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

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Abstract

Background—Achieving healthy weight is recommended for all breast cancer survivors. Previous research on post-diagnosis weight change and mortality had conflicting results.

Materials and methods—We examined whether change in bodyweight in the 18mo 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 18mo post-diagnosis weight until death or June, 2015 (median follow-up [range]: 3 [0–9] years). We divided follow-up into earlier (18–54mo) and later (>54mo) post-diagnosis periods.

Results—Mean (SD) age-at-diagnosis was 59 (11) yrs. 980 women died, 503 from breast cancer. Most women maintained weight within 5% of diagnosis bodyweight; weight loss and gain were equally common at 19% each. Compared to weight maintenance, large losses (≥10%) were associated with worse survival, with hazard ratios (HR) 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 post-diagnosis weight loss is associated with worse survival in both earlier and later post-diagnosis periods, independent of treatment and prognostic factors.

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Impact—Weight loss and gain are equally common after breast cancer, and weight loss is a consistent marker of mortality risk.

Keywords

Body Weight Changes; breast cancer; survival; mortality; life style

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 post-menopausal 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 post-diagnosis weight gain or loss are heterogeneous. In almost all studies, post-diagnosis weight loss predicts worse survival, (6–11) though not without exception. (12) Similarly, post-diagnosis 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) Further, 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.

The present study examines weight change in the 18 months following 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 post-diagnosis 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, co-morbidities, chemotherapy treatment and breast cancer subtype. Additionally, we evaluate whether the influence of post-diagnostic weight change on survival varies over the course of follow-up, examining separate associations earlier (18–45 months) and later (≥54 months) post-diagnosis.

MATERIALS AND METHODS

Study population

We included all women ages 18–80 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 post-diagnosis (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, standard deviation [SD] 2 weeks from diagnosis). We defined the "post-diagnosis" as the weight closest to 18 months post-diagnosis within 3 months (mean [SD] 18 [1] months). "Post-diagnosis weight change" was the difference of the post-diagnosis and at-diagnosis weights. From weights measured ~12 months pre-diagnosis (range 6–30 months, mean [SD] 11 [5] months pre-diagnosis]) we calculated pre-diagnosis BMI.

Our main exposure was percent weight change after diagnosis computed as "post-diagnosis 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 gain (≥10%).

Mortality outcomes

For mortality outcomes, we used data from the KPNC mortality file, comprised 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 pre-diagnosis 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 post-diagnosis) 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 post-diagnostic 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 post-diagnosis, determined empirically and through inspection of Kaplan-Meier curves to be a meaningful cut-point).

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 pre-diagnostic 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 hazard ratio estimates and was not included in the final multivariable model.

To assess non-linearity, 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, and stable weight (<5% change from at-diagnosis weight) as reference.

To examine heterogeneity by patient characteristics (race/ethnicity, age, co-morbidities, 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 et al(18) from the 3-marker immunohistochemistry and substituted grade for Ki67 as proposed at the St. Gallen's Consensus Conference(19). Subtypes were defined as: 1) Surrogate Luminal A (well/moderately differentiated, ER+/PR+ and Her2−); 2) Surrogate Luminal B (poorly/undifferentiated, ER+ or PR+ and PR− or Her2+); 3) HER2+, endocrine negative (ER−/PR− and Her2+); and 4) 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 post-diagnosis, 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 pre-diagnosis BMI influenced findings. Finally, as the effects of weight loss later in the post-diagnosis period may differ, we evaluated weight changes between 12 and 24 months post-diagnosis with subsequent death. We used SAS software version 9.3 (SAS, Inc., Cary, NC) 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 following diagnosis, 19% of women lost >5% of bodyweight (mean [SD] weight loss: 18 [12] pounds); 19% gained >5% of bodyweight (mean [SD] weight gain: 15 [9] pounds); and 62% maintained a stable weight (mean [SD] weight change: 0 [5] pounds). Table 1 shows participant characteristics by weight change category. Compared to 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 co-morbidities. 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 to 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 multi-variable adjustment, the positive 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 18–54 months post-diagnosis) and later (≥54 months post-diagnosis) periods of follow-up. Post-diagnosis weight loss ≥10% was associated with worse survival earlier (HR, 2.63 [95% CI, 2.12–3.26]) and later in follow-up, though 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 bodyweight, a significant adverse association emerged after 3 years (Supplemental Table S1).

