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Post Diagnosis Weight Gain and Breast Cancer Recurrence In Women with Early Stage Breast Cancer

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ABSTRACT

PURPOSE: To examine whether weight gain after diagnosis of breast cancer affects the risk of breast cancer recurrence.

PATIENT AND METHODS: Patients included 3215 women diagnosed with early stage breast cancer (Stage I > 1 cm., II, and IIIA) who were enrolled either in an observational cohort of breast cancer survivors or were part of the comparison group of a dietary intervention trial to prevent breast cancer recurrence. We computed weight change from 1 yr prior to diagnosis to study enrollment. Delayed entry Cox proportional hazards models were used to evaluate associations of categories of weight change with time to recurrence, controlling for known prognostic factors.

RESULTS: Neither moderate (5-10%) nor large (>10%) weight gain (HR 0.8, 95%CI, 0.6 to 1.1; HR 0.9, 95% CI, 0.7 to 1.2, respectively) after breast cancer diagnosis was associated with an increased risk of breast cancer recurrence in the early years post diagnosis (median time of 73.7 months from diagnosis).

CONCLUSION: Our research provides evidence that weight gain commonly seen in the first several years following a breast cancer diagnosis does not increase a woman's risk for breast cancer recurrence in the first 5-7 years post diagnosis. However, this research does not address the effects of weight gain on overall survival or on the risk of other new cancers, other prognostic outcomes of concern to the breast cancer survivor.

Introduction

Several comprehensive reviews of the evidence relating body weight to breast cancer prognosis [1-4] have concluded that overweight status at the time of breast cancer diagnosis is associated with a poorer prognosis. These reviews report that roughly two-thirds of the studies conducted in the last decade have shown that higher body mass index (BMI) or body weight (overweight or obesity) are significant risk factors for recurrent disease or decreased survival [1;3;4], with only 25% showing a null effect and 10% suggesting a significant inverse association [3]. However, two recent randomized clinical trials, which offer the advantages of large populations in which clinical prognostic factors are well defined, have found an effect of obesity only on overall survival [5] or only on new contralateral breast disease, but not recurrence [6]. Several plausible mechanisms have been proposed to support the effect of body weight on breast cancer growth. Among them is the hypothesis that excess adipose tissue contributes to increased circulating bioavailable estrogen, through conversion of precursor adrenal androgens and reduced sex hormone binding globulin concentration [7]. In addition, it is hypothesized that visceral obesity increases both insulin and insulin–like growth factors(IGF-I, IGF-II) which stimulate the synthesis of sex steroid hormones [3] which are involved in the regulation of normal and malignant growth of epithelial breast cells [8;9]. Fasting serum insulin concentration has been directly associated with an increase in both distant recurrence and death in women previously treated for breast cancer [10]. In addition, it has been postulated that obese women may be under-dosed in terms of chemotherapy and/or radiation treatment, resulting in reduced therapeutic response [11;12]. Obesity has also been associated with later stage and larger tumors at the time of diagnosis [13;14], both known to be important predictors of disease recurrence.

There is also substantial evidence that weight gain often occurs in women after a diagnosis of breast cancer, and is reportedly most prevalent in women who are premenopausal at diagnosis and among those who receive chemotherapy as part of their treatment [15;16]. Average weight gains measured post-chemotherapy in the early years post diagnosis have been reported to be between 2.9 kg and 4.4 kg, with one third patients gaining more than 5 kg [3;17].

While weight at diagnosis has been linked to a poorer prognosis, few studies have specifically addressed whether weight change following diagnosis further influences prognosis independently of other factors. The few studies that have addressed this issue have generally had small numbers of women, have not used the same prognostic outcomes measures and have reported inconsistent results [18-23]. The largest study to date was from the Nurse's Health Study Cohort (NHS), in which self-reported body weight measures were obtained in a sub-sample of over 5000 generally healthy women who were subsequently diagnosed with breast cancer and followed for a median of 9 years. An intriguing finding from this study [24] was that a gain in BMI post-diagnosis was related negatively to prognosis in women who reported never smoking but not in the women who reported ever smoking. The current report investigates the specific effects of post diagnosis weight change on breast cancer recurrence using data collected from two large studies of breast cancer survivors.

