the initial prediagnosis weight. A weight change of <5% of the prediagnosis weight was considered weight stable (reference group). These categories were chosen because they are commonly used for weight loss recommendations to reduce risk of obesity, heart disease, diabetes, and cancer. NHS women were excluded from the analysis if they were diagnosed before 1990 to ensure comparability of treatment standards [$n = 2{,}965$ (16%)]. In addition, we eliminated women with missing weight measurements [$n = 2{,}408$ (13%)] and those who had stage IV breast cancer [n = 45 (<1%)], thus leaving 12,915 breast cancer survivors as the final analytic sample size.

Sociodemographic, lifestyle, and clinical characteristics of the overall pooled cohort and by U.S. cohorts and SBCSS were summarized by frequency distributions for categorical variables and means with SDs for continuous variables. The χ^2 tests were used to determine whether covariates varied across weight gain categories.

The multivariable analysis involved 3 steps. First, delayed entry Cox proportional hazards regression models with time since diagnosis as the time scale were used to estimate study-specific adjusted HRs and 95% confidence intervals (CI). The entry date was the date of the postdiagnosis weight measurement. The exit date was the date of death or date of last contact (i.e., date of last follow-up survey or date of last registry linkage, whichever was most recent). We assessed whether there was heterogeneity in the association between weight change and mortality and time at postdiagnosis weight measurement via inclusion of appropriate cross-product (interaction) terms in the regression model and found no evidence of effect heterogeneity. Similarly, we assessed whether there was heterogeneity in the weight change effect over time (since diagnosis: <5 and >5 years) and found no appreciable variation in effect.

Second, a meta-analysis was conducted with study-specific HRs using inverse variance weights in random-effects models (20). The *Q*-test statistic was used to test for

heterogeneity in risk estimates across studies (21). Third, if no evidence for heterogeneity was observed, then individual data from the 4 cohorts were combined, and a pooled analysis was conducted for the weight change–outcome associations of interest using delayed entry Cox proportional hazards regression models stratified by study. If evidence for heterogeneity was observed ($P < 0.05$), then results from the random-effects meta-analysis and study-specific analyses were presented. There was heterogeneity when all sites were pooled, which was eliminated when Shanghai data were removed. Therefore, we present pooled data for U.S. sites and Shanghai separately.

We examined the possibly nonlinear relation between weight change and mortality with restricted cubic splines. We *a priori* specified 4 knots, noting that in practice, 3 to 5 knots should adequately represent most phenomena likely to be observed in medical studies. We used the software default for knot location (fifth, 35th, 65th, and 95th percentiles of weight change distribution), noting that results are generally insensitive to knot locations unless they are placed in an extremely nonuniform way over the covariate space (22, 23).

Covariates were selected on the basis of *a priori* assumptions, and models were fully adjusted for age at diagnosis, AJCC stage, race/ethnicity, menopausal status, hormone receptor status, number of positive nodes, treatment, prediagnosis BMI, and smoking history. We evaluated possible effect modification in the associations between weight change and mortality outcomes by hormone receptor status (ER+ vs. ER–), comorbidity status (at least one comorbidity vs. none), prediagnosis BMI (normal vs. overweight), and smoking (ever vs. never). Heterogeneity in association between individual levels of weight change and survival by potential effect modifiers (e.g., comorbidity yes/no) was assessed via inclusion of cross-product terms in the Cox regression models ($P_{contrast}$).

Results

Over a mean (SD) follow-up time of 8.1 (4.0) years, 1,603 deaths were confirmed (1,040 deaths due to breast cancer). Mean time (range) to death was 6.7 (1.5–17.2) years from diagnosis.

U.S. sites and Shanghai differed significantly on several baseline characteristics (Table 1). As expected, mean body size, as measured by prediagnosis weight [71.1 kg (United States) vs. 60.0 kg (Shanghai)] and BMI [26.4 kg/m^2 (United States) vs. 23.8 kg/m^2 (Shanghai)] were significantly different ($P < 0.0001$). However, there was no significant difference in pre- to postdiagnosis weight change [1.7 kg (United States) vs. 1.5 kg (Shanghai); $P = 0.93$]. In both the United States and China, weight gain was more common than weight loss p33.7% gain vs. 15.0% loss (United States) and 36.6% gain vs. 13.9% loss (Shanghai)].