In cubic spline analyses treating percent weight change as a continuous exposure, we found a significant, non-linear relationship of weight change to mortality. Any degree of weight loss was strongly associated with all-cause (Figure 2) and breast cancer-specific death (Supplemental Figure 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 body weight was not associated with breast-cancer specific (HR, 1.09 [95% CI, 0.81–1.45]) and 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 (Supplemental 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+ (Supplemental 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 post-diagnosis produced similar associations (data not shown).

DISCUSSION

This study of 12,590 breast cancer survivors is the largest U.S.-based cohort to examine the association of post-diagnosis weight change and mortality. We found the association of post-diagnosis weight change varied over follow-up. For women who lost weight, the hazard ratios were highest in the earlier post-diagnosis 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 post-diagnosis). For moderate weight loss (>5–10%), risk of death was significantly increased in the earlier post-diagnosis period, but not later. Weight gain was not associated with death in the earlier post-diagnosis 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 haven’t assessed intentionality of weight loss. Ongoing trials in Europe (5, 20) and the U.S. (3) should help to determine whether intentional weight loss improves breast cancer survival.

Though 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 post-diagnosis period – intentional or 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 following diagnosis was most strongly associated with mortality in the earlier period of follow-up (18 to 54 months post-diagnosis); however, the association of large weight loss with worse survival persisted even into the later follow-up period (≥54 months post-diagnosis).

With regards to post-diagnosis weight gain, associations with survival have been inconsistent. For example, a recent meta-analysis concluded post-diagnosis weight gain ≥10% of bodyweight was associated with higher all-cause mortality only for women whose

BMI at diagnosis was <25 kg/m2. There was no association with breast cancer-specific mortality or among women with BMI ≥25 kg/m2 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 since few (6%) breast cancer survivors gain ≥10% of diagnosis bodyweight.

We found no evidence of variation by breast cancer subtype, though 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 bodyweight by 18- or 36-months post-diagnosis had higher mortality compared to women with stable bodyweight; 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) 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 post-diagnosis) than later. (7) The LIBCSP data also suggest that excess cardiovascular (CVD) mortality among breast cancer survivors (compared to women without a breast cancer history) only becomes evident 7 years post-diagnosis, (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 since weight gain increases circulating estrogen, hyperinsulinemia and inflammatory cytokine production. (28) However, there were few overweight women who gained >5% of diagnosis bodyweight.

