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Postdiagnosis Weight Change and Survival Following a Diagnosis of Early-Stage Breast Cancer

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Abstract

Background: Achieving a healthy weight is recommended for all breast cancer survivors. Previous research on postdiagnosis weight change and mortality had conflicting results.

Methods: We examined whether change in body weight in the 18 months following diagnosis is associated with overall and breast cancer–specific mortality in a cohort of $n = 12{,}590$ stage I–III breast cancer patients at Kaiser Permanente using multivariable-adjusted Cox regression models. Follow-up was from the date of the postdiagnosis weight at 18 months until death or June 2015 [median follow-up (range): 3 (0–9) years]. We divided follow-up into earlier (18–54 months) and later (>54 months) postdiagnosis periods.

Results: Mean (SD) age-at-diagnosis was 59 (11) years. A total of 980 women died, 503 from breast cancer. Most women maintained weight within 5% of diagnosis body weight; weight loss and gain were equally common at 19% each. Compared with weight maintenance, large losses (≥10%) were associated with worse survival, with HRs and 95% confidence intervals (CI) for all-cause death of 2.63 (2.12–3.26) earlier and 1.60 (1.14–2.25) later in follow-up. Modest losses (>5%–<10%) were associated with worse survival earlier [1.39 (1.11–1.74)] but not later in follow-up [0.77 (0.54–1.11)]. Weight gain was not related to survival. Results were similar for breast cancer–specific death.

Conclusion: Large postdiagnosis weight loss is associated with worse survival in both earlier and later postdiagnosis periods, independent of treatment and prognostic factors.

Impact: Weight loss and gain are equally common after breast cancer, and weight loss is a consistent marker of mortality risk. *Cancer Epidemiol Biomarkers Prev; 26(1); 44–50. ©2016 AACR.*

See all the articles in this *CEBP Focus* section, "The Obesity Paradox in Cancer: Evidence and New Directions."

Introduction

As the breast cancer survivor population grows (1), strategies to promote health and prolong life become increasingly important (2). With obesity an established risk factor for postmenopausal breast cancer, research has turned to the potential benefits of weight loss among survivors (3–5). In observational studies, breast cancer patients with stable weight following diagnosis consistently have the best survival, but results for postdiagnosis weight gain or loss are heterogeneous. In almost all studies, postdiagnosis weight loss predicts worse survival (6–11), although not without exception (12). Similarly, postdiagnosis weight gain predicts worse survival in some (7, 10, 11), but not all (8, 9), studies. Differences in timing of exposure and duration of follow-up may contribute to inconsistencies (8, 9, 11). Furthermore, the influence of weight change on survival may differ depending on how much time has elapsed since diagnosis (7). Methodologic limitations to existing studies include self-reported or recalled weights (7, 8, 11, 12); inadequate control for tumor characteristics (11); recruiting survivors substantially after diagnosis (8); only examining weight gain (13); or combining gains and losses as a single exposure (14). Rarely are sample sizes large enough to stratify by stage or characteristics that might clarify differences across subgroups of patients.

This study examines weight change in the 18 months after diagnosis and subsequent survival in a large, population-based cohort of women with early stage (I–III) invasive breast cancer within Kaiser Permanente Northern California (KPNC), an integrated health system. We selected 18 months postdiagnosis for comparability with other studies and to avoid active treatment and potential alterations in physical activity and diet habits during the first year after diagnosis. Our large sample provides statistical power to stratify by stage, comorbidities, chemotherapy treatment, and breast cancer subtype. In addition, we evaluated whether the influence of postdiagnostic weight change on survival varies over the course of follow-up, examining separate associations earlier (18–54 months) and later (>54 months) postdiagnosis.

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Materials and Methods

Study population

We included all women ages 18 to 80 years at KPNC diagnosed with a first primary stage I–III invasive breast cancer between 2005 [when the electronic medical record (EMR) was implemented] and 2013 ($n = 14{,}572$). Women with a prior history of other invasive cancers were excluded. We required weight and height within 3 months of diagnosis and 18 months postdiagnosis ($n = 12{,}671$) and information on smoking and hormone receptor status, leaving 12,590 women for analysis. The KPNC institutional review board approved the study.

