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Determinants of Weight Gain during Adjuvant Endocrine Therapy and Association of Such Weight Gain with Recurrence in Long-Term Breast Cancer Survivors

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Abstract

We conducted a retrospective study of breast cancer survivors to determine risk factors for weight gain during endocrine therapy and the association of such weight gain with recurrence.

Background—Weight gain is a negative prognostic factor in breast cancer (BC) patients. Risk factors for weight gain during adjuvant endocrine therapy (ET) and the extent to which such weight gain is associated with disease recurrence remain unclear.

Methods—We retrospectively identified a cohort of women diagnosed with stage I–III, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative BC between January 1997 and August 2008, who had received initial treatment at MD Anderson, had completed 5 years of ET, and had remained free of locoregional or distant relapse or contralateral BC for 5 years after diagnosis. Weight change at the end of 5 years of ET was measured as the percent change of weight from the start of ET, and a weight gain of >5% was considered clinically significant. Multivariable logistic regression and Cox proportional hazards models were used to assess the determinants of such weight gain and the risk of recurrence after 5 years.

Results—Among 1,282 long-term BC survivors, 432 (33.7%) had a weight gain of >5% after 5 years of ET. Women who were premenopausal at diagnosis were 1.40 times more likely than women who were postmenopausal at diagnosis to have a weight gain of >5%. Asian women had the lowest risk of gaining weight. The recurrence risks of patients who gained weight and those who did not were not significantly different.

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Conclusions—Premenopausal BC patients had an increased risk of weight gain after 5 years of ET, but BC patients who had a weight gain of >5% did not have an increased risk of disease recurrence.

Keywords

weight gain; adjuvant endocrine therapy; disease recurrence; early-stage breast cancer

Introduction

Weight gain is prevalent among breast cancer (BC) survivors, with 50–96% of survivors reporting weight gain after a diagnosis of or during treatment for primary BC.^{1–8} Weight gain is considered to be a negative prognostic factor in BC patients.^{9,10} The public health implications of obesity and breast cancer are immense.¹¹ Weight gain could possibly adversely affect survival among breast cancer survivors with an elevated risk of recurrence and mortality.^{12–16} Although several studies have assessed weight gain in BC survivors, the causal factors underlying such weight gain remain elusive. However, possible explanations include fatigue, reduced physical activity, and increased caloric intake associated with behavioral or treatment-related factors.¹⁷

Studies of the relationship between weight change and BC outcomes have yielded inconsistent findings.^{18–21} Different timings of the post-diagnostic weight change measures and the highly selected populations of patients with good prognosis are also likely to contribute to the varied findings. Most studies of weight gain in BC patients have assessed weight change during or after adjuvant chemotherapy.^{10, 22, 23} Predictors of weight gain after BC was analyzed in the Women's Healthy Eating and Living (WHEL) study, a prospective randomized clinical trial that included BC patients within 4 years of their diagnosis with their weight recorded 1 year prior to diagnosis, at study enrollment and over a period of 6 years, which reported an association of weight gain with chemotherapy irrespective of the types or regimens, whereas tamoxifen was not significantly associated.²³ Another study reported associations of weight gain after chemotherapy in patients with a younger age at diagnosis and with a premenopausal status²⁴, supporting that there is weight gain with chemotherapy. However, the published data on weight gain determinants specifically during adjuvant endocrine therapy (ET) are very limited.

The association of weight gain with BC recurrence is inconclusive.^{14, 25, 26} A study that combined participants from the WHEL study and from the Life after Cancer Epidemiology (LACE) study suggested there was no increase in risk of disease in the first 5–7 years post diagnosis in early stage BC.²¹ However, the weight change was not specifically examined during ET. Therefore, the objectives of our study were to identify risk factors for weight gain specifically after 5 years of ET and to determine the extent to which such weight gain was associated with disease recurrence in long-term BC survivors.