Methods

Study Population:

Study participants included 3215 women previously treated for breast cancer who were part of one of two on-going studies: 1742 women are from the Life After Cancer Epidemiology (LACE) Study, an observational cohort study examining behavioral risk factors related to breast cancer recurrence and 1473 women who were randomly assigned to the comparison arm of the Women's Healthy Eating and Living (WHEL) Study, a randomized diet intervention trial testing whether a low-fat, plant-based diet can influence risk for breast cancer recurrence and survival [25]. Because the two studies had the same inclusion/exclusion criteria, we combined the samples to improve power and strengthen the findings.

All women were recruited between 1995 and 2002 to either the LACE or WHEL studies. Eligibility criteria for both studies included: being 18-70 yrs of age at enrollment; having been diagnosed with early stage primary breast cancer (Stage I $\geq$ 1 cm, or Stage II or IIIA) within 39 months of enrollment for LACE and within 48 months for WHEL; having completed breast cancer treatment and being free of recurrence (based on recent mammography and clinical examination); and having had no other cancers within 5 years prior to enrollment. In addition, breast cancer surgery had to have been either a total mastectomy or breast sparing surgery followed by breast radiation, and had to include evaluation of axillary or sentinel node for disease staging. If relevant, participants must have completed chemotherapy and all other cancer treatment, with the exception of SERM therapy before study enrollment.

The LACE study participants received no intervention during the report period, whereas the WHEL comparison group participants received print materials advising them to consume a diet

consistent with current general dietary recommendations for cancer prevention (five servings of vegetables and fruit daily, 20 g/d fiber, and <30% energy from fat).

Further details on both LACE and the WHEL Study inclusion criteria, and data collection methods are provided elsewhere [25;26]. The institutional review boards of all the participating institutions approved procedures for this study, and written informed consent was obtained from all study participants prior to enrollment.

Weight Measurements

Weight assessments used in these analyses include weight one year prior to diagnosis (pre-diagnosis weight) and weight at study enrollment. Pre-diagnosis weight was collected in the same manner in both WHEL and LACE: women self-reported based on retrospective recall. Weight and height at enrollment into the LACE study were self-reported based on self-measurement. Women were instructed to stand with bare feet against the wall and use a ruler pressed firmly on their head and to place a piece of tape where the ruler touches the wall. The measurement was to be recorded to the nearest half-inch by placing the zero end of the tape measure at the bottom of the wall and measuring up until the point of the bottom of the tape. 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. Weight and height at enrollment into WHEL was measured (in light clothing without shoes) by trained research staff in a clinic setting on balance beam scales, according to standard procedures [27].

Covariates:

We obtained information on medical prognostic factors either through electronic data sources available from Kaiser Permanente (LACE) or from medical chart review (WHEL and LACE participants who were not Kaiser members). Data included size, histology, lymph node

involvement and distant metastasis, estrogen and progesterone receptor status, HER2/Neu status, and treatments (summary of surgical procedures, dates and types of chemotherapy, radiation therapy, and type of hormonal therapy). Tumor stage was calculated according to the American Joint Committee on Cancer (AJCC) (4th edition of manual for staging of Cancer). Both LACE and WHEL studies obtained smoking history from self-report through questionnaires

Outcome Assessment

For these analyses, breast cancer recurrence includes a local/regional cancer recurrence, distant recurrence/metastasis, development of a contralateral breast primary or death from breast cancer if a recurrence was not previously reported. For WHEL, outcome events were probed during semi-annual telephone interviews with study participants, conducted by the clinical site coordinator or designee and included probes for information on any hospitalization or medical diagnoses. Any reported recurrence or new primary cancer triggered a confirmation telephone interview with the study participant or her designee. Two independent oncologists reviewed medical records for all reported recurrences or new primary cancers. If disagreement occurred, the study pathologist from the WHEL Study coordinating center adjudicated the outcome.

For LACE, outcomes were ascertained by a mailed semi-annual health status update questionnaire that asked women to report any events occurring in the preceding six months. These included recurrences and hospitalizations for any condition. LACE members who reported any event were telephoned to complete a new event report. Medical records were then reviewed to verify the outcome, which the study medical oncologist confirmed. All non-respondents to the semi-annual health status questionnaire were called to complete a report by telephone. In both studies death certificates were used to confirm cause of death due to breast cancer.

Statistical Analysis

All analyses were run separately for each individual study sample, as well as for the combined sample. LACE and WHEL datasets were compared on baseline medical and demographic characteristics; differences between datasets were controlled for in analyses combining datasets.

The final sample was limited to those women who had a complete dataset on height, weight at 18 years, weight at pre-diagnosis, weight at study entry, age at diagnosis, stage, treatment methods, and tamoxifen use. This resulted in a reduction in combined sample size of n= 3057 in the final model, as 158 were missing progesterone or estrogen receptor status.

