Does Switching from Tamoxifen to an Aromatase Inhibitor Result in Weight Change in Postmenopausal Breast Cancer Patients?

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Abstract: *Background*: Women treated with early stage breast cancer often gain weight following diagnosis. Tamoxifen and aromatase inhibitor (AI)-treated patients experience similar weight gains in randomized clinical trials after five years of adjuvant therapy. How switching therapies affects weight change is uncertain.

Purpose: To determine the degree of weight change at the time of switching from tamoxifen to an aromatase inhibitor during adjuvant hormonal therapy, and to identify possible associations.

Methods: Retrospective review of postmenopausal women with non-metastatic, invasive, hormone receptor-positive breast cancer sequenced from tamoxifen to an AI. Weights and height were recorded while on tamoxifen, 12 and 6 months prior to switching, at the time of the switch and 6 and 12 months post-switch. Variables included age at diagnosis, adjuvant chemotherapy, body-mass index (BMI), antidepressant use, co-morbidities, and menopausal status.

Results: Data on 80 eligible patients revealed mean weight change from 12 months prior to 12 months post-switch was 0.7 kg (95%CI: -0.16, 1.5 kg, p=.11) with most of the change occurring before the switch. No significant difference was found between weights obtained from the time of switch to 12 months after (mean change -0.1 kg; 95% CI: -0.74, 0.53, p=.75). No association with age, stage, BMI, menopausal status, specific AI, duration of tamoxifen, adjuvant chemotherapy, alcohol or antidepressant use was found.

Conclusions: While patients switching from tamoxifen to an AI experienced modest weight gain in the 12 months prior to the switch, they did not experience further significant weight change after 12 months on an AI.

Keywords: Weight gain, postmenopausal breast cancer hormone therapy, survivorship.

INTRODUCTION

When first reported in 1978 [1], weight gain was an unexpected finding after treatment for early stage breast cancer. Now it is a well-recognized complication of adjuvant therapy, particularly adjuvant chemotherapy [2-8]. Women with a breast cancer diagnosis appear to experience greater weight gain than women without breast cancer, despite an overall tendency for women to gain weight over time—particularly after menopause [9]. Weight gain in women represents a serious health threat for a number of reasons. In postmenopausal women without a diagnosis of cancer increased weight has been associated with increased risk of developing and dying from breast cancer [10]. Additionally, weight gain is associated with altered body image: women about to start adjuvant hormonal therapy commonly express concern about hormonal management and the risk of subsequent weight gain.

A number of studies, predominantly retrospective, have defined factors associated with weight gain after a diagnosis of localized breast cancer, including the use of adjuvant chemotherapy, pretreatment menopausal status, chemo-therapy-induced menopause, younger age at diagnosis, and lower body mass index (BMI) prior to breast cancer treatment as independent variables associated with weight gain [2-8,10-12]. Few of these studies are clear with respect to the timing of weight gain. Makari-Judson and colleagues demonstrated that 71% of women gained weight with a median gain of 1.5 kg at one year and 2.7 kg at two years after diagnosis, with little weight gain thereafter [12]; others have described a similar plateau [5].

Hormonal therapy, predominantly tamoxifen, was not found to be a significantly contributing variable in the aforementioned studies or others; few patients received therapy with aromatase inhibitors (AI). Studies of tamoxifen in the prevention setting found no significant difference in weight gain in healthy women receiving tamoxifen compared with placebo [13], nor was there a difference when tamoxifen was evaluated in early stage breast cancer [14].

Tamoxifen is a selective estrogen receptor modulator (SERM) and thus has both estrogenic and anti-estrogen effects. AIs reduce the production of postmenopausal estrogen by inhibiting aromatase, the enzyme responsible for the conversion of androstenedione and testosterone to estrogens. When compared to another hormonal breast cancer treatment, megesterol, which inhibits estrogen by blocking ACTH, there was significantly less weight gain in women receiving AIs compared with those treated with megestrol [15]. In a large prospective randomized study of the AI anastrazole and tamoxifen in the adjuvant treatment

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of early-stage breast cancer, no differences in weight gain were seen between the two agents [16].

One approach to the use of AI agents in the adjuvant therapy of breast cancer is sequencing; that is, switching from tamoxifen to an AI after two to three years of the SERM. While a large randomized study in early-stage invasive breast cancer of adjuvant therapy with exemestane after two or three years of tamoxifen compared with continued tamoxifen did not yield a difference in weight gain between the arms [17], results were noted for five years of therapy, and did not assess weight changes surrounding the time the agents were switched, leaving the dynamics of weight change at the time of the switch from a SERM to an agent without estrogenic activity unreported. The timing of this switch occurs at the time that previous work suggests a plateau in weight change is reached [5, 12].

