Is There a Difference in the Association between Percent Mammographic Density and Subtypes of Breast Cancer? Luminal A and Triple-Negative Breast Cancer

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Abstract

Background: **Mammographic density is a potentially modifiable risk factor for breast cancer. To what extent mammographic density is a predictor for both hormone receptor-positive and hormone receptor-negative tumors is unclear. Even less is known about whether mammographic density predicts subtypes of breast cancer defined by expression status of the three receptors: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER-2).**
Methods: **We estimated the association of percent mammographic density with subtypes of invasive breast cancer among 479 population-based female breast cancer patients and 376 control subjects ages 35 to 64 years. The expression status of ER, PR, and HER-2 was assessed using immunohistochemistry methods in a single laboratory. We considered ER+ or PR+ plus HER-2- tumors as luminal A breast cancer and ER-/PR-/HER-2- tumors as triple-negative breast cancer. We used unconditional logistic regression methods to estimate odd ratios (95% confidence intervals) for both case-control and case-case comparisons.**
Results: **Mammographic density was associated with increased risk of both invasive breast cancer subtypes, luminal A and triple-negative, in the case-control analysis. Results from case-case comparisons yielded no differences between the two subtypes among all women combined or in analyses done separately by race (White versus African American women) or menopausal status (premenopausal versus postmenopausal women; all P values > 0.05).**
Conclusions: **Our results suggest that percent mammographic density is positively associated with both luminal A and triple-negative breast cancer.** (Cancer Epidemiol Biomarkers Prev 2009;18(2):479–85)

Introduction

Gene expression studies with cDNA microarray technology have segregated breast cancers into several subtypes based on variations in gene expression patterns (1–4). These subtypes differ in prognosis and survival (1, 4, 5). Women with ''luminal A'' cancers, one of the main subtypes, have better prognosis, whereas those diagnosed with ''basal-like'' breast cancers have poorer prognosis than all other subtypes.

Tumors of these two major subtypes have different immunohistochemical profiles. Luminal A tumors typically express estrogen receptor (ER+) and progesterone receptor (PR+) but have low expression of human epidermal growth factor receptor-2 (HER-2/*neu*, also known as ERBB2, and referred to HER-2 throughout this article) (6). Basal-like tumors typically show low expression of ER, PR, and HER-2 but exhibit high expression of genes characteristic of the basal epithelial cell layer, including expression of HER-1 and/or cytokeratins 5/6 (6).

Mammographic density, a quantitative measure of connective and epithelial tissue in the breast, is a strong risk factor for breast cancer (7) and is commonly represented as the percent of total breast tissue on mammogram that is dense. Women with high percent mammographic density are four to six times more likely to develop breast cancer compared with those with very low density (7–10). Given that percent mammographic density is related to hormone-related factors such as menopausal status (11) and use of postmenopausal hormone therapy (12, 13) and tamoxifen (14), one might expect it to be predominantly associated with luminal A breast tumors. However, one study has shown that high mammographic density is a strong risk factor for both ER+ and ER- breast cancer (15). Furthermore, in another study, high density was not associated with HER-2 status (16). Neither of these studies has provided data for subtypes defined jointly by ER and PR status or for subtypes defined by ER, PR, and HER-2.

We therefore decided to examine the association of percent mammographic density with subtypes of breast

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cancer defined by three markers (ER, PR, and HER-2). We used these markers to define luminal A and triple-negative tumors. In the absence of data on basal cytokeratins, the latter subgroup represents a proxy for basal-like tumors.

