SHORT-TERM (6 MONTHS) EFFECTS OF TAMOXIFEN ON THE CONTRALATERAL BREAST PARENCHYMA IN PATIENTS WHO HAVE UNDERGONE SURGERY FOR BREAST CANCER: SIGNIFICANCE OF MAMMOGRAPHY IN THE RADIOLOGIC EVALUATION OF BREAST PARENCHYMA

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ABSTRACT

Objective: Our aim is to radiologically evaluate the effects of tamoxifen on the contralateral breast parenchyma in patients who have undergone surgery for breast cancer.

Materials and Methods: We examined the mammograms of 121 women; 88 of them had breast cancer and 33 were healthy controls. The patients were grouped as follows; I: patients who received tamoxifen therapy after surgery, II: patients who did not take tamoxifen and III: healthy controls. The breast parenchyma area, the visualization of Cooper's ligaments and lactiferous ducts were evaluated in all 3 groups and analyzed statistically in order to determine the changes in breast density.

Results: In patients who had undergone tamoxifen therapy, compared to non-tamoxifen patients, there was a prominent reduction in breast parenchyma ($p<0.0001$). This effect was more significant in premenopausal women ($p<0.005$). The effect of tamoxifen was most evident at the first 6th month follow-up.

Conclusion: Tamoxifen reduces breast parenchyma and mammography is an objective method for demonstrating this reduction as a decrease in breast density.

Key Words: Tamoxifen, Breast carcinoma, Mammography, Breast parenchyma.

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer in women, and the second leading cause of female mortality in North America (1,2). Statistics for breast cancer in the United States show a recent downward trend in mortality and a leveling off in the incidence of breast cancer (3). Better treatment and diagnosis at earlier, more curable stages due to improved screening modalities have been credited with the favorable direction of these statistical changes (3).

Tamoxifen reduces the incidence of breast cancer and plays an important role in controlling breast cancer (3,4). Tamoxifen is a nonsteroidal antiestrogenic compound. It was synthesized in 1966 in Great Britain (5) and was initially developed as an antifertility agent (6,7). Tamoxifen antagonizes estrogenic effects in the breast, and competes with and inhibits the

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molecular-proliferative activity of endogen estrogen in tumor cells. It behaves as an estrogen agonist in relation to bone and the lipid profile (3,8).

The mammographic appearance of the breast gained interest in recent years, and is thought to be a marker for breast cancer risk (9,10). The long-term effects of tamoxifen on the breast parenchyma can be evaluated in mammographic examinations.

Women with prior history of breast cancer have an approximately three times greater risk of developing cancer of the opposite breast, compared to women without breast cancer (11). In patients treated with tamoxifen, there is 30% reduction in the incidence of contralateral breast cancer, compared with those not treated with this drug (3,12). Finally, tamoxifen is said to decrease the breast parenchyma and this reduction increases the efficacy of the follow-up mammograms (13).

The aim of this study is to radiologically evaluate the effects of tamoxifen on the contralateral breast parenchyma in patients who have undergone surgery for breast cancer.

METHODS AND MATERIAL

We retrospectively reviewed the mammograms of 121 women. Eighty-eight of these women had breast cancer and had undergone modified radical mastectomy, partial mastectomy or wide excision. Fifty-one of these 88 breast cancer patients received tamoxifen treatment after surgery. The other 33 women were healthy and followed as controls.

The patients were divided into 3 groups. Group I consisted of 51 women who had received postoperative tamoxifen therapy. Group II (control group) consisted of 37 breast cancer patients who had not received tamoxifen therapy. Group III (control group) consisted of 33 healthy women who had a similar age distribution and menstruation status with the breast cancer patients.

Mammograms of the contralateral breasts were evaluated before and after surgery in group I and group II, and the follow-up mammograms of the left breast were evaluated in group III once a year for at least 2 years. Two radiologists reviewed the mammographic examinations. Mammograms were taken with Senographe DMR scanner (General Electric Medical Systems, Milwaukee, WI).

The changes in breast parenchyma were examined on the mediolateral oblique projections by evaluating the changes in the area of breast parenchyma, the degree of visualization of Cooper's ligaments and lactiferous ducts.

The area of breast parenchyma was estimated by multiplying the length of the longest horizontal axis by that of the longest vertical axis on the mediolateral oblique view (13). The changes in the area of breast parenchyma were grouped as:

(1) Decrease of more than 20%,
(2) Decrease of less than 20% and,
(3) No change (Fig. 1).