We therefore undertook this retrospective review to determine if there is a change in weight associated with sequencing to an aromatase inhibitor after treatment with tamoxifen at the time of the switch, and to describe factors that might be associated with this change.

PATIENTS AND METHODS

This study was a retrospective chart review of 80 breast cancer patients identified by their medical oncologist as having been sequenced from tamoxifen to an AI and meeting eligibility criteria. The study was conducted at the D'Amour Center for Cancer Care, Springfield, Massachusetts and was approved by the Institutional Review Board which waived informed consent.

Eligible women had a prior diagnosis of early stage (AJCC I, II or III) estrogen and/or progesterone receptor positive breast carcinoma, had started on tamoxifen then were sequenced onto an AI—anastrazole, exemestane, or letrozole—and were postmenopausal at the time of starting the AI. Patients had received therapy with the AI for twelve months or more at the time of the review. Women who did not have weights recorded, had metastatic disease or had discontinued the AI with less than 6 months of treatment were excluded from this review.

Information compiled included age at diagnosis of breast cancer, stage, tumor characteristics (grade, Her2/*neu* status by immunohistochemistry or fluorescence *in situ* hybridization, size, lymph node involvement), type of surgery (breast conserving therapy or mastectomy), and use of radiation and specific adjuvant therapy, including chemotherapy and chemotherapy regimen. Comorbidities were documented and included diabetes, thyroid disease, as well as use of antidepressants including use of selective serotonin reuptake inhibitors (SSRIs) and tobacco use. Menopausal status was classified according to treatment-induced menopause (due to either chemotherapy or surgery), naturally-experienced menopause, or postmenopausal at the time of diagnosis.

Patients fell into several treatment groups based on time of switch from tamoxifen to an AI. These were defined as 1) less than 2 yrs of tamoxifen, 2) 2-3 years of tamoxifen, 3) more than 3 but less than 5 years of tamoxifen, and 4) 5 years or longer on tamoxifen. Weight and height were collected every 6 months starting one year before switch and continuing one year after.

Analysis of the Study and Statistical Considerations

Descriptive analyses were undertaken in order to determine distributions of variables collected during this retrospective study. Univariate measurements employed *T* tests, paired or unpaired (for continuous variables), chi-square tests for nominal data, Pearson correlation, or simple logistic regression, as appropriate. Multivariate regression models were constructed employing stepwise forward linear regression in order to determine independently-associated variables of significance.

RESULTS

Characteristics of the 80 women in the study are shown in Table **1**. Mean weight change from 12 months prior to switching hormonal agents to 12 months post-switch was 0.7 kg (95%CI: -0.16, 1.5 kg, p=.15). Most of this change was experienced prior to the switch (mean change from 12 months prior to switch 0.8 kg, 95%CI: 0.14, 1.5 kg, p=.03). No further change in weight was observed after the switch (mean weight change from the switch to 12 months post-switch -0.1 kg, 95%CI: -0.82, 0.46, p=.29).

Current smokers (n = 9) lost weight over the 2-year observation period (mean change -1.6 kg, p=.043), with decreased mean weight seen both in the 12 months prior to the switch (mean change -0.7 kg, p=.11) and the 12 months after the switch (mean change -0.9 kg, p=.40). Those with a history of hypothyroidism (n = 3) gained weight significantly over the 24 months of observation (mean change 4.9 kg, 95%CI: 0.78, 9.0, p=.04), but without gain for the 12 months of observation after the switch (mean change -1.3 kg, 95%CI: -4.5, 1.8, p=.35).

Stage of disease was not associated with change of weight over the full 24 month observation period, but was for the 12 months prior to the switch (p=.017), with the bulk of the change affecting patients with stage III disease (mean change in the 12 months prior to the switch 3 kg, 95%CI: 0.91, 5.1, p=.03). Stage IIIB patients gained significant weight (mean change over the 2 years of observation 9.9 kg, 95%CI: 2.3, 14.6, p=.0002), although there were only 3 cases in the series. No association with age, BMI, classification of menopausal status, specific AI employed, duration of tamoxifen treatment, adjuvant chemotherapy or chemotherapy type, method of local control or use of radiation therapy, alcohol or antidepressant use, or other co-morbidities was found, and no factor was identified that was associated with weight change over the year after the switch.

Stepwise multivariate regression determined that history of hypothyroidism (p=.050) and current smoking history (p=.056) were associated with weight change over the 2 years of observation. Similar results were found when only the 12 months prior to the switch were considered. No variables were associated with weight change in the 12 months following the switch.

