

# Reduction of breast density following tamoxifen treatment evaluated by 3-D MRI: preliminary study<sup>☆</sup>

Jeon-Hor Chen<sup>a,b</sup>, Yeun-Chung Chang<sup>c</sup>, Daniel Chang<sup>a</sup>, Yi-Ting Wang<sup>c</sup>, Ke Nie<sup>a</sup>,  
Ruey-Feng Chang<sup>d</sup>, Orhan Nalcioglu<sup>a</sup>, Chiun-Sheng Huang<sup>e,\*</sup>, Min-Ying Su<sup>a</sup>

<sup>a</sup>Tu & Yuen Center for Functional Onco-Imaging and Department of Radiological Science, University of California Irvine, Irvine, CA 92697, USA

<sup>b</sup>Department of Radiology, China Medical University Hospital, Taichung 40407, Taiwan

<sup>c</sup>Department of Medical Imaging, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei 10617, Taiwan

<sup>d</sup>Department of Computer Science and Information Engineering, National Taiwan University, Taipei 10617, Taiwan

<sup>e</sup>Department of Surgery, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei 10617, Taiwan

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## Abstract

This study analyzed the change in breast density in women receiving tamoxifen treatment using 3-D MRI. Sixteen women were studied. Each woman received breast MRI before and after tamoxifen. The breast and the fibroglandular tissue were segmented using a computer-assisted algorithm, based on T1-weighted images. The fibroglandular tissue volume (FV) and breast volume (BV) were measured and the ratio was calculated as the percent breast density (%BD). The changes in breast volume ( $\Delta$ BV), fibroglandular tissue volume ( $\Delta$ FV) and percent density ( $\Delta$ %BD) between two MRI studies were analyzed and correlated with treatment duration and baseline breast density. The  $\Delta$ FV showed a reduction in all 16 women. The  $\Delta$ %BD showed a mean reduction of 5.8%. The reduction of FV was significantly correlated with baseline FV ( $P < .001$ ) and treatment duration ( $P = .03$ ). The percentage change in FV was correlated with duration ( $P = .049$ ). The reduction in %BD was positively correlated with baseline %BD ( $P = .02$ ). Women with higher baseline %BD showed more reduction of %BD. Three-dimensional MRI may be useful for the measurement of the small changes of  $\Delta$ FV and  $\Delta$ %BD after tamoxifen. These changes can potentially be used to correlate with the future reduction of cancer risk.

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## 1. Introduction

Mammographic density (MD) is a function of abundance of epithelial and connective tissue in the breast. MD has been proven as an independent risk factor for breast cancer [1–5]. Most of the current knowledge about breast density has been obtained using mammography. The relationship between MD and breast cancer risk is well established. Women with extensive dense breast tissue visible on a mammogram have a cancer risk 1.8 to 6.0 times that of women with low density [5]. Boyd et al. [6] found a 2% increase in relative breast

cancer risk for every 1% increase in percent mammographic density (PMD). With the relationship established by the epidemiology evidence [1–5], research effort has been devoted to incorporate breast density into risk assessment models [7–10]. It was found that a risk model based on breast density alone adjusted for age and ethnicity was as accurate as the Gail model [9], and a new model that can estimate 5-year risk for invasive breast cancer has also been developed [10].

For women who had been diagnosed with breast cancer, their cancer risk in the contralateral breast is increased [11–13], with the cumulative incidence of 15.4% at 20 years [11]. The risk among women diagnosed at younger age (<50 years old) had a cumulative probability of nearly 40% after 15 years [14]. Adjuvant hormonal therapy is commonly used for preventing secondary cancer in patients with hormone receptor-positive breast cancer. Tamoxifen is a selective

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\* Corresponding author. Department of Surgery, National Taiwan University Hospital, Taipei 10617, Taiwan.