Weight change exposures

Medical assistants measured height and weight at each visit. Body mass index (BMI) was computed in kilograms per squared height in meters (kg/m^2). When patients had multiple weights, we defined "at-diagnosis" as the weight closest to diagnosis but prior to any treatment [mean 0 months, SD 2 weeks from diagnosis]. We defined as "postdiagnosis" the weight closest to 18 months postdiagnosis [mean (SD) 18 (1) months]. "Postdiagnosis weight change" was the difference of the postdiagnosis and at-diagnosis weights. From weights measured approximately 12 months prediagnosis [range 6–30 months, mean (SD) 11 (5) months prediagnosis)], we calculated prediagnosis BMI.

Our main exposure was percent weight change after diagnosis computed as "postdiagnosis weight change" divided by "at-diagnosis weight" multiplied by 100. As in prior studies (7, 9, 13), we created five categories: large losses (≥10% of body weight); modest losses (>5%–<10%); stable weight (within 5%); modest gains (>5%–<10%); and large gains (≥10%).

Mortality outcomes

For mortality outcomes, we used data from the KPNC mortality file, composed of data from the California State Department of Vital Statistics, U.S. Social Security Administration, and KPNC healthcare utilization. We designated death as "breast cancer–specific" when breast cancer was a primary or contributing cause. We verified deaths (including cause) and searched for persons lost to follow-up using death certificates from each state through June 30, 2015 (15).

Covariates

We gathered information from the KPNC Cancer Registry and EMR on prognostic factors, including disease stage, tumor characteristics, adjuvant chemotherapy, radiation, surgery, race/ethnicity, and age at diagnosis. Smoking and alcohol history (current, former or never) are routinely available in the EMR; we chose the values closest to date of diagnosis ± 3 months. We calculated the Charlson Comorbidity Index (16) in the prediagnosis year ± 3 months and dichotomized as any versus none.

Statistical analysis

We used Cox regression models to examine associations between weight change and all-cause and breast cancer–specific death. We calculated person-time from the second weight measurement (~18 months postdiagnosis) until death or June 30, 2015. In analyses of breast cancer–specific mortality, we censored subjects who died from other causes at date of death. We tested for violations of proportional hazards with variable × time interactions. We detected a violation for our main exposure; thus, overall results are the average association of postdiagnostic weight change during the entire subsequent period of follow-up. We additionally report associations separately by duration of follow-up, evaluating interactions of weight change with follow-up time (dichotomized before/after the median follow-up of 3 years, i.e., 54 months postdiagnosis, determined empirically and through inspection of Kaplan–Meier curves to be a meaningful cutpoint).

We included confounding variables in our final models *a priori*, based on previous literature, and compared models controlling for age at diagnosis and race/ethnicity to those additionally adjusted for prediagnostic BMI, comorbidities at diagnosis, alcohol, smoking, adjuvant cancer treatment (chemotherapy and/or radiation), and tumor characteristics [stage (I, II, or III), grade (well, moderately, or poorly/undifferentiated), and hormone receptor and HER2 status]. Type of surgery (mastectomy or lumpectomy) did not alter HR estimates and was not included in the final multivariable model.

To assess nonlinearity, we used the likelihood ratio test to compare models with linear terms for percent weight change to models with linear and cubic spline terms. These restricted cubic splines (17) had four knots at the weight change values of 10% and 20% loss and gain; stable weight (<5% change from at-diagnosis weight) was the reference.

To examine heterogeneity by patient characteristics (race/ethnicity, age, comorbidities, BMI, and stage, all recorded at diagnosis) as well as by adjuvant chemotherapy and breast cancer subtype, we introduced product terms for weight change categories and stratification variables into regression models. We evaluated statistical significance with likelihood ratio tests. For breast cancer subtypes, we used categories adapted by Prat and colleagues (18) from the 3-marker IHC and substituted grade for Ki67 as proposed at the St. Gallen's Consensus Conference (19). Subtypes were defined as: (i) surrogate Luminal A (well/moderately differentiated, ER$^+$/PR$^+$ and Her2$^-$); (ii) surrogate Luminal B (poorly/undifferentiated, ER$^+$ or PR$^+$ and PR$^-$ or Her2$^+$); (iii) HER2$^+$, endocrine negative (ER$^-$/PR$^-$ and Her2$^+$); and (iv) triple-negative breast cancer, TNBC (ER$^-$/PR$^-$, and Her2$^-$).