Methods

Study Design and Patients

This retrospective study was performed with the approval of MD Anderson's Institutional Review Board (PA13-0424). Using the Breast Cancer Management System database in the Department of Breast Medical Oncology at MD Anderson, we identified 1,282 women who were diagnosed with early stage (I-III), hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative BC between January 1997 and August 2008 and who received their initial treatment at MD Anderson to help diminish a selection bias.²⁷ HR-positive tumors were those that were either estrogen receptor-positive or progesterone receptor-positive as determined by immunohistochemistry using institutional cut-offs. HER2 status had been assessed by immunohistochemistry or by fluorescence in situ hybridization when available and determined to be positive or negative on the basis of institutional cut-offs and guidelines that were current at the time of diagnosis. Patients self-reported their race at the time of registration. By inclusion criteria, all patients were 18–90 years old at diagnosis, had completed 5 years of ET, and were disease-free 5 years after diagnosis. Body mass index (BMI) was classified according to World Health Organization criteria.²⁸ Underweight was defined as a BMI of $<18.5 \text{ kg/m}^2$; normal, $18.5\text{--}24.9 \text{ kg/m}^2$; overweight, $25\text{--}29.9 \text{ kg/m}^2$; and obese, $>30 \text{ kg/m}^2$. Menopausal status was recorded at the time of diagnosis and defined as pre-, peri-, or postmenopausal by the attending physician following guidelines that were current at the time of diagnosis²⁹; women who were perimenopausal were grouped with women who were premenopausal. We excluded patients who had received any treatment for BC prior to their initial visit to MD Anderson, those who initiated ET more than 1 year after their diagnosis, those who had received ET prior to their BC diagnosis (e.g., for chemoprevention), those who had any disease recurrence within 5 years of diagnosis, those who had concurrent second primary cancers of any site, and those with missing demographic, tumor, and/or treatment details.

Outcomes of Interest

The two outcomes of interest of this study were weight gain specifically after 5 years of ET and recurrence-free survival (RFS). Weight change percentages were calculated as $[(\text{weight after ET} - \text{weight before ET}) / \text{weight before ET}] \times 100$. A weight gain of $>5\%$ was considered clinically relevant, as this cut-off has been reported in previous studies aiming to improve health outcomes among overweight and obese individuals^{30–32} and because this value has been used to evaluate the effects of weight change in BC survivors.^{19, 21, 23, 33, 34} We reviewed patients' charts to verify their weights assessed by direct measurement during clinic visits within 90 days of starting and ending ET. RFS was defined as the time from diagnosis to any locoregional recurrence (including invasive ipsilateral tumor and invasive locoregional tumor) or distant recurrence or death from any cause.³⁵ Patients with no recurrence were censored at last follow-up.

Statistical Analysis

Univariate logistic regression analyses were used to evaluate the crude association between weight change and patients' demographic, clinical, and treatment characteristics. Variables with p -values of <0.25 in the univariate analysis were included in a multivariable model.

^{36, 37} Backward selection criteria were used to retain variables in the multivariable model using a 0.05 significance level. Owing to their clinical significance, chemotherapy, surgery, and ET were retained in the multivariable model regardless of whether they had *p*-values of <0.25 in the univariate analysis. A log-rank test was used to compare the survival probabilities of patients with a weight gain of >5% with those of patients with a weight change of ≤5%. A multivariable Cox proportional hazards regression model with adjustment for other baseline covariates was used to evaluate the association between weight gain and RFS. *P*-values of <0.05 indicated statistical significance. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and STATA version 12 (Statacorp, College Station, TX).