At approximately 2 years postdiagnosis, 50% of U.S. women remained weight-stable, regardless of their prediagnosis BMI (Table 2). In both populations, postdiagnosis weight gain was more common in normal weight women than in overweight women, whereas conversely, weight loss was more common in overweight women than normal weight women (Table 2). Also in both populations, postmenopausal women were more likely to lose weight and less likely to gain weight than premenopausal women. In U.S. sites only, women with comorbidities were more likely to lose weight (19%) after a breast cancer diagnosis and less likely to gain weight (27%) than women without comorbidities (13% lose and 37% gain), and women diagnosed with later stage (stage II or III) cancer were more likely to have large weight gains than women with stage I cancer. In Shanghai, weight loss and weight gain were both more common among women with stage III cancers than those with stage I and II cancers.

For U.S. sites and Shanghai, both weight loss and weight gain were associated with an increased risk of overall mortality, suggesting a U-shaped relationship (Fig. 1; $P_{nonlinearity} < 0.0001$). In both countries, remaining weight stable was associated with the lowest risk. The risk for mortality increased gradually with increasing weight gain. In contrast, risk increased markedly as weight loss increased.

Weight loss and breast cancer–specific mortality, non–breast cancer mortality, and overall mortality

Weight loss ≥10% (mean = 11.64 kg) was related to overall mortality in the U.S. sites (HR, 1.41; 95% CI, 1.14–1.75) and in Shanghai (HR, 3.25; 95% CI, 2.24–4.73; Table 3). For Shanghai, as 86% of deaths were due to breast cancer, effects for overall mortality were similar to those with breast cancer–specific mortality (HR, 3.60; 95% CI, 2.39–5.42). For U.S. sites, ≥10% weight loss was associated only with non–breast cancer mortality (HR, 1.62; 95% CI, 1.21–2.19; data not shown) and not with breast cancer mortality (HR, 1.13; 95% CI, 0.83–1.56). We further stratified effects of weight loss on overall mortality by ER status, baseline comorbid status, smoking status, and prediagnosis BMI. No differences in effects were seen by ER status (data not shown). Women who ever smoked and had ≥10% weight loss had an increased risk of death (HR, 1.58; 95% CI, 1.20–2.09), whereas women who never smoked had no increased risk (Table 4). When women were stratified by prediagnosis BMI, moderate weight loss (5%–10%, mean = 4.9 kg) was associated with an increased risk for normal weight women, but not overweight women, in both the U.S. sites and Shanghai ($P_{contrast} = 0.05$ and 0.14, respectively). Large weight loss was associated with increased risk in both populations, regardless of prediagnosis weight. In sensitivity analyses, removing the underweight women (BMI < 20 kg/m^2), and removing all deaths that occurred in the first year after measurement did not alter results (data not shown).

For the U.S. sites, large weight loss was associated with an increased risk of overall mortality in women with existing comorbidities (HR, 1.70; 95% CI, 1.29–2.23) but not in women without comorbidities (HR, 1.13; 95% CI, 0.77–1.65). We conducted sensitivity analyses excluding