To address confounding by severe illness leading to large weight loss or large weight gain and to death, we stratified by stage, comorbidity, and smoking. Since follow-up began 18 months postdiagnosis, our design excluded early deaths. We additionally reported results for earlier and later periods of follow-up to examine whether the influence of weight changes on mortality varies over time. We also considered whether adjustment for at-diagnosis instead of prediagnosis BMI influenced findings. Finally, as the effects of weight loss later in the postdiagnosis period may differ, we evaluated weight changes between 12 and 24 months postdiagnosis with subsequent death. We used SAS software version 9.3 (SAS, Inc.) for all statistical analyses.

Results

Baseline characteristics

Of the 12,590 early-stage breast cancer survivors in our study, 980 died, 503 due to breast cancer. In the 18 months after diagnosis, 19% of women lost >5% of body weight [mean (SD) weight loss: 18 (12) pounds]; 19% gained >5% of body weight [mean (SD) weight gain: 15 (9) pounds]; and 62% maintained a stable weight [mean (SD) weight change: 0 (5) pounds]. Table 1

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Table 1. Characteristics by category of weight change in the KPNC population of breast cancer patients diagnosed from 2005 to 2013 ($N = 12,590$)

	Large loss (≥10%)	Modest loss (>5%–<10%)	Stable (within 5%)	Modest gain (>5%–<10%)	Large gain (≥10%)	Total
N	827	1,536	7,836	1,645	746	12,590
			Mean or median			
Median (range) of follow-up, years	3 (0–9)	3 (0–9)	3 (0–9)	3 (0–9)	4 (0–8)	3.4 (0–9)
Median age at diagnosis, years	61	60	60	56	54	59
Median change (pounds)	−28	−12	0.10	11	24	0
			Percent			
History of alcohol drinking						
Never	47	49	45	42	46	45
Former	3	2	3	2	2	2
Current	50	49	52	56	51	52
History of smoking						
Never	55	57	59	54	61	60
Former	35	33	30	30	30	31
Current	10	10	11	16	8	9
Diagnosis BMI category						
Obese	54	47	35	28	22	37
Overweight	28	29	31	33	34	31
Normal weight	18	24	33	38	40	32
Underweight	0.1	1	1	2	3	1
Race/Ethnicity						
White	71	68	64	68	68	66
Black	11	7	7	7	10	7
Hispanic	8	11	10	9	11	10
Asian	11	14	18	15	10	16
Other	0	1	1	1	1	1
Comorbidities, yes/no	18	16	12	11	9	13
Tumor stage						
I	45	50	58	57	58	55
II	39	37	33	35	33	35
III	16	13	9	8	9	10
Breast cancer subtype[a]						
Surrogate Luminal A	43	48	48	47	43	47
Surrogate Luminal B	37	34	36	36	38	36
Her2+, endocrine negative	6	5	5	5	4	5
Triple negative	14	13	11	12	14	12
Chemotherapy	54	52	43	47	55	46
Radiotherapy	34	40	43	42	34	42

[a]Definitions adapted by Prat and colleagues (18) from the 3-marker IHC plus grade subtypes in the St. Gallen's Consensus Conference; we separated breast cancer into subtypes as follows: (i) surrogate Luminal A (well or moderately differentiated and ER^+ and PR^+ and $Her2^-$); (ii) surrogate Luminal B (poorly or undifferentiated ER^+ or PR^+ and any of PR^-, $Her2^+$); (iii) HER2-positive, endocrine negative (ER^-, PR^-, and $Her2^+$); and (iv) triple negative (ER^-, PR^-, and $Her2^-$).

shows participant characteristics by weight change category. Compared with women who maintained or gained weight, women who lost weight were slightly older at diagnosis, more likely to have stage II or III than stage I cancer, be overweight/obese, and have comorbidities. Women who gained large amounts of weight were younger with lower at-diagnosis BMI.

Overall weight change and outcomes

Table 2 shows the association of weight change over the entire follow-up period with mortality. In age and race/ethnicity–adjusted models, compared with stable weight, large (≥10%) and modest (>5%–<10%) losses were associated with increased risk of all-cause death [HR, 2.95 (95% CI, 2.47–3.52) and HR, 1.26 (95% CI, 1.04–1.53)] and breast cancer–specific death [HR, 3.01 (95% CI, 2.34–3.87) and HR, 1.42 (95% CI, 1.09–1.83)]. After multivariable adjustment, the adverse association of large losses persisted for breast cancer–specific [HR, 2.13 (95% CI, 1.65–2.76)] and all-cause death [HR, 2.24 (95% CI, 1.87–2.69)], but associations attenuated for modest losses for breast cancer–specific [HR, 1.24 (95% CI, 0.95–1.61)] and all cause death [HR, 1.15 (95% CI, 0.95–1.39)]. Overall, there was no increased risk of death for large or modest weight gain.