We computed weight change from 1 y pre-diagnosis to study entry and body mass index (BMI, wt[kg]/ht[m^2]) both for 1 y pre-diagnosis and at study entry. Percent (%) of weight change was calculated as (weight at study entry - weight at 1 y pre-diagnosis) / (weight at 1 y pre-diagnosis) multiplied by 100. One participant whose weight change was greater than 100 lbs. between diagnosis and entry into the study due to gastric bypass surgery was eliminated from the analyses.

T-tests were conducted to determine univariate predictors of weight gain, and univariate predictors of recurrence were determined with log-rank test, adjusted for the varying entry times. All tests are two-sided, with $p<0.05$ considered statistically significant. Hazard ratios (HR) and 95% CI of a breast cancer event for percent weight gain were computed, controlling for covariates using the Delayed Entry Cox proportional hazards model [28;29]. The delayed entry model adjusts for the fact that a woman who enrolled in our study *t* years after the diagnosis of her original breast cancer was not under observation for a possible recurrence prior to *t* years. Formal tests for interactions with % weight gain and other covariates, including study population (LACE or WHEL) were conducted using likelihood ratio (LR) tests. Non-linear trends of %

weight gain with recurrence were tested by including these terms as linear (centered) in a univariate model, and using likelihood ratio tests to determine the significance of adding a quadratic (centered) term. Analyses were conducted using STATA software, version 8.2 (College Station, TX). Time (in years) from diagnosis to breast cancer recurrence was the endpoint of interest. Women who did not recur were censored at the earliest of drop-out date, date of death (from causes other than breast cancer) or July 31, 2004.

Results

Tables 1 and 2 present results by individual study population. Results in Table 3 and 4 are presented for the combined sample to simplify presentation, since predictors of weight gain and recurrence were similar across the two groups. Results in Table 5 are again presented by individual study to demonstrate the consistency of weight gain effects across the two study populations.

Table 1 describes characteristics of the each study population. Median time between diagnosis and study entry was ~ 2 years in both studies, while follow-up time since diagnosis was just greater than 5 years in LACE and just greater than 7 years in WHEL.

The two samples differed with regard to age and stage at diagnosis with fewer women having Stage I and more women having Stage II or IIIA disease in WHEL than in LACE. Mean age at diagnosis in LACE was 58.8 yrs compared to 51.1 years for WHEL. Many of the other differences reported in Table 1 are not clinically significant (i.e., months from diagnosis, tumor size, nodal status and smoking status) and likely result from large sample sizes or are the result of age differences (menopausal status , hormone receptor status), or stage differences (treatment modalities).

Table 2 presents anthropometric characteristics for each study sample. Generally, differences between the two samples were not clinically significant. Height and weight at age 18, pre-diagnosis, and at study entry were similar between the two groups. Between 1 yr-pre-diagnosis and study entry (median = 33.9 months), mean weight gain differed between the two samples and was approximately 1.4 kg greater in WHEL (3.17kg) than in LACE (1.81kg). In both samples, weight gain between 1 yr-pre-diagnosis and study entry increased with increasing time, stabilizing at approximately 3 years post-diagnosis.

Women were overweight, on average with a mean BMI in the combined sample of 27.4 kg/m^2 at study entry. Between age 18 and 1 yr-pre-diagnosis, self-reported weight increased substantially from 55.3 kg to 70.6 kg. Between 1 yr-pre-diagnosis and study entry, 43.5 % of the women remained weight stable ($\pm$ 5%), 44.0% gained >5% of their body weight and only 12.5% of the women lost weight.

Table 3 presents univariate predictors of weight change from pre-diagnosis to study entry in the combined sample. Weight gain varied by height, pre-diagnosis BMI, age, treatment, menopausal status, and estrogen receptor status. Women who had the lowest BMI pre-diagnosis gained the highest percentage of body weight from pre-diagnosis to study entry, while those who had the highest BMI pre-diagnosis gained the least weight. Younger and premenopausal women were more likely to have greater weight gain than older or postmenopausal women. Women who received chemotherapy had greater gains in body weight than those who received radiation therapy alone.

When predictors of recurrence were examined, uncontrolled for covariates (Table 4), established factors associated with better prognosis such as early stage disease, fewer number of positive nodes and positive estrogen and progesterone receptor tumor status were each inversely related to recurrence, as was current tamoxifen use. Weight change was not associated with recurrence.

