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Pre-diagnosis body mass index, post-diagnosis weight change, and prognosis among women with early stage breast cancer

Bette J. Caan,

Division of Research, Kaiser Permanente Medical Program of Northern California, 2000 Broadway, Oakland, CA 94612, USA

Marilyn L. Kwan,

Division of Research, Kaiser Permanente Medical Program of Northern California, 2000 Broadway, Oakland, CA 94612, USA

Georgina Hartzell,

Division of Research, Kaiser Permanente Medical Program of Northern California, 2000 Broadway, Oakland, CA 94612, USA

Adrienne Castillo,

Division of Research, Kaiser Permanente Medical Program of Northern California, 2000 Broadway, Oakland, CA 94612, USA

Martha L. Slattery,

Department of Internal Medicine, University of Utah, 375 Chipeta Way Suite A, Salt Lake City, UT 84108, USA

Barbara Sternfeld, and

Division of Research, Kaiser Permanente Medical Program of Northern California, 2000 Broadway, Oakland, CA 94612, USA

Erin Weltzien

Division of Research, Kaiser Permanente Medical Program of Northern California, 2000 Broadway, Oakland, CA 94612, USA

Bette J. Caan: bette.caan@kp.org; Marilyn L. Kwan: marilyn.l.kwan@kp.org

Abstract

Objective—We examined the association between body mass index (BMI) around the time of diagnosis, weight change post-diagnosis, and breast cancer prognosis in a prospective cohort study of 1,692 breast cancer survivors.

Methods—Pre-diagnosis weight, weight at study entry, and height was obtained from mailed questionnaires and then weight change and BMI were calculated. After approximately seven years of follow-up, 207 recurrences, 99 deaths due to breast cancer, and 162 deaths due to any cause were reported. Delayed entry Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI), controlling for treatment and known prognostic factors.

Results—Being obese one year before diagnosis was associated with an increased risk of death from any cause (HR = 1.6; 95% CI: 1.1–2.3) and a suggestion of increased risk of death from breast cancer (HR = 1.6; 95% CI: 0.9–2.7). However, weight gain up to four years after a breast cancer diagnosis was not associated with an increased risk of recurrence or death from any cause nor did moderate weight loss (5–10%) decrease risk of these outcomes. There was some evidence

that women who had larger weight losses ($\geq 10\%$) between pre-diagnosis and study entry had an increased risk of recurrence (HR = 1.7; 95% CI 1.0–2.6) and death due to any cause (HR = 2.1; 95% CI 1.3–3.4) compared to being weight stable. This elevated risk was more pronounced among women who were obese before diagnosis (BMI ≥ 30 kg/m²) or who had ER– or PR– tumors.

Conclusion—We found that being obese before breast cancer diagnosis was associated with increased risk of recurrence and poorer survival, corroborating results from previous studies. However, weight gain after diagnosis did not confer additional risk. Body weight pre-diagnosis appears to be the strongest predictor of an adverse breast cancer prognosis.

Keywords

BMI; Weight gain; Breast cancer; Prognosis; Recurrence; Survival; Death

Introduction

Substantial evidence exists that weight gain often occurs in women after breast cancer diagnosis. This increase in weight is most common among pre-menopausal women at diagnosis as well as those who receive chemotherapy as part of their treatment [1,2]. The average weight gains measured in the early post-chemotherapy years have been reported to range from 1.7 to 4.4 kg, with one-third of patients gaining more than 5 kg [3–6]. Although the majority of the breast cancer literature to date has suggested that higher body mass index (BMI) or body weight (overweight or obese) at diagnosis is associated with a poorer prognosis [3,7–16], few studies have specifically addressed whether weight change following diagnosis influences outcomes.

Among the limited number of studies that have examined the potential association between weight change and breast cancer prognosis, many are based on data collected more than 20 years ago when weight gains among breast cancer patients were much larger. Most studies have reported inconsistent results based on small sample sizes and use of non-uniform prognostic outcome measures [17–24]. The Nurses' Health Study, which is the largest and among the most recent study to date, collected self-reported body weight measures in a sub-sample of over 5,000 generally healthy women who were subsequently diagnosed with breast cancer and followed for a median of nine years [22]. They reported an intriguing finding that a gain in BMI post-diagnosis was associated with poorer prognosis in women who reported never smoking but not in women who reported ever smoking. We recently conducted a study using two separate cohorts of breast cancer survivors (Life After Cancer Epidemiology [LACE] and the comparison group of the WHEL [Women's Healthy Eating and Living] study) [24] examining the effect of weight change from one year prior to diagnosis to study enrollment (approximately two years after diagnosis) on breast cancer recurrence among 3,215 women diagnosed with early stage breast cancer (Stage I ≥ 1 cm, II, or IIIA). We found no association between moderate (5–10%) or large ($\geq 10\%$) weight gain and risk of breast cancer recurrence up to seven years post-diagnosis.