Table 1. Characteristics of the analytic sample in the ABCPP

	Overall ($N = 12,915$)	U.S. sites pooled ($N = 8,429$)	Shanghai ($N = 4,486$)	
	Mean (SD)	Mean (SD)	Mean (SD)	P^a
Age at diagnosis, y	57.0 (10.5)	58.9 (10.3)	53.5 (10.0)	<0.0001
Height, m	1.6 (0.1)	1.6 (0.1)	1.59 (0.1)	<0.0001
Prediagnosis BMI, kg/m^2	25.5 (5.0)	26.4 (5.4)	23.8 (3.5)	<0.0001
Prediagnosis weight, kg	67.2 (14.3)	71.1 (15.1)	60.0 (9.0)	<0.0001
Postdiagnosis weight, kg	68.8 (14.7)	72.8 (15.6)	61.5 (9.0)	<0.0001
Weight change pre to post, kg	1.6 (6.3)	1.7 (6.9)	1.5 (4.7)	0.93
Time from diagnosis to post, y	2.1 (0.7)	2.4 (0.6)	1.6 (0.3)	<0.0001
	n (%)	*n* (%)	*n* (%)	P^a
Weight change				
Stable (within 5%)	6,539 (50.6)	4,318 (51.2)	2,221 (49.5)	<0.0001
Moderate loss (5%–10%)	1,197 (9.3)	770 (9.1)	427 (9.5)	
Large loss (≥10%)	700 (5.4)	501 (5.9)	199 (4.4)	
Moderate gain (5%–10%)	2,316 (17.9)	1,421 (16.9)	895 (20.0)	
Large gain (≥10%)	2,163 (16.8)	1,419 (16.8)	744 (16.6)	
Race/ethnicity				
Non-Hispanic white	7,470 (57.8)	7,470 (88.6)	0 (0.0)	<0.0001
Non-Hispanic black	221 (1.7)	221 (2.6)	0 (0.0)	
Asian	4,701 (36.4)	215 (2.6)	4,486 (100.0)	
Hispanic	272 (2.1)	272 (3.2)	0 (0.0)	
Other	251 (1.9)	251 (3.0)	0 (0.0)	
Education				
Less than college graduate	6,473 (50.1)	2,293 (27.2)	4,180 (93.2)	<0.0001
College graduate or higher	6,441 (49.9)	6,135 (72.8)	306 (6.8)	
Menopausal status at diagnosis				
Premenopausal	4,155 (32.2)	1,965 (23.3)	2,190 (48.8)	<0.0001
Postmenopausal	8,342 (64.6)	6,046 (71.7)	2,296 (51.2)	
Unknown	418 (3.2)	418 (5.0)	0 (0.0)	
Stage of breast cancer				
I	5,835 (46.6)	4,248 (51.4)	1,587 (37.1)	<0.0001
II	5,118 (40.8)	3,062 (37.1)	2,056 (48.1)	
III	1,581 (12.6)	947 (11.5)	634 (14.8)	
Hormone receptor status				
ER+, PR+	7,489 (60.8)	5,193 (65.7)	2,296 (52.1)	<0.0001
ER–, PR+	589 (4.8)	255 (3.2)	334 (7.6)	
ER+, PR–	1,719 (14.0)	1,138 (14.4)	581 (13.2)	
ER–, PR–	2,518 (20.4)	1,320 (16.7)	1,198 (27.2)	
Adjuvant treatment				
None	1,924 (15.1)	1,602 (19.4)	322 (7.2)	<0.0001
Chemotherapy only	4,400 (34.5)	1,671 (20.2)	2,729 (60.8)	
Radiation only	2,422 (19.0)	2,393 (28.9)	29 (0.6)	
Both	4,006 (31.4)	2,600 (31.5)	1,406 (31.3)	
Hormonal therapy				
No	4,242 (33.2)	2,145 (25.9)	2,097 (46.9)	<0.0001
Yes	8,526 (66.8)	6,148 (74.1)	2,378 (53.1)	
Nonsedentary physical activity				
None	1,752 (14.7)	598 (7.9)	1,154 (26.4)	<0.0001
<4.6 h	2,268 (19.0)	1,881 (24.9)	387 (8.9)	
4.6 to <15.6 h	3,500 (29.4)	2,264 (30.0)	1,236 (28.3)	
≥15.6 h	4,395 (36.9)	2,804 (37.2)	1,591 (36.4)	
Smoking history				
Never	8,430 (65.4)	4,063 (48.4)	4,367 (97.3)	<0.0001
Ever	4,458 (34.6)	4,339 (51.6)	119 (2.7)	

(Continued on the following page)

Table 1. Characteristics of the analytic sample in the ABCPP (Cont'd)

	Overall ($N = 12,915$) Mean (SD)	U.S. sites pooled ($N = 8,429$) Mean (SD)	Shanghai ($N = 4,486$) Mean (SD)	P^a
Diabetes				
No	11,530 (93.0)	7,376 (93.2)	4,154 (92.6)	0.20
Yes	867 (7.0)	536 (6.8)	331 (7.4)	
Hypertension				
No	8,520 (68.6)	5,096 (64.3)	3,424 (76.3)	<0.0001
Yes	3,894 (31.4)	2,833 (35.7)	1,061 (23.7)	
Myocardial infarction				
No	9,410 (95.2)	5,162 (95.7)	4,248 (94.7)	0.03
Yes	471 (4.8)	234 (4.3)	237 (5.3)	
Stroke				
No	9,773 (97.8)	5,398 (98.1)	4,375 (97.5)	0.07
Yes	216 (2.2)	106 (1.9)	110 (2.5)	
Any comorbidity				
No	7,930 (64.4)	4,733 (60.5)	3,197 (71.3)	<0.0001
Yes	4,376 (35.6)	3,088 (39.5)	1,288 (28.7)	

[a]From Kruskal–Wallis test for continuous variables and Pearson χ^2 test for categorical variables.

WHEL participants who did not have data on myocardial infarction or stroke, which may have caused some misclassification on comorbid status. After exclusion of WHEL data, results were similar for women with comorbidities (HR, 1.65; 95% CI, 1.24–2.20) and without comorbidities (HR, 1.55; 95% CI, 1.02–2.34).

