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ARTICLE

Mammographic Breast Density and Subsequent Risk of Breast Cancer in Postmenopausal Women According to Tumor Characteristics

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Background Few studies that investigated the associations between breast density and subsequent breast cancer according to tumor characteristics have produced inconclusive findings. We aimed to determine whether the associations between breast density and subsequent breast cancer varied by tumor characteristics.

Methods We included 1042 postmenopausal women diagnosed with breast cancer between June 1, 1989, and June 30, 2004, and 1794 matched control subjects from the Nurses' Health Study, an ongoing prospective cohort study of 121701 registered female nurses across the United States. Breast density was estimated from digitized images using computerized techniques. Information on breast cancer risk factors was obtained prospectively from biennial questionnaires before the date of cancer diagnosis for case subjects and matched control subjects. Polychotomous logistic regression was used to assess associations of breast density with tumor subtypes based on invasiveness, histology, size, grade, receptor status, and involvement of lymph nodes. All tests of statistical significance were two-sided.

Results The risk of breast cancer increased progressively with increase in percent breast density (P_{trend} < .001). Women with higher breast density (≥50%) showed a 3.39-fold (odds ratio = 3.39, 95% confidence interval = 2.46 to 4.68) increased risk of breast cancer compared with women with lower breast density (<10%). The associations between breast density and breast cancer risk were stronger for in situ compared with invasive tumors ($P_{heterogeneity}$ < .01), high-grade compared with low-grade tumors ($P_{heterogeneity}$ = .02), larger (>2 cm) compared with smaller (≤2 cm) tumors ($P_{heterogeneity}$ < .01), and estrogen receptor–negative compared with estrogen receptor–positive tumors ($P_{heterogeneity}$ = .04). There were no differences in associations by tumor histology, involvement of lymph nodes, and progesterone receptor and HER2 status ($P_{heterogeneity}$ > .05).

Conclusions The findings suggest that higher mammographic density is associated with more aggressive tumor characteristics and also with in situ tumors.

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Mammographic breast density is a well-established and strong predictor of breast cancer risk (1–4). Appearance of the breast on the mammogram is a reflection of the amount of fat, connective tissue, and epithelial tissue in the breast (3). Light (non-radiolucent) areas on the mammogram represent the fibrous and glandular tissues ("mammographically dense"), whereas, the dark (radiolucent) areas are primarily fat. Women with breasts of 75% or greater percent density (proportion of the total breast area that appears dense on the mammogram) are at four- to sixfold greater risk of breast cancer compared with women with more fat tissues in the breasts (3,5,6). The increased risk of breast cancer persists for 10 years or more after density assessment in both pre- and postmenopausal women and is independent of other breast cancer risk factors (6).

Breast cancer is a heterogeneous disease; different pathological subtypes of breast cancer have distinct clinico-morphological features that make their detection and treatment challenging and influence survival of the patients (7–11). Some epidemiological risk factors for breast cancer, such as age, menopausal status, body mass index (BMI) after menopause, age at birth of first child, past use of postmenopausal hormones (PMHs), and alcohol consumption, have shown associations only with certain tumor subtypes, suggesting etiologic heterogeneity (12–15). It is poorly understood whether breast density differentially affects the risk of certain pathological subtypes of breast cancer.

To further address this issue, we analyzed prospective data in postmenopausal women from the Nurses' Health Study to determine if there are differences in the association between breast

CONTEXT AND CAVEATS

Prior knowledge

Women with higher mammographic breast density are at increased risk of breast cancer. However, it is not clear whether the risk varies by certain pathological subtypes of tumors.

Study design

A prospective nested case–control study design within the Nurses' Health Study cohort to analyze postmenopausal women for associations of breast density with breast cancer risk according to tumor subtypes based on invasiveness (in situ or invasive), histological type (ductal or lobular), size (≤2 or >2 cm), grade (1, 2, or 3), receptor status (estrogen receptor, progesterone receptor , and HER2), and involvement of lymph nodes (none or any).

Contribution

Women with higher breast density (≥50%) showed a 3.39-fold increase in breast cancer risk compared with women with lower breast density (<10%). The association between breast density and breast cancer risk was stronger for aggressive tumor characteristics such as higher grade, estrogen receptor–negative status, and larger (>2 cm) size.

Implication

Identification of subtype-specific breast cancer risk factors may help in developing new prevention strategies.

Limitations

The results are restricted to postmenopausal women and do not apply to premenopausal women. Associations between breast density and breast cancer risk by combined receptor status were not examined because of insufficient statistical power.

From the Editors

density and subsequent risk of breast cancer according to the tumor's invasiveness, histological type, grade, size, involvement of lymph nodes, and the status of estrogen receptor (ER), progesterone receptor (PR), and HER2.

Participants and Methods

The Nurses' Health Study is a prospective cohort that was established in 1976 and follows 121 701 registered female nurses in the United States, aged 30–55 years at enrollment. After initial questionnaire administration, the information on breast health risk factors (BMI, reproductive history, age at menopause, PMH use, smoking, and alcohol use) and any diagnoses of cancer or other diseases was updated biennially. More detailed description of the cohort has been published elsewhere (3,12,16).