Results

Patient Characteristics

The selection of the patient population is depicted in Figure 1, and patient characteristics are provided in Table 1. The median follow-up time from the date of diagnosis was 11.2 years (quartile [Q] 1, 9.4; Q3, 13.3), and the median follow-up time from 5 years after diagnosis was 6.2 years (Q1, 4.4; Q3, 8.3). Among the 1,282 long-term BC survivors included in the study, 432 (33.7%) had a weight gain of >5%, and 850 (66.3%) had a weight change of ≤5%. In both groups, about 60% of patients were overweight or obese at diagnosis, and about 40% of patients had a normal weight at diagnosis. Patients who had a weight gain of >5% were younger than those with a weight change of ≤5%. Patients who had a weight gain of >5% were also more likely to be premenopausal at diagnosis. Overall, the two groups had similar race distributions; however, the group of patients who gained weight had a lower proportion of Asian women. Patients with stage II or III disease or grade 3 tumors were more likely to have a weight gain of >5% than patients with stage I disease or grade 1 or 2 tumors were. Tumor histology distribution did not differ significantly between the two groups. Compared with patients who had a weight change of ≤5%, patients who had a weight gain of >5% were more likely to have received chemotherapy, tamoxifen, or a sequential ET regimen and less likely to have received an AI. In terms of locoregional therapy, patients who gained weight were more likely than patients who did not gain weight to have undergone a mastectomy; the proportion of patients who received radiation therapy did not differ between the groups.

Univariate Analysis for Associations between Patient Characteristics and Weight Change

The results of the univariate analysis are given in Table 2. Premenopausal status, stage II or III disease, grade 3 tumor, and chemotherapy increased the likelihood of a weight gain of >5%. Although both age and menopausal status at diagnosis were significantly associated with weight gain, owing to high correlation between these two factors³⁸, we decided to proceed with menopausal status only, as it plays a larger role than age in treatment decisions.¹⁰ Compared with white women, African American women and Hispanic women were similarly more likely to gain weight, whereas Asian women were less likely to gain weight. Patients who received ET with an AI were less likely than those who received tamoxifen to gain weight. Interestingly, BMI at diagnosis and radiation therapy were not associated with weight gain during ET.

Multivariable Analysis for Associations between Patient Characteristics and Weight Change

The results of the multivariable analysis are shown in Table 3. Women who were premenopausal at diagnosis were 1.40 times more likely than women who were postmenopausal at diagnosis to have a weight gain of >5% (odds ratio, 1.40; 95% confidence interval, 1.01–1.93; $p=0.040$). Asian women were less likely than women of other races to gain weight. No tumor characteristics were associated with weight gain in the presence of other variables in the multivariable model. The odds of gaining weight did not differ significantly between patients who did or did not undergo chemotherapy or mastectomy. The specific type of ET agent (tamoxifen, AI, or sequential therapy) was not significantly associated with weight gain after 5 years of adjuvant ET.

Survival Analysis

Kaplan-Meier analysis revealed that, compared with women with a weight change of $\leq 5\%$, those with a weight gain of >5% were not at an increased risk of recurrence after completing 5 years of ET (Figure 2). After adjustment for significant baseline risk factors and pre-specified treatment variables, the multivariable Cox proportional hazards model showed that a weight gain of >5% did not significantly increase recurrence risk (hazard ratio, 0.95; 95% confidence interval, 0.62–1.47; $p=0.829$).

Discussion

The results of our study suggest that the risk of weight gain during ET is higher among BC patients who were premenopausal at diagnosis than among those who were postmenopausal. In addition, compared with those who had a weight change of $\leq 5\%$, BC patients who had a weight gain of >5% during ET did not have a higher risk of disease recurrence. This study helps in understanding the relationship of weight gain specifically during ET and its implication on disease recurrence.