E-mail address: [huangcs@ntu.edu.tw](mailto:huangcs@ntu.edu.tw) (C.-S. Huang).

estrogen receptor modulator (SERM) that is used to prevent estrogen from binding to the receptor and is the most commonly used adjuvant hormonal therapy for hormone receptor-positive breast cancers. It has been demonstrated to reduce the incidence of contralateral breast cancers in breast cancer patients and to prevent cancer risk by as much as 50% in healthy women [15,16]. Tamoxifen and other estrogen receptor modulators, such as raloxifene, have also been shown to decrease breast density particularly in premenopausal woman [17–21]. The underlying mechanism is not well known yet, but reducing the proliferative activity of breast tissues seems to be one major reason [22–24].

A few studies assessing the change in breast density after adjuvant hormonal therapy using mammography have been reported. Most studies found a consistent reduction of breast density in premenopausal women taking tamoxifen either as a preventive measure against or as part of their treatment for breast cancer [19–21]. The evaluation of breast density based on mammogram bears some major problems, including tissue overlapping, positioning difference of the woman, variation in the degree of compression, as well as calibration of mammography units and the setting of kilovolt potential and milliamperere second used to acquire the mammogram [25]. MRI provides a three-dimensional view of the breast with strong soft tissue contrast distinguishing between fibroglandular and fatty tissues. As such, MRI does not suffer from the problems with mammography that come from the projection nature and hence may be advantageous for evaluating the change in breast density after receiving adjuvant hormonal therapy. The goal of this study was to use an MR-based method to measure the change in breast density following tamoxifen treatment.

## 2. Materials and methods

### 2.1. Study subjects

This retrospective study was approved by the institutional review board of our institution and was HIPAA compliant. All patients gave written informed consent for participating in the MRI study. The enrollment criteria were patients who had completed cancer treatment and received tamoxifen as adjuvant hormonal therapy and who had a pretreatment study and one post-treatment MRI study done at the breast center. In a period of 2.5 years (October 2006 to March 2009), 17 women were identified. All subjects had histologically confirmed, hormone receptor-positive breast cancer and were prescribed to take tamoxifen (20 mg oral tablet per day) for 5 years. One subject was excluded due to incomplete coverage of the whole breast in the baseline MRI study. The remaining 16 women (age 33–51, mean 43 years) were analyzed in this study. None of these 16 subjects had received any form of chemotherapy prior to or during the tamoxifen treatment period. Of the 16 subjects, 12 received unilateral mastectomy and four received breast-conserving surgery prior to the tamoxifen treatment. In this study

only the contralateral normal breast without any surgical intervention was analyzed.

The follow-up MRI was performed for surveillance purposes, and the duration between pretreatment and follow-up studies ranged from 8 to 26 months ( $17.5 \pm 5.7$  months). Three subjects had the treatment in less than 1 year (8–11 months). Eleven were in between 1 and 2 years; and two were more than 2 years (25 and 26 months).

### 2.2. MRI study protocol

All MRI studies were acquired with a 1.5-T MR scanner (Signa Excite HD, GE Healthcare, Milwaukee, WI, USA) with a dedicated eight-channel breast coil. The axial view T1-weighted images without fat suppression were used for the analysis of breast density in this study. The data were collected before the contrast injection. The parameters were TR/TE/TI=7.4/3.3/23 (ms), slice thickness=2.0 mm, image matrix=512×512 with pixel resolution of 0.625 mm, FOV=30 cm. Depending on the size of breasts, some adjustments in TR, TE and FOV were made. The number of slices varied according to the size of the breast (around 56 slices). The total imaging time for this imaging sequence was approximately 3 min.

### 2.3. Methods for breast segmentation and breast density measurement

The analysis procedures include segmentation of the breast from the body and segmentation between fibroglandular and fatty tissues within the breast. Firstly, the number of MRI slices (along the superior–inferior direction) containing the breast was defined. The first superior slice and the last inferior slice were determined when a layer of fatty breast tissue could be identified compared to the layer of body fat. Non-breast subcutaneous fat on the chest typically displays homogenous thickness across the chest wall. The selection had to ensure that no portion of the breast was excluded. Next, the lateral posterior margin of bilateral breasts was defined. The middle slice of the image sequence containing the most breast tissues was selected, and a horizontal line was drawn through the dorsal boundary of the sternum, resulting in a horizontally cut image. The horizontal line defined on this image was then applied to all other slices.