Given the limited and relatively non-comparable literature regarding weight gain and breast cancer prognosis, we decided to expand and build upon our first study [24] by examining exclusively in the LACE cohort the associations between (1) BMI one year prior to diagnosis and post-diagnosis and risk of recurrence, death due to breast cancer, and death due to any cause and (2) weight change post-diagnosis on recurrence and death due to any cause. Furthermore, considering the fairly established association between overweight status at diagnosis and poorer prognosis, we wanted to determine whether the relationship between weight change and breast cancer prognosis varies by obesity around diagnosis as well as tumor hormone receptor and smoking status.

Materials and methods

Study cohort

The LACE cohort consists of 2,288 women diagnosed with invasive breast cancer between 1997 and 2000 and recruited primarily from the Kaiser Permanente Northern California (KPNC) Cancer Registry (82%) and the Utah Cancer Registry (12%). Additionally, a subset of women who declined participation in the Women's Healthy Eating and Living (WHEL) Trial, a dietary intervention trial to reduce risk for breast cancer recurrence, was a third source of participants (6%).

Eligibility criteria included being 18–70 years at enrollment; having been diagnosed with early stage, invasive primary breast cancer (Stage I $\geq$ 1 cm., Stage II, or Stage IIIA) 11–39 months before study enrollment; having completed their breast cancer treatment (except for adjuvant hormonal therapy) and being free of recurrence (based on recent mammography and clinical examination); and having had no history of other cancers within five years prior to enrollment. In addition, the breast cancer surgery had to have been either a total mastectomy or a breast sparing surgery followed by radiation, with an evaluation of axillary or sentinel node for disease staging. Subsequently, after medical record review, any woman who had a breast cancer recurrence, new breast primary, or death within the time between diagnosis and three months after enrollment was excluded.

Between January 2000 and April 2002, 5,656 women who were presumed to meet the LACE eligibility criteria were sent a recruitment package. Of these, 2,614 (46%) agreed to participate and completed the questionnaires. Subsequent medical record review to confirm eligibility resulted in 326 exclusions. Reasons for exclusions were breast cancer recurrence, new primary breast cancer, or death within the time between diagnosis and three months after enrollment into the study cohort (37%), incorrect stage (34%), other cancer within the five years before enrollment (10%), prior breast cancer (6%), more than 39 months since diagnosis (6%), incomplete demographic and medical data (3%), still receiving treatment (2%), and language difficulty (2%). The remaining 2,288 women constitute the LACE cohort. This analysis was restricted to 1,692 (74%) women who had a complete dataset on height, weight at 18 years, weight at one year pre-diagnosis, weight at study entry, age at diagnosis, hormone receptor status, breast cancer stage, number of positive nodes, treatment (chemotherapy and/or radiation therapy), and tamoxifen use. The 1,692 women who comprise the study sample have no significant differences compared to the LACE sample as a whole on major demographic and breast cancer risk factors (data not shown). Subjects entered the cohort on average 1.90 years after diagnosis (range: 0.92–3.24 years) and were subsequently followed on average five years (range: 0.25–6.86) post-enrollment. Further details on the LACE cohort are provided elsewhere [25]. The study was approved by the institutional review boards of KPNC and the University of Utah.

Weight measurements

Weight assessments used in these analyses include self-reported weight at one year pre-diagnosis as well as self-reported weight at study enrollment. Pre-diagnosis weight was collected through questionnaires in which women retrospectively recalled their weight. Weight and height at enrollment were self-reported from self-measurement as instructed on the questionnaire. For height, women were asked to stand with bare feet against the wall, and using a ruler pressed firmly on their head, to place a piece of tape where the ruler touched the wall. The measurement was to be recorded to the nearest half-inch. For weight, women were asked to record their most recent weight in light clothing without shoes, to the nearest half-pound, from a home or medical office scale.

