

Effect of Raloxifene on Mammographic Density and Breast Magnetic Resonance Imaging in Premenopausal Women at Increased Risk for Breast Cancer

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Abstract

Background: Mammographic density is a risk factor for breast cancer. Mammographic density and breast magnetic resonance imaging (MRI) volume (MRIV) assess the amount of fibroglandular tissue in the breast. Mammographic density and MRIV can be modulated with hormonal interventions, suggesting that these imaging modalities may be useful as surrogate endpoint biomarkers for breast cancer chemoprevention trials. We evaluated the effect of raloxifene on mammographic density and MRIV in premenopausal women at increased risk for breast cancer.

Methods: Mammograms and MRI were obtained at baseline and after 1 and 2 years of 60 mg raloxifene by mouth daily for 27 premenopausal women. Mammographic percent dense area was calculated using a semiquantitative thresholding technique. T₁-weighted spoiled gradient-echo MRI with fat suppression was used to determine breast MRIV using a semiautomatic

method. Mean change in mammographic density and median change in MRIV were assessed by the Wilcoxon signed-rank test.

Results: No significant change in mammographic density was seen after treatment with raloxifene. Mean change after 1 year was 1% [95% confidence interval (95% CI), -3 to +5] and after 2 years was 1% (95% CI, -2 to +5). MRIV decreased on raloxifene. Median relative change in MRIV after 1 year was -17% (95% CI, -28 to -9; *P* = 0.0017) and after 2 years was -16% (95% CI, -31 to -4; *P* = 0.0004).

Conclusions: In high-risk premenopausal women, mammographic density did not change on raloxifene, whereas MRIV significantly declined. Our findings suggest that MRIV is a promising surrogate biomarker in premenopausal women at increased risk for breast cancer and should be investigated further in breast cancer prevention trials. (Cancer Epidemiol Biomarkers Prev 2008;17(7):1696–701)

Introduction

Mammographic density is a well-recognized risk factor for breast cancer and was first described in 1976 by Wolfe using qualitative assessments (1). Semiquantitative methods of measuring mammographic density have since been developed and studies incorporating these techniques have consistently shown a positive association with breast cancer risk. The risk for developing breast cancer for the most dense compared with the least dense breast tissue categories ranges from 1.8 to 6.0, with most studies yielding an odds ratio of ≥ 4.0 (2). Mammographic density is a dynamic value influenced by age, parity (3), menstrual cycle phase (4), menopause (5), insulin-like growth factor pathway (6), body mass index (7), and genetics (8). Endocrine agents that change breast cancer risk also affect mammographic density. Notably, estrogen and progesterone hormone replacement therapy

increases the risk of breast cancer (9) and likewise increases mammographic density (10), whereas tamoxifen, a selective estrogen receptor modulator, decreases the risk of breast cancer as well as mammographic density in both premenopausal and postmenopausal women (11–13). Tamoxifen decreases mammographic density 7.9% compared with a 3.5% decrease in the placebo arm (*P* < 0.01; ref. 11). Changes in mammographic density are noted in the first year after starting tamoxifen. These observations suggest that mammographic density may be useful as a surrogate endpoint biomarker for breast cancer chemoprevention trials.

Breast magnetic resonance imaging (MRI) is another imaging modality that can assess the amount of fibroglandular tissue in the breast [MRI volume (MRIV); ref. 14]. This technique is of interest due to the limitations of mammography, which presents a two-dimensional image of a three-dimensional object. The tomographic images obtained with MRI allow for a more comprehensive assessment of tissue throughout the breast. Although not as extensively studied as mammographic density, MRI also reflects biological effects, and MRI enhancement decreases with age (14) and varies with the menstrual cycle and hormone replacement therapy (15). It should be recognized that the methodology used for

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reporting change on MRI is variable and less well established than for mammographic density (16, 17). Two studies have evaluated the relationship between mammographic density and MRI fibroglandular variables and report high correlation between mammographic density and MRIV. Correlation coefficients ranged from 0.63 to 0.91, with one study noting a stronger correlation in postmenopausal women, indicating that these radiologic studies reflect similar measures of stromal and connective tissue versus fat (14, 18).