Weight gain remained unrelated to recurrence in each individual study population, as well as the combined sample (Table 5) when controlled for age, stage at diagnosis, number of positive nodes, treatment variables, hormone receptor status, and BMI pre-diagnosis. Hazard ratios for the effect of weight gain on recurrence were remarkably consistent across both study populations with no indication for either a moderate (5%-10%) or larger (> 10%) weight gain being associated with an increased risk of recurrence. Results were less consistent across weight loss categories. While there was a significant reduced risk associated with recurrence for a moderate (5-10%) weight loss in WHEL, but not in LACE, both hazard ratios (HR) were less than 1.0 and the point estimate for each HR was included in the 95% confidence intervals of the other. In the combined sample the reduced risk was not significant at the .05 level.

For larger (>10%) weight loss, the HR's were non-significant for each individual study, as well as the combined sample. Weight change was examined for interactions with age, pre-diagnosis BMI, stage, tumor receptor status, chemotherapy treatment status and smoking status. No significant interactions were observed. Study population was also added as a covariate in the model and there was no indication of an interaction effect (p=0.98). These results did not change materially when analyses excluded contralateral new primary breast cancers.

Discussion

In this study, weight gain post-diagnosis was not associated with an increased risk of breast cancer recurrence. While we are one of the first studies to report the effect of weight gain occurring past initial treatment on recurrence, our results are limited to recurrences in the first 5-7 years post- diagnosis, and we did not examine the impact of weight gain on other adverse outcomes of concern to breast cancer survivors, such as the occurrence of other new cancers or overall survival. Rather in an attempt to better understand the underlying mechanism that may be specific to weight gain and breast cancer, we focused on a more homogeneous outcome that included only breast cancer events.

It should also be noted that because women did not enter either LACE or WHEL studies until they had completed chemotherapy and/or radiation treatment, our results cannot be generalized to recurrences that may have occurred in that initial post-diagnosis treatment period. While it is possible that those with large weight gains recurred more rapidly and are not represented in our sample, this seems unlikely because the correlation between time to study entry and weight gain is low ($r = 0.16$) and average weight gains increased as time from diagnosis to study entry increased.

A further limitation is that we used self-reported weight; however, our data corroborate previous studies which have demonstrated excellent correlation ($r=0.90$-0.99) between self-reported and measured weight [30;31]. For women enrolled in the LACE Study, the correlation between the woman's self-report of her weight one year prior to diagnosis and a measured weight abstracted from the medical record close to the time of diagnosis was extremely high ($r=0.94$) and the mean self-reported weight was only 2% (1.5 kg) lower than the mean weight in the medical

record. For WHEL women, the correlation between self-reported and measured weight at study entry was r=0.99.

The literature regarding post-diagnosis weight gain and prognosis [18-24] is not extensive and it is difficult to compare results across studies, because the studies often used different measures to evaluate prognosis. Some examined only overall survival, while others use disease-free, relapse-free or recurrence- free survival, and even among the latter three, definitions often vary across study.

To exemplify the difficulty in comparison across studies, the most recent and largest study to date [24] reported that among women in the Nurses' Health Study (NHS) who developed breast cancer and self-reported both a pre-diagnosis weight (up to 4 years before) and a post-diagnosis weight (1 to 4 years after), increase in BMI was related to recurrence for a median gain of 6 lbs. (HR 1.40) and for a median gain of 17 lbs. (HR 1.53, p for trend =.04). However this relationship was found only in the 40% of the sample who reported never smoking while no relationship between weight gain and recurrence was found in the 60% of women who had ever smoked and quit or in women who were current smokers. In contrast, we found no association in any of the aforementioned smoking sub-groups. However, the NHS definition of recurrence included death from breast cancer or any new reported cancer of the lung, liver, bone or brain but excluded any local recurrences in the ipsilateral breast or any new primaries in the contralateral breast. These latter two categories of events account for almost 50% of the recurrence endpoints in our study. While many of the new reported cancers in the NHS are likely to be a distant breast cancer recurrence, some of those events are likely not to be a breast cancer event at all, but a new primary in these organs. Differences in the definition of recurrence endpoints between studies may account for our differing results.