Covariates

Information on medical prognostic factors was obtained either through electronic data sources available from Kaiser Permanente or from medical chart review for the non-Kaiser participants. Data included tumor size, histology, number of positive lymph nodes and any metastasis, hormone receptor status, and treatments. Treatment data included surgical procedures and associated dates, as well as types and dates of chemotherapy, radiation therapy, and hormone therapy. Tumor stage was calculated according to the American Joint Committee on Cancer (AJCC) (3rd edition of manual for staging of cancer). Data on menopausal status (pre-menopausal, post-menopausal) and smoking status (never, past, current) were obtained from the mailed baseline questionnaire at cohort entry. Physical activity was assessed (MET-hrs per week) from a mailed questionnaire modeled loosely on the Arizona Activity Frequency Questionnaire [26] and was divided into four domains: job or work-related activities (including volunteer work), non-work routine activities, recreational activities, and transportation.

Outcome assessment

For these analyses, three prognostic outcomes were considered: new breast cancer event, hereafter referred to as recurrence, death due to breast cancer, and death due to any cause. Recurrence includes a local/regional cancer recurrence, distant recurrence/metastasis, and development of a contralateral breast primary; death due to breast cancer includes death due to breast cancer as the primary or secondary cause on the death certificate; and death due to any cause is all deaths including those from breast cancer. Recurrences were ascertained by a mailed semi-annual (until April 2005) and annual (after April 2005) health status update questionnaire that asked participants to report any events occurring in the period since their last questionnaire. When needed, participants receiving care outside of Kaiser Permanente who reported any event were contacted to obtain permission to view their protected health information. Medical records were then reviewed to verify the outcome. All non-respondents to the health status questionnaire were called to complete the questionnaire by telephone. Participant deaths were determined through KPNC electronic data sources available on Kaiser members, a family member responding to a mailed questionnaire, or a phone call on non-Kaiser members. In the event of a long-term non-response, death certificates were requested for those participants outside of Kaiser who may have expired. For all study subjects who were known to have died, copies of death certificates were obtained to confirm death. Among all ascertained deaths, 55% had a primary or secondary cause of death due to breast cancer, with the remaining 45% due to other causes.

Statistical analysis

Weight change from one year pre-diagnosis to study entry was computed, as well as BMI ($\text{wt}[\text{kg}]/\text{ht}[\text{m}^2]$) for both one year pre-diagnosis and at study entry. Percent (%) weight gain was computed as $(\text{weight at study entry} - \text{weight at one year pre-diagnosis}) / (\text{weight at one year pre-diagnosis}) \times 100$. The percent weight gain was separated into categories of $\pm 5\%$, $\pm 5-10\%$, and $\pm >10\%$ and stratified by selected characteristics such as pre-diagnosis BMI and age at diagnosis. These categories of weight gain were chosen because they are commonly used for weight loss recommendations to reduce risk of obesity, heart disease, diabetes, and cancer [27–29]. Follow-up began at date of study entry and ended at date of first confirmed cancer recurrence, date of death, study drop-out date, or 12 March, 2007, whichever occurred first. Hazard ratios (HR) and 95% confidence intervals (CI) of a breast cancer event for BMI one year pre-diagnosis, BMI at study entry, and percent weight gain were computed adjusting for covariates using the delayed entry Cox proportional hazards model [30,31]. The delayed entry model adjusts for the fact that a woman who entered the study t years after the diagnosis of her original breast cancer was not under observation for a possible recurrence prior to t years. A linear test for trend was estimated by modeling

categorical variables of exposure on an ordinal scale. We also examined whether the associations between weight change and prognosis varied by BMI, tumor hormone receptor status, and smoking status by first generating strata-specific estimates and then including interaction terms in the Cox models. CIs not overlapping with 1.00 or p values <0.05 were considered statistically significant. For all analyses, we removed new primaries from the contralateral breast from the recurrence outcome to see if HRs changed significantly.