Materials and Methods

Subject Identification. Women included in the current analysis were African American and White women who participated in the Los Angeles County component of the Women's Contraceptive and Reproductive Experiences Study (17) for whom we obtained mammograms as part of a mammographic density study of Asian American, African American, and White breast cancer cases and controls (9). The Women's Contraceptive and Reproductive Experiences Study was a multicenter, population-based study of invasive breast cancer conducted among women ages 35 to 64 years in five areas of the United States, including Los Angeles County. Eligible cases in this study were U.S.-born White and African American women residing in Los Angeles Country when diagnosed with a first primary invasive breast cancer between June 1994 and August 1998. Controls were selected by random-digit dialing among the residents of Los Angeles Country and were frequency matched to case patients on age and ethnicity. We obtained complete histories of menstrual and reproductive factors, hormone replacement therapy, weight, height, and family history of breast cancer for each participant during in-person interviews conducted as part of the Women's Contraceptive and Reproductive Experiences Study.

Participants in the Los Angeles mammographic density study (9) had undergone diagnostic or prediagnostic mammograms within 5 years of their diagnosis date (cases) or screening mammogram within 5 years before or 1 year after their first date of contact (controls). Of the 1,374 women eligible to participate, we retrieved and scanned one or more mammograms for 949 women (531 case patients and 418 control subjects) using an Omnimedia XRS 6cx scanner (Lumisys) or a Cobrascan CX312T scanner (Radiographic Digital Imaging). We excluded 24 women (20 cases and 4 controls) because their digitized mammogram files were not useable and therefore had mammograms available for 925 women (511 cases and 414 controls). The mammograms were read in batches containing equal proportion of cases and controls from each 5-year age group. We selected the mammograms from the contralateral (nondiseased) breast of the cases. For controls, we randomly selected the right or left breast while assuring that, within each batch, the control laterality distribution represented that of the unaffected (contralateral) breast of the cases. The mammographic density assessments were conducted by Dr. Ursin using a validated computer-assisted method (9). All participants had signed an informed consent as part of their recruitment for the Women's Contraceptive and Reproductive Experiences Study; the study was approved by the Institutional Review Board at the University of Southern California.

Assessment of ER, PR, and HER-2. We requested paraffin-embedded tumor blocks from the pathology laboratories where the breast cancer diagnosis was made. We received tumor tissue for 375 (73%) of the 511 case patients for whom we have mammograms. The status of ER, PR, and HER-2 was determined in Dr. Press' laboratory at the University of Southern California using previously published immunohistochemical methods (18–21). Tumors defined as ER+ or PR+ were those where ≥10% nuclei were specifically immunostained. For ER, this cutoff is equivalent to 10 fmol ER/mg cytosol protein using the dextran-coated charcoal biochemical assay method, which is the standard cutoff traditionally used for ER positivity (18). HER-2 expression status was determined by immunohistochemistry using the 10H8 monoclonal antibody (DAKO; refs. 20, 21) to assess HER-2 membrane protein immunostaining. No (0) or weak (1+) membrane immunostaining was considered low HER-2 expression (HER-2-). Moderate (2+) or strong (3+) membrane immunostaining was considered HER-2 overexpression (HER-2+).

Statistical Analysis. We used *t* tests to evaluate differences in continuous variables and Pearson χ^2 tests to evaluate differences in the frequency distributions of categorical variables comparing cases with controls and comparing cases by subtype of breast cancer.

We used multivariable polychotomous logistic regression methods using data from cases and controls to estimate odds ratios (OR) and corresponding 95% confidence intervals (95% CI) for the association of percent mammographic density with the subtypes of breast cancer defined by ER, PR, and HER-2 status and multivariable dichotomous logistic regression for case-case comparisons by subtype.

We present results for ER+ or PR+, both ER− and PR− (ER−/PR−), HER-2-, HER-2+, luminal A (ER+ or PR+ plus HER-2-), and triple-negative (ER−/PR−/HER-2−) breast cancer. We also performed analysis for the subtypes defined by both ER+ and PR+ (ER+/PR+) instead of either positive of the two. Because results were essentially the same for using either receptor positive compared with using ER+/PR+, we only present results for subtypes defined by the former, either receptor positive.

