Mammographic Patterns as a Predictive Biomarker of Breast Cancer Risk: Effect of Tamoxifen

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Abstract

Mammographic breast density has been shown to be associated with up to a 4- to 6-fold increase in risk of breast cancer, whereas tamoxifen therapy increases disease-free survival and reduces mortality. We have therefore investigated whether these effects are related. To determine the effects of tamoxifen on mammographic density, mammograms from 94 women who had received tamoxifen for breast cancer and 188 women (without breast cancer) who had not received tamoxifen were visually classified according to the criteria of Wolfe. Two controls were age-matched to each case. All of the women were postmenopausal (ages, 50–64 years), neither group was taking hormone replacement therapy, and none of the cases had received chemotherapy. There were significant differences in breast density between cases and controls at the initial mammogram ($P = 0.0001$) but no significant differences at the follow-up mammogram ($P = 0.51$). A significant change to a more lucent pattern had occurred among the case group ($P = 0.0001$). The odds ratio for cancer that was associated with the more dense (P2 and DY) patterns with respect to the more lucent (N1 and P1) patterns was 3.6 (95% confidence interval, 2.11–6.18) at the initial mammogram. This was significantly reduced to 1.5 (95% confidence interval , 1.32–1.70) after treatment with tamoxifen ($P = 0.019$; $\chi^2 = 5.52$). The substantial reduction in breast density with tamoxifen provides evidence that tamoxifen has the capacity to favorably alter postmenopausal breast density toward a more lucent pattern, which is associated with reduced risk of breast cancer. Mammographic pattern is, thus, a potential biomarker of breast cancer risk.

Introduction

The mammographic appearance of the breast has received widespread interest over recent years as a marker of risk for breast cancer. The relative proportions of radiolucent fat and radiodense connective tissue and glandular epithelium within the breast give rise to the variations in the appearance of the breast as seen on mammograms (1, 2). Increased radiological density has been reported to be associated with up to a 4- to 6-fold increase in the risk of breast cancer (3). Apart from age, the factors affecting breast density are not well established. Recent studies have suggested a familial linkage (4), and a low-fat high-carbohydrate diet has been reported to reduce the percentage area of breast density (5). Treatment with HRT[2] has been implicated in increasing breast density (6), although the evidence is not conclusive.

Tamoxifen reduces the risk of a subsequent breast cancer in women who have had breast cancer. The effects of tamoxifen on the breast are primarily antiestrogenic, although some agonist properties at other sites have been demonstrated (7). In five premenopausal women, this chemopreventive agent has been suggested to favorably alter the mammographic appearance of the breast (8). We have studied mammographic patterns of the contralateral breast in a larger group of postmenopausal women treated with tamoxifen and have compared results with healthy age-matched controls. The primary reason for carrying out this study was to determine the sample size required for a dietary intervention study looking at the effects of plant estrogens on mammographic breast patterns, based on the assumption that plant estrogens would act in a way similar to that of tamoxifen on the breast. This was a retrospective study and not of an ideal study design. Ideally, the control group for this study would have consisted of breast cancer patients who were not taking tamoxifen; however, almost all of the women in the United Kingdom of this age are treated with tamoxifen on diagnosis of breast cancer, which necessitated the use of normal controls. Additionally, because of the retrospective nature of this study there were many instances of missing data; for example, an attempt was made to obtain information on the past use of HRT from the notes of cases, but data were not present in all of the notes.

Materials and Methods

Our data came from the breast screening unit at St. Margaret's Hospital, Epping. All of the breast cancer patients at this clinic within the age range of the screening population (50–64 years) were commenced on a course of tamoxifen, irrespective of their nodal status. St. Margaret's Hospital is also taking part in a Medical Research Council breast screening frequency trial (9); participants in this trial are free from breast cancer and screened by mammography on a yearly basis. These women acted as controls to the breast cancer cases. Both groups (cases and controls) were scheduled to have annual mammography.

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[2] The abbreviations used are: HRT, hormone replacement therapy; OR, odds ratio.

Subjects. The case group consisted of 94 women who had been treated by means of surgery and/or radiotherapy for breast cancer, and who had been commenced on tamoxifen (20 mg/day). A control group of 188 women from the Medical Research Council screening trial were matched to the case women by age and menopausal status (two per case) to the nearest year. The age range of the women was 50–64 years, with a mean age of 59 (±3.3) years in cases and controls.