The quantification of breast density was performed using a 3D MRI-based method [26]. Briefly, on the horizontally cut image, a fuzzy c-means (FCM)-based segmentation algorithm with the b-spline curve fitting was applied to obtain the breast boundary and then a dynamic searching algorithm was applied to exclude the skin along the breast boundary. After the breast was segmented from the body, the total breast volume (BV) was calculated.

For fibroglandular tissue segmentation, the adaptive FCM was applied for bias field correction to remove image intensity nonuniformities and for segmentation of the fibroglandular tissue from the surrounding fatty tissue. After completing the segmentation from all imaging slices,

the volume of fibroglandular tissue (FV) was calculated, and the percent breast density (%BD) was obtained by normalizing FV to the BV.

The analysis of breast density in the follow-up MRI study of each patient was done by using her own pretreatment MRI as reference. The number of slices containing the breast was fixed; also, the number of clusters used for fibroglandular tissue segmentation was the same. This was to ensure that the analysis was performed using a matching setting, in order to minimize any variation that may come from the operator.

2.4. Statistical analysis

All analyses were performed using SPSS 15.0 (SPSS, Inc., Chicago, IL, USA). For normality test, the distribution of each parameter was first tested using the Kolmogorov–Smirnov test. Age, follow-up duration, BV at B/L (BV\_B/L), BV at F/U (BV\_F/U), %BD at B/L (%BD\_B/L), %BD at F/U (%BD\_F/U) were already normally distributed. No further transformations were needed for these four parameters. Square-root transformation was applied to FV at B/L (FV\_B/L) and to FV at F/U (FV\_F/U) to ensure normal distribution for further statistical comparison. The stepwise linear regression was utilized to investigate the relationship between the changes in (sqrt) FV with baseline BV, baseline (sqrt) FV, age and treatment duration. The change in %BD was analyzed in the same way to investigate the association with baseline BV, baseline %BD, age and treatment duration. A *P* value of less than .05 was regarded as statistically significant.

3. Results

The results measured in the baseline and the follow-up studies are summarized in Table 1. The baseline BV ranged from 69 to 688 cm<sup>3</sup> (358±174 cm<sup>3</sup>). The follow-up BV ranged from 73 to 633 cm<sup>3</sup> (331±157 cm<sup>3</sup>). The baseline FV ranged from 19 to 272 cm<sup>3</sup>, and the follow-up FV ranged from 9 to 175 cm<sup>3</sup>. The baseline %BD ranged from 5.1% to 39.5% (22.1±2.6%). The follow-up %BD ranged from 2.6% to 30.8% (16.3±3.3%). The absolute reduction of %BD ( $\Delta\%$  BD) was 5.8%±3.8% compared to the baseline MRI. Seven

Table 1  
Mean value and range of breast volume, fibroglandular tissue volume and percent breast density in pretreatment (B/L) and follow-up MRI studies

	B/L	F/U	<i>P</i>
Breast volume (cm <sup>3</sup> )	69–688 (366) [358±174]	73–633 (327) [331±157]	.01
Fibroglandular tissue volume (cm <sup>3</sup> )	19–272 (53) [79±66]	9–175 (45) [52±41]	<.001
Breast density (%)	5.1–39.5% (23.6%) [22.1±2.6 (%)]	2.6–30.8% (16.3%) [16.3±3.3 (%)]	<.001

The range (median) of each raw data set is shown. The breast volume and percent density are normally distributed, and the mean±standard deviation (in brackets) is also shown. The fibroglandular volume is not normally distributed, and the square root transformation is applied before performing the *t* test.

subjects showed  $\Delta\%$ BD of less than 5%; seven showed between 5% and 10%; and two showed larger than 10%. Overall, the group mean of BV, FV and %BD between the baseline and the follow-up MRI all showed significant reduction (Table 1).

