Mammographic Density and Estrogen Receptor Status of Breast Cancer

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Abstract

Background: **The density of breast tissue on a mammogram is a strong predictor of breast cancer risk and may reflect cumulative estrogen effect on breast tissue. Endogenous and exogenous estrogen exposure increases the risk of estrogen receptor (ER)–positive breast cancer. We determined if mammographic density is associated more strongly with ER-positive breast cancer than with ER-negative breast cancer.**

Methods: **We analyzed data from 44,811 participants in the San Francisco Mammography Registry of whom 701 developed invasive breast cancer. Mammographic density was measured using the Breast Imaging Reporting and Data System (BI-RADS) classification system (1 = almost entirely fat, 2 = scattered fibroglandular, 3 = heterogeneously dense, 4 = extremely dense). We tested for associations between mammographic density and ER-positive and ER-negative breast cancer separately. Analyses were adjusted for age, body mass index, postmenopausal hormone use, family history of breast cancer, menopausal status, parity, and race/ethnicity.**

Results: **Mammographic density was strongly associated with both ER-positive and ER-negative breast cancers. Compared with women with BI-RADS 2, women with BI-RADS 1 (lowest density) had a lower risk of ER-positive cancer [adjusted hazard ratio (HR), 0.28; 95% confidence interval (95% CI), 0.16-0.50] and ER-negative cancer (adjusted HR, 0.17; 95% CI, 0.04-0.70). Women with BI-RADS 4 (highest density) had an increased risk of ER-positive breast cancer (adjusted HR, 2.21; 95% CI, 1.64-3.04) and an increased risk of ER-negative breast cancer (adjusted HR, 2.21; 95% CI, 1.16-4.18).**

Conclusion: **Surprisingly, women with high mammographic density have an increased risk of both ER-positive and ER-negative breast cancers. The association between mammographic density and breast cancer may be due to factors besides estrogen exposure.**
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Introduction

Mammographic breast density is one of the strongest known risk factors for breast cancer. Studies have consistently shown that women with increased mammographic breast density have higher risk of breast cancer compared with women of similar age with lower breast density (1-3). The risk of breast cancer remains increased for up to 10 years after the determination of breast density on a mammogram (2).

Mammographic density may be influenced by estrogen. Mammographic density decreases after menopause (4). Formulations of postmenopausal hormone replacement therapy (HRT) that include estrogen plus progesterone increase mammographic density (5-7). Tamoxifen, a selective estrogen receptor (ER) modulator that has antiestrogenic effects in the breast, decreases mammographic density (8-10). Thus, high mammographic density may be associated with breast cancer because it is a marker of estrogen effects on breast tissue (11).

Risk factors for ER-positive and ER-negative breast cancers may be distinct (12). Increasing age and postmenopausal HRT have been associated with an increased risk of developing an ER-positive tumor (13, 14). Selective ER modulators are protective against ER-positive but not ER-negative breast cancers and may even increase the risk of ER-negative breast cancer risk (15, 16). If mammographic density is a risk factor for breast cancer because it represents cumulative effect of both endogenous and exogenous estrogens on the breast and estrogen is associated with an increased risk of ER-positive breast cancer, then mammographic breast density should be a stronger risk factor for ER-positive than ER-negative breast cancers. We tested this hypothesis by prospectively comparing the strength of the association between mammographic breast density and *invasive* ER-positive and ER-negative tumors among women who participated in the San Francisco Mammography Registry, a population-based mammography registry.

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Materials and Methods

Population. The San Francisco Mammography Registry includes 13 radiology facilities in San Francisco and has been operating since 1995. Demographic, clinical, and risk factor information, mammographic interpretations, and cancer outcomes obtained through linkage with the regional population-based Surveillance, Epidemiology, and End Results program are collected for all women undergoing screening or diagnostic mammography in San Francisco.

Women who had reading of mammographic density associated with at least one of their mammograms taken before January 1, 2002 were included in this study. Mammographic density measurements were done on 47% of the women in the database. The density measurements were done routinely at 11 of the 13 of the facilities participating in the registry. At these 11 facilities, density was read on >95% of the mammograms. The other two sites, which include the largest site, do not routinely assess mammographic density and were therefore excluded from the analysis. We excluded all women who had a diagnosis of breast cancer prior to their first mammographic density measurement because treatments for breast cancer including tamoxifen and radiation may alter breast density.

