

Tamoxifen and Mammographic Breast Densities¹

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Abstract

The extent of breast tissue density on mammograms is one of the strongest risk factors for breast cancer. The aim of this analysis was to evaluate whether tamoxifen can affect mammographic breast density. Subjects were participants in the National Surgical Adjuvant Breast Project Breast Cancer Prevention Trial (BCPT), recruited and followed at the Breast Center of Saint-Sacrement Hospital in Quebec City, Canada. The Breast Cancer Prevention Trial is a double-blind trial in which women at high risk of breast cancer were randomized to receive either 20 mg tamoxifen per day or placebo. Mammograms were taken before treatment began and yearly thereafter. For the purpose of this analysis, Wolfe's parenchymal pattern and the percentage of the breast showing tissue densities were assessed by review of pre- and posttreatment mammograms without knowledge of treatment assignment. Among the 69 women included in this analysis, 36 received tamoxifen and 33 received placebo for an average of 3.3 and 3.5 years, respectively. Among women receiving tamoxifen, 16 of 36 (44.4%) changed to a parenchymal pattern of lower density compared with 5 of 33 (15.2%) women receiving placebo ($P = 0.010$). Moreover, in the tamoxifen-treated group, the difference in the percentage of the breast showing tissue densities between the pre- and posttreatment mammograms reached -9.4% on average compared with a reduction of -3.6% in the placebo group ($P = 0.010$). Our data show that tamoxifen can reduce high-risk mammographic features. Breast densities should be evaluated as possible early markers of the preventive effect of selective estrogen receptor modulators.

Introduction

Tamoxifen, a SERM,³ can reduce the incidence of breast cancer. Among women with the disease, 5 years of tamoxifen

reduces the incidence of breast cancer in the opposite breast by $\sim 47\%$ (1). Similarly, among women with a high risk of breast cancer, the National Surgical Adjuvant Breast Project BCPT reported that tamoxifen reduced the incidence of breast cancer by 45% after an average follow-up of 3.6 years (2). However, randomized Italian and British trials have not observed such a preventive effect of tamoxifen (3, 4). Recently, raloxifene, another SERM, has been shown to reduce breast cancer incidence among postmenopausal women (5).

Tamoxifen could affect the incidence of diagnosis of breast cancer by intervening at different moments in the carcinogenic process from the early changes in breast epithelial cells to later stages when invasive cancer is already developed but yet undiagnosed. Given the effectiveness of tamoxifen in the treatment of women with clinical invasive breast cancer (1), tamoxifen appears likely to also have a therapeutic effect on preclinical but as yet undetected lesions. Successful treatment of these undetected preclinical lesions would lead to a reduction in the number of women subsequently diagnosed with breast cancer. Most of the reduction in incidence of diagnosis of breast cancer observed shortly after the beginning of tamoxifen administration could be linked to this therapeutic effect. The possible effect of tamoxifen on breast tissue changes that occur earlier in the carcinogenic process is not yet as clear but needs to be determined because such an effect would result in true prevention of the disease by reducing the occurrence of new invasive cancers.

The aim of this analysis was to determine whether tamoxifen could affect breast tissue as reflected on the mammogram as breast densities. The extent of breast densities on the mammogram is one of the strongest risk factors for breast cancer (6–16). Breast cancer risk has been shown repeatedly to increase substantially with the percentage of the breast showing tissue densities and to be higher in women with the radiologically dense P2 or DY parenchymal patterns than in those with the N1 or P1 patterns. This association of breast densities with breast cancer risk is suggested to derive from the association of breast densities with epithelial hyperplasia (with and without atypia) and carcinoma *in situ* (16, 17). A reduction in high-risk mammographic features after the administration of tamoxifen would support the idea that this drug can alter breast tissue and prevent the development of new invasive breast cancers.

Materials and Methods

Eligibility. The analysis was based on participants in the BCPT recruited and followed at the Breast Center of Saint-Sacrement Hospital in Quebec City, Canada. The BCPT trial is described in detail elsewhere (2). In brief, participants were women ages 35 years or older at randomization and had a risk of developing invasive breast cancer equal to or greater than the 5-year risk of 60-year-old women (1.7%). The level of breast cancer risk was assessed by use of a modified form of the Gail model (18), based on information concerning breast cancer risk factors such as the number of first-degree relatives with breast cancer, nulliparity or age at first live birth, number of breast

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³ The abbreviations used are: SERM, selective estrogen receptor modulator; BCPT, Breast Cancer Prevention Trial; IGF-I, insulin-like growth factor I.

biopsies, histological diagnosis of atypical hyperplasia, and age at menarche. Women diagnosed with lobular carcinoma *in situ* were automatically eligible. Postmenopausal hormone therapy, oral contraceptives, or androgens should never have been used or had been discontinued for at least 3 months prior to randomization.

