Tamoxifen in women with breast cancer and mammographic density

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Summary

Purpose of investigation: To evaluate the effect of tamoxifen on mammographic density using a qualitative and a semiquantitative method. *Methods:* Mammograms from 148 women treated for breast cancer before and after surgery were reviewed: 68 were administered tamoxifen; 80 did not receive tamoxifen. The mammograms were classified in one of the four BIRADS density categories by two radiologists blinded to the treatment and by a computer-assisted method after digitizing images. *Results:* At mammographic one-year-follow-up density was reduced in both groups and remained stable in the following years. A comparison of mammograms performed before surgery and after one year showed a statistically significant difference in density reduction between the tamoxifen and the non-tamoxifen-treated group. Good agreement was obtained between the qualitative and semiquantitative method. *Conclusion:* Breast density reduction observed in women treated with tamoxifen may help in the detection of small tumors in dense breasts by means of reducing the masking effect of parenchyma.

Key words: Mammographic density; Breast cancer; Tamoxifen.

Introduction

High breast density has been reported as one of the greatest breast cancer risk factors: a radiologically assessed breast density of more than 50% has an attributable risk of approximately 30% [1]. Dense breast tissue furthermore reduces the ability to detect small cancers due to possible "masking" [2]. A reduction in breast density may lower the risk of breast cancer and increase the possibility of detecting small breast neoplasms. In 1976 Wolfe first described the association between a qualitative classification of dense mammographic patterns and the risk of breast cancer [3] and several other cohort studies have confirmed this association [4]. However, whether breast density is an independent risk factor or if it is linked to other risk factors is still unclear [3, 5]. Mammographic breast density can be caused by various internal and external factors, and research is under way to determine whether it is the result of genetic and/or environmental factors, lifestyle factors, hormonal levels at different phases of a woman's life or a result of her reproductive history [6, 7]. Many authors have shown interest in the evaluation of the effects of exogenous hormone drug administration on breast mammographic density in women with previously excised breast cancers mainly for two reasons: 1) patients with a personal history of cancer have a relatively high-risk of a new breast cancer and mammograms are definitively important to assess each new little alteration suggestive of tumor; 2) follow-up by mammography is mandatory and unavoidable, and mammograms acquired before and after treatment are accessible to be compared. In particular special attention has been paid to tamoxifen citrate, a selective estrogen-receptor modulator (SERM) which has been evaluated for its efficacy as an adjuvant treatment in women with breast cancer [8] and as a prophylactic treatment in women considered to be at high risk for subsequent disease [9] or at average risk for breast cancer [10]. Whereas hormone replacement therapy (HRT) seems to increase breast density, tamoxifen seems to reduce breast density [4, 11] even though the changes that occur are reversible [12]. Boyd *et al*. [5] and Chow *et al.* [13] both concluded that "tamoxifen causes a decrease in mammographic density with use; an effect that is better quantitated by semiquantitative criteria or computer-aided calculation of digitized images". Byng *et al*. proposed an "analysis of digitized mammograms which facilitate computer analysis" in order to detect small changes in breast density [1]. Whether a reduction in mammographic density is associated with a reduced individual risk of breast cancer is still unclear. However, tamoxifen-induced reduction in density can be a marker for the effectiveness of action in the single patient and also facilitate the reading of mammograms and thereby the ability to detect early breast cancer. The aim of this study was to evaluate the possibility to assess the effect of tamoxifen on breast density during and after completion of therapy using a qualitative (BIRADS) and semiquantitative (computer-aided calculation of digitized images) method.

