Original Study

Determinants of Weight Gain During Adjuvant Endocrine Therapy and Association of Such Weight Gain With Recurrence in Long-term Breast Cancer Survivors

Akshara Raghavendra,[1] Arup K. Sinha,[1,2] Janeiro Valle,[3] Yu Shen,[4] Debu Tripathy,[1] Carlos H. Barcenas[1]

Abstract

We conducted a retrospective study of breast cancer survivors to determine the 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. The 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. **Patients and Methods:** We retrospectively identified a cohort of women with a diagnosis of stage I-III, hormone receptor–positive, human epidermal growth factor receptor 2-negative BC from January 1997 to August 2008, who had received initial treatment at the MD Anderson Cancer Center, had completed 5 years of ET, and had remained free of locoregional or distant relapse or contralateral BC for $\geq$ 5 years after diagnosis. The weight change at the end of 5 years of ET was measured as the percentage of the change in weight from the start of ET, with a weight gain of $>$ 5% 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:** Of 1282 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 had gained weight and those who had not were not significantly different. **Conclusion:** Premenopausal BC patients had an increased risk of weight gain after 5 years of ET; however, BC patients with a weight gain of $>$ 5% did not have an increased risk of disease recurrence.

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Introduction

Weight gain is prevalent among breast cancer (BC) survivors, with 50% to 96% of survivors reporting weight gain after a diagnosis or during treatment of 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 BC are immense.[11] Weight gain could possibly adversely affect survival among BC 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 postdiagnostic weight change measures and the highly selected

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[1]Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX
[2]Department of Biostatistics, The University of Texas School of Public Health, Houston, TX
[3]Department of Internal Medicine, University of Miami, Miami, FL
[4]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX

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Address for correspondence: Carlos H. Barcenas, MD, MS, Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1354, Houston, TX 77030
E-mail contact: CHBarcenas@mdanderson.org

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populations of patients with a good prognosis are also likely to have contributed to the varied findings. Most studies of weight gain in BC patients have assessed the weight change during or after adjuvant chemotherapy.[10,22,23] The predictors of weight gain after BC were analyzed in the Women's Healthy Eating and Living (WHEL) study, a prospective randomized clinical trial that included BC patients within 4 years of diagnosis with their weight recorded 1 year before the diagnosis, at study enrollment, and for a period of 6 years. The WHEL study reported an association of weight gain with chemotherapy, irrespective of the type or regimen.[23] In contrast, tamoxifen was not significantly associated with weight gain.[23] Another study reported associations of weight gain after chemotherapy in patients with a younger age at diagnosis and with a premenopausal status,[24] supporting the idea that weight gain occurs 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 the Life after Cancer Epidemiology (LACE) study suggested that no increase in the risk of disease was present in the first 5 to 7 years after diagnosis in those with early-stage BC.[21] However, the weight change during ET was not specifically examined. Therefore, the objectives of our study were to identify the 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.

Patients and Methods

Study Design and Patients

The present retrospective study was performed with approval of the MD Anderson Cancer Center's institutional review board (approval no. PA13-0424). Using the Breast Cancer Management System database in the Department of Breast Medical Oncology at the MD Anderson Cancer Center, we identified 1282 women with a diagnosis of early-stage (stage I-III), hormone receptor−positive (HR^+), human epidermal growth factor receptor 2−negative ($HER2^-$) BC from January 1997 to August 2008, who had received their initial treatment at MD Anderson to help diminish a selection bias.[27] HR^+ tumors were those that were either estrogen receptor−positive or progesterone receptor−positive as determined by immunohistochemistry using institutional cutoffs. HER2 status was assessed by immunohistochemistry or fluorescence in situ hybridization when available and determined as positive or negative on the basis of institutional cutoffs and guidelines that were current at the time of diagnosis. Patients self-reported their race at the time of registration. By the inclusion criteria, all the patients were aged 18 to 90 years at diagnosis, had completed 5 years of ET, and were disease free 5 years after diagnosis. Body mass index (BMI) was classified according to the World Health Organization criteria.[28] Underweight was defined as a BMI of < 18.5 kg/m^2; normal, 18.5 to 24.9 kg/m^2; overweight, 25 to 29.9 kg/m^2; and obese, > 30 kg/m^2. Menopausal status was recorded at the diagnosis and was defined as pre-, peri-, or postmenopausal by the attending physician using the guidelines that were current at that time.[29] Women who were perimenopausal were grouped with women who were premenopausal. We excluded patients who had received any treatment for BC before their initial visit to MD Anderson, those who had initiated ET > 1 year after their diagnosis, those who had received ET before their BC diagnosis (eg, for chemoprevention), those who had had any disease recurrence within 5 years of diagnosis, those with concurrent second primary cancers at any site, and those with missing demographic, tumor, and/or treatment details.

Outcomes of Interest

The 2 outcomes of interest for the present study were weight gain, specifically after 5 years of ET, and recurrence-free survival (RFS). The weight change percentages were calculated as [(weight after ET − weight before ET)/weight before ET] × 100. A weight gain of $> 5\%$ was considered clinically relevant, because this cutoff 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' medical records to verify their weight as assessed by direct measurement during clinic visits within 90 days of starting and ending ET. RFS was defined as the interval from diagnosis to any locoregional recurrence (including invasive ipsilateral tumor and invasive locoregional tumor) or distant recurrence or death from any cause.[35] Patients without recurrence were censored at their last follow-up visit.

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 $< .25$ on univariate analysis were included in a multivariable model.[36,37] Backward selection criteria were used to retain variables in the multivariable model using a .05 significance level. Because of their clinical significance, chemotherapy, surgery, and ET were retained in the multivariable model, regardless of whether they had a P value of $< .25$ on 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 $\leq 5\%$. A multivariable Cox proportional hazards regression model with adjustment for other baseline covariates was used to evaluate the association between weight gain and RFS. $P < .05$ was considered to indicate 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 the patient characteristics are listed in Table 1. The median follow-up time from the date of diagnosis was 11.2 years (quartile [Q] 1, 9.4 years; Q3, 13.3 years), and the median follow-up time from 5 years after diagnosis was 6.2 years (Q1, 4.4 years; Q3, 8.3 years). Of the 1282 long-term BC survivors included in the present study, 432 (33.7%) had a weight gain of $> 5\%$, and 850 (66.3%) had a weight change of $\leq 5\%$. In both groups, ~60% of patients were overweight or obese at diagnosis, and ~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 $\leq 5\%$. Patients who had a weight gain of $> 5\%$ were also more likely to be