Tests for trend were conducted by fitting ordinal values corresponding to categories of percent mammographic density in our models and testing whether the coefficient (slope of the dose response) differed from zero.

We tested for homogeneity of trends by race and menopausal status using a likelihood ratio test, comparing the fit of a model with a trend variable for mammographic density with the fit of a model where mammographic density was allowed to vary according to the categories of the potential effect modifier.

We adjusted for the following variables, selected *a priori*, as potential confounders in all our multivariable polychotomous and dichotomous logistic regression models: age at mammogram in 5-year age groups (categorical), first-degree family history of breast cancer (no first-degree family history, mother or sister with breast cancer), body mass index (reported for the date 5 years before reference date, in kg/m^2, continuous), age at menarche (≤13, >13 years), parity [never/ever had a full-term (>26 weeks) pregnancy], age at first full-term pregnancy (≤30, >30 years), menopausal status, and hormone therapy (current, past, never), and race (White,

Table 1. Frequency distribution of breast cancer cases ages 35 to 64 years from Los Angeles County by tumor subtypes

	Cases (n = 352), n (%)	Cases by race, n (%)		
		White (n = 194)	African American (n = 158)	P*
ER and PR				
ER+ or PR+	225 (63.9)	137 (70.6)	88 (55.7)	0.004
ER-/PR-	127 (36.1)	57 (29.4)	70 (44.3)	
HER-2				
HER-2−	290 (82.4)	168 (86.6)	122 (77.2)	0.02
HER-2+	62 (17.6)	26 (13.4)	36 (22.8)	
ER, PR, and HER-2				
Luminal A (ER+ or PR+ plus HER-2−)	184 (52.3)	121 (62.4)	63 (39.9)	0.0004
Luminal B (ER+ or PR+ plus HER-2+)	41 (11.6)	16 (8.2)	25 (15.8)	
Triple-negative (ER−/PR−/HER-2−)	106 (30.1)	47 (24.2)	59 (37.3)	
ER−/PR−/HER-2+	21 (6.0)	10 (5.2)	11 (7.0)	

*P ascertained from Pearson χ^2 test.

African American). In our previous analysis (22), we examined the associations between these potential confounders and percent mammographic density among these control subjects. All of them were associated with percent mammographic density either among all these control subjects or among one of the subgroups defined by age (<50 versus ≥50 years), except for age at menarche (22). We included age at menarche in our multivariable models because it is an established risk factor for breast cancer (23, 24). In addition, we adjusted for the laterality of the breast where the mammogram was from.

Because several potential confounders had missing values, we calculated the unadjusted ORs of percent mammographic density associated with breast cancer first including and then excluding the subjects with missing values. We found the unadjusted estimates were quite similar. Therefore, we excluded 43 women (20 case patients and 23 control subjects) who had undergone simple hysterectomy, 3 women (2 case patients and 1 control subject) with unknown menopausal status, 2 case patients with missing weight information, 1 control subject with missing age at first full-term pregnancy, 4 women (1 case patient and 3 control subjects) with

Table 2. Characteristics of controls and breast cancer cases ages 35 to 64 years from Los Angeles County