The change in BV, FV and %BD between the baseline and the follow-up MRI for each patient was calculated, and the results are summarized in Table 2. The stepwise linear regression was used to check the relationship between the changes in (sqrt) FV with baseline BV, baseline (sqrt) FV, age and the follow-up duration. The results showed that the reduction of FV and (sqrt) FV was correlated with baseline FV (*P*<.001) (Fig. 1) and with the duration of tamoxifen treatment (*P*=.03). Patients with a higher baseline density showed a greater reduction. When normalized to the baseline FV, the  $\Delta\%$ FV reduction ranged from 9.0% to 72.0%. This percentage change in (sqrt) FV was significantly correlated with the duration of treatment (*P*=.049) (Fig. 2). Patients receiving a longer tamoxifen treatment had a greater FV reduction. The  $\Delta\%$ BD was also correlated with baseline %BD (*P*=.02). A case example is illustrated in Fig. 3. The results suggest that tamoxifen treatment causes significant reduction in breast density and that the reduction is positively correlated with baseline density and treatment duration.

4. Discussion

Although MD is an independent risk factor for breast cancer, the link between change in breast density and the modified risk is less known [3,27–30]. It was found that an increase in BI-RADS density category within 3 years is associated with an increase in breast cancer risk, and a decrease in density is associated with a decreased risk [29]. Tamoxifen is known to reduce breast cancer risk. However, it was not clear whether the reduced breast density can be used as a surrogate marker to predict the protective effect. Recently, the missing link was elucidated by a study by Cuzick et al. [31] which reported the density results analyzed from the International Breast Cancer Intervention Study (IBIS-1) trial in the 2008 San Antonio Breast Cancer Symposium. This trial enrolled 7154 high-risk women and randomized them to receive tamoxifen or placebo for 5 years. It was shown that women who had at least a 10%

Table 2  
Changes in breast volume, fibroglandular tissue volume and percent breast density between the baseline and follow-up MRI of each patient

	Range (median)	Mean±S.D. [95% CI]	<i>P</i>
BV(B/L)–BV(F/U), cm <sup>3</sup>	–17.8 to 94.6 (25.6)	26.7±35.5 [7.7–45.6]	.01
FV(B/L)–FV(F/U), cm <sup>3</sup>	4.7 to 97.0 (14.7)	26.6±24.8 [13.0–40.3]	<.001
BD(B/L)–BD(F/U), %	0.3 to 11.9 (5.5)	5.8±3.8 (%) [3.7–7.8]	<.001