The data were analyzed as a cohort study. For all women included, we selected the first mammogram in the data set after January 1, 1995 as the main predictor. The last possible follow-up time was July 1, 2002. Follow-up time for women who developed invasive breast cancer was calculated as the time between their first mammogram with Breast Imaging Reporting and Data System (BI-RADS) density measurement and the date of invasive breast cancer diagnosis. Follow-up time for women who did not develop cancer was censored on July 1, 2002. The latter date was selected because it was known that completeness of cancer reporting would be >95% to the Northern California Surveillance, Epidemiology, and End Results registry prior to July 1, 2002.

Cancers occurred from <1 month after the index mammogram up to 7.5 years after the index mammogram. The mean time between mammogram and diagnosis of breast cancer was ~1.9 years. For women who were not diagnosed with breast cancer, the mean time between index mammogram and the last follow-up date was ~3.8 years.

Measurements. Breast density was classified using BI-RADS categories of almost entirely fat (1), scattered fibroglandular densities (2), heterogeneously dense (3), and extremely dense (4). Demographic information and a breast health history were obtained by questionnaire at each screening examination. The questionnaire includes questions about history of breast cancer, menopausal status, parity, history of breast cancer in first-degree relatives and age at diagnosis of the woman's relative, current postmenopausal HRT use, height, and weight. Body mass index (BMI) was calculated from self-reported height and weight. We used women's self-report of their menopausal status. For women who did not report menopausal status, those ages ≥55 years at the time of mammography were assumed to be postmenopausal. Women ages 50 to 54 years were considered postmenopausal if both ovaries had been removed, if they reported their periods had stopped permanently, or if they were taking HRT. Women were considered ''current HRT users'' if they self-reported HRT use at a screening examination.

We included all invasive breast cancers diagnosed between January 1, 1995 and July 1, 2002 and reported to the regional Northern California Surveillance, Epidemiology, and End Results program. ER and progesterone receptor (PR) status of breast cancers were collected from the regional Surveillance, Epidemiology, and End Results program. Women who developed carcinoma *in situ* were not included in this analysis.

Statistical Analysis. We compared age between unaffected women and women who developed ER-positive breast cancer and between unaffected women and women who developed ER-negative breast cancers using ANOVA. For all other analyses in Table 1, we adjusted for age, because baseline age was different among ER-positive cases and controls. We calculated age-adjusted rates for dichotomous and categorical variables (race/ethnicity, HRT, family history, and parity) and used logistic regression models adjusted for age alone to test the significance of the observed differences. We calculated age-adjusted means for continuous variables using linear regression models. In each case, we used women without breast cancer as the baseline group. To test the association between mammographic density and age, we used ANOVA. We adjusted all other demographic and risk factors in Table 2 for age, because age is strongly correlated with mammographic density. To test each variable for association with mammographic density and adjust the association for age, we used ordinal logistic regression models in which the outcome was BI-RADS category and each variable was tested separately with age as the only other covariate in the model. Analyses comparing baseline characteristics and mammographic density across different ethnic groups were done with Caucasians as the comparison group, because this was the largest subgroup.

We used Cox proportional hazards models to assess the association between breast density and ER-positive, ER-negative, PR-positive, and PR-negative breast cancer and all invasive breast cancers. Breast density was entered into the model as a categorical variable. In all of the analyses, we used BI-RADS category 2 (scattered fibroglandular densities) as the comparison group because this was the largest group. BMI was entered into the model as a continuous variable. Parity was entered into the models as nulliparity versus history of at least one childbirth. Family history was also entered as a dichotomous variable: history of at least one first-degree relative with breast cancer versus no first-degree relatives with breast cancer.