Previous studies have shown that premenopausal status at BC diagnosis is a strong predictor of weight gain,¹⁰ although this association remains under discussion.^{39–43} In our study, premenopausal status at diagnosis was associated with significant weight gain. Studies of BC patients receiving tamoxifen have found weight gain to be more highly correlated with premenopausal status than with postmenopausal status at diagnosis.⁴⁴ One study of women on tamoxifen reported weight gain in 61% of premenopausal as compared to 39% of postmenopausal women ($p=0.0001$).⁴⁵ A second study showed significant weight gain in patients receiving tamoxifen vs. no tamoxifen ($p<0.05$) and this effect was more pronounced in premenopausal women.⁴⁶ A third study reported that the percentages of groups of BC survivor's age ≤ 49 years, 50–59 years, or ≥ 60 years at diagnosis who gained weight were 43%, 39%, and 33%, respectively⁴⁷ which all correlates with our findings. In the present study, the univariate analysis revealed that both younger age and premenopausal status at diagnosis were significantly associated with a weight gain of >5%; however, we included only menopausal status in the multivariable model as it has a more important role in choosing a particular ET and age is correlated with menopausal status.

Differences in weight gain amongst race/ethnicity were also assessed. In our study, Asian women had a significantly lower risk of gaining weight during 5 years of ET compared to women of other races. Among women with BC from the WHEL study, Asian Americans had a smaller risk of weight gain with chemotherapy than women of other races.²³ The correlation of race with weight gain suggests that demographic and genetic factors are correlated with weight change in BC survivors as well as in the general population.⁴¹

Although mastectomy did show an association with weight gain in the univariate analysis, such association did not hold in the multivariable analysis. Studies of younger breast cancer patients who underwent a mastectomy compared to older patients, found that the younger women tended to have worse body image.^{48–55} Others have shown that undergoing a mastectomy may have an impact on appearance and satisfaction.^{54, 56–61} Changes in the body image of a breast cancer patient may have an impact on weight gain.⁶²

For HR-positive BC, ET commonly includes an aromatase inhibitor (AI)⁶³, usually exemestane, anastrozole, or letrozole⁶⁴, for postmenopausal women, and tamoxifen or AI plus ovarian suppression^{4, 64, 65} for premenopausal women. Some BC patients may initiate ET with tamoxifen and then switch in a sequential manner to an AI, or vice versa⁶⁶, depending on different clinical scenarios, such as becoming postmenopausal during ET, or because of toxicities. As expected, patients receiving AIs were more likely to have been postmenopausal at diagnosis, and those receiving tamoxifen were more likely to be premenopausal. However, we found no significant differences in weight change among patients receiving tamoxifen alone, AI alone, or sequential therapy with tamoxifen and AI. In the univariate analysis tamoxifen showed correlation with weight gain but not in the multivariable analysis; this may be attributed to the fact that tamoxifen is essentially a surrogate for premenopausal status, which could be why it correlates with weight gain in the univariate analysis. Our finding is similar to what is reported in the literature. The ATAC trial, a large randomized study of early stage postmenopausal BC, showed that 20% of patients receiving tamoxifen alone gained 2 to 5kg, and 20.8% on AI alone had the same weight gain ⁶⁷over a period of 5 years of ET, implying that there was no difference in weight gain with regard to the type of ET. Another randomized study of postmenopausal women who were disease free after 2 to 3 years of tamoxifen were randomly assigned to switch to exemestane or continue with tamoxifen until 5 years of treatment were completed, reported that 55.3% of patients receiving tamoxifen and 51.5% of patients receiving exemestane had a > 5% weight gain at 5 years.^{2, 7} These weight gains were self-reported and did not have a fixed definition of weight gain which complicates comparisons among studies.

It is noteworthy from the above studies that weight gain is potentially not related to the type of endocrine therapy, but could be due to more comprehensive reasons like lifestyle factors including diet, exercise routine and socio demographic characteristics comprising of age, marital status, education and menopausal status.⁶⁸ Also attributable reasons for weight gain due to AI mentioned in a recent systemic analysis related it to a prevalent side effect of musculoskeletal pain due to aromatase inhibitors leading to decline in physical activity,⁶⁹ which in turn can contribute to energy imbalance.⁴

In our study, patients with weight gains of >5% after 5 years of ET were not at an increased risk of recurrence. A similar result was reported combining the comparison cohort of the WHEL's study and the LACE study having no effect of weight gain after initial treatment on recurrence.²¹ However, previous studies have identified weight gain as a risk factor for BC recurrence^{70, 71}; in one of these studies, BMI gain was a significant determinant of recurrence ($p=0.0008$).⁷⁰ It would be difficult to compare these findings among studies as different measures were used to determine weight change.