Randomization. Study subjects were recruited and randomized between June 1992 and August 1997 to receive either tamoxifen or placebo. Neither the patients nor the investigators knew the group to which the women were randomized. Women randomized to the tamoxifen group were to receive the drug at a dose of 20 mg per day for 5 years. However, treatments were terminated early and unblinded because of the observed tamoxifen-associated reduction in the incidence of breast cancer diagnosis at the time of an interim analysis (2).

Initial Evaluation and Follow-Up. At initial evaluation, women completed a self-administered questionnaire on demographic characteristics, medical and reproductive history, and life style. All women had a bilateral mammogram within 180 days prior to randomization. Follow-up visits occurred at 3 months and 6 months after the beginning of treatment, and every 6 months thereafter. Bilateral mammograms were taken annually. Most women followed at Saint-Sacrement Hospital had their initial and follow-up mammograms at the same radiology clinic (Clinique Radiologique Audet).

End Points. The main end point for this analysis was the change in the morphology of breast tissue as assessed from mammograms. Mammographic features of breast tissue evaluated included Wolfe's mammographic parenchymal pattern (6, 7) and the percentage of the breast showing tissue densities (8–12, 15).

Mammographic features were assessed by one of us (J.B.), who has experience in such readings, *i.e.*, Wolfe's parenchymal pattern and the percentage of the breast showing densities, which is evaluated using 22 scores (score 0 for 0%, score 5 for 1–9%, score 10 for 10–14%, score 15 for 15–19% . . . score 90 for 90–94%, and score 95 for 95–100% of the breast with densities; Refs. 8, 10, and 19). This assessment was made from the pretreatment and posttreatment mammograms. The posttreatment mammograms corresponded to the last mammograms taken while the woman was under treatment or within 2 months of treatment cessation. The craniocaudal and mediolateral mammograms of only one breast were reviewed. The mammograms of the right or left breast were chosen at random for review except for the four women diagnosed with invasive breast cancer. For these women, the mammograms of the unaffected breast were used to assess features.

The pre- and posttreatment mammograms of each participant were reviewed simultaneously without knowledge of treatment assignment or of any other information on women. The mammograms of each woman were reviewed twice. The second review was done without knowledge of the outcome of the first review. The results of the two reviews were then compared. When parenchymal pattern differed or when the absolute difference in the percentage of the breast showing densities exceeded 10%, mammograms were reexamined to obtain final assessment of mammographic features. Otherwise, the average of the percentage of the breast of the two independent reviews and the consistent parenchymal pattern were used as final assessment of features. The weighted kappa comparing the first and second assessment of parenchymal pattern in four categories was 0.82 for the pretreatment mammograms and 0.83 for the posttreatment mammograms. The intraobserver intraclass correlation coefficients for the assessment of the

Table 1 Characteristics of treatment groups at randomization^a

Characteristics	Tamoxifen <i>n</i> = 36	Placebo <i>n</i> = 33
Age at baseline (yr)	50.9 ± 8.0	50.3 ± 6.4
At least one first-degree relative with breast cancer (%)	75	75.8
History of at least one breast biopsy (%)	52.8	42.4
Nulliparity (%)	36.1	24.2
Age at first live birth ^b (yr)	26.1 ± 4.2	24.6 ± 4.6
Age at menarche (yr)	12.8 ± 1.6	12.9 ± 1.7
Body mass index	25.1 ± 3.1	25.3 ± 4.5
Alcohol consumption (drinks/week)	3.1 ± 4.5	3.9 ± 5.0
Wolfe's parenchymal pattern (%)		
N1 or P1	5.6	12.1
P2	52.8	51.5
DY	41.7	36.4
Mean percentage of the breast with mammographic densities	60.3 ± 18.5	60.5 ± 24.2
Duration of treatment (yr)	3.3 ± 1.5	3.5 ± 1.2

^a ± values are means ± SD.

^b Among women who had at least one child.

percentage of the breast showing densities were 0.92 and 0.89 for the pre- and posttreatment mammograms, respectively.

Data Analysis. Women in the two treatment groups were compared on the basis of the change in breast densities between the pre- and posttreatment mammograms. Change in parenchymal pattern was expressed in terms of the proportion of women for whom the pattern changed from a dense to a less dense category, *i.e.*, from a DY pattern at the pretreatment mammograms to a P2, P1, or N1 pattern at the posttreatment mammograms, from a P2 pattern to a P1 or N1 pattern, or from a P1 to an N1 pattern. The difference between treatment groups in the proportion of women for whom the pattern changed was tested using Fisher's exact test. Multivariate logistic regression allowed evaluation of potential confounding effect of covariates.