To test the strength of mammographic density and other potential risk factors as predictors of ER-positive versus ER-negative breast cancers, we generated polytomous models. In these models, we classified ER-positive and ER-negative cancers as distinct outcomes and compared the women who developed each of these with women who did not develop breast cancer. The final model included all of the same covariates included in the multivariate Cox proportional hazards models described above but also included follow-up time entered as a covariate. After estimating the model, we used Wald

Table 1. Comparison of baseline characteristics and mammographic density among women who remained unaffected and women who developed either ER-positive or ER-negative cancers

Characteristic*	Women without breast cancer (n = 44,110)	Women with ER-positive breast cancer (n = 504)	$P^{\dagger}$	Women with ER-positive breast cancer (n = 118)	$P^{\ddagger}$
Age, mean (SD)	53.5 (11.9)	57.9 (12.2)	<0.001	54.9 (12.6)	0.21
First-degree relative with cancer (%)	15.0	25.1	<0.001	24.4	0.004
Current hormone therapy use (%)	22.6	29.5	0.003	16.7	0.90
Nulliparity (%)	30.5	36.3	0.006	26.8	0.96
Premenopausal (%)	42.0	43.3	0.59	41.7	0.20
BMI, mean (SD)	27.1 (6.2)	27.2 (6.8)	0.74	28.4 (7.4)	0.02
Race (%)					
White	52.4	68.3		43.8	
Asian	20.6	18.2	<0.001	10.3	0.07
Latina/Hispanic	18.2	8.5	<0.001	20.4	0.73
African American	8.6	3.7	<0.001	12.5	0.17
Native American	0.2	0		0	
Mammographic density (%)					
BI-RADS 1	7.2	2.3	0.001	0.9	0.034
BI-RADS 2	44.5	39.4	—	42.0	—
BI-RADS 3	40.8	43.9	0.002	34.2	0.72
BI-RADS 4	7.4	13.1	<0.001	9.6	0.048

NOTE: All variables are presented as age-adjusted proportions or means. Statistical tests for association with ER-positive and ER-negative cancers are adjusted for age.

*All characteristics age-adjusted except for age.

†Ps for comparison of women with ER-positive breast cancer versus women without breast cancer.

‡Ps for comparison of women with ER-negative breast cancer versus women without breast cancer.

statistic to test the hypothesis that a particular covariate (e.g., breast density) was equivalent for both ER-positive and ER-negative breast cancers. A significant P value for this test implies that the covariate has a different strength of association for ER-positive versus ER-negative breast cancers.

Statistical analysis was done using Stata software (version 6). All statistical tests were two sided.

Results

Of the 44,811 women included in the analysis, 701 women developed invasive breast cancer. Of these, 504 were reported to have developed ER-positive disease, 118 had ER-negative tumors, and ER status was either not tested or could not be ascertained in 79 of the cases. In univariate analyses, women who developed ER-positive breast cancer were older by ~4 years. In age-adjusted analyses, women who developed ER-positive cancers were more likely to be taking hormones, to have had a first-degree relative with breast cancer, to be nulliparous, and to be Caucasian compared with women who did not develop breast cancer (Table 1). Women who developed ER-negative breast cancer were more likely to have had a first-degree relative with breast cancer.

Mammographic density decreased with age and was inversely related to BMI after adjustment for age (Table 2). Women who used HRT were more likely to have higher mammographic density, as were women who were nulliparous and women with a family history of breast cancer. Even after adjustment for age, postmenopausal women had significantly lower mammographic density than premenopausal women (Table 2).

Table 2. Association of demographic characteristics and breast cancer risk factors with mammographic density

	BI-RADS 1 (n = 3,203)	BI-RADS 2 (n = 19,932)	BI-RADS 3 (n = 18,332)	BI-RADS 4 (n = 3,344)	P
Age, mean (SD)	61.0 (12.1)	56.1 (11.9)	50.8 (10.9)	46.8 (9.5)	<0.001
Family history, first-degree relative (%)	12.9	14.1	16.2	16.5	<0.001
BMI, mean (SD)	32.0 (7.9)	28.6 (6.4)	25.4 (4.8)	22.7 (3.8)	<0.001
HRT (%)	19.9	21.3	27.1	25.5	<0.001
Nulliparity (%)	27.6	25.7	34.6	44.1	<0.001
Premenopausal (%)	35.0	40.2	43.6	43.8	<0.001
Race (%)					
White	49.7	51.5	54.1	50.5	
Asian	10.7	15.8	2.8	33.9	<0.001
Latina	21.7	22.1	15.4	10.3	<0.001
African American	16.8	10.2	6.6	5.1	<0.001
Native American	0.4	0.2	0.1	0.04	0.001

NOTE: All variables are presented as age-adjusted proportions or means.