We further explored multivariable-adjusted effects of large weight loss on overall mortality by dividing women into 4 groups based on comorbidity status (yes/no) and initial BMI status (normal/overweight) and comparing them with women in the same comorbid/BMI category who remained weight stable for the U.S. sites (Fig. 2). Overweight women with comorbid conditions and normal weight women without comorbid conditions who lost weight were at increased risk of overall mortality. Normal weight women with comorbid conditions who had large weight loss were also at increased risk of poorer survival, but the risk was nonsignificant. The only group without increased risk was women who did not have a comorbid condition and were initially overweight. In these women, large weight loss was associated with a nonsignificant decreased risk of overall mortality (HR, 0.78; 95% CI, 0.46–1.30).

Weight gain and breast cancer–specific and overall mortality

In the U.S. sites, weight gain $\geq$10% (mean = 10.5 kg) was marginally related to overall mortality (HR, 1.15; 95% CI, 0.98–1.35) but not breast cancer–specific mortality (HR, 1.03; 95% CI, 0.84–1.26; Table 3). A similar magnitude of risk was observed in Shanghai for overall mortality (HR, 1.16; 95% CI, 0.84–1.62) and breast cancer–specific mortality (HR, 1.25; 95% CI, 0.88–1.77) but neither were significant. When we further examined effects of weight gain on overall mortality by prediagnosis BMI, comorbid status, ER status, and smoking status, there were no interactions with weight gain in either population (Table 4, ER results not shown). Women who gained $\geq$10% and were normal weight had a trend toward higher risk of overall mortality (HR, 1.24; 95% CI, 0.98–1.56) compared with their overweight counterparts (HR, 1.04; 95% CI, 0.83–1.31), but the difference between the groups was not significant ($P_{contrast} = 0.12$). Categorizing women into 4 groups by both prediagnosis BMI and comorbid status did not change these findings; only normal weight women were at increased risk regardless of comorbid status (data not shown). In sensitivity analyses, we excluded underweight women (BMI < 20 kg/m^2), and results were unchanged (data not shown).

Discussion

This study of nearly 13,000 women with breast cancer showed a U-shaped relationship between postdiagnosis weight change and all-cause mortality. It is the largest to date and the first among United States and China breast cancer study populations to suggest that weight maintenance in the first few years after diagnosis is associated with the most favorable outcomes. The majority of previous studies reporting on weight loss and breast cancer outcomes have been cautious in their interpretation, but have all suggested, as this report does, that weight loss is also associated with poorer breast cancer outcomes (1, 10–12, 24). One study reports more than 5 times the risk of overall mortality and more than 7 times the risk of breast cancer mortality for women who lose >5% of their prediagnosis weight than women who remain relatively stable (within 5%; ref. 24). This study is the first to further explore results by both comorbid status and initial weight, enabling better identification of women at highest risk of poor outcomes due to weight loss.

The association of weight gain with poorer breast cancer outcomes has been reported previously (1, 8, 11, 12).