As the amount of breast parenchyma decreases, Cooper's ligaments and lactiferous ducts become more visible (Fig. 2). Through this data, the visualization of Cooper's ligaments and lactiferous ducts were grouped as:

(1) Remarkable visualization,
(2) Subtle visualization, and
(3) No change.

The correlation between group I, II, III and the classified parameters related to the changes in the breast parenchyma were analyzed statistically. The significance of the data was assessed by the Chi-square test ($p<0.05$ was accepted as significant). Fischer's Exact Test was used to determine whether tamoxifen-induced parenchymal reduction was more prominent in premenopausal or in postmenopausal women ($p<0.05$ was accepted as significant).

The time interval of the most distinct effect of tamoxifen on breast parenchyma was also assessed. The changes in the area of breast parenchyma were evaluated in the follow-up mammograms and evaluated with Repeated Analysis of Variance test.

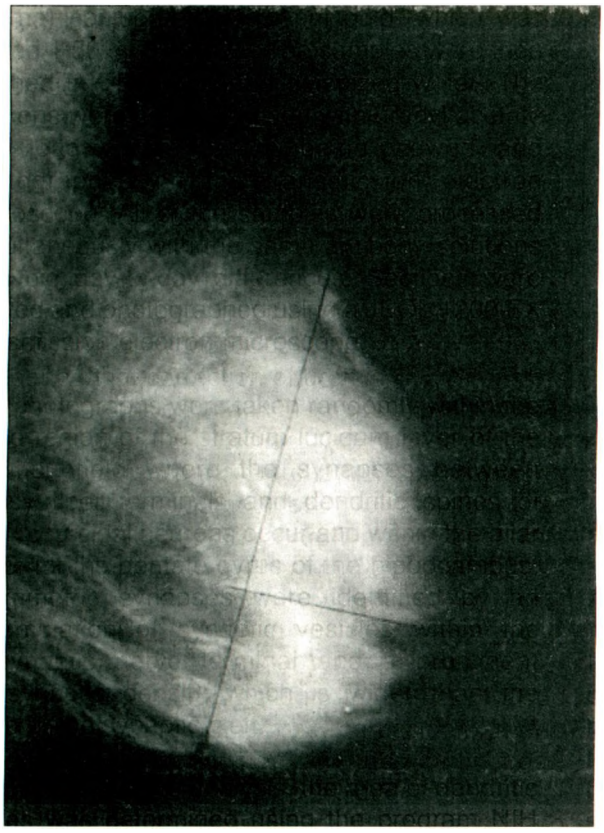

Fig. 1: The area of breast parenchyma was estimated by multiplying the length of the longest horizontal axis by that of the longest vertical axis on the mediolateral oblique view.

RESULTS

The mean age of the patients in group I was 55.1 years (range, 35-75); of group II, 56.3 years (range, 33-75) and of group III, 53.3 years (range, 46-65).

Eight women in group I and one woman in group II were excluded because they had fatty replaced radiolucent breast parenchyma.

Of the 43 women in group I, 11 (25.6%) showed no change, 11 (25.6%) showed a decrease between 10-20% and 21 (48.8%) showed a decrease greater than 20%. In group II, no change in parenchymal area was assessed in 32 (88.9%) of 36 women, a decrease of 10-20% was found in 4 (11.1%) women. No woman had a decrease greater than 20%. In the healthy control group (group III), all of the 33 (100%) women showed no change (Table I).

Through this data, a remarkable statistical significance was observed between the changes in the area of the breast parenchyma and the groups ($p<0.0001$). Compared with non-tamoxifen patients and the healthy control group, there was a marked decrease in the breast parenchyma of patients who had undergone tamoxifen treatment (Figs, 2, 3). There was no significant difference between the non-tamoxifen patients and healthy women ($p>0.05$) (Table I).

Table I: Distribution of the Changes in Parenchymal Area According to the Groups.

	No change	10-20% reduction	>20% reduction	TOTAL
Tamoxifen-treated patients (Group I)	11 (25.6%)	11 (25.6%)	21 (48.8%)	43
Non-tamoxifen patients (Group II)	32 (88.9%)	4 (11.1%)	0 (0%)	36
Healthy patients (Group III)	33 (100%)	0 (0%)	0 (0%)	33

(Chi-square=34.171, $p<0.0001$)

All of the 43 women included in our study had estrogen receptor (ER) positive tumors. Of the 43 cases in group I, 27 received only tamoxifen treatment, 8 received tamoxifen therapy combined with chemotherapy and 8 received tamoxifen treatment combined with chemotherapy and radiotherapy. In group II, 15 women received only radiotherapy, five received only chemotherapy, 6 received radiotherapy combined with chemotherapy and 10 had no treatment.