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 post-diagnosis revealed similarly adverse associations of large weight loss. Our follow-up began 18 months following 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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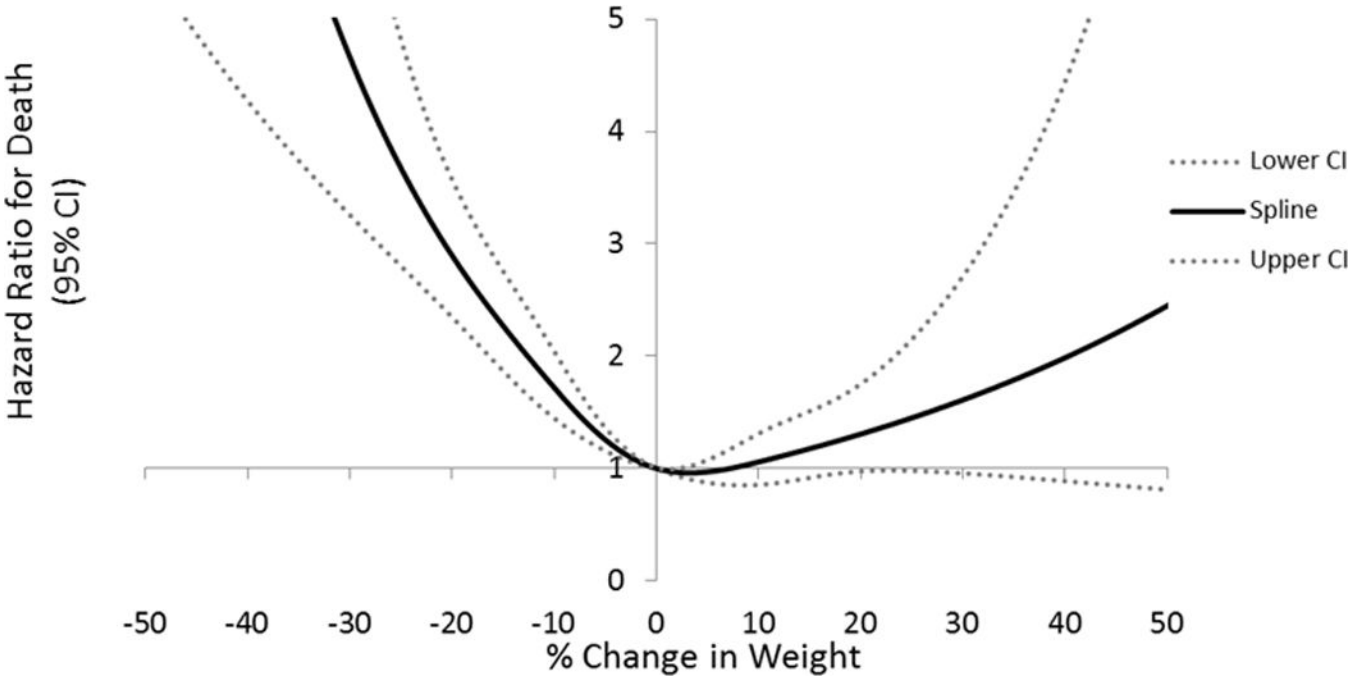

Figure 1. Post-Diagnosis Weight Change Category and All-cause Mortality by Period of Follow-Up

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 radiation therapy (yes/no), and pre-diagnosis BMI.