Weight change in earlier and later follow-up periods

The association of weight change with mortality varied over follow-up ($P < 0.05$ for time × weight change interaction). Figure 1 reports separate associations in earlier (between 18 and 54 months postdiagnosis) and later (>54 months postdiagnosis) periods of follow-up. Postdiagnosis weight loss ≥10% was associated with worse survival earlier [HR, 2.63 (95% CI, 2.12–3.26)] and later in follow-up, although HRs attenuated later [HR, 1.60 (95% CI, 1.14–2.25)]. Modest losses (>5%–<10%) were associated with worse survival earlier [HR, 1.39 (95% CI, 1.11–1.74)], but not later in follow-up [HR, 0.77 (95% CI, 0.54–1.11)]. Weight gain was not associated with death in the full study population. Among overweight women who gained >5%–<10% of body weight, a significant adverse association emerged 54 months after diagnosis (Supplementary Table S1).

In cubic spline analyses treating percent weight change as a continuous exposure, we found a significant, nonlinear relationship of weight change to mortality. Any degree of weight loss was strongly associated with all-cause (Fig. 2) and breast cancer–specific death (Supplementary Fig. S1), while large weight gain had an adverse association only in the upper exposure range. For example, the spline estimates suggested gaining 10% of diagnosis

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Table 2. Association of postdiagnosis weight change with breast cancer–specific and all-cause mortality

	HR (95% CI)									
	Large loss (≥10%)		**Modest loss (>5%–<10%)**		**Stable (within 5%)**		**Modest gain (>5%–<10%)**		**Large gain (≥10%)**	
	HR (95% CI)									
Breast cancer–related death										
# Events, at risk 503/12,950	Events	*N*	Events	*N*	Events	*N*	Events	*N*	Events	*N*
	79	827	73	1,536	264	7,836	57	1,645	30	746
Age/race-adjusted[a]	3.01 (2.34–3.87)		1.42 (1.09–1.83)		Ref.		1.01 (0.76–1.34)		1.14 (0.78–1.67)	
Multivariable[b]	2.13 (1.65–2.76)		1.24 (0.95–1.61)		Ref.		1.06 (0.79–1.41)		0.98 (0.67–1.44)	
All-cause death										
# Events, at risk	Events	*N*	Events	*N*	Events	*N*	Events	*N*	Events	*N*
980/12,950	159	827	133	1,536	534	7,836	102	1,645	52	746
Age/race-adjusted[a]	2.95 (2.47–3.52)		1.26 (1.04–1.53)		Ref.		0.94 (0.76–1.17)		1.11 (0.84–1.48)	
Multivariable[b]	2.24 (1.87–2.69)		1.15 (0.95–1.39)		Ref.		0.96 (0.78–1.19)		0.98 (0.74–1.31)	

[a]Adjusted for age at diagnosis (categorical) and race.

[b]Additionally adjusted for alcohol, smoking status, comorbidities, prediagnosis body mass index (categorical), stage, grade, receipt of adjuvant chemotherapy (yes/no), receipt of radiotherapy (yes/no), and tumor characteristics (ER, PR, and HER2 status).

body weight was not associated with breast cancer–specific [HR, 1.09 (95% CI, 0.81–1.45)] or all-cause mortality [HR, 1.06 (95% CI, 0.85–1.31)], while gaining 25% of diagnosis body weight was marginally associated with breast cancer–specific [HR, 1.62 (95% CI, 1.00–2.63] and all-cause mortality [HR, 1.45 (95% CI, 0.98–2.15)].

Analyses by subgroup

We stratified analyses by subgroups, including age, stage, BMI, and race/ethnicity measured at diagnosis, as well as receipt of adjuvant chemotherapy. We observed stronger associations of large weight loss among younger women (<55 years) for breast cancer–specific ($P_{interaction} = 0.04$) and all-cause death ($P_{interaction} = 0.02$) and women with stage III cancer for all-cause death ($P_{interaction} = 0.01$; Table 3). Large losses had consistently adverse associations with survival and weight gain had no association (Supplementary Table S2). We did not find any significant interactions by breast cancer subtype, but it should be noted that power was limited for the less common subtypes, particularly $HER2^+$ (Supplementary Table S3).