Table 2. Percent weight change by selected cohort characteristics in the ABCPP

	U.S. sites ($N = 8,429$)						Shanghai ($N = 4,486$)					
	Weight stable; within 5% ($n = 4,318$)	Moderate weight loss; >5%–10% ($n = 770$)	Large weight loss; ≥10% ($n = 501$)	Moderate weight gain; >5%–10% ($n = 1,421$)	Large weight gain; ≥10% ($n = 1,419$)		Weight stable; within 5% ($n = 2,221$)	Moderate weight loss; >5%–10% ($n = 427$)	Large weight loss; ≥10% ($n = 199$)	Moderate weight gain; >5%–10% ($n = 895$)	Large weight gain; ≥10% ($n = 744$)	
	Row%	Row%	Row%	Row%	Row%	P^a	Row%	Row%	Row%	Row%	Row%	P^a
Prediagnosis BMI												
Underweight	52.9	5.6	2.1	19.8	19.8	<0.0001	38.6	3.2	1.0	23.6	33.7	<0.0001
Normal	52.3	7.0	3.3	17.9	19.5		46.0	8.2	3.4	22.9	19.6	
Overweight	51.1	10.3	6.5	16.3	15.8		59.4	13.8	6.5	14.4	5.9	
Obese	48.9	12.5	11.4	14.8	12.4		59.3	15.7	12.3	9.8	3.0	
Smoking categories												
Never	51.7	9.1	6.3	16.9	16.1	0.36	50.0	9.5	4.4	19.9	16.1	<0.0001
Ever	50.8	9.2	5.7	16.8	17.6		31.1	10.1	5.0	21.0	32.8	
Any comorbidity												
No	50.3	7.7	5.3	17.5	19.3	<0.0001	47.2	7.4	3.1	22.4	19.8	<0.0001
Yes	53.9	11.6	7.4	15.7	11.3		55.1	14.7	7.8	13.8	8.5	
Education categories												
Less than college	40.3	8.9	5.7	18.3	26.9	<0.0001	49.0	9.5	4.4	20.1	16.9	0.15
College grad or higher	55.3	9.2	6.1	16.3	13.1		55.9	9.5	4.6	17.3	12.8	
ER status												
Positive	51.7	9.3	5.9	16.5	16.5	0.04	50.2	9.9	4.5	19.4	16.0	0.31
Negative	48.5	8.7	5.7	17.9	19.2		48.4	8.9	4.2	21.3	17.3	
Unknown/missing	54.3	7.8	7.3	18.3	12.4		43.8	9.4	4.7	15.6	26.6	
Menopausal status at diagnosis												
Premenopausal	40.1	6.9	4.0	20.1	28.9	<0.0001	44.3	5.9	2.3	23.7	23.7	<0.0001
Postmenopausal	55.5	10.2	6.4	15.8	12.2		54.5	12.9	6.5	16.3	9.8	
Unknown	41.9	4.6	8.9	17.5	27.3		0.0	0.0	0.0	0.0	0.0	
Stage of breast cancer												
I	54.4	9.5	6.0	15.8	14.3	<0.0001	52.0	9.2	4.2	19.8	14.8	0.006
II	47.4	9.0	6.1	18.2	19.4		50.2	9.4	4.1	19.9	16.4	
III	47.2	7.9	5.6	17.7		21.5	42.6	10.9	5.4	20.4	20.8	

[a]From Pearson χ^2 test.

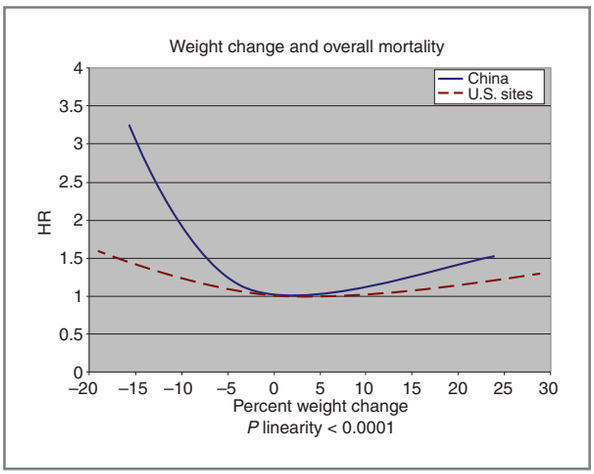

Figure 1. HR and 95% CI for percent weight change and overall mortality for U.S. sites and Shanghai, China, using restricted cubic splines with knots at −10.7, 0, 4.7, and 18.2 percent change for U.S. sites and −9.4, 0, 5.3, and 16.4 percent change for Shanghai with 0 percent change as the reference in the ABCPP. Models adjusted for age at diagnosis, AJCC stage, race/ethnicity, menopausal status, hormone receptor status, nodal positivity, chemotherapy, radiation therapy prediagnosis BMI, and smoking.

However, our results suggest that compared with women who remain weight stable, a woman must experience substantial weight gain before an increased risk of death is observed. Several mechanisms have been postulated through which weight gain may influence survival, including enhanced conversion in the adipose tissue of androgens to estrogens (25–27), as well as decreased levels of sex hormone–binding globulin and increased insulin and insulin-like growth factors and inflammatory factors (28).

Similar to our findings, several other studies have also found that normal weight women are the most susceptible to weight gain after a breast cancer diagnosis (10, 13, 29, 30). We also found that normal weight women are at highest risk of experiencing the negative effects of weight gain on overall mortality outcomes, as previously reported in an NHS analysis (8). Thus, the prevailing recommendation that women should not gain excessive amounts of weight postdiagnosis is supported by our data, and prevention of weight gain appears to be an evidence-based public health goal for breast cancer survivors.