Raloxifene, another selective estrogen receptor modulator, has been recently found to be effective in breast cancer prevention (19). Evaluation of the effect of raloxifene on mammographic density has been conducted in postmenopausal women at risk for osteoporosis and/or cardiovascular disease. In the largest cohort ($n = 280$), Jackson et al. determined that no increase in mammographic density occurred in women on raloxifene as opposed to those on combined hormone replacement therapy, whereas in smaller cohorts mammographic density declined from baseline on raloxifene or showed no significant change. The methodology to assess change in mammographic density in these studies included semiquantitative and, in some cases, purely qualitative means to describe mammographic density (20-22). Although raloxifene has not been shown to have a large effect on mammographic density in these studies, the effect of raloxifene on mammographic density in premenopausal women is unknown. Based on the ability of tamoxifen to reduce mammographic density to an even greater degree in premenopausal versus postmenopausal women (11), we postulated that raloxifene would reduce mammographic density and MRIV in premenopausal women at increased risk for invasive breast cancer.

Materials and Methods

Trial Design. Participants enrolled in a phase II trial of raloxifene in premenopausal women at high risk for developing invasive breast cancer. Details of the study have been reported previously (23-26). In brief, all participants provided written informed consent. Eligible patients had an increased risk of breast cancer by at least one of the following criteria: Gail model risk assessment of $\geq 1.7\%$ over 5 years, a family history consistent with hereditary breast cancer, or a histologically documented diagnosis of lobular carcinoma *in situ*, atypical ductal hyperplasia, or locally treated ductal carcinoma *in situ*. Subjects were required to have regular menstrual cycles (defined as 26-35 days) for the 6 months preceding enrollment in the trial. Premenopausal status was additionally verified by a follicle-stimulating hormone level <20 mIU/mL. Raloxifene was administered orally at 60 mg/d with 1,250 mg/d calcium for 2 years. Because raloxifene is contraindicated in women who are or may become pregnant due to possible teratogenic effects, all women were required to use nonhormonal birth control for the duration of the study and for 3 months after completion. After stopping raloxifene, subjects were followed off-drug for 1 year.

Imaging Studies. Standard four-view bilateral film-screen mammograms were obtained in the follicular phase of the menstrual cycle at baseline before treatment,

after 1 and 2 years of raloxifene treatment, and 1 year after cessation of raloxifene. The cranio-caudal view of one breast was selected for digitization. The denser breast was chosen at baseline and this same breast was followed over the course of the study. For patients who had had no prior surgery, the side with greater density was selected. For patients who had undergone breast surgery for noninvasive cancer or other reasons, mammograms of the unaffected side were selected and digitized. Mammograms were scanned with a Better Light Digital Scan Back through a Nikon 4×5 camera using a resolution of 267 pixels per inch and saved as TIFF files.

Digitized mammograms were analyzed using the scripting language of the MEDx image analysis and visualization software package (Medical Numerics). Using this program, the skin/air interface was manually outlined. This region was then interactively thresholded by segmenting the image based on gray level and applying a tint over the fibroglandular densities above the specified threshold. The percentage of the breast occupied by fibroglandular tissue (percent mammographic density) was calculated. Percent mammographic density was determined independently by two radiologists (C.K.C. and C.E.G.) masked to the subject's duration on raloxifene as well as current use of raloxifene.

Breast MRI was done on the same day as the mammogram. T₁-weighted spoiled gradient-echo fat suppressed MRI using gadolinium contrast with images at 3 mm intervals were obtained. The MRIV was determined using an automated classification and calculation method developed by our group. We have compared previously our automated tissue classification method with manually generated tissue classification by two experienced radiologists and found 94.95% agreement (27). Due to the high concordance of these measurements, the current study did not include further assessment of interobserver or intraobserver variability in determining MRIV. The same breast was evaluated for change in mammographic density and MRIV.

Statistics. The change in mammographic density was calculated as the difference in the percent density. The change in MRIV was determined by subtracting the earlier MRIV from the later MRIV and dividing by the earlier MRIV to adjust for large changes in MRIV associated with large baseline MRIV values. Changes over time in paired images were tested for a mean change of zero using the Wilcoxon signed-rank test. Correlation between mammographic density at baseline and clinical factors age and body mass index was also evaluated. The association between mammographic density and MRIV was determined by Spearman rank correlation. Intraradiologist reproducibility of the determination of mammographic density for the baseline mammograms was assessed as well as interradiologist correlation for change in mammographic density from baseline to 1 year on raloxifene using Spearman rank correlation.