In sensitivity analyses, we found stronger associations with weight loss among never-smokers. Controlling for at-diagnosis BMI or defining exposure as weight change from 12 to 24 months postdiagnosis produced similar associations (data not shown).

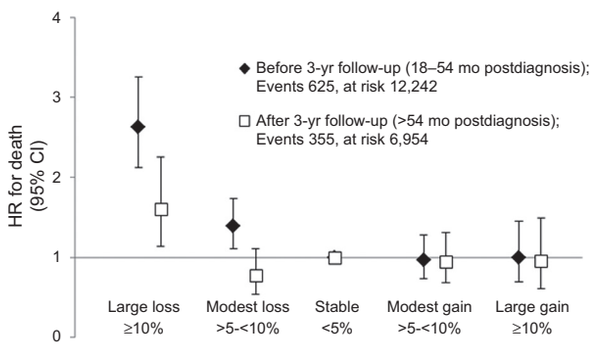

Figure 1.

Postdiagnosis weight change category and all-cause mortality by period of follow-up. Model adjusted for age at diagnosis (continuous), race, smoking status, alcohol intake, stage (in BMI subgroup), grade, comorbidities, tumor characteristics, receipt of chemotherapy (yes/no), receipt of radiotherapy (yes/no), and prediagnosis BMI.

Discussion

This study of 12,590 breast cancer survivors is the largest U.S.-based cohort to examine the association of postdiagnosis weight change and mortality. We found the association of postdiagnosis weight change varied over follow-up. For women who lost weight, the HRs were highest in the earlier postdiagnosis period, from 18 to 54 months. However, large weight loss (≥10%) remained associated with worse survival even in the later period of follow-up (>54 months postdiagnosis). For moderate weight loss (>5%–10%), risk of death was significantly increased in the earlier postdiagnosis period, but not later. Weight gain was not associated with death in the earlier postdiagnosis period; later in follow-up an adverse association emerged, but only for overweight women. Results were similar for death due to breast cancer.

The increased risk of death with large weight loss and the lack of a decreased risk with modest weight loss are consistent with previous observational studies (8–12). It is possible that large weight loss reflects treatment and disease burden rather than voluntary improvement in lifestyle behaviors. Indeed, with few exceptions (11), observational studies have not assessed the intentionality of weight loss. Ongoing trials in Europe (5, 20) and the United States (3) should help to determine whether intentional weight loss improves breast cancer survival.

Although we did not have information on intentionality, we found large weight loss was consistently harmful across all subgroups. This suggests that even among overweight/obese women, there may be patients for whom weight loss has an adverse rather than protective influence on survival after breast cancer. One reason for this could be that during the cancer trajectory, alterations in nutrient intake and absorption impact energy metabolism and mobilization. Surgery, radiotherapy, and chemotherapy may lead to reduced physical activity, reduced appetite, nausea, diarrhea, and other symptoms that could produce weight loss, or, even in the absence of weight loss, loss of muscle (21, 22). Weight loss during treatment is associated with chemotherapy-related toxicity and decreased survival (23, 24). Patients may need some degree of metabolic reserve to withstand active treatment, and weight loss in the early postdiagnosis period, intentional or

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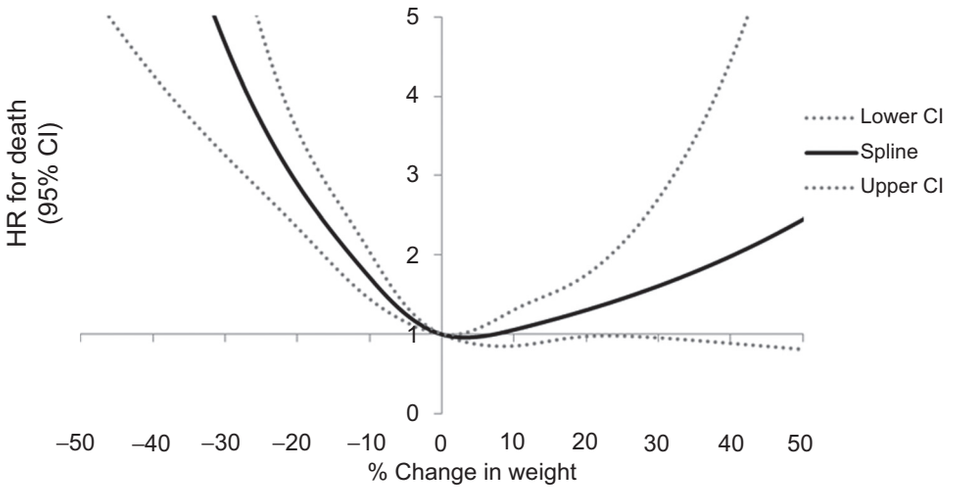