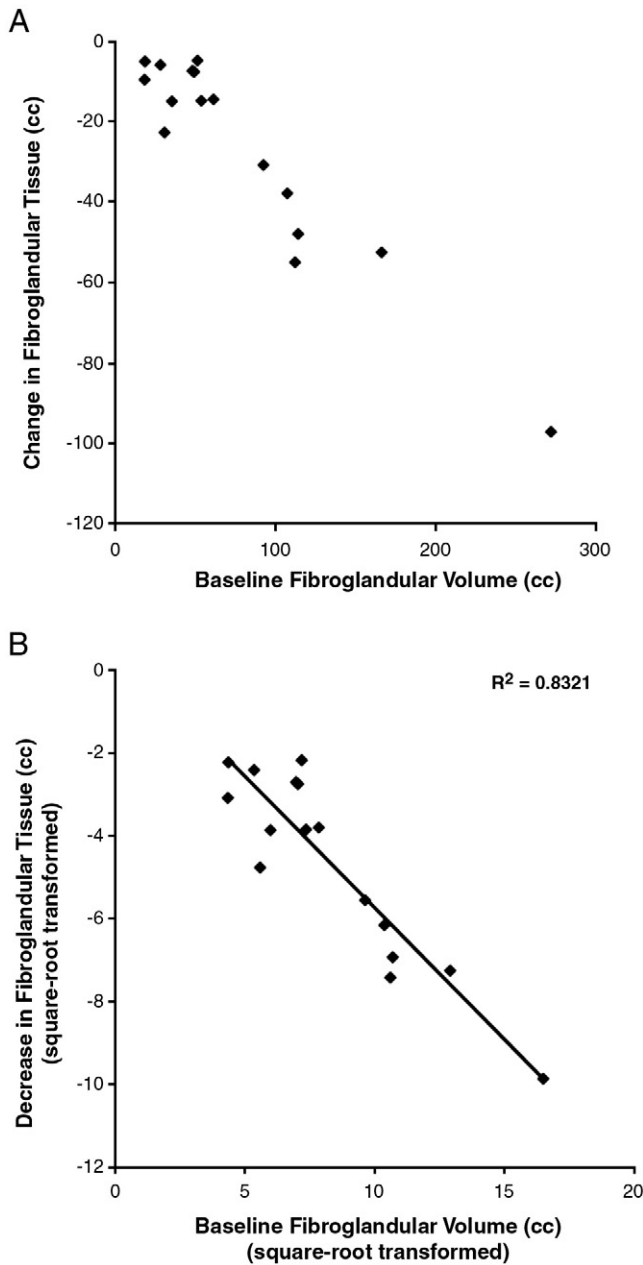


Fig. 1. (A and B) The reduction of FV and square root-transformed FV was positively correlated with baseline FV and baseline square root-transformed FV, respectively.

reduction in MD over the first 12 to 18 months of tamoxifen prophylaxis had a 63% reduction in breast cancer risk ( $P=.002$ ), whereas other women who had <10% reduction in MD had no benefit from tamoxifen treatment ( $P=.89$ ). It was noted that most of the density reduction occurred during the first 18 months of treatment. The impact of tamoxifen on risk reduction thus seems to be predictable by the changes in MD during the first 18 months of treatment [31]. In our study, the average treatment duration of tamoxifen was 17.5 months.

Despite all the encouraging results reporting the role of MD, breast density can also be measured by other imaging

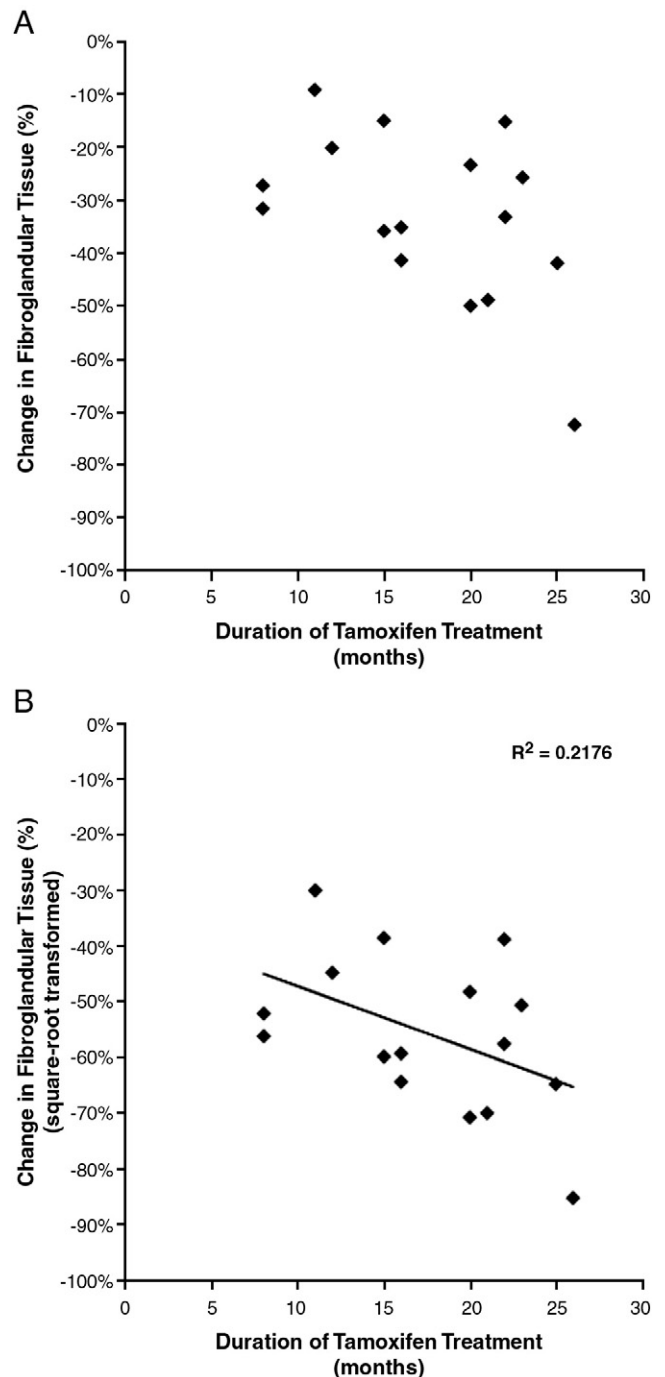


Fig. 2. (A and B) The percentage reduction in FV and square root-transformed FV was significantly correlated with the duration of treatment.