Results

Table 1 presents characteristics of the study population. The mean age at diagnosis was 58.3 years, with a mean time from diagnosis to study entry of 22.7 months. On average, women were followed for almost seven years after diagnosis. Overall, women gained weight since age 18 with the mean weights at age 18, one year pre-diagnosis, and study entry being 54.9 kg, 71.3 kg, and 72.9 kg, respectively. The average BMI of the study participants at one year pre-diagnosis was 26.9 kg/m² and at enrollment was 27.5 kg/m². Of the participants who reported menopausal status at diagnosis, 26.3% were pre-menopausal and 73.7% were post-menopausal. Of the total study population, 69.2% were ER+/PR+. Forty-six percent (46.7%) of the women were diagnosed with Stage I breast cancer, while 50.2% and 3.1% had Stage II and Stage IIIA, respectively.

The distribution of weight gain by selected characteristics is shown in Table 2. About half (47%) of the women remained weight stable ($\pm 5\%$) regardless of whether their BMI was above or below 30 kg/m² one year before diagnosis. However, of the women under 30 kg/m², 38.9% gained at least 5% of their body weight, compared to 25.9% gaining the same amount among women over 30 kg/m². Younger and pre-menopausal women were more likely to gain at least 5% of their body weight than older or post-menopausal women ($p < 0.001$). Women diagnosed with cancer stage greater than Stage I as well as women who underwent chemotherapy gained more weight ($p < 0.05$). Hormone receptor status did not have a significant effect on weight gain.

Being obese one year before diagnosis was associated with a statistically significant increased risk of death from any cause (HR = 1.6; 95% CI: 1.1–2.3) and a marginally significant risk of death from breast cancer (HR = 1.6; 95% CI: 0.9–2.7) after adjusting for stage, age at diagnosis, tamoxifen use, treatment, number of positive nodes, hormone receptor status, physical activity, and smoking status (Table 3). In a test for linear trend, increasing BMI before diagnosis was associated with a statistically significant increased risk of death due to any cause (p for trend = 0.03) and a suggestion of increased risk of both recurrence and death due to breast cancer (borderline statistically significant). In contrast, no statistically significant trends were found for an increased risk of either recurrence, death due to breast cancer, or death due to any cause with BMI at study entry (Table 3).

Weight gain after a breast cancer diagnosis did not increase the risk of recurrence or death due to any cause, and moderate weight loss (5–10%) did not confer any benefit. Women who lost at least 10% of their body weight between pre-diagnosis and study entry had a significantly increased risk of recurrence (HR = 1.7; 95% CI: 1.0–2.6) and death due to any cause (HR = 2.1; 95% CI: 1.3–3.4) compared to being weight stable after adjustment for stage, age at diagnosis, tamoxifen use, treatment, number of positive nodes, hormone receptor status, pre-diagnosis BMI, smoking, and physical activity. Linear tests for trend of increasing weight loss elevating risk for both recurrence and death due to any cause were marginally statistically significant (Table 4). After removing all women who were diagnosed with a recurrence or death due to any cause during the first year after entry into the cohort, the relationship with women who lost at least 10% of their weight and recurrence was attenuated (HR = 1.5; 95% CI: 0.9–2.5) and no longer significant, although the risk for death

due to any cause remained statistically significant (HR = 2.1; 95% CI: 1.2–3.6). We also examined the relationships between BMI and weight change with recurrence after removing the contralateral breast primaries ($n = 14$) from the recurrence definition, and results were essentially unchanged (data not shown).

When we further examined the associations of weight change and recurrence and death from any cause by BMI prior to diagnosis, again no increased risk of recurrence or death was observed for weight gain among either the obese or non-obese groups (Table 5). The increased risk associated with weight loss of at least 10% was statistically significant only among obese women for both recurrence (HR = 2.5; 95% CI: 1.2–5.1) and death from any cause (HR = 2.8; 95% CI: 1.4–5.6), although interactions for weight change between obese and non-obese were not statistically significant (Table 5). Assessing the associations for weight change and recurrence and death from any cause by tumor hormone receptor status revealed that the associations between weight loss of at least 10% and recurrence (HR = 2.1; 95% CI: 1.0–4.4) and death (HR = 2.5; 95% CI: 1.1–5.5) were statistically significant in the ER–, PR– group (Table 6), although again interactions between weight change and hormone receptor status for both outcomes did not achieve statistical significance. We examined weight change by smoking status (ever smoked versus never smoked), and no significant interactions were observed; subgroup findings were similar to the group as a whole (data not shown).