In group I, 19 women were premenopausal and 24 women were postmenopausal. In group II, 13 women were premenopausal and 23 were postmenopausal. In group III, 18 women were premenopausal and 15 were postmenopausal. Of the 19 premenopausal patients in group I, 18 showed a decrease in the area of breast parenchyma and one showed no change. Of the 24 postmenopausal patients in group I, 13 showed a decrease in the area of breast parenchyma and 11 showed no change. According to this data, a more prominent parenchymal decrease was assessed in premenopausal women ($p<0.05$).

In healthy patients, neither premenopausal nor postmenopausal women showed a change in

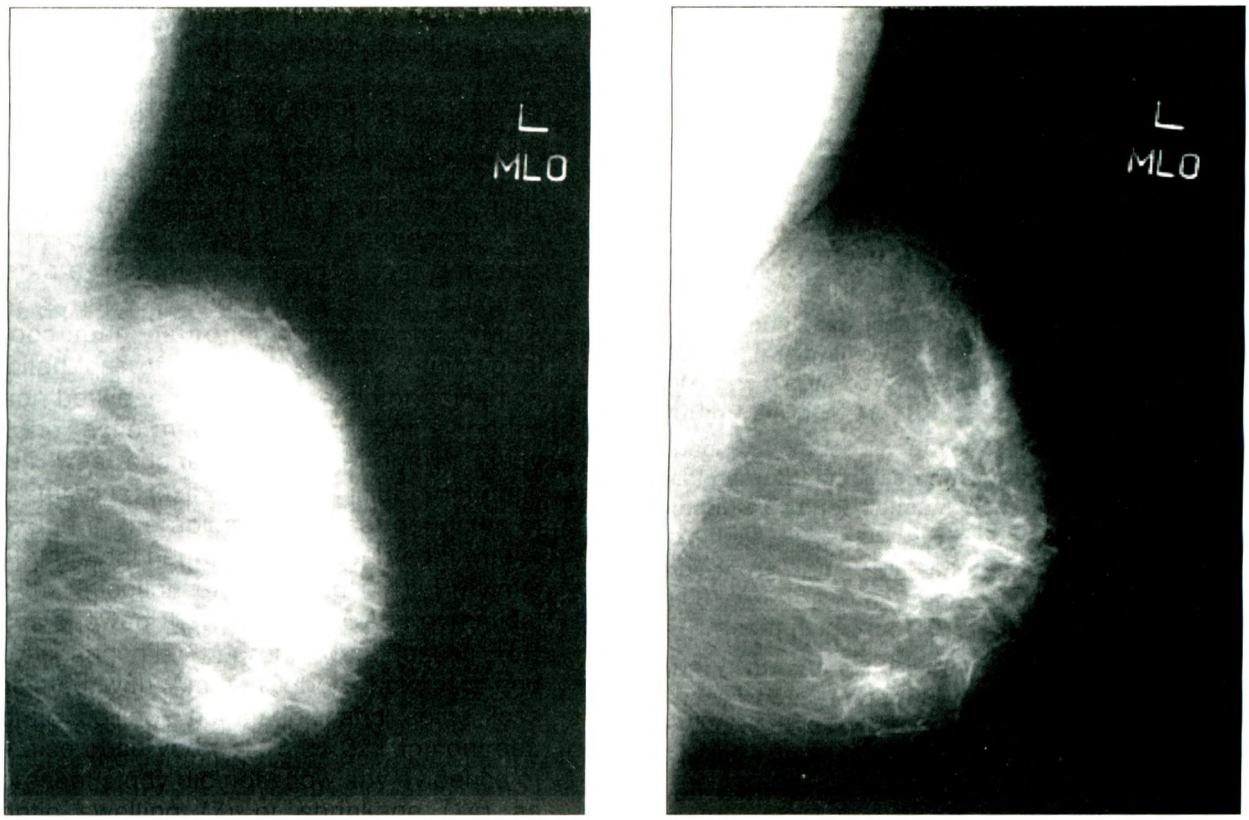

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Fig. 2a-2b: The reduction in parenchymal area and the remarkable visualization of Cooper's ligaments and lactiferous ducts, in the left mammograms, before tamoxifen treatment and after 6 months.

their breast parenchyma. The changes in the visualization of the lactiferous ducts in the Cooper's ligaments are shown in Table II and III respectively.