DISCUSSION

Early studies suggesting weight gain in women treated for early stage breast cancer with tamoxifen were small

Table 1. Patient Characteristics

Characteristic		Value
Mean age		53 (range: 33-81)
Mean weight 12 months prior to switch		72.8 kg (range: 42.6-136.2)
Mean BMI 12 months prior to switch		28.6 kg/m^2 (range: 18.9-53.9)
Stage:		
	I	35
	II	37
	III	8
ER +		80
PgR+		60
Her2/*neu*+	0	52
	1+	1
	2+	9
	3+	0
	Unknown	17
Local therapy	Mastectomy	35
	Breast conservation	45
Radiation therapy		56
Adjuvant chemotherapy		49
Chemotherapy regimens*	AC	30
	AC+T	12
	CAF	3
	Others	4
Menopause	Chemotherapy induced amenorrhea	25
	Premenopausal at time of diagnosis then experiencing natural menopause	8
	Premenopausal at time of diagnosis then experiencing surgical menopause within 6 months of starting an AI	2
	Premenopausal at time of diagnosis then experiencing surgical menopause more than 6 months before starting an AI	0
	Postmenopausal at time of diagnosis	45
Duration of tamoxifen therapy	< 2 years	14
	2-3 years	29
	3-5 years	20
	> 5 years	17
Aromatase inhibitor	Exemestane	45
	Anastrazole	20
	Letrozole	15
Hypothyroidism		3
Depression		9
Hypertension		13
Cigarette use	Never smoker	49
	Past use, now non-smoker	22
	Current smoker	9
Alcohol use	Non-drinker	27
	< 3 drinks/week	45
	3+ drinks/week	8
Antidepressant use		18

*Abbreviations: AC: doxorubicin/cyclophosphamide; AC + T, doxorubicin/cyclophosphamide followed by paclitaxel: CAF: cyclophosphamide, doxorubicin, fluorouracil.

[18, 19]; other investigators describe reports from patients suggesting difficulty in achieving weight loss while on tamoxifen [20]. Large randomized trials including National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 (in patients with invasive breast cancer) and NSABP P-1 (the tamoxifen prevention trial) did not reveal significant differences in weight gain between patients treated with tamoxifen for five years and those who were not. The ATAC trial comparing anastrazole to tamoxifen usage over five years [16] and the BIG-98 trial comparing letrozole to tamoxifen over five years [21] have not revealed a difference in weight gain. Finally, the Intergroup Exemestane Study did not find a significant difference in weight over 5 years between patients treated with five years of adjuvant tamoxifen and those treated with two to three years of tamoxifen followed by exemestane [17]. In a smaller study by Francini *et al.* [22], women who had received two years of tamoxifen were randomly assigned either to continue on tamoxifen or switch to exemestane and monitored for changes in body weight, composition and lipid profiles. While all of the women in this study were either overweight or obese, the mean BMI of 29 kg/m^2 was similar to that in our series. There was no difference in weight in the women who continued on tamoxifen while those sequenced to exemestane experienced a non-significant weight decrease 12 months later, despite a significant decrease in body fat.

The purpose of our study was to evaluate the weight change dynamic at the time of hormonal therapy switch. The current results do not show reveal a statistically significant weight change in this sample of postmenopausal women sequenced from tamoxifen to an AI over the two years of observation surrounding the switch. A modest weight gain was seen in the 12 months prior to switching therapies, but none thereafter. Our previous data, based on both pre-and postmenopausal patients, suggests that not only do postmenopausal patients tend to gain relatively little weight, but that little weight change occurs in the third year after diagnosis [12], which would account for the majority of the patients in this series. Subgroups with significant weight changes—current smokers, hypothyroid history, and stage III patients—represent small proportions of our study population; this, combined with a small data set analyzed by stepwise techniques, yields results that should be considered as hypothesis-generating only, given the risk of compromised *p*-values.

Our study is limited in its ability to address many of the variables potentially associated with weight gain. Caloric intake and energy expenditure were assumed to be relatively constant over the two year period of the study for each patient. Recent efforts at determining the impact of aerobic exercise interventions in breast cancer survivors have not yielded changes in BMI or weight [23-25] despite sustained changes in exercise patterns and body composition.

CONCLUSION

Avoiding weight gain is, and should continue to be, an important goal for both breast cancer survivors and their clinicians, but weight gain should not constitute a factor when considering the most appropriate choice of adjuvant hormonal therapy. Our study did not show a significant difference in weight change for women on tamoxifen sequenced to an AI. Future prospective studies should address changes in weight distribution as well as body composition in breast cancer survivors on AI agents, particularly years after diagnosis.

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CONFLICTS OF INTEREST

The authors to not have any conflicts of interest to declare.

REFERENCES

[1] Dixon JK, Moritz DA, Baker FL. Breast cancer and weight gain: an unexpected finding. Oncol Nurs Forum 1978; 5: 5-7.