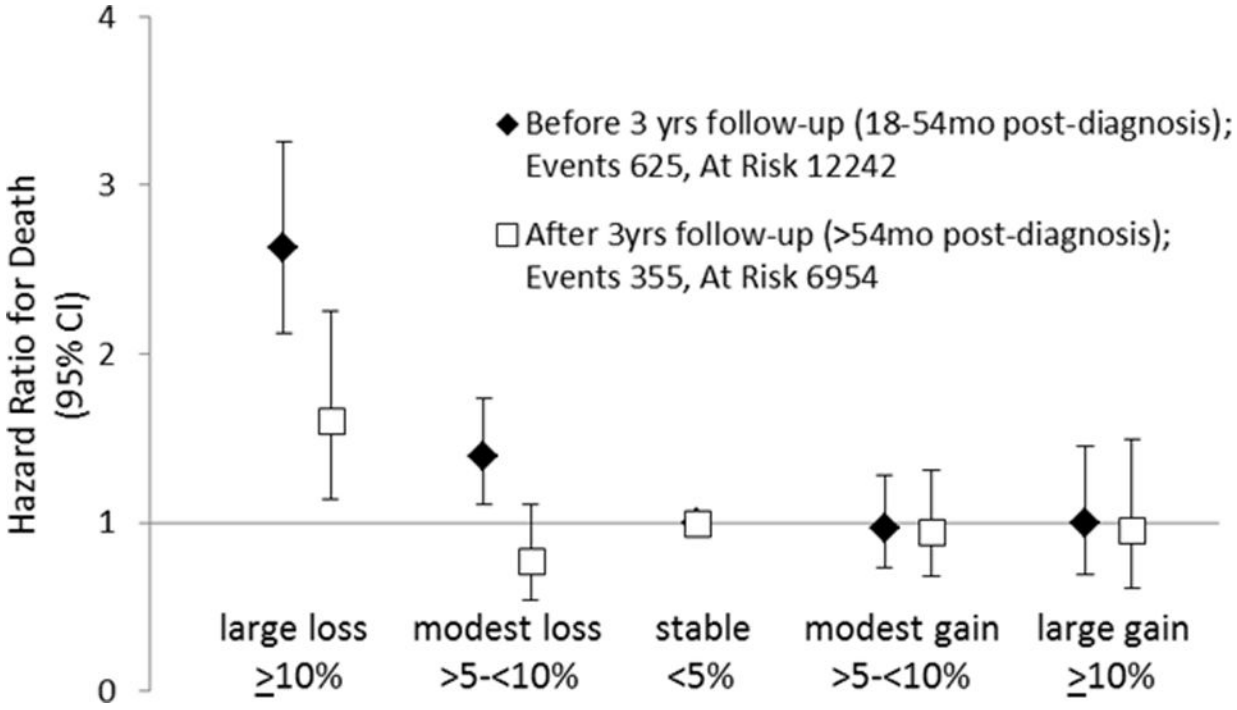

Figure 2. Post-Diagnosis Weight Change and All-cause Mortality (n=12,590; deaths=980)

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 radiation therapy (yes/no), and at-diagnosis BMI

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Table 1

Characteristics by category of weight change in the Kaiser Permanente Northern California population of breast cancer patients diagnosed from 2005–2013 (N=12,590)

	Large Loss (≥10%)	Modest Loss (>5–<10%)	Stable (within 5%)	Modest Gain (>5–<10%)	Large Gain (≥10%)	Total
N	**827**	**1536**	**7836**	**1645**	**746**	**12590**
			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						

	Large Loss (≥10%)	Modest Loss (>5–<10%)	Stable (within 5%)	Modest Gain (>5–<10%)	Large Gain (≥10%)	Total
N	**827**	**1536**	**7836**	**1645**	**746**	**12590**
I	45	50	58	57	58	55
II	39	37	33	35	33	35
III	16	13	9	8	9	10
Breast Cancer Subtype[1]						
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
Radiation Therapy	34	40	43	42	34	42

[1]Definitions adapted by Prat et al from the 3-marker immunohistochemistry plus grade subtypes in the St. Gallen's Consensus Conference we separated breast cancer into subtypes as follows: 1) Surrogate Luminal A (well or moderately differentiated and ER+ and PR+ and Her2−); 2) Surrogate Luminal B (poorly or undifferentiated ER+ or PR+ and any of PR−, Her2+); 3) HER2 positive, endocrine negative (ER−, PR−, and Her2+); and 4) Triple negative (ER−, PR−, and Her2−).

Table 2

Association of Post-Diagnosis Weight Change With Breast-Cancer-specific & All-cause Mortality Hazard Ratio (95% Confidence Interval)

Large Loss (≥10%)			**Modest Loss (>5–<10%)**		**Stable (within 5%)**		**Modest Gain (>5–<10%)**		**Large Gain (≥10%)**	
Breast Cancer Death					HR (95% CI)					
#Events, At risk 503/12,950	Events	N	Events	N	Events	N	Events	N	Events	N
	79	827	73	1536	264	7836	57	1645	30	746
Age/race-adjusted *	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)	
Multivariate **	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)	
Overall Death										
#Events, At risk 980/12,950	Events	N	Events	N	Events	N	Events	N	Events	N
	159	827	133	1536	534	7836	102	1645	52	746
Age/race-adjusted *	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)	
Multivariate **	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)	

* Adjusted for age at diagnosis (categorical), and race

** Additionally adjusted for alcohol, smoking status, comorbidities, pre-diagnosis body mass index (categorical), stage, grade, receipt of adjuvant chemotherapy (yes/no), receipt of radiation therapy (yes/no), and tumor characteristics (ER, PR and HER2 status)

Table 3

Association of Post-Diagnosis 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%) HR (95% CI)	Modest Gain (>5–<10%)	Large Gain (≥10%)	P Interaction
Breast Cancer Death							
Age at diagnosis							
<55years	181/4856	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	322/7734	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	187/1258	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	229/4378	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	87/6954	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							
<55years	243/4856	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	737/7734	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	240/1258	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	401/4378	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	339/6954	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)	

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 radiation therapy (yes/no), and pre-diagnosis BMI

P-Interaction from likelihood ratio test comparing models with and without interaction terms of weight change category and each subgroup variable