The change in the percentage of the breast with densities was measured by the difference in the percentage of the breast with densities observed on the pre- and posttreatment mammograms (percentage of the breast with densities on the posttreatment mammogram minus the percentage on the pretreatment mammogram). Treatment groups were compared on the basis of the average difference in the percentage of the breast with densities using the *t* test, taking into account inequality in variances when needed. Multiple linear regression was used to explore confounding by covariates.

Results

Overall, 184 women were enrolled in the BCPT at Saint-Sacrement Hospital, and 69 participants were included in this analysis (36 in the tamoxifen group and 33 in the placebo group). Reasons for exclusion were treatment duration of <1 year (*n* = 20), breast implants (*n* = 3), and either pre- or posttreatment mammograms done in clinics other than Clinique Radiologique Audet (*n* = 13). In addition, the pretreatment mammograms were unavailable for 79 women (35 in the tamoxifen group and 44 in the placebo group), mainly because standard policy in the participating radiology clinic is to destroy mammograms after a period of 5 years.

The pretreatment characteristics of the tamoxifen and placebo groups are shown in Table 1. The two groups were similar with respect to most variables assessed. The only characteristics

Table 2 Change in mammographic features after treatment with tamoxifen or placebo

	Percentage of women changing to a parenchymal pattern of lower radiologic density			Mean reduction in the estimated percentage of the breast showing radiological densities		
	Tamoxifen % (n ^a)	Placebo % (n)	P ^b	Tamoxifen Mean ± SD (n)	Placebo Mean ± SD (n)	P ^b
All women	44.4 (36)	15.2 (33)	0.010	-9.4 ± 12.0 (36)	-3.6 ± 5.3 (33)	0.010 ^c
Age at baseline (yr)						
<50	66.7 (21)	18.8 (16)	0.007	-12.1 ± 11.0 (21)	-3.6 ± 4.5 (16)	0.003 ^c
≥50	13.3 (15)	11.8 (17)	1	-5.7 ± 12.6 (15)	-3.5 ± 6.2 (17)	0.540 ^d
Duration of treatment (yr)						
1.0–3.4	38.5 (13)	6.7 (15)	0.069	-6.9 ± 11.1 (13)	-3.3 ± 3.5 (15)	0.282 ^c
3.5–5.0	47.8 (23)	22.2 (18)	0.114	-10.9 ± 12.4 (23)	-3.8 ± 6.6 (18)	0.024 ^c

^a Total number of women in category.

^b Fisher's exact test. All *P*s are two-sided.

^c *t* test with unequal variances.

^d *t* test with equal variances.

that differed slightly between the tamoxifen and the placebo groups were the history of at least one breast biopsy (52.8% versus 42.4%, Fisher exact *P* = 0.472) and nulliparity (36.1% versus 24.2%, respectively; Fisher exact *P* = 0.309). The average duration of treatment was 3.3 and 3.5 years for the tamoxifen and placebo groups, respectively.

Table 2 shows the changes in parenchymal pattern between the pre- and posttreatment mammograms. Among women receiving tamoxifen, 4 of 19 women with a P2 pattern changed to a P1 pattern, and 12 of 15 with a DY pattern changed to a P2 pattern. Thus, 16 of 36 (44.4%) changed to a less dense parenchymal pattern. Among women receiving placebo, only 5 of 12 women with a DY pattern changed to a P2 pattern, and all women with a P2 pattern remained in the same category. Thus, 5 of 33 (15.2%) changed to a less dense parenchymal pattern. This difference between tamoxifen and placebo groups (44.4% versus 15.2%) was statistically significant (*P* = 0.010). Only one woman, in the placebo group, had an increase in pattern density from N1 at pretreatment to P1 at posttreatment. The reduction in parenchymal pattern associated with tamoxifen was much clearer in participants <50 years of age and was apparent even among those who had been treated for 1.0–3.4 years.

In the tamoxifen-treated group, the difference in the percentage of the breast with densities between the pre- and posttreatment mammograms reached -9.4% on average compared with a difference of -3.6% in the placebo group (*P* = 0.010; Table 2). Again, the tamoxifen-associated reduction in breast density appeared clearer in women <50 years of age, and the reduction was apparent after 1.0–3.4 years of treatment. The interaction of treatment with age was not statistically significant (*P* = 0.158).

The strength and statistical significance of the associations of tamoxifen use with the change in parenchymal pattern or with the change in the percentage of the breast with densities remained essentially unchanged when adjustment was made for nulliparity and history of breast biopsy, the two factors that differed slightly between the two treatment groups.