Results

Thirty-seven women enrolled in the trial, and of these, 7 did not start drug. Paired mammograms were available for 27 subjects at baseline and 12 months, 25 subjects at baseline and 24 months, and 19 subjects at baseline and

Table 1. Subject characteristics (n = 27)

Mean (range) age	43 (35-47)
Race	
Caucasian	26
Hispanic	1
Mean (range) body mass index	24 (18-41)
Mean (range) mammographic density, %	39 (7-78)
Risk category	
Gail risk >1.7% (median, %)	20 (2.2)
Family history	1
Ductal carcinoma <i>in situ</i>	3
Lobular carcinoma <i>in situ</i>	3

36 months (1 year off raloxifene). We evaluated MRIV only for those women who also had paired mammograms. Paired MRI were available for 16 subjects at baseline and 12 months, 19 subjects at baseline and 24 months, and 17 subjects at baseline and 36 months (1 year off raloxifene). Characteristics of the 27 subjects included in the study are shown in Table 1.

Change in Mammographic Density. Mean percent mammographic density for the 27 eligible patients at baseline was 39% and 37% for radiologist A (C.K.C.) and radiologist B (C.E.G.), respectively. No significant change in percent mammographic density was seen after 1 or 2 years of treatment with raloxifene by either reader. The mean change from baseline to 1 year was 1% [95% confidence interval (95% CI), -3 to +5] for radiologist A and 2% (95% CI, -4 to +7) for radiologist B. The mean change from baseline to 2 years on raloxifene was 1% (95% CI, -2 to +5) for radiologist A and 6% (95% CI, -0.2 to +13) for radiologist B. Twelve months after cessation of raloxifene, little overall change in mammographic density was recorded (Table 2). No associations between baseline mammographic density and age ($r = -0.02$, $P = 0.91$) or body mass index ($r = -0.27$, $P = 0.18$) were found. Of the 19 subjects with baseline to year 2 MRIV data, 18 have baseline to year 2 mammographic density changes, with the following summary statistics: for radiologist A, mean change, 3%; 95% CI, -1% to 8% ($P = 0.17$) for the null hypothesis of zero mean change; for radiologist B, mean change, 9%; 95% CI, 3-15% ($P = 0.008$). These changes are a little higher than those of the other 7 subjects without MRIV data but not significantly higher ($P = 0.17$ and 0.30, respectively, Wilcoxon rank-sum test); thus, the results are comparable with the entries in Table 2.

To assess the reproducibility and reliability of readers' measurements, both intraradiologist and interradiologist correlations were determined. Radiologist A recalculated percent mammographic density for 27 baseline mammograms. The difference between the initial and rescored

measurements (second set - first set) has a mean of $-0.4 \pm 10\%$ (range, -17% to 39.0%). These differences are consistent with a mean of zero ($P = 0.56$). The 39% at the upper end of the range is an extreme outlier from one subject; the second highest difference is 7%. Interradiologist correlation for change in percent mammographic density from baseline to 1 year was high ($r = 0.63$; $P = 0.0006$). This correlation was also high from baseline to 2 years and 12 months after cessation of raloxifene (Table 3).

Change in MRIV. MRIV significantly decreased while on raloxifene for 1 and 2 years. The median percent change in MRIV from baseline to 1 year was -17% (95% CI, -28 to -9; $P = 0.0017$). The median percent change from baseline to 2 years on raloxifene was -16% (95% CI, -31 to -14; $P = 0.0004$). The median percent change in MRIV from 2 years to 1 year later off of raloxifene was -9% (95% CI, -18 to 20; $P = 0.64$) and not significantly different from the reading at 2 years (Table 4). Body mass index had moderate negative correlations with MRIV at all time points [range, $r = -0.41$ ($P = 0.081$) to $r = -0.56$ ($P = 0.005$)] and no correlation with age at baseline ($r = -0.01$; $P = 0.98$).

Correlation between Mammographic Density and MRIV Measurements. Mammographic density and MRIV measurements were well correlated at all time points: baseline ($r = 0.89$; $P < 0.0001$), 1 year on raloxifene ($r = 0.67$; $P = 0.0005$), 2 years on raloxifene ($r = 0.81$; $P < 0.0001$), and 1 year after stopping study drug ($r = 0.80$; $P = 0.0005$; Fig. 1). However, change in readings over time was not well correlated between mammographic density and MRIV (baseline to year 2: $r = 0.33$; $P = 0.18$).