Among women with the BI-RADS 1, 17 (0.5%) developed breast cancer of which 0.4% were ER positive and 0.06% were ER negative. Of the women with BI-RADS 2, 315 (1.6%) developed breast cancer of which 1.1% were ER positive and 0.29% were ER negative. Among the women with BI-RADS 3 density, 297 (1.6%) developed cancer of which 1.2% were ER positive and 0.25% were ER negative. Of the women with the highest density, 72 (2.2%) developed cancer of which 1.6% were ER positive and 0.4% were ER negative. These numbers are likely to be substantially higher than the true incidence of breast cancer in the population, because women are often diagnosed with breast cancer around the time of mammography.

In multivariate-adjusted analyses, increased mammographic density was associated with increased risk of both ER-positive and ER-negative breast cancers (Table 3). For both types of tumors, there was a progressive increase in risk with increasing density. Although the number of cancers, particularly ER-negative cancers, among women with BI-RADS 1 was low, we found that the association between density and ER-positive and ER-negative cancers was consistent among different density categories. Results adjusting for age and BMI only did not substantially differ from the results of the fully adjusted models, suggesting that other than age and BMI there were no other major confounders of the association between density and either ER-positive or ER-negative cancers.

There was no significant difference between the strength of the association between ER-positive cancers and breast density and the association between ER-negative cancers and breast density by Wald test ($P = 0.73$). When each category of breast density was tested individually, there was still no difference between ER-positive and ER-negative breast cancers (BI-RADS 1, $P = 0.49$; BI-RADS 3, $P = 0.42$; BI-RADS 4, $P = 0.90$). Several variables were significantly more predictive of either ER-positive or ER-negative cancers. African Americans had a lower risk of ER-positive breast cancer compared with Caucasians but a trend toward higher risk of ER-negative disease, a difference that was statistically significant ($P = 0.0002$). Latinas also had a lower risk of ER-positive breast cancer compared with Caucasians but similar risk of ER-negative disease [odds ratio, 0.89; 95% confidence interval (95% CI), 0.55-1.46], a difference that was also significant ($P = 0.001$).

We also tested for an association between mammographic density and breast cancer by PR status. Of the 620 tumors tested for PR status, 451 were PR positive and 169 were PR negative. We found an increased risk of both PR-positive [adjusted hazard ratio (HR), 2.21; 95% CI, 1.58-3.11] and PR-negative (adjusted HR, 1.97; 95% CI, 1.10-3.51) breast cancer for women with BI-RADS 4 compared with women with BI-RADS 2. Among women with BI-RADS 1 density, there was decreased risk of PR-positive cancer (adjusted HR, 0.20; 95% CI, 0.10-0.40) and PR-negative cancer (adjusted HR, 0.35; 95% CI, 0.15-0.81).

Discussion

Our results show that mammographic density is a strong risk factor for both ER-positive and ER-negative breast cancers. The ER status of a tumor may be a marker of its prior exposure to endogenous and exogenous estrogens. If the association between mammographic density and breast cancer is due to estrogen (11), then mammographic density should have been a better discriminator between ER-positive and ER-negative tumors. Therefore, our results suggest that the link between mammographic density and breast cancer may be due to factors other than or in addition to estrogen exposure. These results are consistent with the recent observation that mammographic density does not seem to be strongly associated with serum estradiol levels among postmenopausal women (17). Thus, whereas mammographic density (1, 2) and postmenopausal hormone levels (18) are both strong predictors of breast cancer risk, they may act independently of each other. We also found that the association between breast density and breast cancer was consistent among PR-positive and PR-negative tumors.