modalities. Especially if the change in density measured from the same woman over time will be measured, the consistency of the imaging technique should be a main concern. A recent review article by Kopans [32] raised the question about the accuracy of breast density determined by mammography. The author stressed that studies suggesting a link between MD and risk for breast cancer have methodological flaws and concluded that studies showing small percentage differences between groups are likely to be inaccurate.



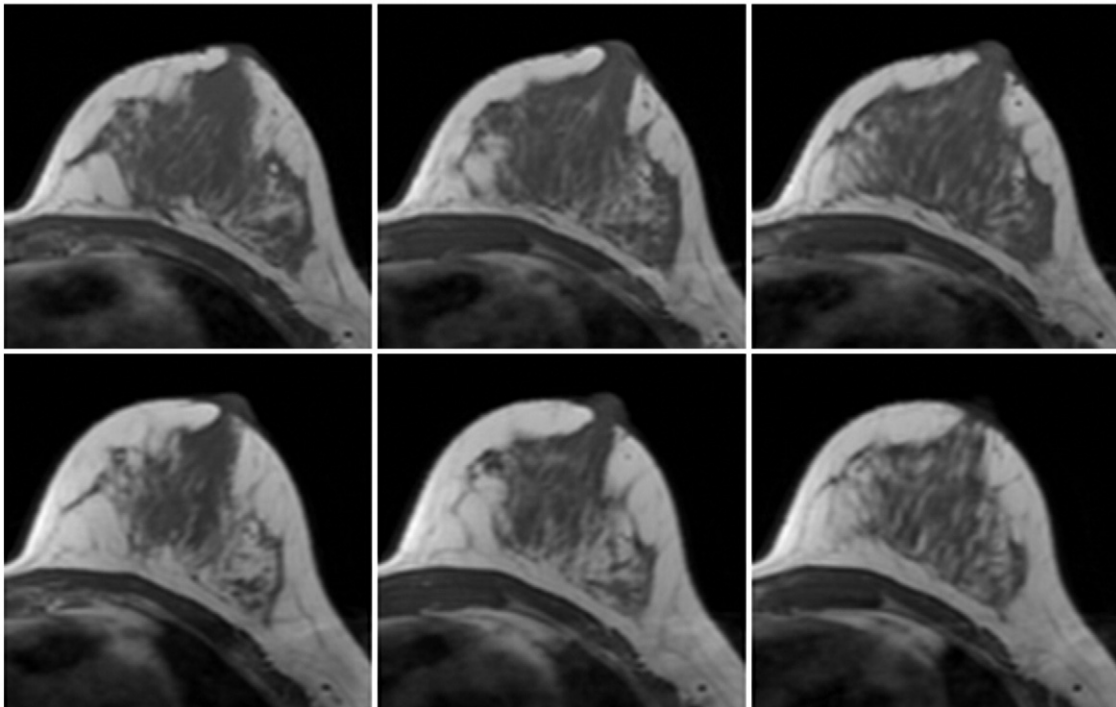


Fig. 3. MR images from a 38-year-old woman with estrogen receptor-positive breast cancer in the right breast who had received breast-conserving surgery prior to her tamoxifen treatment. The upper row shows the baseline MR images of the left breast before the treatment. The lower row shows the MR images 25 months after the treatment. The baseline fibroglandular tissue volume was 114.4 ml and the follow-up was 66.6 ml, with a reduction of 47.8 ml (41.8%). The reduction in percent breast density was 8.4%.