Discussion

In this trial, in premenopausal women at high risk for breast cancer, we found that percent mammographic density did not change on raloxifene, whereas MRIV significantly decreased. Although these results may appear to be discordant with each other, further consideration of each of the imaging modalities and prior intervention studies clarifies these findings and underscores promising aspects of MRIV assessments. Determination of change in MRIV may offer a more reproducible and sensitive measure of breast fibroglandular tissue. Although mammographic density has been embraced as a risk marker for breast cancer and incorporated into standard risk assessments (28), its deficiencies must also be recognized. Mammographic density readings are based on a single two-dimensional image subject to technical manipulation (14). Thus, any

Table 2. Mean change in mammographic density

Time on study	n	Radiologist A		Radiologist B	
		Mean change in % mammographic density (95% CI)	P	Mean change in % mammographic density (95% CI)	P
1 y	27	1 (-3 to 5)	0.93	2 (-4 to 7)	0.86
2 y	25	1 (-2 to 5)	0.58	6 (-0.2 to 13)	0.05
3 y (from year 2 to year 3)	19	-5 (-10 to -0.5)	0.02	-6 (-15 to 34)	0.26

Table 3. Interradiologist correlation for mammographic density

Time on study	<i>r</i> coefficient	<i>P</i>
1 y	0.63	0.0006
2 y	0.62	0.0013
3 y (1 year off raloxifene)	0.39	0.1

given instrumentation of mammograms to obtain mammographic density may influence readings (e.g. digitizing the image, the underlying contrast of the image). Although MRI also are mechanically manipulated, the much larger volume of data makes for a more stable assessment. Thus, although no changes were seen in mammographic density, relatively little data were available for analysis in comparison with MRIV. The statistically significant correlation between the mammographic density and MRIV at all time points on our study shows that they indeed produce similar quantitative evaluations of fibroglandular tissue. The lack of correlation of change in MRIV and mammographic density is likely due to range of measurements in mammographic density, the SD of the changes in mammographic density, and the measurement fluctuation, which taken together, may cloud a potential correlation.

The three-dimensional nature of MRI technology might overcome some of the limitations of mammography, allowing more accurate and stable assessment of fibroglandular volume. The reduction in variation in MRIV compared with mammographic density supports this imaging modality as a more reliable and reproducible surrogate biomarker and thus more amenable as an endpoint in phase II prevention trials, which employ smaller sample sizes.

Additionally, it is important to interpret these results in the scope of literature on endocrine agents and mammographic density. The Study of Tamoxifen and Raloxifene (29) reported that raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer in postmenopausal women at increased risk, yet, unlike tamoxifen, raloxifene has not been found to have an effect on mammographic density. Christodoulakos et al. reported no statistically significant change in mammographic density in postmenopausal women at risk for osteoporosis or cardiovascular disease after 1 year of raloxifene ($n = 48$) compared with controls ($n = 27$) using qualitative measures to score mammographic density (21). Similarly, in a nested pilot study, Freedman et al. found that the mean mammographic density in a subgroup of postmenopausal women participating in an osteoporosis prevention trial did not significantly change in women receiving raloxifene compared with placebo. Mammographic density decreased slightly in both groups over 2 years: -1.3% in the 45 women receiving placebo versus -1.5% in the 45 women receiving raloxifene (20). This study used semiquantita-

tive methods, similar to ours, to determine mammographic density. Typically, the studies with tamoxifen have included larger cohorts of women, both premenopausal and postmenopausal, who are also at increased risk for breast cancer, and tamoxifen has repeatedly been shown to decrease mammographic density. These differences in study populations may contribute to the ability to see a change in mammographic density. An examination of baseline mammographic density across these trials underscores this point.