Table II: The Distribution of the Changes in Cooper's Ligaments According to the Groups

	No change	Minimal visualization	Remarkable visualization	TOTAL
Tamoxifen-treated patients (Group I)	12 (27.9%)	9 (20.9%)	22 (51.2%)	43
Non-tamoxifen patients (Group II)	31 (86.1%)	4 (11.1%)	1 (2.8%)	36
Healthy patients (Group III)	33 (100%)	0 (0%)	0 (0%)	33

(Chi-square=29.101, p<0.0001)

There was a remarkable statistical significance between the visualization of Cooper's ligaments-lactiferous ducts in the groups (p<0.0001). In comparison with the healthy patients and non-tamoxifen group, there was an obvious increase in the visualization of Cooper's ligaments and lactiferous ducts in tamoxifen patients, which supported the decrease in breast parenchyma. No statistically significant difference was found between group II and III according to the visualization of the Cooper's ligaments and lactiferous ducts (p>0.05).

Table III: The Distribution of the Changes in Lactiferous Ducts According to the Groups

	No change	Minimal visualization	Remarkable visualization	TOTAL
Tamoxifen-treated patients (Group I)	12 (27.9%)	11 (25.6%)	20 (46.5%)	43
Non-tamoxifen patients (Group II)	33 (91.7%)	3 (8.3%)	0 (0%)	36
Healthy patients (Group III)	33 (100%)	0 (0%)	0 (0%)	33

Chi-square=34.018, p<0.0001)

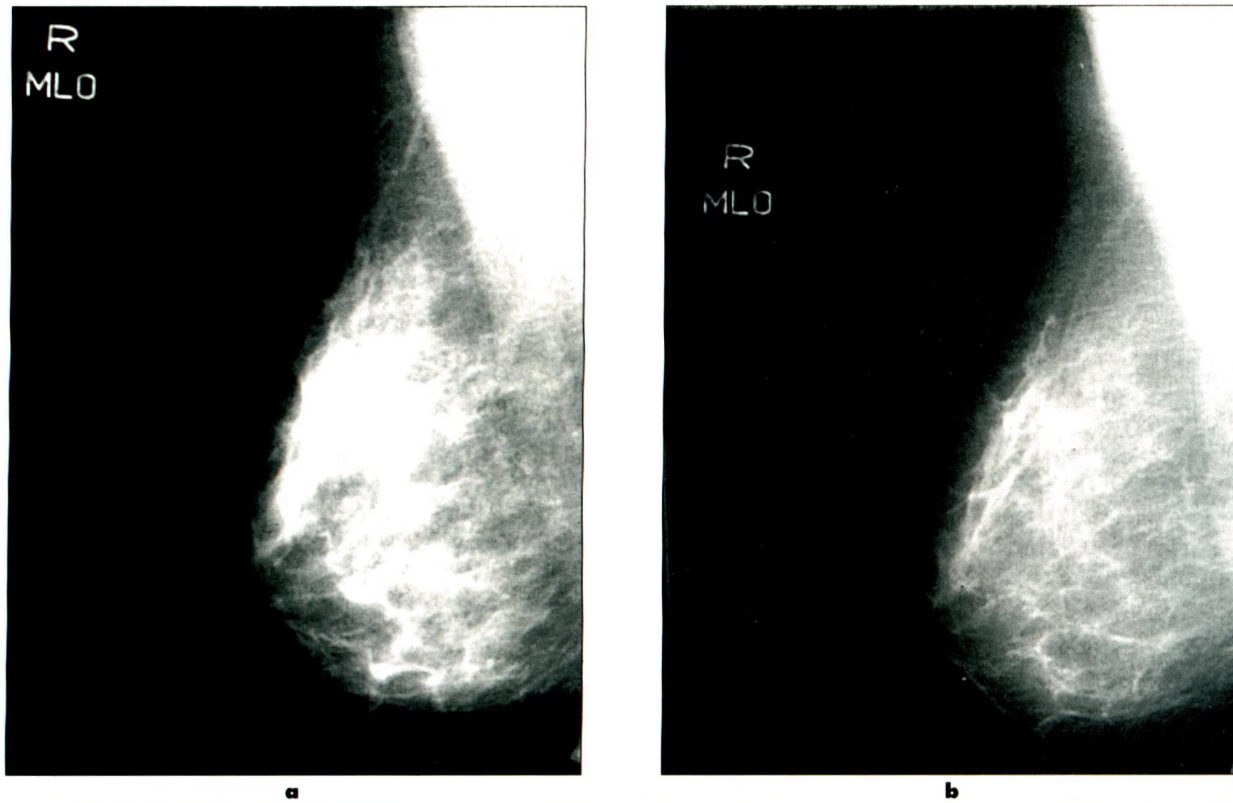

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Fig.3a-3b: The reduction in parenchymal area and the remarkable visualization of Cooper's ligaments and lactiferous ducts, in the right mammograms, before tamoxifen treatment and after 12 months.