Breast cancer cases were confirmed through medical record review by trained personnel. Information on tumor's invasiveness, histology, grade, nodal involvement, tumor size, and ER, PR, and HER2 status was obtained from pathology reports and medical records. For breast cancers with missing receptor data from pathology reports, the receptor status was obtained from immunohistochemical staining performed on paraffin sections of the tumor tissue microarray (TMA) according to a standard protocol (17). For ER and PR, positivity was defined as greater than 10% of tumor cell nuclei staining (17). Moderate (2+) or strong (3+) membrane staining for HER2 in more than 10% of the tumor cells was used as the cutoff to determine HER2 positivity of the tumor (17).

A nested case–control approach was originally used as an efficient design to examine the association between endogenous hormones, breast density, and breast cancer risk (3). We made use of this study to examine the association between breast density and tumor characteristics. Using incidence density sampling, women who did not have any type of cancer at the time of the case subjects' cancer diagnosis (control subjects) were matched 1 : 1 (if women were pre- or postmenopausal and were taking hormones at the time of blood collection) or 1 : 2 (if women were postmenopausal and were not taking hormones at the time of blood collection) with women diagnosed with in situ or invasive breast cancer (case subjects) during the follow-up period from time of blood collection between June 1, 1989, and June 30, 2004 (18). Because the original study was designed to evaluate associations between circulating biomarkers and risk of breast cancer, the case subjects were matched with control subjects on the following variables: age, menopausal status, PMH use (current vs not current) at blood collection, and day and time of blood collection. Selection of case subjects and control subjects occurred on an ongoing basis every 2 years. Women with any type of cancer (other than nonmelanoma skin cancer) at the time of the selection were excluded from this study population.

We attempted to obtain mammograms closest to the time of blood collection from 1612 eligible case subjects and 2857 eligible control subjects. Of those who were eligible, 1504 (93%) case subjects and 2512 (88%) control subjects gave written consent to obtain their mammograms. Of all consenting women, 1446 (96%) case subjects and 2406 (96%) control subjects received mammograms, and usable mammograms were obtained from 1409 (97%) case subjects and 2371 (99%) control subjects. From these 1409 case subjects, only those with the date of the mammogram before the date of diagnosis or in the same month as the date of diagnosis were retained in this study (1305 case subjects, 93%). Nine control subjects with inconsistent data on their menopausal status were excluded. The final study population included 1305 case subjects (87% of 1504 women giving consent) and 2362 matched control subjects (94% of 2512 women giving consent).

Of the 3667 women, 2839 (77%) case subjects and control subjects combined were postmenopausal at the time of both the mammogram and diagnosis (date of diagnosis for case subjects or reference date for control subjects; the diagnosis date for a case subject was the reference date for its matched control subject). A total of 312 (9%) women were premenopausal at both dates, and 515 (14%) women were premenopausal at the time of the mammogram and became postmenopausal before the date of diagnosis or reference date for control subjects; menopausal status at the time of the mammogram was unknown for one woman. Given this distribution, and results from previous studies suggesting possible differences in the association of breast density with pre- and postmenopausal breast cancer (19,20), we restricted our analysis to women who were postmenopausal at the time of both the mammogram and diagnosis (1045 case subjects and 1794 control subjects). Such restriction also controls for potential density changes from the mammogram date to the reference date as a result of menopausal transition (2,21). We further excluded three case subjects

who were ascertained through the National Death Index for whom we did not have medical records or pathology reports. This study was approved by the Committee on the Use of Human Subjects in Research at Brigham and Women's Hospital.

Assessment of Mammographic Breast Density

Screening mammogram before the diagnosis date (for case subjects) or reference date (for matched control subjects) was used for density measurements. The average time between the mammogram date and the date of breast cancer diagnosis was 4.8 years (interquartile range = 2–7 years). The average time between mammogram and the reference date of control subjects was 4.2 years (interquartile range = 1–7 years). To quantify mammographic density, the craniocaudal views of both breasts were digitized at 261 μm per pixel with a Lumisys 85 laser film scanner (Lumisys, Sunnyvale, CA). The Cumulus software (University of Toronto, Toronto, Canada) was used for computer-assisted determination of the percent mammographic density (3,22). During this assessment, the observer was blinded to the participant's case–control status. As reported previously, the measure of mammographic breast density was highly reproducible (within-person intraclass correlation coefficient was 0.93) (3). Because breast densities of the right and left breast for an individual woman are strongly correlated (correlation coefficient = 0.92–0.96 for density estimated from right vs left craniocaudal views) (22), the average percent density of both breasts was used in this analysis.