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Materials and Methods

This study is a retrospective, nonrandomized, blinded review of mammograms from 148 women (age range 41-78 yrs), who were surgically treated for monolateral breast cancer from January 1988 to December 1998 and underwent follow-up evaluation for six years in our department. All mammograms were obtained using the same equipment with the same high quality film-screen combination and amount of compression. Patients, who were hormone-receptor-positive received tamoxifen treatment, whereas patients who were hormone-receptor-negative received no hormonal treatment. The tamoxifen-receiving group consisted of 68 women who received tamoxifen alone or tamoxifen combined with chemotherapy and/or radiation therapy after surgery, administered postoperatively at 20 mg/day for five years. The second group consisted of 80 women who received only chemotherapy and/or radiation therapy after surgery. In both groups there was a homogeneous distribution of pre and postmenopausal patients despite the different age range (tamoxifen-receiving group: age range 41-78 yrs, mean age 58.5 ± 9.3 yrs, median 56.5 yrs; non tamoxifen-treated group: age range 49-78 yrs, mean age 63.9 ± 9.2 yrs, median 63.5 yrs). Ethical approval for the study was granted by the Medical Research Ethics Committee of our University, and informed consent was obtained from all patients. The study is divided in two parts. In the first part of the work mammographic breast density was classified using a qualitative subjective assessment of glandular densities according to the four standard criteria of The American College of Radiology's Breast Imaging Reporting and Data System (BIRADS) and percent density: BIRADS A indicates that the breast is almost entirely fatty (< 10% dense tissue), BIRADS B that there are scattered fibroglandular densities (10-49% dense tissue), BIRADS C that the breast is heterogeneously dense (50-75% dense tissue), and BIRADS D that the breast is extremely dense (> 75% dense tissue). In the second part of the work the analogic film screen mammograms were digitalized and the digitized images were computed and processed with two graphical softwares (Corel Photo-Paint and AutoCad 2004.0.0) for the detection of areas with glandular density, the quantification of their percent of extension and successively for the final classification into one of the four BIRADS categories. Data obtained with the two methods (qualitative and semiquantitative method) were compared. All measurements were made on one craniocaudal view of the unaffected breast taken before surgery and annually for six years for each patient. In the tamoxifen-receiving group, first follow-up was performed one year after the start of tamoxifen therapy and last follow-up one year after completed tamoxifen therapy. In the non-tamoxifen-treated group first follow-up was performed one year after completion of collateral therapies. The mammograms were classified with consensus by two radiologists, both familiar with mammogram reading and with BIRADS classification, and blinded to the treatment the patients had received. Fisher's exact test was used to analyze the associations between categorical variables, the relationship between the groups and variations in mammographic density and the odd ratio (OR) was calculated. The Wilcoxon signed-ranks test was used to evaluate the homogeneity in mammographic density distribution in the groups. Intraclass correlation ICC (two-way mixed) was used to assess the agreement between qualitative and quantitative methods. All statistical analyses were performed using SPSS 13.0 software package (SPSS, Chicago, USA) and a p value < 0.05 was considered significant.

Table 1. — *Variation in density in the tamoxifen-receiving group.*

Qualitative/ semiquantitative method		Mammography after one year A	B	C	D	Total
	A	22/21	0/0	0/0	0/0	22/21
Basal	B	1/2	13/13	0/0	0/0	14/15
mammography	C	0/0	9/9	13/13	0/0	22/13
	D	0/0	0/0	4/4	6/6	10/10
Total		23/23	22/22	17/17	6/6	68/68

Table 2. — Table 2. — *Variation in density in the non-tamoxifen-treated group.*

Qualitative/ semiquantitative method		Mammography after one year A	B	C	D	Total
	A	30/28	0/0	0/0	0/0	30/28
Basal	B	1/3	11/12	0/0	0/0	12/15
mammography	C	0/0	2/1	24/24	0/0	26/12
	D	0/0	0/0	3/3	9/9	12/12
Total		31/31	13/13	27/27	9/9	80/80

Results

Distribution of dense breasts in the tamoxifen (cases) and the non-tamoxifen-treated group (controls) was homogeneous before surgery. Tables 1 and 2 list the distribution of the four BIRADS categories before surgery and at the first follow-up after one year in the cases and in the controls as assessed with the qualitative and semiquantitative method. The variations were stable throughout the remaining five-year follow-up period. At the first follow-up, totally 20 variations in breast density were observed with the qualitative method (14 cases and 6 controls) and 22 with the semiquantitative assessment (15 cases and 7 controls): all variations concerned breast density reduction and no increase was observed with either method. The Wilcoxon signed-rank test showed a statistically significant difference between preoperative and first follow-up mammograms with both the two assessment methods ($p < 0.0001$ and $p < 0.0001$) and a statistically significant difference in breast density reduction was assessed between the cases and the controls ($p = 0.021$). Good agreement in the BIRADS assessment was detected while comparing the qualitative and the semiquantitative method for preoperative mammograms (ICC = 0.994 $p < 0.00001$, ICC = 0.985 $p < 0.00001$) and mammograms at the first follow-up after one year (ICC = 1, ICC = 1), respectively, in cases and controls. There was a statistically significant difference ($p < 0.0001$) between mean age in the two groups, however at the first mammographic follow-up after one year all patients were in menopause. In relation to the median age of 59 yrs in the cases, 12/14 cases of density reduction occurred in patients < 59 yrs while among the controls all the six cases of density reduction occurred in patients < 59 yrs. Fisher's test showed a statistically significant relationship between age and variation in breast density in both groups ($p = 0.035$, $p = 0.004$) with an estimated OR for the cases of 3.2 times (95% CI 1.15-8.86) with qualitative assessment and 2.95 (95% CI 1.13-7.74) with semiquantitative assessment greater than the controls of achieving reduced breast density.