The mean duration of tamoxifen therapy was 18.9 months. Patients in this group had their follow-up mammograms on the 12^{th}, 18^{th}, 24^{th} or 42^{nd} months beginning from the 6^{th} month.

The numerical value of the breast parenchyma was calculated and the changes in the parenchymal area were evaluated in the follow-up mammograms. According to the results, the most obvious decrease in the area of breast parenchyma was seen in the first 6^{th} month mammogram (Fig.2).

There was no significant difference between the 6^{th} and 12^{th}-18^{th} months ($p>0.005$) follow-up results. After 18^{th} month, the decrease in the area of breast parenchyma had a horizontal cours.

DISCUSSION

Tamoxifen is a well-known nonsteroidal antiestrogenic agent that plays an important role in controlling breast cancer. It is also effective in patients in reducing the incidence of contralateral breast cancer, compared to those who have not received this drug (3-8,12). Tamoxifen is particularly used in postmenopausal patients with ER-positive tumors, but it is also used in premenopausal women. The use of adjuvant tamoxifen in patients with ER-negative tumors is not evident. It is shown that, in long-term use of tamoxifen, the 10-year survival rate is increased in patients with both ER-positive tumors and the tumors of unknown ER status (3,4,12,14).

Mammographic density of the breast plays an important role as women who have dense breast parenchyma are found to have a higher risk of cancer, up to 4-6 fold (15). Therefore, by reducing breast density, tamoxifen prevents the development of a new breast cancer (4,9,10,13-18). Another advantage of the reduced density is that mammography becomes more efficient in fatty replaced breasts (4,9,13-20).

This study shows that there is a significant difference in the reduction of breast parenchyma in breast cancer patients receiving tamoxifen treatment compared to breast cancer patients who did not receive tamoxifen treatment and

healthy controls. We found the reduction in the amount of breast parenchyma and improvement in the visualization of both Cooper's ligaments and lactiferous ducts is indicative of reduction of the parenchyma.

Recent studies show that tamoxifen is effective in the reduction of breast parenchyma (4,12,13,14,19,20). In these studies, the authors used different methods in evaluating the parenchymal difference. Chow et al (20) report that semiquantitative or quantitative methods are more efficient than qualitative methods in showing this change. We believe that visual inspection solely may cause standardization problems. Although we found significant difference in the visualization of Cooper's ligaments and lactiferous ducts, we consider that this qualitative approach could have inter and intra observer differences. Measurement of the area of the breast parenchyma is an objective method and it could be easily and effectively used in follow-up of these patients.

While examining the effects of tamoxifen on the breast parenchyma, we also grouped the patients according to their menopausal status. Fatty radiolucent breasts was excluded as there was no breast parenchyma to evaluate. We found that, the reducing effect of tamoxifen is more obvious in premenopausal women ($p<0.005$). This finding may be due to the increased breast density in premenopausal women, while; in postmenopausal women, the reduction in breast parenchyma may not be demonstrated due to the fatty involution. Another point to stress is, whether there is a transition from premenopausal to postmenopausal status during the evaluation. This matter is also emphasized in the study of Ursin et al (14). The investigators, without sufficient data, suggested that the results would not be affected by this transition. All the groups in our study included both pre-and postmenopausal women. We believe that the changes in breast parenchyma due to menopausal status should be similar in both tamoxifen receiving and control groups and the transition would not affect our results.

The relation between the reducing effect of tamoxifen and the time period was also evaluated in our study. Of the 32 women, 10 had no 6th month control mammograms. In 19 cases, the most obvious change in the breast parenchyma was seen in the first 6th month control, while the reduction at the 12th month control was not as remarkable. After this period, the reduction showed a horizontal course (Fig 4). There is some data in the literature that reports the time-dependent radiologic changes due to tamoxifen treatment. Son and Oh reported that the decrease in breast parenchyma was obvious after 6 months (13). Atkinson et al mentioned that the majority of changes in mammographic pattern among the cases was established within 10-25 months of tamoxifen use (19). We believe that, by increasing the number of cases, the frequency and time period of the follow-up mammograms; the radiologic visualization of the tamoxifen-induced breast parenchymal decrease may be debated.

In conclusions, mammographic follow-up of patients who were operated for breast carcinoma and received tamoxifen, shows a significant reduction of breast parenchyma of the contralateral breast. The reduction in breast parenchyma is evident in the first 6th month follow-up. This reduction plays an important role, as it is believed to correlate with a decrease in cancer risk. Mammography can be used as an objective method in monitoring breast parenchyma in patients receiving tamoxifen treatment.

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