Variables	Overall cases vs controls			ER-/PR- vs ER+ or PR+			HER-2+ vs HER-2−			Triple-negative vs luminal A		
	Controls (n = 376)	Cases (n = 479)	P*	ER+ or PR+ (n = 225)	ER-/PR- (n = 127)	P*	HER-2− (n = 290)	HER-2+ (n = 62)	P*	Luminal A (n = 184)	Triple-negative (n = 106)	P*
Age (y), mean†	49.7	48.7	0.10	50.3	46.7	0.0002	49.2	47.9	0.28	50.6	46.9	0.0004
Race, %												
White	60.4	58.5	0.57	60.9	44.9	0.004	57.9	41.9	0.02	65.8	44.3	0.0004
African American	39.6	41.5		39.1	55.1		42.1	58.1		34.2	55.7	
First-degree breast cancer family history,‡ %	9.3	15.7	0.006	14.2	13.4	0.83	14.1	12.9	0.80	14.1	14.2	0.996
Body mass index (kg/m^2), mean†	26.4	25.6	0.05	25.6	26.0	0.55	25.6	26.2	0.46	25.4	26.0	0.43
Age at menarche (y), %												
≤13	77.7	79.5	0.50	81.3	75.6	0.20	79.7	77.4	0.69	81.0	77.4	0.46
>13	22.3	20.5		18.7	24.4		20.3	22.6		19.0	22.6	
Nulliparous, %	17.8	20.3	0.37	19.6	22.1	0.58	21.4	16.1	0.35	20.7	22.6	0.69
Age at first full-term pregnancy among parous women (y), %												
≤30	92.2	86.7	0.02	90.1	82.8	0.08	87.3	88.5	0.82	89.7	82.9	0.14
>30	7.8	13.4		9.9	17.2		12.7	11.5		10.3	17.1	
Menopausal status and HT, %												
Premenopausal	39.4	48.9	0.003	42.2	55.1	0.12	46.6	48.4	0.60	42.4	53.8	0.31
Postmenopausal, never HT	12.0	14.6		15.6	14.2		14.5	17.7		15.2	13.2	
Postmenopausal, former HT	13.8	12.1		14.7	10.2		14.1	8.1		15.2	12.3	
Postmenopausal, current HT	34.8	24.4		27.6	20.5		24.8	25.8		27.2	20.8	

Abbreviation: HT, hormonal therapy including estrogen therapy or estrogen plus progestin therapy.
* P ascertained from Pearson χ^2 test, except where otherwise noted.
† P ascertained from t test.
‡ First-degree breast cancer family history, mother or sister with breast cancer.

Table 3. Adjusted OR (95% CI) of breast cancer associated with percent mammographic density by ER/PR and HER-2 status

Percent density	All cases vs controls			By ER/PR status			
	Controls	Cases	OR (95% CI)	ER+ or PR+ cases	ER+ or PR+ vs controls OR (95% CI)	ER-/PR-cases	ER-/PR- vs controls OR (95% CI)
Overall							
<10	99	76	1.00	39	1.00	19	1.00
10-29	101	109	1.31 (0.86-2.00)	54	1.23 (0.73-2.07)	27	1.30 (0.65-2.60)
30-59	140	218	1.84 (1.22-2.78)	102	1.74 (1.05-2.87)	58	1.99 (1.04-3.84)
≥60	36	76	2.46 (1.40-4.34)	30	2.05 (1.02-4.10)	23	3.01 (1.29-7.02)
P_{trend}			0.0004		0.01		0.005
Race							
White							
<10	57	37	1.00	19	1.00	5	1.00
10-29	56	57	1.39 (0.78-2.49)	32	1.40 (0.69-2.84)	9	1.71 (0.51-5.74)
30-59	91	132	1.84 (1.06-3.20)	65	1.90 (0.96-3.78)	28	2.72 (0.88-8.42)
≥60	23	54	2.87 (1.39-5.94)	21	2.48 (1.01-6.08)	15	5.16 (1.41-18.91)
P_{trend}			0.003		0.03		0.008
African American							
<10	42	39	1.00	20	1.00	14	1.00
10-29	45	52	1.18 (0.62-2.25)	22	0.94 (0.42-2.10)	18	1.08 (0.45-2.61)
30-59	49	86	1.81 (0.96-3.42)	37	1.46 (0.67-3.18)	30	1.62 (0.70-3.78)
≥60	13	22	1.72 (0.67-4.43)	9	1.31 (0.40-4.29)	8	1.49 (0.42-5.29)
P_{trend}			0.06		0.32		0.25
Test for effect modification by race, P			0.38		0.55		0.13

NOTE: Adjusted for age at mammography, first-degree breast cancer family history, body mass index, age at menarche, number of full-term pregnancies, age at first full-term pregnancy, a variable combining menopausal status and hormone therapy use, race, and laterality of mammogram.

missing age at menarche, and 17 women (7 case patients and 10 control subjects) who were adopted or who did not know the breast cancer history of their first-degree family members to maintain a consistent sample size for all statistical analyses. This resulted in 479 cases and 376 control subjects with mammograms who were available for the case-control analyses overall and 352 cases who were available for the analyses by receptor status.