This study is prospective, with a large sample size that includes premenopausal and postmenopausal women of diverse racial and ethnic groups. One limitation of the study is that we used a qualitative rating of breast density that was made by numerous radiologists and has limited replicability (19). However, even with a qualitative measure of breast density, the association with breast cancer risk is strong. Misclassification of the readings may attenuate the association with breast cancer, but this should not have a differential affect on the association between ER-positive and ER-negative tumors.

Table 3. HRs (95% CI) for mammographic density

	BI-RADS 1 (n = 3,203)	BI-RADS 2 (n = 19,932)	BI-RADS 3 (n = 18,332)	BI-RADS 4 (n = 3,344)
All invasive breast cancers (n)	17	315	297	72
Unadjusted HR (95% CI)	0.33 (0.20-0.54)	Reference	1.05 (0.89-1.23)	1.46 (1.13-1.89)
Adjusted HR (95% CI)	0.26 (0.16-0.42)	Reference	1.26 (1.07-1.49)	2.09 (1.59-2.75)
ER-positive breast cancers (n)	13	224	215	52
Unadjusted HR (95% CI)	0.36 (0.20-0.63)	Reference	1.07 (0.88-1.29)	1.48 (1.10-2.01)
Adjusted HR (95% CI)	0.29 (0.16-0.50)	Reference	1.28 (1.05-1.56)	2.11 (1.52-2.92)
ER-negative breast cancers (n)	2	57	45	14
Unadjusted HR (95% CI)	0.22 (0.05-0.89)	Reference	0.87 (0.59-1.29)	1.55 (0.86-2.78)
Adjusted HR (95% CI)	0.17 (0.04-0.70)	Reference	1.05 (0.70-1.59)	2.25 (1.18-4.26)

NOTE: HRs from Cox proportional hazards models are calculated with the BI-RADS 2 category as the reference group. Models were adjusted for age, HRT use, BMI, parity, family history and menopausal status, and race/ethnicity.

The ER status of tumors may be associated with distinct biological subtypes of breast cancer and genetic and risk factor profiles. Classification of tumor subtypes using gene expression profiles has identified ER status as one of the most important variables in clustering the expression profiles (20, 21). BRCA1 mutation carriers develop mostly ER-negative tumors, whereas BRCA2 mutation carriers develop mostly ER-positive tumors (22–24). ER-negative cancers are more common among younger women and among African American women (12). There may also be a differential effect of menopause on risk (25). Postmenopausal risk of ER-positive cancers continue to increase with age, whereas ER-negative cancers do not. Because mammographic density is associated with development of both ER-positive and ER-negative tumors, it suggests that mammographic breast density increases the risk of a biologically diverse and heterogeneous set of tumors.

Mammographic density is a heritable trait (26) with ~60% of the variance explained by genetic factors (26, 27). In addition, first-degree relatives of women with increased mammographic density have increased risk of developing breast cancer (28). Thus, genes that determine breast density may also affect breast cancer risk. Previous studies have shown that mammographic density is associated with higher insulin-like growth factor-I levels in premenopausal women, which are in turn associated with breast cancer (29). Other growth factors that affect the breast have also been shown to be associated with mammographic density. Our results provide indirect evidence that mammographic density may be defined by a set of genes that increase the risk of a diverse set of breast tumors.

The utility of measuring mammographic density to identify women at high risk for breast cancer will depend on the efficacy of preventive interventions that can be offered to women at high risk. Current primary prevention therapies such as tamoxifen and raloxifene seem to be protective against ER-positive breast tumors but not against ER-negative tumors (15, 16). Despite their strong protective effects, selective ER modulators are not being widely used currently, possibly because of the potential harms associated with their use (30). Identifying women who are at specifically increased risk of ER-positive tumors may be important to maximize the potential benefit of selective ER modulators. Because mammographic breast density is associated with increased risk of ER-positive tumors, breast density may be useful to identify women who may benefit from tamoxifen or ralixofene. However, because women with increased density are also at increased risk of ER-negative tumors, preventive therapy with selective ER modulators may not decrease the risk of women destined to be diagnosed with ER-negative breast cancer to the same extent as women destined to have ER-positive breast cancer. The value of measuring breast density to identify women who will benefit from chemoprevention may be established by measuring breast density among participants of large trials of chemoprevention.

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