Of the remaining six studies on weight gain and prognosis [18-23], three reported no relationship [19;20;23], and none of the three that found a negative impact on prognosis [18;21;22], reported a statistically significant effect on recurrence or any outcome measure that included only breast cancer events. A study by Camoriano et al. [18] of 545 node-positive women reported a significant effect of weight gain on overall survival, but not on recurrence; and only for pre-menopausal, but not post-menopausal, women. The remaining two studies had sample sizes of less than 65 and reported a relationship with overall survival [22] or disease-free survival (without defining which events were included) [21]. In addition, all of these studies [18-23] were conducted about 20 years ago when chemotherapy regimens both lasted 1 year and were frequently supplemented with steroids and early weight gains were considerably larger than has been observed in more recent studies where chemotherapy regimens are of shorter duration and are often accompanied by effective adjuvant anti-estrogen therapies. Additionally, these prior studies are constrained by lack of documentation of weight changes beyond 1-year post-diagnosis.

As we have observed, weight gain at the completion of treatment may not fully reflect subsequent weight gain, because women gain weight after their initial treatment, regardless of whether they received chemotherapy. Also, we have generally observed much smaller weight gains at 1 year post-diagnosis than earlier reports, possibly due to the changes in lengths and types of adjuvant therapy, and also because the survivors enrolling in the WHEL Study (and perhaps LACE as well) may have already modified their eating habits toward lower fat and higher vegetable and fruit consumption [32].

Although the main objective of this study was to examine the effect of post-diagnosis weight change on recurrence, and while we report that weight gain does not increase the risk of

recurrence, this does not refute that being overweight or obese at the time of diagnosis is a negative prognostic factor as reported by the majority of previous studies [2;3]. The present study corroborates other studies which have found that the women who are the leanest at the time of diagnosis have the greatest post-diagnosis weight gain [24;33;34]. If weight status at the time of diagnosis is indicative of typical adult weight, modest weight gains post-diagnosis may not negate the benefits of having a normal BMI over a lifetime, particularly if lifetime BMI is accompanied by habitual behaviors associated with a more favorable prognosis.

Secondly, how post-diagnosis weight gain influences the hormonal profile associated with tumor growth is unclear. While McTiernan et al .[7] demonstrate that among postmenopausal breast cancer survivors, being obese (BMI > 30) post-diagnosis was related to an adverse prognostic hormonal profile relevant to breast cancer risk (higher concentrations of estrogens and androgens), this same effect has not been studied in breast cancer survivors who were pre- or peri-menopausal at diagnosis. However, the many previous studies finding no relationship between obesity and the incidence of premenopausal breast cancer [35-37] suggest that excess weight among premenopausal women is not associated with a hormonal profile that promotes breast cancer.

Because weight gain differed by menopausal status in our study (mean difference 2.6%) with significantly greater weight gain in women who are premenopausal at diagnosis the results of the present study may be due in part, to the contribution of premenopausal women. If recurrence is mediated by gonadal hormone status, this may explain our finding that weight gain was not associated with increased risk.

A third possible explanation for our findings is that adjuvant chemotherapy may simultaneously prevent tumor growth, a beneficial effect, but accelerate the aging process, a negative effect,

especially among younger women, thereby leading to similar body composition changes and weight gains over 1-3 years that are typically observed more gradually over the 10-year period encompassing menopause [3].

In summary, we did not observe an association between post-diagnosis weight gain, an exposure which has been inadequately studied, and risk for recurrence of breast cancer in the first 5-7 years post diagnosis. However, it should be noted that the established guidelines of maintaining a healthy weight to prevent diabetes and cardiovascular disease apply to breast cancer survivors as well. While we have provided some plausible biological explanations for our findings, additional research efforts should use a similar prognostic outcome measure to enable better comparisons of results across studies, and improve our ability to gain an understanding of the biological mechanisms underlying the effects of weight gain specific to breast cancer growth. As it is becoming increasingly clear that breast cancer is a heterogeneous disease, defined by tumor subtypes, studies should also focus on the effects of weight gain by hormone receptor status, as well as menopausal status. The relationship between weight and breast cancer prognosis may be more complex than previously thought and the hope is that future studies will be able to shed light on these complex relationships.

Table 1. Demographic and Tumor Characteristics of the Study Sample, Overall and by Study.