Discussion

Our data indicate that tamoxifen can reduce mammographic breast densities after 1–5 years of use. This tamoxifen-associated reduction in breast densities was seen primarily among women <50 years. In a study of 19 premenopausal women with unilateral breast cancer, Ursin *et al.* (20) have also observed a

reduction in the radiological density of the breast in their 5 patients who had received tamoxifen (*P* = 0.10).

The evaluation of mammographic breast densities is subjective and liable to observer variability. To reduce the possibility of bias from observer error, mammograms were reviewed twice independently, and then major differences in assessed features were resolved by a third reading. In addition, mammograms were reviewed without knowing the group to which the women had been randomized. Thus, intraobserver variability in assessment of mammographic features should have been minimized, and errors should be similar whether women received tamoxifen or placebo. Finally, breast densities were assessed without computer assistance. Despite its advantages (14), the strength of the association of breast densities with breast cancer risk tends to be greater when breast densities are measured using the common unassisted method than when measured with computer assistance (21), showing that the two methods are as valid, at least for experienced readers.

Among the 184 women enrolled in the BCPT at our institution, only 69 could be included in this analysis. However, the main reasons for exclusion (unavailability of mammograms, *n* = 92; treatment of <1 year, *n* = 20; and breast implants, *n* = 3) are unlikely to be related to change in mammographic densities. The similarity of women in the treatment and placebo groups are reassuring in this respect. Randomization seems to have been largely successful in balancing treatment groups with respect to baseline characteristics, even after exclusion criteria were applied. Some differences were observed for nulliparity and history of breast biopsies. However, the differences were small, and the tamoxifen-associated changes in mammographic features were essentially unchanged, even after the imbalance in these factors was taken into account in multivariate analysis. Changes in body weight or menopausal status during intervention was not considered in the analysis.

Extensive breast densities have been related to histological characteristics of breast tissue, such as epithelial hyperplasia (with or without atypia), carcinoma *in situ*, and stromal fibrosis (reviewed in Ref. 16). Thus, breast densities appear to be related to breast cancer risk through their association with epithelial proliferation (17). The reduction in mammographic densities seen to follow tamoxifen administration is consistent with the idea that tamoxifen can reduce epithelial proliferation (and stromal fibrosis) in the breast and that the epithelial changes could prevent the development of some new invasive breast cancers.

Tamoxifen could affect breast tissue because of its antiestrogenic action. Tamoxifen is an estrogen receptor modulator, and in the breast, it acts as an antiestrogen (22). Tamoxifen treatment may then have an effect on breast tissue comparable, in some way, with that of a reduction in circulating estrogens. Parity and menopause are associated with reductions in estrogens (23, 24), and both factors are accompanied by reductions in the density of the mammographic parenchymal pattern (16). Administration of a hormonal contraceptive designed to reduce estrogen and progesterone circulating levels has also been reported to be associated with a reduction in the radiological density of the breast (25, 26). In contrast, breast densities have been seen to increase with intake of exogenous estrogens in the form of hormone replacement therapy (16).

The influence of tamoxifen on breast morphology could be mediated through other biological effects of the drug, such as inhibition of IGF-I (27). IGF-I can stimulate cell proliferation *in vivo* and *in vitro* (28). Receptors to IGF-I have been found in ductal epithelium of normal breast tissue (29). IGF-I appears to be related to breast cancer risk primarily among premenopausal women (30), the group in which tamoxifen-associated reductions in breast densities was the clearest. Moreover, Byrne *et al.* (31) reported recently that circulating levels of IGF-I were positively correlated with breast densities, but this association, like the one seen in our results, was confined to premenopausal women.

Our data suggest that breast densities may be useful as early markers in clinical trials evaluating the effect of SERMs for the possible prevention of breast cancer. Already, breast densities have been used as an intermediate marker in some randomized trials of breast cancer prevention with dietary modification (32) and fenretinide (33) and have been proposed as intermediate markers of the possible preventive effect of tamoxifen on breast cancer occurrence (20).

A reduction in breast densities may also facilitate the diagnosis of breast cancer and may result in some underestimation of the effect of tamoxifen (or other SERMs) on breast cancer incidence. Breast cancers developing in women receiving tamoxifen may be easier to detect and thus be detected earlier than those developing in untreated women. Such lead time gained through tamoxifen would tend to artificially increase the age-specific rate of breast cancer diagnosis in tamoxifen-treated women and, consequently, result in some underestimation of the preventive effect of this drug. The extent of the underestimation of the preventive effect would depend on the amount of lead time gained from tamoxifen treatment.

In conclusion, the observed changes in mammographic breast density associated with tamoxifen treatment is consistent with the idea that this medication can reduce epithelial (and stromal) proliferation in breast tissue and, thus, prevent the development of some new invasive breast cancers. Our results also suggest that mammographic breast density should be evaluated as a possible early marker of the preventive effect of SERMs on breast cancer occurrence.

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