Discussion

In this large, prospective cohort study, we observed an approximately 60% increased risk of death from any cause for women who were obese around the time of diagnosis. Similar findings have been reported in several other studies [13–15,32]. Interestingly, gaining weight in the immediate post-diagnosis period (up to four years post-diagnosis) appeared to not be associated with a poorer prognosis. In contrast, for women who were obese before diagnosis, there was some evidence that weight loss ($\geq 10\%$) was associated with a poorer prognosis, resulting in an increased risk of death due to any cause.

Since we are the first to report that weight loss of this magnitude during the short-term survivorship period after breast cancer diagnosis is associated with increased risk of death and is more pronounced among obese compared to non-obese breast cancer patients, caution in interpretation of our findings is warranted. One obvious explanation for significant weight loss being related to increased risk of death could be that the breast cancer disease process itself caused the weight loss, and women whose cancer may have already metastasized but was not yet diagnosed at the time of study entry had greater weight loss. To investigate this possibility, we conducted the same analyses yet removed women who recurred or died within a year of study entry. While results for recurrence were attenuated and no longer significant, results for death due to any cause were unchanged. To explore this possible explanation further, we examined the mean time to recurrence or death by weight change categories to see if women who lost the greatest amount of weight had events that occurred closer to study entry. No significant differences between those who lost at least 10% of their weight and other categories of weight change were apparent. Thus, it is unlikely that these findings were a result of women being sicker at entry into the study. Alternatively, it is also possible that the significant finding of larger weight losses ($\geq 10\%$) being associated with increased risk of death occurred by chance. Although $\geq 10\%$ weight loss was the only category (Table 4) where the confidence interval did not include 1.0, the test for trend for weight loss was not significant at the 0.05 level. We conducted multiple tests in this study, and results must be considered in that context, as in any study. As recommended by Rothman [33,34] and Savitz [35], we did not choose to adjust for multiple comparisons, but

we acknowledge an inflation of the overall Type 1 error rate for the family of tests conducted in this study.

We previously reported that post-diagnosis weight gain did not increase the risk of recurrence in the first five to seven years after diagnosis utilizing data from two different study populations [24]. Our current analysis, which confirms our previous results, expanded on the prior study by extending follow-up time (women in LACE were on average seven years post-diagnosis) and examining the impact of weight change on death due to breast cancer and death due to any cause as well as assessing risk by hormone receptor status, pre-diagnosis BMI, and smoking status.

Weight gain after a breast cancer diagnosis is common, is likely due to increases in fat-free mass [1,36], and has been noted during the first year of diagnosis and up until at least four years post-diagnosis [5,6,37,38]. However, weight gain in the immediate period after a breast cancer diagnosis may not have a similar impact on prognosis as either pre-diagnosis weight, which may be more indicative of a lifetime of being overweight, or weight gains over the adult lifespan [12], which are usually of greater magnitudes and occur over a longer period of time. The literature regarding weight gain post-diagnosis and its effect on prognosis is not extensive and has provided mixed results [17–24]. Most studies were conducted with small samples over 20 years ago when chemotherapy regimens lasted one year and were often supplemented with steroids; thus early weight gains were considerably larger than has been observed in more recent studies with shorter chemotherapy regimens accompanied by effective adjuvant therapies. Two recent studies have been conducted with treatment regimens more comparable to the treatment experience of our study population: the Nurses' Health Study reported an increased risk of breast cancer death with increasing weight gain after breast cancer diagnosis only in those who never smoked [22], and a follow-up study of participants in the Collaborative Women's Longevity Study found an increased risk of dying in breast cancer survivors only among those who gained more than 22 pounds after diagnosis [39]. Twenty-two pounds is a substantial gain since we have observed an average weight gain of 1.7 kg in the LACE Study, which is similar in magnitude to that reported from another cohort study of breast cancer survivors who enrolled women during the same time period as our study [5].