In our study, the association of weight loss with mortality differed slightly by site; in the pooled U.S. cohorts,

Table 3. Delayed entry Cox proportional hazard models for weight change and breast cancer–specific and overall mortality in the ABCPP

	U.S. sites			Shanghai		
	N = 8,354 (757 events)			*N* = 4,441 (279 events)		
Breast cancer–specific mortality	**No. of events**	**HR (95% CI)**	**P_{trend}**	**No. of events**	**HR (95% CI)**	**P_{trend}**
Weight stable						
Within 5%	365	Reference		111	Reference	
Weight loss						
Moderate 5%–10%	68	1.09 (0.84–1.42)	0.29	34	1.54 (1.05–2.28)	<0.0001
Large ≥10%	44	1.13 (0.83–1.56)		31	3.60 (2.39–5.42)	
Weight gain						
Moderate 5%–10%	130	0.97 (0.79–1.19)	0.90	50	1.00 (0.71–1.41)	0.28
Large ≥10%	150	1.03 (0.84–1.26)		53	1.25 (0.88–1.77)	
	N = 8,354 (1,271 events)			*N* = 4,441 (326 events)		
Overall mortality	**No. of events**	**HR (95% CI)**	**P_{trend}**	**No. of events**	**HR (95% CI)**	**95% CI**
Weight stable						
Within 5%	614	Reference		139	Reference	
Weight loss						
Moderate 5%–10%	134	1.20 (0.99–1.45)	0.0003	38	1.35 (0.94–1.94)	<0.0001
Large ≥10%	101	1.41 (1.14–1.75)		37	3.25 (2.24–4.73)	
Weight gain						
Moderate 5%–10%	201	0.98 (0.83–1.15)	0.38	55	0.93 (0.68–1.28)	0.52
Large ≥10%	221	1.15 (0.98–1.35)		57	1.16 (0.84–1.62)	

NOTE: Models adjusted for age at diagnosis, race, menopausal status, stage, hormone receptor status, positive nodes, treatment (chemotherapy, radiation therapy, both), prediagnosis BMI, and smoking.

Table 4. Delayed entry Cox proportional hazard models for overall mortality, stratified by comorbid status, prediagnosis BMI, and smoking history

	U.S. sites					Shanghai				
	Comorbidity		No comorbidity			Comorbidity		No comorbidity		
	N = 3,031 (584 events)		*N* = 4,715 (589 events)			*N* = 1,275 (97 events)		*N* = 3,165 (229 events)		
	No. of events	HR (95% CI)	No. of events	HR (95% CI)	$P_{contrast}$[a]	No. of events	HR (95% CI)	No. of events	HR (95% CI)	$P_{contrast}$[a]
Weight stable										
Stable	290	Reference	276	Reference		40	Reference	99	Reference	
Weight loss										
Loss 5%–10%	75	1.24 (0.95–1.60)	55	1.29 (0.96–1.73)	0.80	15	1.34 (0.73–2.44)	23	1.43 (0.90–2.28)	0.84
Loss ≥10%	66	1.70 (1.29–2.23)	32	1.13 (0.77–1.65)	0.05	20	3.68 (2.09–6.47)	17	2.89 (1.71–4.89)	0.36
Weight gain										
Gain 5%–10%	89	0.98 (0.77–1.25)	97	1.00 (0.79–1.26)	0.68	13	1.22 (0.64–2.33)	42	0.82 (0.57–1.19)	0.26
Gain ≥10%	64	1.10 (0.83–1.45)	129	1.17 (0.94–1.46)	0.17	9	1.46 (0.67–3.18)	48	1.05 (0.73–1.51)	0.53
	Underweight/normal; *N* = 3,962 (550 events)		Overweight/obese; *N* = 4,392 (721 events)			Underweight/normal; *N* = 2,984 (199 events)		Overweight/obese; *N* = 1,457 (127 events)		
	No. of events	HR (95% CI)	No. of events	HR (95% CI)	$P_{contrast}$[a]	No. of events	HR (95% CI)	No. of events	HR (95% CI)	P[a]
Weight stable										
Stable	256	Reference	358	Reference		72	Reference	67	Reference	
Weight loss										
Loss 5%–10%	52	1.59 (1.17–2.16)	82	1.05 (0.82–1.33)	0.05	22	1.74 (1.07–2.83)	16	0.99 (0.57–1.72)	0.14
Loss ≥10%	27	1.74 (1.16–2.60)	74	1.40 (1.09–1.81)	0.36	16	4.08 (1.07–2.83)	21	2.62 (1.58–4.36)	0.38
Weight gain										
Gain 5%–10%	97	1.06 (0.84–1.35)	104	0.88 (0.70–1.09)	0.21	40	0.99 (0.67–1.47)	15	0.91 (0.51–1.62)	0.71
Gain ≥10%	118	1.24 (0.98–1.56)	103	1.04 (0.83–1.31)	0.12	49	1.20 (0.83–1.75)	8	1.42 (0.67–3.00)	0.90
	Ever smoked; *N* = 4,298 (737 events)		Never smoked; *N* = 4,029 (527 events)			Ever smoked		Never smoked		
	No. of events	HR (95% CI)	No. of events	HR (95% CI)	$P_{contrast}$[a]					
Weight stable										
Stable	351	Reference	260	Reference		Not calculable—too few smokers in Shanghai population				
Weight loss										
Loss 5%–10%	76	1.20 (0.94–1.54)	58	1.23 (0.92–1.65)	0.89					
Loss ≥10%	61	1.58 (1.20–2.09)	40	1.27 (0.91–1.79)	0.22					
Weight gain										
Gain 5%–10%	115	1.00 (0.80–1.23)	85	0.98 (0.76–1.25)	0.98					
Gain ≥10%	134	1.20 (0.97–1.48)	84	1.03 (0.80–1.33)	0.56					