Personal Details and Past Use of HRT. Information on personal details such as menopausal status and past use of HRT was gathered from hospital notes written at the time of diagnosis in the cases. Questionnaires with some relevant data (but not past use of HRT) had been filled in at the time of mammography by the controls. Data for all of the variables were not always available for each subject. As much information as possible on the past use of HRT among the case women was obtained because of the possibility that the cessation of HRT before breast cancer treatment began may have influenced changes in mammographic pattern (10–13).

Exclusion Criteria. Women not eligible to be included in the study were those who were pre- or perimenopausal (*i.e.,* who had had a menstrual period in the twelve months preceding mammography), those on HRT, and (for the case group alone) those who had received chemotherapy as part of their treatment.

Mammography. Mammograms were classified visually by one of us (R. W.) according to the four categories of the Wolfe pattern (2). Mammograms from the cases and controls were classified separately, and, because of logistic problems of blinding the mammograms (*e.g.,* case notes had been more frequently used), the radiologist knew: (*a*) which mammograms were cases and which were controls at the time of classification; and (*b*) the order (initial/follow-up) in which the mammograms had been taken (see note below on reproducibility). Mammograms of the contralateral breast (cases) and of both breasts (controls) were classified. For the controls, a single assessment of a mammographic pattern was made from the combined impression from both breasts. A slight variation between the two breasts occurred occasionally; however, in no instance was the difference greater than a Wolfe category. Had there been a difference, the mammograms from that subject would not have been used. All of the case initial mammograms were those taken before the commencement of tamoxifen treatment. Mammograms taken approximately 19.6 months (cases) and 14.3 months (controls) after the initial mammogram were used as the follow-up observation.

Reproducibility. Reproducibility of the Wolfe pattern classification was assessed by reclassifying a randomly selected group of approximately 13% of the mammograms. The same radiologist (R. W.) reclassified the mammograms and was unaware of the original classification, of case/control status, and of which mammogram (initial or follow-up) the films were. Mammograms from one breast only were reclassified for both the cases and controls.

Data Analysis. A numerical score was assigned to each Wolfe pattern; 1 for the most lucent (N1) pattern, 2 for P1, 3 for P2, and 4 for the most dense (DY) pattern. Codes were also assigned to each variable for which data had been collected. *t* tests and ANOVA were carried out using the Systat 5.2 statistical package. ORs associated with the more dense P2 and DY patterns, compared with the more lucent N1 and P1 patterns, were calculated as an estimate of relative risk, and χ^2 was used to test for significance.

Table 1 History of HRT use among the case women

Change in Wolfe pattern	Previous use of HRT (n = 41)	
	Yes	No
	15	26
More dense	0 (0%)	1 (4%)
Less dense	3 (20%)	8 (31%)
No change	12 (80%)	17 (65%)

Results

Past Use of HRT. For 41 of the cases, we had information on the use of HRT before their treatment for breast cancer; no information was available for the remaining 53 women. Of the 41 cases, 15 women had previously taken HRT and stopped on diagnosis, and of these, 3 (20%) changed to a more lucent pattern with tamoxifen. Twenty-six of the cases had never received HRT; 8 (31%) of these changed toward a more lucent pattern, and 1 became more dense with tamoxifen (Table 1). There was, therefore, no clear effect of the previous use of HRT on change in breast density. Data were not available on the past use of HRT for the controls.

Mammographic Breast Density: Wolfe Pattern Distribution. The majority of the cases and controls at both the initial and follow-up mammograms were classified into either the P1 or P2 Wolfe pattern classifications, with the minority being classified into the least dense N1 pattern or the most dense DY pattern (Table 2).

Changes with Time and Treatment. At the initial mammogram, the cases had significantly more dense breasts than the controls; mean score for cases = 2.75 (SD, 0.73), and mean score for controls = 2.27 (SD, 0.83; P = 0.0001; Table 2). Thirty-one (33%) of the case women changed from one Wolfe pattern to another between the two mammograms, of which 29 became less dense. Ten (5%) of the control women changed, of which only two became less dense. Hence, there was a significant change toward a less dense pattern in the case group (P = 0.0001) after treatment with tamoxifen, and a slight but nonsignificant change toward a more dense pattern in the controls (P = 0.058; Table 2). The change in pattern that occurred between the initial and follow-up mammograms in the case women was significantly different from the change that occurred in the controls (P = 0.0001). There was no significant difference in mean score between the cases and controls at the follow-up mammogram (2.37 and 2.30, respectively; P = 0.51; Table 2).