Strengths of the LACE study include being one of the few existing cohorts of early-stage breast cancer survivors and one of the first studies to assess the effect of weight gain occurring past initial treatment. It should be noted that since women did not enter the cohort until they had completed chemotherapy and/or radiation treatment (on average two years post-diagnosis), our results cannot be generalized to outcomes that may have occurred in the initial post-diagnosis treatment period. Our results also cannot be generalized to weight gains that women may experience after the first four years post-diagnosis. Another limitation is that weight was self-reported, yet the correlation between self-report of pre-diagnosis weight and measured weight abstracted from medical records around the time of diagnosis was extremely high ($r = 0.94$). In addition, the mean self-reported weight was only 2% (1.5 kg) lower than the mean weight in the medical record. Furthermore, the data from this study confirm previous studies which have demonstrated excellent correlation ($r = 0.90$ – 0.99) between self-reported and measured weight [40,41].

In summary, our study findings show that being obese before breast cancer diagnosis was associated with increased risk of death due to any cause and a suggestion of an increase risk of death due to breast cancer, which corroborates results from previous studies. Additionally, weight gain after a breast cancer diagnosis did not further increase risk of a poorer prognosis. Body weight pre-diagnosis, which presumably reflects long-term lifestyle habits rather than short-term weight change that occurs in the immediate post-diagnosis

period, appears to be the strongest predictor of an adverse breast cancer prognosis. While there was some evidence that substantial weight loss after diagnosis was related to poorer prognosis and was strongest for obese women and women with ER– or PR– tumors, these findings need to be confirmed in other independent datasets before breast cancer survivors who are obese and otherwise healthy are advised against weight loss. Future studies should also examine the effect of weight change post-diagnosis on prognosis by both weight status at diagnosis and by tumor subtype, since for the latter, it is well-recognized that breast cancer is a heterogeneous disease and risk factors for prognosis may well vary by tumor subtype.

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Table 1Characteristics of the LACE Cohort ($n = 2,288$)

	<i>n</i>	Mean (SD)
Months from diagnosis to study entry	2,288	22.7 (6.7)
Months of follow-up ^a	2,288	83.9 (20.2)
Age at diagnosis (years)	2,288	58.3 (11.0)
Height (cm)	2,287	162.9 (6.9)
Weight at age 18 (kg)	2,240	54.9 (7.8)
Weight at one year pre-diagnosis (kg)	2,262	71.3 (16.2)
Weight at study entry (kg)	1,927	72.9 (16.3)
Change in weight pre-diagnosis to study entry (kg)	1,905	1.7 (7.6)
BMI at one year pre-diagnosis (kg/m ²)	2,262	26.9 (5.9)
BMI at study entry (kg/m ²)	1,928	27.5 (5.8)
Change in BMI pre-diagnosis to study entry (kg/m ²)	1,906	0.6 (2.8)
Tumor size (cm)	2,250	2.1 (1.3)
	<i>n</i>	%
Menopausal status at diagnosis ^b		
Pre-menopausal	520	22.8
Post-menopausal	1,458	63.8
Unknown/missing	307	13.4
Tamoxifen use		
Never	508	22.4
Past	153	6.7
Current	1,610	70.9
Treatment		
No radiation/no chemotherapy	395	17.8
Chemotherapy only	423	19.0
Radiation only	552	24.8
Both chemotherapy and radiation	855	38.4
Surgery		
Mastectomy	1,125	49.2
Conserving	1,162	50.8
Number of positive nodes		
0	1,363	63.2
1–3	567	26.3
4–6	122	5.7
7–9	37	1.7
≥10	67	3.1
Tumor size (cm)		
0 to < 2	1,206	53.6
2 to < 3	626	27.8

	<i>n</i>	Mean (SD)
3 to < 4	208	9.2
4 to < 5	104	4.6
≥5	106	4.7
Stage		
I	1,067	46.7
II	1,147	50.2
IIIA	70	3.1
Hormone receptor status		
ER+, PR+	1,551	69.2
ER+, PR−	305	13.6
ER−, PR+	38	1.7
ER−, PR−	348	15.5
Smoking history		
Never	897	53.2
Past	673	39.9
Current	116	6.9

^aMonths of follow-up defined as months from diagnosis to recurrence, death, or 12 March 2007, whichever came first

^bPre-menopausal status defined as date of diagnosis one year or less after date of last menstruation or date of last menstruation after date of diagnosis; post-menopausal status defined as date of diagnosis more than one year after date of last menstruation

Abbreviations: ER = Estrogen-receptor; PR = Progesterone receptor

Table 2Percent weight gain by selected characteristics in the LACE Cohort ($n = 1,692$)