Measurement of breast density using MRI has been reported by several groups [18,33–39]. Differently from MD, MRI provides full 3D coverage of the breast, and with the use of appropriate segmentation procedures, the breast volume and fibroglandular tissue volume can be measured. Several studies have compared the density measured by MRI and mammography. A recent study from 138 high-risk women by Khazen et al. [33] has shown a significant correlation between MD and the density calculated from MRI ( $r=0.78$ ). Another study of 35 patients by Klifa et al. [39] also showed similar findings. Studies reporting the measurement of changes in breast density using MRI are scarce. A recent article by Eng-Wong et al. [18] found that, in women receiving raloxifene, MD did not show any change, but the fibroglandular tissue volume measured by MRI showed a significant reduction. Based on the findings, they suggested that MR breast density is more sensitive in detecting small changes; thus it may provide a promising surrogate biomarker and should be investigated further in breast cancer prevention trials [18]. Our study also showed decreased fibroglandular tissue volume  $\Delta$ FV after tamoxifen treatment. The mean  $\Delta$ %BD was 5.8% after 17 months of follow-up in our study.

The 3D MR-based method used in this study [26] has small measurement errors. The average standard deviation for breast volume and percent density measurements was in the range of 3–4% among three trials of one operator or among three different operators. When tested for different

breast morphologies, including fatty breast, the method still showed a small variation (Fig. 4).

Many studies have reported the reduction in MD after tamoxifen treatment. Cuzick et al. [17] investigated MD in asymptomatic high-risk women receiving tamoxifen for chemoprevention. They showed a greater density reduction in the tamoxifen group (7.9%) than in the placebo group (3.5%) within 18 months of treatment ( $P<.001$ ). Meggiorini et al. [40] studied 148 women and found a statistically significant difference in density reduction between the tamoxifen and the nontamoxifen-treated group after 1 year of treatment. Similarly, Chow et al. [41] studied 28 high-risk women taking tamoxifen for 2 years and found that digitized MD scores showed a 4.3% decrease per year ( $P=.0007$ ). In a study of women under age of 50, Brisson et al. reported that the mean  $\Delta$ %BD was  $-12.1\pm 11\%$  for the treatment group and was  $-3.6\%\pm 4.5\%$  for the control group ( $P<.01$ ) [19]. Another study performed by Son and Oh [21] evaluated the effects of 20 mg/day tamoxifen in 102 patients and 50 control patients, and showed that 60% of tamoxifen-treated women demonstrated a marked decrease in breast density on mammography as compared to 36% of control patients.

Our study also showed that the change in fibroglandular tissue volume ( $\Delta$ FV) was correlated with baseline FV and the duration of treatment, with women showing higher  $\Delta$ FV when their baseline FV was higher or when duration of treatment was longer. Brisson et al. [19] studied 36 women and found that tamoxifen-associated reduction in breast

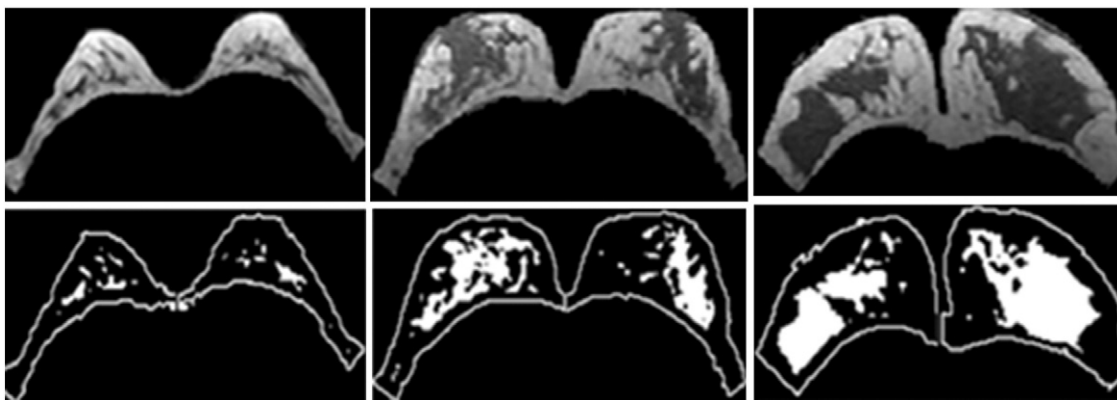


Fig. 4. Intra-operator variations on the measurement of the percent density in three different breast morphologies. The percent density variation is 2.2% for a 49-year-old Caucasian woman with fatty breast (left), 1.3% for a 49-year-old Asian woman with intermingled fat and fibroglandular tissue (middle), and 3.7% for a 33-year-old Asian woman with dense breast (right).