All statistical significance levels (P values) reported are two-sided. All analyses were done using the SAS Statistical Package version 9.1 (SAS Institute).

Results

Frequency Distribution of Cases by Tumor Subtypes. Among 352 cases who had available receptor status, tumors from 225 (63.9%) women were classified as ER+ or PR+ and 127 (36.1%) as ER-/PR-. Further, tumors from 184 (52.3%) women were classified as luminal A, 106 (30.1%) as triple-negative, 41 (11.6%) as luminal B, and 21 (6.0%) were classified as ER−/PR−/HER-2+ breast cancer (Table 1). White women tended to have tumors classified as luminal A (62.4%), whereas, among African American cases, luminal A (39.9%) and triple-negative (37.3%) breast cancer were both common.

Characteristics of Controls and Cases. Women with ER+ or PR+ tumors were on average older than those diagnosed with ER-/PR- tumors (P = 0.0002), whereas women with luminal A tumors were older than those with triple-negative cancers (P = 0.0004; Table 2). Compared with African American patients, White patients were more likely to have ER+ or PR+ (P = 0.004) and HER-2− (P = 0.02) or luminal A breast cancer (P = 0.0004).

Associations between Percent Mammographic Density and Breast Cancer Risk Overall and by ER/PR and HER-2 Separately Overall, and as reported previously for the full study from which this subset came (9), percent mammographic density was positively associated with the risk of breast cancer (P_{trend} = 0.0004; Table 3). Women with ≥60% mammographic density were 2.46 (95% CI, 1.40-4.34) times more likely to have breast cancer than those with <10% mammographic density. This positive association with mammographic density was present for ER+ or PR+ as well as ER-/PR- breast cancer and for both HER-2− and HER-2+ breast cancer. Furthermore, case-case comparisons suggested that there was no difference in the association between percent mammographic density and breast cancer risk by either ER/PR or HER-2 status (all P_{trend} values > 0.30).

Associations between Percent Mammographic Density and Luminal A and Triple-Negative Breast Cancer Risk. Percent mammographic density was positively associated with both luminal A and triple-negative breast cancer (P_{trend} = 0.02 and 0.007, respectively; Table 4). Case-case comparisons suggested that there was no difference in this association between luminal A and triple-negative breast cancer (P_{trend} = 0.44).

Similar positive associations with both luminal A and triple-negative breast cancer were observed when analyses were restricted to White, African American, premenopausal, or postmenopausal women separately (Table 4). Further, neither the effect modification on these two subtypes by race (P = 0.63 and 0.75) nor by menopausal status (P = 0.69 and 0.29) was statistically significant. The associations were similar when restricted to nulliparous and parous women separately (results not shown).

Table 3. Adjusted OR (95% CI) of breast cancer associated with percent mammographic density by ER/PR and HER-2 status (Cont'd)