Figure 2.
Postdiagnosis weight change and all-cause mortality ($n = 12,590$; deaths = 980). Model adjusted for age at diagnosis (continuous), race, smoking status, alcohol intake, stage (in BMI subgroup), grade, comorbidities, tumor characteristics, receipt of chemotherapy (yes/no), receipt of radiotherapy (yes/no), and at-diagnosis BMI.

not, may combine with the metabolic burden of treatment and recovery to adversely impact the transition into survivorship. Consistent with this hypothesis, we found large weight loss in the 18 months after diagnosis was most strongly associated with mortality in the earlier period of follow-up (18–54 months postdiagnosis); however, the association of large weight loss with worse survival persisted even into the later follow-up period (>54 months postdiagnosis).

With regards to postdiagnosis weight gain, associations with survival have been inconsistent. For example, a recent meta-analysis concluded postdiagnosis weight gain ≥10% of body-weight was associated with higher all-cause mortality only for women whose BMI at diagnosis was <25 kg/m^2. There was no association with breast cancer–specific mortality or among women with BMI ≥25 kg/m^2 at diagnosis (13). This meta-analysis did not address weight loss. Our study also found an adverse association of weight gain, but only later in follow-up and only among women with at-diagnosis BMI 25–<30 kg/m^2. In our analysis, power was limited to evaluate large weight gain as few (6%) breast cancer survivors gain ≥10% of diagnosis body weight.

We found no evidence of variation by breast cancer subtype, although power was limited in less common subgroups (i.e., HER2$^+$). Contrary to our finding that weight gain was not associated with survival, a pooled analysis of 6,295 5-year survivors of early-stage ER$^+$ cancer found that weight gain ≥10% was associated with late recurrence (25). Consistent with our results, the Shanghai Breast Cancer Survival Study found women with TNBC who lost ≥5% of body weight by 18 or 36 months postdiagnosis had higher mortality compared with women with stable body weight; weight gain was not associated with mortality.

A key limitation of ours and other studies of weight change is the lack of information on body composition (26). Even for a patient with stable weight, there may be considerable loss/gain of skeletal muscle and/or fat. At-diagnosis sarcopenia (loss of muscle mass, strength, and function) predicts worse survival (27). Sarcopenia combined with subsequent muscle loss may explain the adverse associations with weight loss: skeletal muscle is a key tissue for insulin-mediated glucose uptake and muscle loss may contribute to systemic inflammation and insulin resistance, which are associated with poor breast cancer outcomes (28–31).

Table 3. Association of postdiagnosis weight change and all-cause and breast cancer–specific mortality by age and stage