Discussion

Mammographic breast density is associated either with an increased risk of benign proliferative breast disease that includes a wide range of pathological conditions associated with varying risk of breast carcinoma [14] and with an increased risk of false-negative results at mammography, and a substantial decline in mammographic sensitivity for cancer detection. A reduction in breast density would therefore be important and desirable to reduce both the risk for benign proliferative disease and diagnostic errors. This study showed a statistically significant difference in breast density reduction between the tamoxifen and the non-tamoxifen-treated group (p = 0.021) thus confirming previous studies concerning reduction in mammographic breast density using tamoxifen in women with breast cancer and in healthy women at high risk for breast cancer [4, 11, 13]. All changes in breast density were observed at the first follow-up after one year both in the cases and in the control; these data disagree with Cuzick *et al.* [4] who reported the greatest breast density reduction within 18 months of treatment and a continued reduction in density until 54 months of treatment but this difference may be explained by the different characteristics of the patient population and by the fact that all patients in our study were in menopause at the first follow-up. Nonetheless our study is a nonrandomized review, a fact that may have influenced the results: the tamoxifen-receiving group all had hormone-receptor-positive breast cancer, whereas the non-tamoxifen-treated group had hormone-receptor-negative breast cancer. One year after completed tamoxifen treatment no further changes in breast density were observed. The effect seems not to be reverted in postmenopausal women, whereas the reversibility of the effect in premenopausal women still requires further investigation. Fisher's exact test performed on the results obtained in the cases shows a statistically significant relationship between patient age and variation in breast density with a greater breast density reduction in younger and premenopausal women that may be linked to different types of density. The definition "dense breast" refers in fact to a quantitatively and qualitatively highly heterogeneous group: quantitatively it depends on the relative amounts of fat, connective and epithelial tissue and water content. Fat is radiologically lucent and appears dark on a mammogram, whereas connective, epithelial tissue and water are radiologically dense and appear light. Qualitatively there are dense breasts containing mainly connective tissue or mainly mammary-gland tissue with varying water content which characterizes breasts of women of reproductive age. It is possible that the different composition of the so-called dense breast causes a different response to menopause and to hormonal therapy as dense breasts with more mammary-gland tissue combined with an elevated percentage of water have been reported to be more sensitive than other combinations to age, hormonal situation and hormone treatments [15]. To evaluate mammographic density and tamoxifen-based treatment, a qualitative assessment of mammographic density is required. However, classification in categories has certain limitations because the reading of mammograms is operator-dependent and because it is difficult to measure small variations, which are particularly important in preventive treatments. Some authors have proposed computerized methods for this purpose, which have proved very helpful [1, 13, 14]. Despite the criticism subjective interpretation of mammograms has received, a qualitative classification and assessment of percent of mammographic density is useful in daily clinical practice, and in a team of experts, differences in readings are insignificant. Nonetheless the possibility that a simple digitalization process and the availability of two simple image softwares may offer to semiquantitative assessment of breast density is in our opinion to be noted as this method may avoid mammogram reader dependence. In our work a very good agreement in the BIRADS assessment was obtained with the two methods, probably because of the great experience of the readers. Moreover the semiquantitative assessment method may be more valid when compared to a subjective one performed by radiologists with less experience even if requiring a further training in breast density assessment. In our study, the greatest reduction in breast density was achieved after 12 months in postmenopausal women who received 20 mg/day tamoxifen with both the qualitative and semiquantitative method. Additional research is needed to assess the minimum dose and treatment time required to obtain the necessary reduction in density in order to improve diagnostic accuracy in very dense breasts, and areas of ongoing investigation include evaluating a potential specific treatment before mammographic examinations.

Conclusion

A substantial reduction in breast density in women treated with tamoxifen verified both with a subjective qualitative method and with a semiquantitative method could reduce the "masking" effect in the detection of small tumors.

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