By HER-2 status					
ER-/PR- vs ER+ or PR+ OR (95% CI)	HER-2− cases	HER-2− vs controls OR (95% CI)	HER-2+ cases	HER-2+ vs controls OR (95% CI)	HER-2− vs HER-2+ OR (95% CI)
1.00	44	1.00	14	1.00	1.00
1.22 (0.55-2.71)	70	1.44 (0.88-2.34)	11	0.70 (0.29-1.69)	2.06 (0.79-5.40)
1.28 (0.61-2.69)	133	1.98 (1.23-3.18)	27	1.29 (0.59-2.84)	1.51 (0.64-3.56)
1.52 (0.59-3.91)	43	2.53 (1.32-4.84)	10	1.71 (0.59-4.93)	1.37 (0.44-4.27)
0.40		0.002		0.19	0.75
1.00	20	1.00	4	1.00	1.00
1.40 (0.36-5.40)	37	1.55 (0.78-3.08)	4	0.95 (0.21-4.39)	2.26 (0.43-11.97)
1.80 (0.51-6.35)	79	2.10 (1.08-4.06)	14	1.94 (0.49-7.66)	1.44 (0.33-6.23)
1.94 (0.47-7.96)	32	3.25 (1.40-7.54)	4	2.02 (0.34-11.90)	2.01 (0.32-12.76)
0.33		0.004		0.29	0.70
1.00	24	1.00	10	1.00	1.00
1.16 (0.40-3.40)	33	1.15 (0.55-2.38)	7	0.63 (0.20-1.95)	1.66 (0.46-6.02)
1.10 (0.41-2.93)	54	1.77 (0.87-3.61)	13	0.95 (0.33-2.73)	1.72 (0.54-5.49)
1.00 (0.23-4.40)	11	1.35 (0.44-4.10)	6	1.26 (0.29-5.54)	0.78 (0.14-4.28)
0.98		0.18		0.68	0.88
0.34		0.37		0.51	0.94

Discussion

Our results suggest that percent mammographic density is positively associated with both luminal A and triple-negative breast cancer as defined by ER, PR, and HER-2. We found no evidence that the association was stronger for one subtype.

Besides different prognosis (1, 4, 5) and different immunohistochemical profiles (6) between luminal A and basal-like breast cancer, gene expression studies have reported that these two subtypes may be associated with different carcinogenic pathways (2, 3). The ER signaling pathway is highly activated in luminal A tumors, and the estrogen-responsive genes that have

Table 4. Adjusted OR (95% CI) of luminal A and triple-negative breast cancer associated with percent mammographic density

Percent density	Controls	Luminal A vs controls		Triple-negative cases vs controls		Triple-negative cases vs luminal A
		Cases	OR (95% CI)	Cases	OR (95% CI)	OR (95% CI)
Overall						
<10	99	27	1.00	17	1.00	1.00
10-29	101	49	1.62 (0.92-2.86)	21	1.09 (0.52-2.29)	0.74 (0.30-1.83)
30-59	140	85	2.05 (1.17-3.59)	48	1.81 (0.91-3.63)	0.98 (0.42-2.28)
≥60	36	23	2.22 (1.04-4.78)	20	2.96 (1.21-7.23)	1.38 (0.47-4.01)
P_{trend}			0.02		0.007	0.44
Race						
White						
<30	113	44	1.00	13	1.00	1.00
≥30	114	77	1.68 (0.99-2.88)	34	1.96 (0.87-4.45)	1.31 (0.54-3.19)
African American						
<30	87	32	1.00	25	1.00	1.00
≥30	62	31	1.33 (0.69-2.63)	34	1.84 (0.93-3.66)	1.43 (0.60-3.40)
Test for effect modification by race, *P*			0.63		0.75	0.94
Menopausal status						
Premenopausal						
<30	52	20	1.00	17	1.00	1.00
≥30	96	58	1.47 (0.75-2.90)	40	1.42 (0.66-3.05)	0.88 (0.36-2.17)
Postmenopausal						
<30	148	56	1.00	21	1.00	1.00
≥30	80	50	1.70 (1.00-2.91)	28	2.32 (1.13-4.76)	1.54 (0.64-3.71)
Test for effect modification by menopausal status, *P*			0.69		0.29	0.20

NOTE: Adjusted for age at mammography, first-degree breast cancer family history, body mass index, age at menarche, number of full-term pregnancies, age at first full-term pregnancy, a variable combining menopausal status and hormone therapy use, race, and laterality of mammogram.