NOTE: Models adjusted for age at diagnosis, race, menopausal status, stage, hormone receptor status, positive nodes, treatment (chemotherapy, radiation therapy, both), pre-diagnosis BMI, and smoking. Prediagnosis BMI and smoking are not included as covariates in the respective stratified models.

[a]$P_{contrast}$ derived from inclusion of cross-product terms in the Cox proportional hazard models.

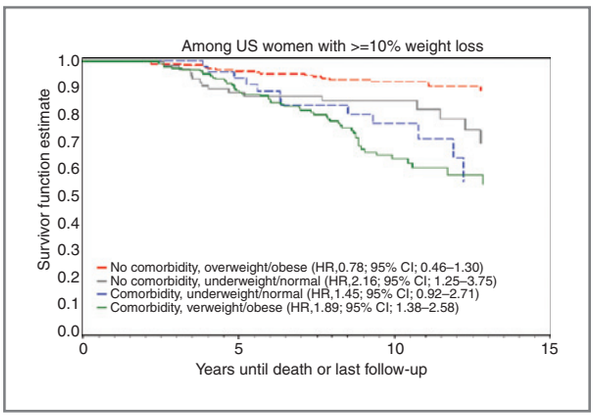

Figure 2. Adjusted survival curves for comorbidity status and prediagnosis BMI category among U.S. women with ≥10% weight loss in the ABCPP.

the increased risk in overall mortality was seen in women with existing comorbid conditions, whereas in Shanghai, the increased risk in mortality was seen regardless of comorbid status. This may partially explain why in the United States we only observed an increased risk in overall mortality and not breast cancer–specific mortality, suggesting that women who have comorbid conditions and lose weight are dying of causes most likely related to their comorbidity rather than their breast cancer. Our hypothesis is further supported by removing the WHEL women from the stratified comorbidity analyses due to having no information on MI or stroke. In this sensitivity analysis, no differences in the effects of weight loss by comorbid status were observed, thus suggesting that MI and stroke are key conditions for which negative effects of weight loss are seen. Because most women survive breast cancer, risk of death due to causes other than breast cancer is of important prognostic value.

One potential explanation for our observed risk of higher mortality among breast cancer survivors who lose weight is that, as a result of both the breast cancer and its associated treatments, some women develop cachexia or pre-cachexia, resulting in not only weight loss but substantial loss of lean body mass (LBM). Exaggerated losses of LBM in breast cancer survivors are hypothesized to be related to chronic inflammation, insulin resistance, and decreases in physical activity (31).

In addition, low levels of LBM in patients with cancer have been associated with increased toxicity to anticancer therapy (32, 33) and higher occurrences of metabolic syndrome-related comorbid conditions (11, 34), with both mechanisms potentially leading to reduced rates of survival (35). Recent data suggest that LBM, similar to proposed effects of fat mass in breast cancer progression, may exert a powerful endocrine, immune, and hormonal influence within the body (36). Of note, the association of weight loss with increased mortality has also been reported in several recent observational studies that have not been restricted to only breast cancer survivors (37–40).