Our study has the limitations inherent to a retrospective observational analysis, such as potential selection biases, however, since all BC survivors were disease free and received ET for 5 years, we considered this to be a very homogeneous study population. Our study design is unique as we decided to focus specifically on weight change during the 5 years of ET and we did not consider the weight at diagnosis, or prior to diagnosis. Therefore, some patients may have gained weight during their initial treatment (i.e., surgery, chemotherapy, and radiation) prior to starting ET, which may complicate the comparing of our study results with other investigators who have studied weight gain after BC treatment. As a strength, our study included BC survivors for whom highly annotated clinicopathological data were available, and we used very specific time points to determine weight changes after ET.

Our findings suggest that, regardless of their baseline BMI or ET regimen, BC patients who are premenopausal at diagnosis have an increased risk of weight gain after 5 years of ET. Compared with patients with weight changes of ≤5% after ET, those with weight gains of >5% are not at an increased risk of recurrence. The findings of our study could be used to identify patients who may derive the most benefit from lifestyle interventions and specific weight management programs by help increase providers' and patients' awareness and knowledge of weight change during breast cancer treatment and its potential clinical implications. Counseling on lifestyle changes could be considered a health goal for premenopausal BC survivors and may help improve BC patients' enroll to these weight management services. Weight management programs and clinical trials of health education materials, such as those offered at our institution, could also benefit premenopausal BR survivors. The associations between weight gain and BC prognosis may be more heterogeneous than previously reported, and future studies of weight gain among BC patients should focus on identifying the underlying biological mechanisms of these associations.

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Clinical Practice Points

- This study helps identify breast cancer patients who may be at higher risk of gaining weight after 5 years of endocrine therapy and who may derive the most benefit from lifestyle interventions and weight management programs.
- This study also helps increase providers' and patients' awareness and knowledge of weight change during breast cancer treatment and its potential clinical implications.
- The results of this study may stimulate the development of practice tools and resources to help oncologists address weight change with their breast cancer patients and help enroll them into weight management programs.

Figure 1.
Patient cohort selection.

Figure 2.
Recurrence-free survival by weight change.

Table 1**Patient Characteristics by Weight Change**

Characteristics	All patients (n = 1,282)	Patients with weight change (n = 850)	5%	Patients with weight gain >5% (n = 432)	P
Age at diagnosis, years					<0.001
Mean (SD)	56.4 (11.0)	57.5 (11.0)		54.2 (11.7)	
Median (Q1-Q3)	57.0 (49.0–64.0)	58.0 (50.0–65.0)		54.0 (47.0–62.0)	
BMI					0.478
Normal or underweight	499 (38.9)	325 (38.2)		174 (40.3)	
Overweight or obese	783 (61.1)	525 (61.8)		258 (59.7)	
Race					0.060
White	977 (76.2)	637 (74.9)		340 (78.7)	
African American	106 (8.3)	72 (8.5)		34 (7.9)	
Hispanic	127 (9.9)	82 (9.7)		45 (10.4)	
Asian	69 (5.4)	57 (6.7)		12 (2.8)	
Native American	3 (0.2)	2 (0.2)		1 (0.2)	
Menopausal status					<0.001
Postmenopausal	979 (76.4)	675 (79.4)		304 (70.4)	
Premenopausal	303 (23.6)	175 (20.6)		128 (29.6)	
Disease stage					0.008
I	780 (60.8)	539 (63.4)		241 (55.8)	
II or III	502 (39.2)	311 (36.6)		191 (44.2)	
Tumor grade					0.017
I	137 (10.7)	103 (12.1)		34 (7.9)	
II	806 (62.9)	538 (63.3)		268 (62.0)	
III	339 (26.4)	209 (24.6)		130 (30.1)	
Histology					0.069
Ductal	957 (74.6)	631 (74.2)		326 (75.5)	
Lobular	128 (10.0)	90 (10.6)		38 (8.8)	
Mixed	125 (9.8)	74 (8.7)		51 (11.8)	
Other *	72 (5.6)	55 (6.5)		17 (3.9)	
Chemotherapy	702 (54.8)	443 (52.1)		259 (60.0)	0.008
Endocrine therapy					<0.001
T	392 (30.6)	251 (29.5)		141 (32.6)	
AI	662 (51.8)	469 (55.2)		193 (44.7)	
Sequential AI and T	228 (17.8)	130 (15.3)		98 (22.7)	
Radiation therapy	869 (67.8)	582 (68.5)		287 (66.4)	0.461
Surgery					0.021
Lumpectomy	696 (54.3)	481 (56.6)		215 (49.8)	
Mastectomy	586 (45.7)	369 (43.4)		217 (50.2)	