The effect of time on change in mammographic pattern was examined (Fig. 1). More cases than controls had a time interval between the two mammograms that was greater than 25 months. It is clearly evident from Fig. 1*a*, however, that the majority of changes in mammographic pattern among the cases were established within 10–25 months of tamoxifen use, with only a small number of changes occurring with greater than 30 months of tamoxifen use. To determine whether there were any effects of a longer time interval between mammograms in the cases compared with the controls, we looked at a truncated group consisting of 36 cases whose time interval between the two mammograms was 12–15.5 months (inclusive) and compared them with 72 controls (two per case) that were closely matched for age and time intervals. The mean age of the truncated cases and controls was 58.5 (±3) and 58.9 (±3) years, respectively, and the mean time interval between mammograms was 13.94 (±1.14) and 13.95 (±1.14) months, re-

Table 2 Percentage distribution of Wolfe pattern and mean score at initial and follow-up mammograms for the cases and controls

	% distribution of mammographic Wolfe pattern								Wolfe pattern score, mean (SD)		Change in score, mean (SD)	*P*, initial *vs.* follow-up[a]
	Initial				Follow-up				Initial	Follow-up		
	N1	P1	P2	DY	N1	P1	P2	DY				
Cases (n = 94)	7.4	20.2	62.8	9.6	19.1	27.7	50.0	3.2	2.75 (0.73)	2.37 (0.83)	−0.37 (0.67)	0.0001
Controls (n = 188)	19.7	38.3	37.2	4.8	18.1	38.8	37.8	5.3	2.27 (0.83)	2.30 (0.83)	0.03 (0.23)	0.058
P, case vs. control[b]									0.0001	0.51	0.0001	

[a] *P* for the significance of change in mammographic pattern.
[b] *P* for the significance of difference in mean score between cases and controls at the initial and follow-up mammograms, and *P* for the significance of difference between cases and controls in the mean change in mammographic pattern.

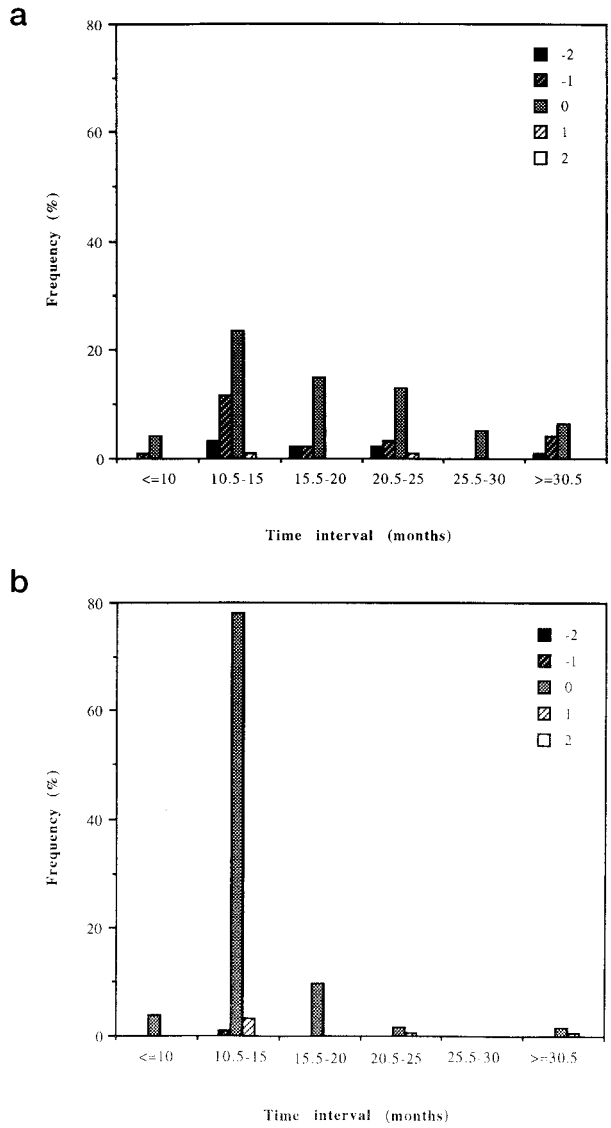

Fig. 1. Effect of time interval between mammograms on change in mammographic patterns.

spectively. This truncated group gave essentially the same results as the whole study group; mean scores for truncated cases and controls at initial mammogram was 2.81 (SD, 0.71) and 2.31 (SD, 0.88), respectively (P = 0.004); mean scores at follow-up mammograms were 2.33 (SD, 0.86) and 2.33 (SD, 0.90), respectively (P = 1.00).