	# Events/*N*	Large loss (≥10%)	Modest loss (>5%–<10%)	Stable (within 5%)	Modest gain (>5%–<10%)	Large gain (≥10%)	$P_{interaction}$
				HR (95% CI)			
Breast cancer–related death							
Age at diagnosis							
<55 years	181/4,856	2.43 (1.51–3.09)	1.69 (1.10–2.57)	Ref.	0.78 (0.49–1.24)	1.10 (0.66–1.84)	0.04
>55 years	322/7,734	2.10 (1.54–2.86)	1.04 (0.75–1.46)	Ref.	1.40 (0.97–2.02)	0.84 (0.46–1.51)	
Stage							
III	187/1,258	2.22 (1.47–3.37)	1.68 (1.13–2.49)	Ref.	0.90 (0.50–1.60)	1.39 (0.78–2.47)	0.24
II	229/4,378	2.42 (1.65–3.54)	1.21 (0.82–1.81)	Ref.	1.10 (0.73–1.65)	0.84 (0.47–1.50)	
I	87/6,954	1.37 (0.67–2.84)	0.41 (0.16–1.03)	Ref.	1.12 (0.61–2.05)	0.61 (0.19–1.99)	
All-cause death							
Age at diagnosis							
<55 years	243/4,856	2.95 (2.01–4.34)	1.57 (1.08–2.28)	Ref.	0.69 (0.45–1.05)	1.12 (0.72–1.75)	0.02
>55 years	737/7,734	2.21 (1.80–2.72)	1.05 (0.84–1.31)	Ref.	1.10 (0.86–1.40)	0.88 (0.60–1.29)	
Stage							
III	240/1,258	2.16 (1.49–3.14)	1.65 (1.16–2.35)	Ref.	0.91 (0.55–1.50)	1.42 (0.87–2.34)	0.01
II	401/4,378	2.45 (1.86–3.25)	1.13 (0.83–1.52)	Ref.	0.84 (0.60–1.17)	0.78 (0.50–1.23)	
I	339/6,954	2.48 (1.80–3.42)	0.80 (0.55–1.15)	Ref.	1.07 (0.77–1.50)	0.86 (0.48–1.55)	

NOTE: Adjusted for age at diagnosis (continuous), race, smoking status, alcohol intake, stage (in BMI subgroup), grade, comorbidities, tumor characteristics, receipt of adjuvant chemotherapy (yes/no), receipt of radiotherapy (yes/no), and prediagnosis BMI. $P_{interaction}$ from likelihood ratio test comparing models with and without interaction terms of weight change category and each subgroup variable.

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Furthermore, the type of fat loss (e.g., subcutaneous versus visceral) may differentially influence survival. The relation of changes in weight and body composition to survival is an ongoing area of research that furthers our understanding of mechanisms and how to target interventions.

As noted earlier, the association of large weight loss with worse survival was more pronounced earlier in follow-up. One prior study examined temporal patterns of mortality in breast cancer survivors: the Long Island Breast Cancer Study Project (LIBCSP) found a stronger influence of weight change on survival earlier in follow-up (within 2 years postdiagnosis) than later (7). The LIBCSP data also suggest that excess cardiovascular (CVD) mortality among breast cancer survivors (compared with women without a breast cancer history) only becomes evident 7 years postdiagnosis (32), providing further evidence that mortality associations vary over time. Later in follow-up, overweight women in our study who gained weight experienced higher all-cause and breast cancer–specific mortality; we speculate that with additional follow-up all women gaining substantial weight might experience worse survival due to CVD (already a contributing cause for 30% of deaths) and perhaps late recurrence as weight gain increases circulating estrogen, hyperinsulinemia, and inflammatory cytokine production (28). However, there were few overweight women who gained >5% of diagnosis body weight.

An important strength of our study was frequent weighing by medical assistants, allowing us to match prospectively collected weights to index dates and harmonize exposure timing across participants. In contrast, other studies used self-reported or recalled weight. We addressed some limitations of prior studies by controlling for adjuvant chemotherapy and tumor characteristics and identifying patients at diagnosis (8). We also had sufficient statistical power to examine separate weight gain and loss categories. Our large sample was racially and ethnically diverse, enhancing generalizability.

Among limitations, we lacked information on adjuvant endocrine therapy, disease recurrence, or intentionality of weight loss. However, sensitivity analyses examining weight changes between 12 months (when treatment is typically complete and disease-induced weight loss less likely) and 24 months postdiagnosis revealed similarly adverse associations of large weight loss. Our follow-up began 18 months after diagnosis, thereby excluding early deaths and partially mitigating confounding by severe disease. Also, stratified analyses showed similar associations of large weight loss with mortality regardless of stage. Large weight loss was significantly associated with worse survival in both earlier and later periods of follow-up; however, associations were stronger closer to diagnosis. One interpretation is that the harms of weight loss wane over time; another is that patients susceptible to harm are depleted from the risk set later in follow-up.

In conclusion, large weight loss among breast cancer survivors was associated with worse survival, even later in follow-up. While upcoming trials will provide information about the effect of intentional weight loss in overweight/obese breast cancer survivors, many patients may also experience large weight loss regardless of intervention. Research should examine the changes in body composition that accompany weight loss among breast cancer survivors and how changes in body composition influence long-term prognosis after a diagnosis of breast cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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