density was apparent after 1.0–3.4 years of treatment ( $6.9 \pm 11.1\%$ ). With 3.5–5 years of treatment, the density was further reduced to  $10.9 \pm 12.4\%$ . Similarly, Cuzick et al. [17] found that breast density further reduced from 7.8% after 18 months to 13.7% after 54 months of treatment. The reason why women with higher baseline FV showed a greater  $\Delta$ FV was not clear. Since MD may reflect cumulative estrogen effect on the breast tissue, it was anticipated that tamoxifen might work more effectively on women with denser breast. There was also a significant correlation between baseline %BD and the reduction of  $\% \Delta$ BD. For measurement of breast density over time, using either mammography or MRI, a consistent breast segmentation is crucial in order to calculate the %BD accurately. This is usually difficult in longitudinal follow-up studies due to variation in patient's positioning that might lead to different coverage in mammography. Whether a higher reduction of FV or %BD will correlate with a lower cancer risk in the future warrants further investigation.

In our study, 16 patients showed different degrees of density reduction with seven subjects showing  $\Delta\%BD$  of less than 5%; seven showed between 5% and 10%; and two showed larger than 10%. The difference in density reduction might be accounted for by the fact that breast response following tamoxifen may vary due to variation in the liver enzyme necessary to metabolize tamoxifen into an active form [42].

In our study, none of the 16 subjects had received chemotherapy prior to or during their tamoxifen treatment period. Many studies have found the association of breast density with ovarian function. Various chemotherapy agents, especially the alkylating category, have been associated with premature ovarian failure [43–45]. Through this effect, the breast density may be reduced.

Besides density reduction, decrease in enhancement of the fibroglandular tissue has also been reported following treatment with selective estrogen receptor modulators [46,47]. In a study of 10 peri- or postmenopausal patients who received a short-term tamoxifen medication, six

patients showed a significant decrease in enhancement [46]. However, in a study which analyzed the influence of breast density on background enhancement at MRI in pre- and postmenopausal women [48], no correlation was found.

Tamoxifen and other estrogen receptor modulators can also affect body fat distribution [49,50]. In a study of 50 postmenopausal women, after 1 year, subjects receiving raloxifene had a slight reduction of fat mass in the trunk and central region and an increase in the legs and, in relation to the control group, had significantly lower values of adiposity in the trunk and abdominal region [49]. Tamoxifen was found to induce fatty liver. Increased hepatic steatosis was detected in 15 (44%) of 34 patients after 3 months of tamoxifen therapy [50]. In our study, the slight reduction in breast volume (Tables 1 and 2) following tamoxifen treatment might be accounted for by its effect on body fat distribution.

In this study, we did not have a control group. It would be interesting to compare such variations with variations measured between baseline and follow-up in the tamoxifen-treated subjects. Once we know what the %change is in normal volunteers (repositioning in the MRI device), then we can conclude that %change measured in the treated population is due to treatment effect. Our density methodology article [26], however, has shown that body position dependence, performed in two volunteers at five different positions, had small variation in the range of 3–4%.

Other limitations existing in our study include the following. (1) The study was based on retrospective review with a small number of patients. (2) The duration for the F/U MRI after the tamoxifen treatment was not consistent. (3) Body mass index (BMI) was not considered. However, all subjects did not show obvious body weight change during their treatment period.

In conclusion, our preliminary data based on 3D MR method showed a significant reduction in FV and %BD after tamoxifen treatment, and the density reduction was positively correlated with baseline density. Since breast density is affected by many variables, it is difficult to estimate a

woman's risk based on the measure of density at one time point. When the baseline density of a woman is known to serve as her own control, a reliable method, such as 3D MRI, may be used to measure changes over time. For a patient receiving adjuvant hormonal therapy, such a method may be very helpful to evaluate her own benefit in terms of reducing breast density and thus cancer risk.

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