Relative Risks Associated with Dense and Lucent Breast Patterns. The OR (as an estimate of relative risk) associated with the more dense P2 and DY patterns *versus* the less dense N1 and P1 patterns was 3.6 (95% confidence interval, 2.11–6.18) at the initial mammogram. This was significantly reduced to 1.5 (95% confidence interval, 1.32–1.70) by the follow-up mammogram (P = 0.019, χ^2 = 5.52 for the difference between the two ORs; Table 2).

Reproducibility. Pearson correlation between the original and the repeat classifications was 0.88.

Discussion

This study comprised mammograms of the contralateral breast in patients with breast cancer who were being treated with tamoxifen. The ideal control group for such cases would have been patients with breast cancer who were not being treated with tamoxifen. However, nearly all of the women in the United Kingdom of this age are treated with tamoxifen on a diagnosis of breast cancer. Consequently, healthy women were necessarily used as the control group. Mammograms from the contralateral breast for the cases but from both breasts for the controls were classified in this study; however, it was unlikely to have biased the results because there was no within-person variation in Wolfe-pattern category. Elsewhere, "hardly any" left-right differences were found (14). The case women in this study had a longer time interval between the initial and follow-up mammograms than the controls. However, an analysis of a truncated group of closely age- and time-interval-matched cases and controls (two controls per case) showed the same effects in terms of a significant reduction in breast density among the cases but no change in controls. To be able to quantitatively evaluate change in mammographic patterns, an ordinal score was created based on the Wolfe patterns. A continuous measure such as computerized determination (5) or planimetry of hand-outlined areas (15) would have been preferable. Nevertheless, repeatability of the visual method was high with a correlation of 0.88 between original and repeat classifications. The fact that it was possible to detect a significant change using this general classification of mammographic breast density highlights the importance of these findings and the need for future studies to further quantify the assessment.

This is the first study to show a reduction in mammographic breast density with tamoxifen in postmenopausal women, although a previous small study of five premenopausal women also showed a favorable effect (8). Gonadotropin-releasing hormone agonists (16) and a low-fat high-carbohydrate diet (5) have also been shown to bring about a reduction in breast density, and treatment with HRT has been implicated

in increasing breast density (10–13) and in preventing the fatty involution of the breast (17).

It is well documented that weight gain is common among women diagnosed with breast cancer (18) and that, as weight increases, breasts tend to become more lucent (19). Unfortunately, we do not have data regarding initial and follow-up weights for the study women; therefore, the possibility of weight gain among the cases cannot be discounted as a factor that may have contributed to the changes toward more lucent breast patterns. Weight gain does, however, tend to be greater among women who receive chemotherapy and among women who were premenopausal at the time of diagnosis (20), but the few studies looking at tamoxifen and weight gain have provided conflicting results (18). The degree of weight gain among postmenopausal women who were not on chemotherapy would appear insufficient to cause more than a small part of the observed change in pattern in this study (18).

One of the aims of tamoxifen treatment is to reduce the risk of breast cancer in the contralateral breast (21). In the present report, the average breast density of the case women receiving tamoxifen changed to approach the level of the normal screening population represented by our controls, and ORs for breast cancer were reduced. The reduction in the OR for cancer, from 3.6 to 1.5, is similar to that reported in the literature for the reduction in risk of a subsequent breast cancer in patients given tamoxifen (22).

An additional benefit of reducing breast density may relate to the effectiveness of mammographic breast screening. If dense mammographic patterns reduce the sensitivity of the detection of breast cancers by mammography, mechanisms by which the density of the breast could be reduced may provide benefits in terms of diagnosis at an earlier physiological stage and, thus, improved survival rates from breast cancer (23–24). Furthermore, mammographic breast density may be potentially predictive of breast cancer and may be useful in evaluating the efficacy of potential chemoprevention agents. A soy protein diet containing isoflavones produces similar effects in terms of circulating hormones to those effects induced by tamoxifen (25); therefore, it may be plausible that these isoflavones could alter the breast parenchyma in a similar, and favorable, way to that of tamoxifen.

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