[2] Knobf MK, Mullen JC, Xistris D, Moritz DA. Weight gain in women with breast cancer receiving adjuvant chemotherapy. Oncol Nurs Forum 1983; 10: 28-33.

[3] Huntington MO. Weight gain in patients receiving adjuvant chemotherapy for carcinoma of the breast. Cancer 1985; 56: 472-4.

[4] Heasman KZ, Sutherland HJ, Campbell JA, Elhakim T, Boyd NF. Weight gain during adjuvant chemotherapy for breast cancer. Breast Cancer Res Treat 1985; 5: 195-200.

[5] Goodwin PJ, Panzarella T, Boyd NF. Weight gain in women with localized breast cancer—a descriptive study. Breast Cancer Res Treat 1988; 11: 59-66.

[6] Camoriano JK, Loprinzi CL, Ingle JN, Therneau TM, Krook JE, Veeder MH. Weight change in women treated with adjuvant therapy or observed following mastectomy for node-positive breast cancer: J Clin Oncol 1990; 8: 1327-34.

[7] Levine EG, Raczynski JM, Carpenter JT. Weight gain with breast cancer adjuvant treatment. Cancer 1991; 67: 1954-9.

[8] Hupperets PS, Wils J, Volovics L, *et al*. Adjuvant chemohormonal therapy with cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF) with or without medroxyprogesterone acetate for node-positive breast cancer patients. Ann Oncol 1993; 4: 295-301.

[9] Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. N Eng J Med 2003; 348: 1625-38.

[10] Kroenke CH, Chen WY, Rosner B, Holmes MD. Weight, weight gain, and survival after breast cancer diagnosis. J Clin Oncol 2005; 23: 1370-8.

[11] Kumar NB, Allen K, Cantor A, *et al*. Weight gain associated with adjuvant tamoxifen therapy in stage I and II breast cancer: fact or artifact? Breast Cancer Res Treat 1997; 44: 135-43.

[12] Makari-Judson G, Judson CH, Mertens WC. Longitudinal patterns of weight gain after breast cancer diagnosis: observations beyond the first year. Breast J 2007; 13: 258-65.

[13] Day R. Quality of life and tamoxifen in a breast cancer prevention trial: a summary of findings from the NSABP P-1 study. National Surgical Adjuvant Breast and Bowel Project. Ann NY Acad Sci 2001; 949: 143-50.

[14] Fisher B, Costantino J, Redmond C, *et al*. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen–receptor-positive tumors. N Engl J Med 1989; 320: 479-84.

[15] Buzdar A, Jonat W, Howell A, *et al*. Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in post menopausal women with advanced breast cancer: results of overview analysis of two phase III trials. Arimidex Study Group. J Clin Oncol 1996; 14: 2000-11.

[16] Baum M, Buzdar A, Cuzick J, *et al*. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early stage breast cancer: Results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. Cancer 2003; 98: 1802-10.

[17] Fallowfield LJ, Bliss JM, Porter LS, *et al*. Quality of life in the Intergroup Exemestane Study: a randomized trial of exemestane versus continued tamoxifen after 2 to 3 years of tamoxifen in postmenopausal women with primary breast cancer. J Clin Oncol 2006; 24: 910-7.

[18] Hoskin, PJ, Ashley S, Yarold, JR. Weight gain after primary surgery for breast cancer—effect of tamoxifen. Breast Cancer Res Treat 1992; 22: 129-32.

[19] Rose DP, Connolly JM, Cheblowski RT, *et al*. The effects of a low fat dietary intervention and tamoxifen adjuvant therapy on the serum estrogen and sex-binding globulin concentrations of postmenopausal breast cancer patients. Breast Cancer Res Treat 1993; 27: 253-62.

[20] Matthews KA, Abrams B, Crawford S, *et al*. Body mass index in mid-life women: relative influence of menopause, hormone use, and ethnicity. Int J Obes Relat Metab Disord 2001; 25: 863-73.

[21] The Breast International Group (BIG) 1-98 Collaborative Group. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med 2005; 353: 2747-57.

[22] Francini G, Petrioli R, Montagnini A, *et al*. Exemestane after tamoxifen as adjuvant hormonal therapy in postmenopausal women with breast cancer: effects on body composition and lipids. Br J Cancer 2006; 95: 153-8.

[23] Rogers LQ, Hopkins-Price P, Vicari S, *et al*. Physical activity and health outcomes three months after completing a physical activity behavior change intervention: persistent and delayed effects. Cancer Epidemiol Biomarkers Prev 2009; 18: 1410-8.

[24] Courneya KS, Mackey JR, Bell GJ, *et al*. Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes. J Clin Oncol 2003; 21: 1660-8.

[25] Courneya KS, Segal RJ, Mackey JR, *et al*. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized clinical trial. J Clin Oncol 2007; 25: 4396-404.

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