	OVERALL (N=3215)		LACE (N=1742)		WHEL (N=1473)	
Continuous	**N**	**Mean(SD)**	**N**	**Mean(SD)**	**N**	**Mean(SD)**
Months from DX to study entry,	3215	22.9 (9.8)	1742	22.5 (6.7)	1473	23.4 (12.5)*
Months of follow-up[1]	3215	73.7 (24.6)	1742	63.0 (13.7)	1473	86.5 (28.3)**
Age at diagnosis	3215	55.3 (10.7)	1742	58.8 (10.7)	1473	51.1 (8.9)**
Categorical	**N**	**%**	**N**	**%**	**N**	**%**
Age at DX (years)						
< 50	1066	33.1	378	21.7	688	46.7**
≥ 50	2149	66.9	1364	78.3	785	53.3
Smoking Status at Study Entry[2]						
Never	1738	54.1	928	53.3	810	55.0**
Past	1273	39.6	694	39.8	579	39.3
Current	189	5.9	119	6.8	70	4.8
Missing/unknown	15	0.5	0.1	0.1	14	1.0
Menopausal Status at DX[3]						
Pre-menopausal	835	26.0	404	23.2	431	29.3**
Post-menopausal	1823	56.7	1116	64.1	707	48.0
Unknown/missing	557	17.3	222	12.7	335	22.7
Tamoxifen use at DX						
Never	916	28.5	389	22.3	527	35.8**
Past	213	6.6	114	6.5	99	6.7
Current	2086	64.9	1239	71.1	847	57.5
Treatment						
No radiation / no chemotherapy	484	15.1	321	18.4	163	11.1*
Chemotherapy only	724	22.5	328	18.8	396	26.9
Radiation only	739	23.0	449	25.8	290	19.7
Both chemotherapy and radiation	1268	39.4	644	37.0	624	42.4
Surgery type						
Mastectomy	1629	50.7	868	49.8	761	51.7
Conserving	1586	49.3	874	50.2	712	48.3

Table 1 (cont.) Demographic and Tumor Characteristics of the Study Sample, Overall and by Study.

	OVERALL (N=3215)		LACE (N=1742)		WHEL (N=1473)	
	N	**%**	**N**	**%**	**N**	**%**
Number of positive nodes						
Node negative	1974	61.4	1128	64.8	846	57.4**
1-3	864	26.9	437	25.1	427	29.0
4-6	202	6.3	93	5.3	109	7.4
7-9	62	1.9	29	1.7	33	2.2
≥ 10	113	3.5	55	3.2	58	3.9
Tumor size (cm)						
(0, 2)	1681	52.3	958	55.0	723	49.2**
[2,3)	892	27.8	469	26.9	423	28.8
[3,4)	315	9.8	159	9.1	156	10.6
[4,5)	150	4.7	80	4.6	70	4.8
≥ 5	174	5.4	76	4.4	98	6.7
Tumor size (cm), mean (SD)	3212	2.2 (1.4)	1742	2.1 (1.3)	1470	2.3 (1.4)**
Stage of Breast Cancer						
I	1406	43.7	837	48.1	569	38.6**
II	1693	52.7	861	49.4	832	56.5
IIIA	116	3.6	44	2.5	72	4.9
Hormone receptor status						
Estrogen (+)						
No	674	21.8	288	17.6	386	26.6**
Yes	2419	78.2	1352	82.4	1067	73.4
Unknown/missing (not included in Comparison)	122	3.8	102	5.9	20	1.4
Progesterone (+)						
No	941	30.7	474	29.2	467	32.5*
Yes	2121	69.3	1150	70.8	971	67.5
Unknown/missing (not included in Comparison)	153	4.8	118	6.8	35	2.4

Abbreviations: DX, Diagnosis

* $P < .05$ for difference between LACE and WHEL

** $P < .01$ for difference between LACE and WHEL

[1] Months of follow-up defined as months from diagnosis to recurrence, study end, or inactive date.

[2] Smoking status defined by subject having smoked at least 100 cigarettes in lifetime.

[3] Pre-menopausal status defined as date of DX one year or less before date of last menstruation or date of last menstruation after date of DX; post-menopausal status defined as date of DX more than one year after date of last menstruation.

Table 2. Anthropometric Characteristics of the Study Sample.