been reported up-regulated in this pathway include *ESR1* and the estrogen-induced gene *TFF1*. The basal-like tumors are characterized by overexpression of several genes in the p21 (*CDKN1A*) pathway that play a critical role in cell proliferation and DNA replication (*MCM3, MCM4, MCM7*, and *MAD2L1*). One gene in this pathway (*SKP2*) encodes a protein involved in the degradation of another cyclin-dependent kinase inhibitor p27 (*CDKN1B*) and one study has suggested that overexpression of this protein in breast tumors is associated with poor prognosis (25).

Previous epidemiologic studies have found that hormone-related risk factors such as postmenopausal hormone therapy (26), nulliparity (27–30), and late age at first full-term pregnancy are positively associated with ER+/PR+ (28, 31, 32) but not associated with ER-/PR- breast cancer. Further, Millikan et al. (33) found that parity and younger age at first full-term pregnancy were associated with a decreased risk of luminal A type (ER+/PR+ and HER-2−) but increased risk of basal-like breast cancer (ER−, PR−, HER-2−, HER-1+, and/or cytokeratins 5/6+).

Postmenopausal hormone therapy (12, 34, 35), nulliparity, and late-onset pregnancies (36, 37) have been associated previously with increased mammographic density. These hormone-related factors may increase breast cancer risk through a pathway that includes increased mammographic density. Thus, we hypothesized that mammographic density would be more strongly associated with luminal A subtype breast cancer than with the triple-negative subtype.

However, we found no difference in the association of percent mammographic density with luminal and triple-negative breast cancer. Our findings are consistent with a prospective study from San Francisco showing that mammographic density is associated with both ER+ and ER- breast cancer (15). It is also consistent with another study conducted in North Carolina, which reported that mammographic density was not associated with HER-2 status (16).

Although the biological mechanisms that underlie the association of mammographic density with breast cancer risk are unknown, it is clear that, although mammographic density is responsive to hormones (12, 14, 38) and therefore ought to be associated with luminal A cancer, it also has a strong inherited component (39). Whether there is a stronger genetic component for the mammographic density among women who develop triple-negative breast cancer than for those who develop luminal A breast cancer is unknown. Data from mammographic screening studies on interval and screen-detected cancers provide some indirect support for our findings that triple-negative cancers are associated with high mammographic density. Interval breast cancer is more common in women with dense mammograms, whereas women with screen-detected breast cancer tend to have less dense mammograms (40, 41). Further, basal-like breast tumors may be more frequent in interval breast cancers than in cancers detected at screening (42, 43).

A strength of our study was that ER, PR, and HER-2 status used in our analysis were all assessed in a single laboratory by immunohistochemistry using the same cutoff for a positive receptor status for all case patients.

Several limitations of this study must be considered. When we did analyses by receptor subtypes, 27% of case patients were excluded due to unavailable paraffin-embedded tissue, which is similar to that reported by previous studies conducted within the Surveillance, Epidemiology and End Results registries (44, 45) or conducted using receptor status measured at a single laboratory (46). We think that it is unlikely that the association between mammographic density and subtypes of breast cancers differed by whether pathology samples were available; therefore, we think this is an unlikely source of bias. Another weakness is that we did comparisons between luminal A and triple-negative (ER−, PR−, and HER-2−) instead of the basal-like subtype that was defined as ER−, PR−, HER-2−, HER-1+, and/or cytokeratins 5/6+ (6, 33) or more extensive gene expression markers (1, 47). However, there have been no published data to support neither correlation between mammographic density and cytokeratins 5/6 nor the association between mammographic density and HER-1.

In conclusion, our results suggest that percent mammographic density is positively associated with both luminal A and triple-negative breast cancer. Understanding the etiology of mammographic density could therefore be useful in elucidating the early carcinogenic process for both of these subtypes of breast cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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