Additional explanations have been hypothesized as to why weight loss among breast cancer survivors with comorbid conditions is associated with poorer outcomes. Women with existing comorbid conditions are known to receive less extensive breast cancer treatment (41), and as chemotherapy is associated with weight gain (30, 42–44), the lack of weight gain or weight loss may be an indicator for treatment that is not the standard of care (41). In addition, women with comorbid conditions at the time of breast cancer diagnosis are more likely to be subsequently hospitalized for chemotherapy toxicity, infection and fever, neutropenia, anemia, all of which increase the risk of weight loss (45) and decrease survival. Unfortunately, data were unavailable on treatment adherence/effectiveness or treatment toxicity to explore this further. Finally, comorbidity itself among breast cancer survivors increases the risk of mortality (46–48), and certain comorbid conditions such as chronic obstructive pulmonary disease (COPD; ref. 49) and kidney failure (50) are known to be associated with weight loss.

While the weight loss observed in this study could be nonvolitional and may be an early marker of cancer cachexia, comorbid overweight women appear to be at risk for weight loss. These results raise questions about the safety of intentional weight loss in the early period postdiagnosis for breast cancer survivors presenting with a comorbid condition or for women who already have low levels of LBM. While weight loss strategies are typically recommended to women who are overweight and have comorbid conditions but do not have breast cancer (51, 52), the success or safety in women who concurrently have comorbid conditions and breast cancer has yet to be shown. In fact, several researchers have now documented a puzzling phenomenon, termed the "obesity paradox," in which overweight or even obese individuals with established diseases such as cardiovascular disease, heart failure, and stroke have a better prognosis compared with normal weight or underweight subjects, despite the associations between obesity and these health care conditions (53, 54). In one recent study among patients with type II diabetes and cardiovascular comorbidity, not only did overweight and obese patients have a lower mortality than patients with normal weight but also weight loss and weight stability were associated with increased mortality and morbidity (55).

Our data indicate that large weight loss in women who are leaner is associated with worse survival, regardless of comorbid status, suggesting that overweight may confer some protection. Others have noted that being overweight may be associated with improved survival during recovery from adverse conditions (56, 57) and with improved prognosis for other adverse events (58, 59). In one large cohort of more than 41,000 surgical ICU patients, being overweight or mildly obese was associated with decreased risk of 60-day in-hospital mortality (56). Such findings may be due to greater nutritional reserves playing a beneficial compensatory role in these patients or protection due to higher LBM associated with overweight

(60). More studies are needed to understand the underlying biologic mechanisms of weight loss on mortality.

Limitations of this study are that we only evaluated weight change at one time point postdiagnosis (on average 2 years postdiagnosis). There is evidence that women who initially lose weight may regain their weight (61–64), such that the increased risk in mortality we observed with weight loss may in fact be related to a yo–yo pattern of initial loss and subsequent regain. Further research should examine prognostic effects of long-term weight patterns in breast cancer survivors. We also were unable to disentangle effects of nonvolitional versus intentional weight loss; however, studies of intentional weight loss among breast cancer survivors are currently underway (65, 66), and results should be forthcoming to shed light on this question. Furthermore, because this analysis was a pooled analysis, we only had information on the most common comorbidities: hypertension diabetes, and cardiovascular disease. Thus, our analyses on comorbid status are limited to these comorbidities. Finally, there is a possibility that our results were biased by illness-induced weight loss before weight change measurement ("reverse causation"). However, in a sensitivity analysis, we removed all deaths that occurred in the first year after measurement, and results were essentially unchanged. A major strength of this pooled study is its size and inclusion of women from both United States and China, which allowed us to further explore and understand effects of weight change by comorbid status and prediagnosis BMI across different treatment settings.

In summary, both weight gain and weight loss are associated with poorer overall survival in the United States and China. Although risks varied slightly across countries and across specific weight and comorbid status categories, the overall results suggest that remaining weight stable, at least in the early years postdiagnosis, is associated with better overall survival. At present, the prevention of weight gain should be recommended to all women, regardless of initial body size, especially in light of the data that that show leaner women are most likely to gain weight after a breast cancer diagnosis. Clinicians should be aware that some women with breast cancer may be at risk of weight loss, especially those with comorbid conditions, and that there is an increase in mortality associated with weight loss in these women. Large weight change, as with big shifts in other medical indicators, should be monitored closely. Similar to strategies for chemotherapy, weight control strategies for breast cancer survivors are not universal to all women and should be personalized to the individual's prognostic profile and medical history.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): B.J. Caan, X.O. Shu, J.P. Pierce, E.M. Poole, M.D. Holmes, W.Y. Chen
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): B.J. Caan, M.L. Kwan, R.E. Patterson, S.J. Nechuta, C.H. Kroenke, E.K. Weltzien, C.P. Quesenberry, Jr, W.Y. Chen
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Study supervision: B.J. Caan, J.P. Pierce

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