	<i>n</i>	Large weight loss ≥10%	Moderate weight loss 5%, < 10%	Weight stable 0%, < 5%	Moderate weight gain 5%, < 10%	Large weight gain ≥10%
BMI one year pre-diagnosis (kg/m ²) ^a						
< 30	1,283	5.3	8.4	47.4	17.6	21.3
≥30	409	13.2	13.7	47.2	12.5	13.4
Age at diagnosis ^a						
> 55	1,041	7.7	11.1	52.7	14.8	13.7
≤ 55	651	6.5	7.5	38.7	18.9	28.4
Chemotherapy treatment ^a						
No	733	8.1	10.5	52.2	14.6	14.6
Yes	959	6.6	9.1	43.6	17.7	23.0
Tamoxifen use						
Never	370	8.1	8.4	50.0	13.5	20.0
Past	106	4.7	8.5	42.5	19.8	24.5
Current	1,216	7.1	10.2	47.0	16.9	18.8
Stage ^b						
I	800	6.7	9.2	51.9	14.8	17.4
II	847	7.8	10.0	43.0	18.2	21.0
IIIA	45	Too few observations to report				
Menopausal status at diagnosis ^{a,c}						
Pre-menopausal	352	4.8	6.8	41.2	18.5	28.7
Post-menopausal	1,118	7.2	11.3	51.2	15.7	14.6
Unknown/missing	222	10.8	6.3	37.8	16.2	28.8
Hormone receptor status						
ER+, PR+	1,152	7.3	9.7	47.1	16.6	19.3
ER- or PR-	540	7.0	9.6	47.8	15.9	19.6

^aChi-square test significant at $p < 0.0001$ ^bChi-square test significant at $p < 0.05$

^cPre-menopausal status defined as date of diagnosis one year or less after date of last menstruation after date of diagnosis; post-menopausal status defined as date of diagnosis more than one year after date of last menstruation

Abbreviations: BMI = Body mass index; ER = Estrogen-receptor; PR = Progesterone receptor

Delayed-entry Cox proportional hazard models^a for BMI and recurrence, death from breast cancer, and death from any cause

Table 3

<i>n</i>	Recurrence			Breast cancer death			Death from any cause		
	# Events	HR	95% CI	# Events	HR	95% CI	# Events	HR	95% CI
<i>BMI one year pre-diagnosis</i>									
Normal	760	79	Referent	30	Referent	58	Referent		
< 25 kg/m ²									
Overweight	520	70	1.3 (0.9, 1.8)	30	1.4 (0.8, 2.3)	50	1.2 (0.8, 1.7)		
25–30 kg/m ²									
Obese	409	58	1.3 (0.9, 1.9)	30	1.6 (0.9, 2.7) ^b	52	1.6 (1.1, 2.3) ^c		
≥30 kg/m ²									
Test for trend			<i>p</i> = 0.10			<i>p</i> = 0.08			<i>p</i> = 0.03
<i>BMI at study entry</i>									
Normal	651	76	Referent	27	Referent	50	Referent		
< 25 kg/m ²									
Overweight	571	74	1.0 (0.7, 1.4)	36	1.4 (0.8, 2.3)	60	1.2 (0.8, 1.8)		
25–30 kg/m ²									
Obese	467	57	1.0 (0.7, 1.4)	27	1.2 (0.7, 2.1)	50	1.3 (0.8, 1.9)		
≥30 kg/m ²									
Test for trend			<i>p</i> = 0.83			<i>p</i> = 0.53			<i>p</i> = 0.22

^a Adjusted for stage, age at diagnosis, tamoxifen use, treatment (chemotherapy/radiation therapy), number of positive nodes, ER status, smoking history, and MET-hours per week of non-sedentary activities

^b *p* ≤ 0.10

^c *p* ≤ 0.05

Abbreviations: HR = Hazard ratio; CI = Confidence interval; BMI = Body mass index

Table 4
Delayed-entry Cox proportional hazard models^a for weight gain and recurrence and death from any cause