For example, in the IBIS-I, a tamoxifen chemoprevention trial, evaluation of mammographic density included 818 premenopausal and postmenopausal women with a baseline mammographic density of ~42%, whereas in the Freedman et al. raloxifene study baseline mammographic density ranged from 8.1 to 13.5%, ~4-fold lower than the women at high risk for breast cancer (11, 20). This difference in baseline mammographic density reflects the dissimilar risk profiles of the women enrolled in these trials and raises the question that perhaps the mammographic density in the raloxifene-treated women may not be elevated enough to detect a significant change. It is also possible that raloxifene as a chemopreventive works through a mechanism that does not affect mammographic density, although this seems unlikely given the similarity in mechanism of action to tamoxifen.

Our study is the first to report on the effects of raloxifene on mammographic density and MRIV in premenopausal high-risk women and the first to assess change in MRIV in a prospective intervention trial. Additional strengths of our trial include our well-defined study population, timing of imaging studies to the menstrual cycle, and same-day imaging for mammograms and MRI. However, our study also had several limitations. Based on the number of evaluable subjects in our study, we could only detect a change in mammographic density greater than 7%. Although this is similar to the magnitude of reduction seen in trials of tamoxifen on breast density, our trial did not have sufficient power to detect smaller reductions in mammographic density. We had no control group or historical series to suggest the natural history of MRIV in a similar cohort over time without intervention. Based on a study of women participating in the Canadian National Breast Screening Study, the estimated average annual reduction in percent mammographic density for premenopausal women is ~1% (5), whereas the natural history of MRIV over time is unknown.

Future directions of research should be aimed at further understanding the histologic correlates of mammographic density and MRIV. Boyd et al. (30) showed that the risk of hyperplasia (with or without atypia) or carcinoma *in situ* in biopsies is related to increasing mammographic density, providing the first significant link to histologic data. Further work has evaluated the link between breast tissue/fluid and mammographic

Table 4. Median change in breast MRIV

Time on study	<i>n</i>	Median % change	Range (95% CI)	<i>P</i>
1 y	16	-17	-64 to 12 (-28 to -9)	0.0017
2 y	19	-16	-57 to 25 (-31 to -14)	0.0004
3 y (from year 2 to year 3)	17	-9	-23 to 28 (-18 to 20)	0.64

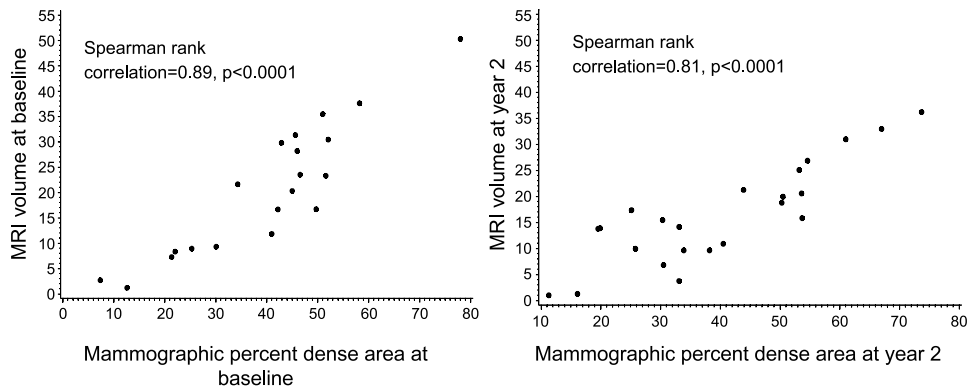


Figure 1. Correlation between mammographic density and MRIV.

density (31-33). These results support the hypothesis that mammographically dense breast tissue reflects the degree of stromal and epithelial proliferation and may be closely linked to growth factor activity.

These findings are important because they are the only report on changes in breast MRIV with a prevention agent. Our results raise important considerations for planning prevention intervention trials because this technique may offer a highly sensitive method to identify promising agents that should be moved forward into larger-scale testing. Although breast MRI is, on average, five times more expensive than mammogram, if this technique can be employed thoughtfully in targeted studies, it may provide reliable data that ultimately reduce research costs. For example, a highly precise test for efficacy will allow design of phase II trials requiring smaller numbers of subjects. MRIV may be a more informative surrogate biomarker for breast cancer risk than mammographic density. Breast MRI will be of increasing relevance because recent American Cancer Society guidelines now recommend breast cancer screening with MRI in addition to mammogram in high-risk women (34). These changes will increase the use of MRI and thus the need to better understand how these images can be evaluated prospectively and used clinically.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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BLOOD CANCER DISCOVERY

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