	OVERALL (N=3215)		**LACE (N=1742)**		**WHEL (N=1473)**	
	N	**Mean(SD)**	**N**	**Mean(SD)**	**N**	**Mean(SD)**
Height (cm)	3215	163.4 (6.8)	1742	162.8 (6.8)	1473	164.1 (6.6)**
Weight at age 18 (kg)	3215	55.5kg (8.0)	1742	55.0 (7.8)	1473	56.0 (8.2)**
Weight at one year pre-DX (kg), mean	3215	70.8 (15.8)	1742	71.4 (15.9)	1473	70.0 (15.8)*
Weight at study entry (kg),	3215	73.2 (16.6)	1742	73.2 (16.5)	1473	73.2 (16.8)
Change in weight pre-DX to study entry (kg),)	3215	2.4 (7.45)	1742	1.817.6)	1473	3.17 (6.9)**
Change in weight (kg) by years from pre-DX to Study Entry						
1.5 - <3 yr.	1861	1.59 (3.04)	1100	1.19 (6.09)	761	2.17 (6.32)**
3 - <4 yr.	939	3.26 (8.29)	589	2.95 (8.65)	350	4.57 (7.55)**
4 - <5 yr.	357	4.27 (7.38)	53	2.26 (7.76)	304	4.62 (7.27)
% Weight gain from pre-DX to study entry						
	N	**%**	**N**	**%**	**N**	**%**
< -10%	191	5.9	124	7.1	67	4.6
(-5%,-10%]	290	9.0	173	9.9	117	7.9
[-5%, 5%]	1461	45.4	820	47.1	641	43.5
(5%, 10%]	555	17.3	286	16.4	269	18.3
> 10%	718	22.3	339	19.5	379	25.7

* P < .05 for difference between LACE and WHEL

** P < .01 for difference between LACE and WHEL

Table 3. Predictors of Percentage Weight Change.

		% Weight Change from pre-DX to Study Entry		
	N	**Mean**	**SD**	**p-value**
Height (cm)				
< 163	1620	3.4	9.8	0.011
≥ 163	1595	4.2	9.9	
BMI 1 y pre-DX (kg/m^2)				
≤ 18.5	36	6.6	8.5	<0.001
(18.5, 25)	1544	5.3	9.1	
[25, 30)	927	3.3	9.9	
≥ 30	708	1.0	10.8	
BMI at Study Entry (kg/m^2)				
≤ 18.5	32	-5.1	7.5	<0.001
(18.5, 25)	1287	1.2	7.8	
[25, 30)	1046	4.8	9.4	
≥ 30	850	6.9	11.8	
Age at DX				
< 50	1066	5.9	10.5	<0.001
≥ 50	2149	2.8	9.4	
Smoking Status at Study Entry*				
Never	1738	3.5	9.6	0.092
Past	1273	4.1	10.0	
Current	189	4.6	11.2	
Chemotherapy treatment				
No	1223	2.5	9.5	<0.001
Yes	1992	4.6	10.0	
Radiation treatment				
No	1208	3.7	9.9	0.584
Yes	2007	3.9	9.8	
Tamoxifen Status at Study Entry				
Never	916	4.3	10.2	0.004
Past	213	5.5	9.7	
Current	2086	3.4	9.7	
Stage				
I	1406	3.5	9.8	0.405
II	1693	4.0	9.8	
IIIA	116	4.0	10.2	

Table 3 (cont.) Predictors of Percentage Weight Change

		% Weight Change from pre-DX to Study Entry		
	N	**Mean**	**SD**	**p-value**
No. Positive Nodes				
Negative (0)	1974	3.8	9.9	0.802
1-3	864	3.7	9.5	
4-6	202	4.6	9.2	
7-9	62	3.6	9.9	
>9	113	3.5	12.1	
Menopausal status at DX†				
Premenopausal	835	5.6	10.2	<0.001
Postmenopausal	1823	3.0	9.3	
Unknown/missing	557	3.9	10.7	
Hormone receptor status				
Estrogen (+) or progesterone (+)				
No‡	561	4.3	10.1	0.211
Yes	2528	3.7	9.7	
Estrogen (+) receptor status				
No	674	4.6	10.0	0.021
Yes	2419	3.6	9.7	
Progesterone (+) receptor status				
No	941	3.7	9.8	0.682
Yes	2121	3.8	9.7	

Abbreviations: BMI, body mass index; DX, Diagnosis.

* Smoking status defined by subject having smoked at least 100 cigarettes in lifetime.

† Premenopausal status is defined as date of DX one year or less after date of last menstruation or date of last menstruation after date of DX.; postmenopausal status defined as date of DX more than one year after date of last menstruation.

‡ Tumor negative for both estrogen and progesterone receptor.

Table 4. Univariate Predictors of Recurrence.