NOTE: Data are no. of patients (%) unless otherwise indicated.

Abbreviations: SD, standard deviation; Q1, quartile 1; Q3, quartile 3; BMI, body mass index; T, tamoxifen; AI, aromatase inhibitor.

* Other histologies were invasive mucinous and invasive tubular.

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Table 2

Results of the Univariate Analysis for Associations between Patient Characteristics and Weight Change

Variable	OR	CI	P
Age at diagnosis (continuous variable)	0.97	0.96–0.98	<0.001
BMI			
Normal or underweight	Ref.		
Overweight or obese	0.92	0.72–1.16	0.478
Race			
White	Ref.		
African American	0.88	0.57–1.35	0.575
Hispanic	1.03	0.70–1.51	0.888
Asian	0.39	0.21–0.75	0.004
Menopausal status			
Postmenopausal	Ref.		
Premenopausal	1.65	1.26–2.15	<0.001
Disease stage			
I	Ref.		
II or III	1.37	1.08–1.73	0.009
Tumor grade			
I	Ref.		
II	1.56	1.03–2.37	0.037
III	1.94	1.24–3.04	0.004
Histology			
Ductal	Ref.		
Lobular	0.79	0.53–1.19	0.263
Mixed	1.33	0.91–1.95	0.143
Other	0.60	0.34–1.04	0.070
Chemotherapy			
No	Ref.		
Yes	1.36	1.08–1.72	0.010
Endocrine therapy			
T	Ref.		
AI	0.73	0.56–0.95	0.019
Sequential AI and T	1.32	0.94–1.84	0.106
Radiation therapy			
No	Ref.		
Yes	0.91	0.71–1.17	0.459
Surgery			
Lumpectomy	Ref.		
Mastectomy	1.32	1.04–1.66	0.020

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; T, tamoxifen; AI, aromatase inhibitor.

Table 3

Results of the Multivariable Analysis for Associations between Patient Characteristics and Weight Change

Variable	OR	CI	P
Menopausal status			
Postmenopausal	Ref.		
Premenopausal	1.40	1.01–1.93	0.040
Race			
White	Ref.		
African American	0.84	0.54–1.29	0.419
Hispanic	0.95	0.64–1.41	0.800
Asian	0.35	0.19–0.67	0.002
Endocrine therapy			
T	Ref.		
AI	0.83	0.61–1.13	0.237
Sequential AI and T	1.33	0.95–1.88	0.100
Chemotherapy			
No	Ref.		
Yes	1.16	0.90–1.51	0.245
Surgery			
Lumpectomy	Ref.		
Mastectomy	1.23	0.96–1.56	0.107

Abbreviations: OR, odds ratio; CI, confidence interval; T, tamoxifen; AI, aromatase inhibitor.