<i>n</i>	Recurrence		Death from any cause			
	<i>n</i> = 1,689 (207 events)		<i>n</i> = 1,689 (160 events)			
	# Events	HR	95% CI	# Events	HR	95% CI
%Weight gain from pre-diagnosis to study entry						
Weight stable						
Within 5%	799	100	Referent		Referent	
Weight gain						
Gain 5–10%	277	30	0.8 (0.5, 1.2)	32	1.2 (0.8, 1.9)	
Gain ≥ 10%	327	35	0.8 (0.5, 1.2)	20	0.7 (0.4, 1.2)	
Test for trend			<i>p</i> = 0.99			<i>p</i> = 0.08
Weight loss						
Loss 5–10%	164	19	0.9 (0.6, 1.5)	15	1.1 (0.6, 1.9)	
Loss ≥ 10%	122	23	1.7 (1.0, 2.6) ^b	23	2.1 (1.3, 3.4) ^b	
Test for trend			<i>p</i> = 0.09			<i>p</i> = 0.09

^aAdjusted for stage, age at diagnosis, tamoxifen use, treatment (chemotherapy/radiation therapy), number of positive nodes, ER status, PR status, smoking history, and MET-hours per week of non-sedentary activities

^b*p* ≤ 0.05

Abbreviations: HR = Hazard ratio; CI = Confidence interval; BMI = Body mass index

Delayed-entry Cox proportional hazard models^a for weight gain and recurrence and death from any cause, by pre-diagnosis body mass index

Table 5

	Recurrence			Death from any cause		
	Obese (≥30 kg/m ²)			Obese (≥30 kg/m ²)		
	HR	95% CI	Not Obese (< 30 kg/m ²) n =1,283 (149 events)	HR	95% CI	Not Obese (< 30 kg/m ²) n =1,283 (110 events)
%Weight gain from pre-diagnosis to study entry						
Weight stable						
Within 5%			Referent			Referent
Weight gain						
Gain 5–10%	0.7	(0.2, 1.9)	0.9	(0.5, 1.4)	1.1	(0.4, 2.8)
Gain ≥ 10%	1.0	(0.4, 2.4)	0.8	(0.5, 1.2)	0.8	(0.3, 2.1)
Weight loss						
Loss 5–10%	0.5	(0.2, 1.4)	1.1	(0.6, 2.0)	0.4	(0.1, 1.5)
Loss ≥ 10%	2.5	(1.2, 5.1) ^b	1.4	(0.7, 2.8)	2.8	(1.4, 5.6) ^b
p for interaction		p = 0.47			p = 0.40	

^a Adjusted for stage, age at diagnosis, tamoxifen use, treatment (chemotherapy/radiation therapy), number of positive nodes, ER status, smoking history, and MET-hours per week of non-sedentary activities

^b p ≤ 0.05

Abbreviations: HR = Hazard ratio; CI = Confidence interval; BMI = Body mass index

Delayed-entry Cox proportional hazard models^a for weight gain and recurrence and death from any cause, by tumor hormone receptor status

Table 6

	Recurrence			Death from any cause		
	ER+/PR+	ER- or PR-		ER+/PR+	ER- or PR-	
	<u>n = 1,152 (123 events)</u>	<u>n = 540 (84 events)</u>		<u>n = 1,152 (98 events)</u>	<u>n = 540 (64 events)</u>	
	HR	95% CI	HR	95% CI	HR	95% CI
%Weight gain from pre-diagnosis to study entry						
Weight stable						
Within 5%		Referent		Referent		Referent
Weight gain						
Gain 5–10%	0.7	(0.4, 1.3)	0.8	(0.4, 1.6)	1.1	(0.6, 1.9)
Gain ≥ 10%	0.6	(0.4, 1.1) ^b	1.2	(0.7, 2.2)	0.7	(0.4, 1.3)
Weight loss						
Loss 5–10%	0.8	(0.4, 1.5)	1.1	(0.5, 2.4)	1.0	(0.5, 2.0)
Loss ≥ 10%	1.3	(0.7, 2.5)	2.1	(1.0, 4.4) ^c	1.8	(0.9, 3.3) ^b
<i>p</i> for interaction		<i>p</i> = 0.53				<i>p</i> = 0.95

^a Adjusted for stage, age at diagnosis, tamoxifen use, treatment (chemotherapy/radiation therapy), number of positive nodes, ER status, PR status, smoking history, and MET-hours per week of non-sedentary activities

^b *p* ≤ 0.10

^c *p* ≤ 0.05

Abbreviations: HR = Hazard ratio; CI = Confidence interval; BMI = Body mass index; ER = Estrogen receptor; PR = Progesterone receptor