	N	%	HR (95% CI)
BMI one year pre-DX (kg/m^2)			
≤ 18.5	5	13.9	1.4 (0.6, 3.4)
(18.5, 25)	154	10.0	Referent
[25, 30)	93	10.0	1.0 (0.8, 1.3)
≥ 30	89	12.6	1.3 (1.02, 1.7)
BMI at study entry (kg/m^2)			
≤ 18.5	5	15.6	1.5 (0.6, 3.6)
(18.5, 25)	141	11.0	Referent
[25, 30)	96	9.2	0.9 (0.7, 1.1)
≥ 30	99	11.7	1.1 (0.9, 1.4)
% Weight gain from pre-DX to study entry *			
< -10%	23	12.0	1.1(0.7,1.8)
[-10%,-5%)	24	8.3	0.7 (0.5,1.1)
[-5%, 5%]	163	11.2	Referent
(5%, 10%]	51	9.2	0.8 (0.6, 1.1)
> 10%	80	11.3	1.0 (0.8, 1.3)
Height (cm)			
< 163	152	9.4	Referent
≥ 163	189	11.9	1.2 (1.0, 1.5)
Age at DX (years)			
≤ 50	132	12.5	Referent
> 50	209	9.7	0.8 (0.7, 1.1)
Smoking status at study entry†			
Never	192	11.1	Referent
Past	121	9.5	0.8 (0.5, 1.3)
Current	24	12.7	0.7 (0.5, 1.1)
Tamoxifen use at study entry			
Never	124	13.7	Referent
Past	30	14.1	1.1 (0.8, 1.7)
Current	187	9.0	0.7 (0.6, 0.9)
Treatment			
No radiation / no chemotherapy	41	8.5	Referent
Chemotherapy only	72	10.1	1.1 (0.8, 1.7)
Radiation only	54	7.3	0.9 (0.6, 1.3)
Both chemotherapy and radiation	174	13.7	1.7 (1.2, 2.3)

Table 4 (cont.) Univariate Predictors of lapse

	N	%	HR (95% CI)
Stage of breast cancer			
I	87	6.2	Referent
II	221	13.1	2.2 (1.7, 2.8)
IIIA	33	28.5	5.0 (3.4, 7.5)
Number of positive nodes			
Node negative	154	7.9	Referent
1-3	87	10.1	1.3 (1.0, 1.7)
4-6	38	18.8	2.6 (1.8, 3.7)
7-9	17	27.4	3.9 (2.4, 6.4)
≥ 10	45	39.8	6.5 (4.7, 9.1)
Hormone receptor status			
Estrogen (+)			
No	100	15.0	Referent
Yes	235	9.7	0.7 (0.5, 0.8)
Progesterone (+)			
No	127	13.5	Referent
Yes	206	9.7	0.7 (0.6, 0.9)
Menopausal Status at DX‡			
Premenopausal	96	11.5	Referent
Postmenopausal	179	9.8	0.9 (0.7, 1.1)
Unknown/missing	66	12.0	1.0 (0.7, 1.4)

Abbreviations: DX, Diagnosis; HR, Hazard Ratio; CI, Confidence interval

P-values based on unweighted, log-rank test for delayed entry model.

* Does not differ once stratified by years from pre-DX to study entry.

† Smoking status defined by subject having smoked at least 100 cigarettes in lifetime.

‡ Premenopausal status is defined as date of DX one year or less after date of last menstruation or date of last menstruation after date of DX; postmenopausal status defined as date of DX more than one year after date of last menstruation.

Table 5. Delayed Entry Cox Proportional Hazards Model for Breast Cancer Relapse, by % Change in Weight*, OVERALL and by Individual Study Populations

	OVERALL (N=3057; 333 Events)		LACE (N=1619; 141 Events)		WHEL (N=1438; 192 Events)	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
% Weight change from pre-DX to study entry						
Weight stable						
[-5%, 5%]	1.0	Referent	1.0	Referent	1.0	Referent
Weight gain						
(5%, 10%]	0.8	(0.6, 1.1)	0.9	(0.5, 1.4)	0.8	(0.5, 1.2)
> 10%	1.0	(0.7, 1.3)	0.8	(0.5, 1.3)	1.1	(0.7, 1.5)
Weight loss						
(5%,10%]	0.7	(0.4, 1.0)	0.9	(0.5, 1.6)	0.5	(0.2, 0.9)
>10%	1.0	(0.7, 1.6)	1.4	(0.7, 2.5)	0.7	(0.3, 1.4)

N=3057; 333 Recurrences or new primaries.

DX: Diagnosis

CI: Confidence interval

*Model controlled for stage, age, pre-DX BMI, tamoxifen use, treatment, number of positive nodes, progesterone and estrogen receptor status.

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