Covariate Information

Information on breast cancer risk factors was obtained from the biennial questionnaires before the date of the breast cancer diagnosis for case subjects and their matched control subjects. Covariate information on smoking, alcohol use, PMH use, BMI, menopausal status, and family history of breast cancer was obtained from the most recently completed questionnaire available before the reference date. Women were considered to be postmenopausal if they reported: 1) no menstrual periods within the 12 months before blood collection with natural menopause, 2) bilateral oophorectomy or 3) hysterectomy with one or both ovaries retained, and 4) were 54 years or older for ever-smokers or 56 years or older for never-smokers (23,24). Ninety percent of the study participants who had a natural menopause were postmenopausal at these ages. Menopausal status and PMH use at the time of the mammogram were assessed by using data from biennial questionnaires before the date of the mammogram.

Statistical Analysis

We used Wilcoxon–Mann–Whitney test to analyze the difference in breast density distributions in case subjects and control subjects. Distribution of breast density categories among case subjects and control subjects were compared with χ^2 test. We used unconditional logistic regression to analyze the association between breast density and breast cancer risk while adjusting for matching variables and potential confounders. The risk estimates are presented as odds ratios (ORs) and their corresponding 95% confidence intervals (CIs). Given the incidence density sampling and rare nature of breast cancer, the odds ratios approximate the relative risks n this study. Variables that previously showed statistically significant associations with either breast cancer or breast density were considered as potential confounders. We included the following potential confounders in the fully adjusted logistic regression models: age at diagnosis (continuous, years), BMI (continuous, kg/m^2), age at menarche (<12, 12, 13, or >13 years), parity and age at first birth or age at the end of the first pregnancy lasting 6 months or longer were modeled as nulliparous (no children, 1–4 children with age at first birth <25 years, 1–4 children with age at first birth of 25–29 years, 1–4 children with age at first birth of ≥30 years, ≥5 children with age at first birth of <25 years, or ≥5 children with age at first birth of ≥25 years), PMH use (never, ever, or unknown), age at menopause (<46 years, 46 to <50 years, 50 to <55 years, ≥55 years, or unknown), family history of benign breast disease (yes or no), alcohol consumption (0, <5, 5 to <15, or ≥15 g/d), and smoking status (ever vs never). The reduced model included only age and BMI at diagnosis (for case subjects) or reference date (for control subjects) as covariates.

Initially, breast density was categorized into five different groups (<10%, 10%–24%, 25%–49%, 50%–74%, and ≥75%). However, because of a very small number of women in the highest breast density category (≥75%) and similar risk estimates for the two highest breast density categories (50%–74% and ≥75%), the logistic regression analyses presented are those with the highest two breast density categories combined. Missing data for age at menarche (six case subjects and nine control subjects) were substituted with the median age at menarche among the control subjects. Missing data for smoking (two case subjects and eight control subjects) were substituted with ever-smoker, because greater than 50% of the control subjects were ever-smokers. Women with missing alcohol use data (41 case subjects and 62 control subjects), missing age at menopause (19 case subjects and 27 control subjects), and missing PMH use data (34 case subjects and 47 control subjects) were included as a separate "unknown" category in the multivariable logistic regression analysis. In a secondary analysis of association between breast density and breast cancer risk, we excluded women diagnosed with breast cancer within 2 years of their mammogram.

Differences in the association of breast density with pathological subtypes of breast cancer were investigated using polychotomous (multinomial) logistic regression (3,25). The outcome was classified based on the invasiveness of the tumor (invasive or in situ), histological type (ductal or lobular), grade (1, predominantly differentiated; 2, moderately differentiated; and 3 poorly differentiated), tumor size (≤2 or >2 cm), receptor status (ER-positive [ER$^+$] or ER-negative [ER$^-$], PR-positive [PR$^+$] or PR-negative [PR$^-$], and HER2$^+$ or HER2$^-$), and nodal involvement (none or any). We did not analyze the association between breast density and breast cancer risk by combined ER and PR (ER/PR) or ER, PR, and HER2 (ER/PR/HER2) status because the small number of tumors in some subsets did not provide sufficient power to draw meaningful conclusions (ER$^+$/PR$^+$, n = 508 tumors; ER$^+$/ER$^-$, n = 125 tumors; ER$^-$/PR$^+$, n = 22 tumors; ER$^-$/PR$^-$, n = 121 tumors). Each of the analyses (with the exception of the tumor grade) had three endpoints (controls and two breast cancer categories of interest, eg, ER$^+$ or ER$^-$ breast cancer). Analysis by tumor grade had four end points (controls, grade 1, grade 2, and grade 3). Breast tumors with undetermined histology (n = 12 tumors), undetermined invasiveness

of the tumor (n = 3), unknown lymph nodes involvement (n = 221 tumors), tumor grade (n = 225 tumors), tumor size (n = 165 tumors), and borderline or unknown receptor status (n = 225 tumors for ER, n = 227 tumors for PR, and n = 467 tumors for HER2) were excluded from the polychotomous regression analysis. Tumors with both ductal and lobular features were not included in the analysis by tumor histology (n = 40 tumors). To test whether the association differed by tumor characteristic, we used polychotomous logistic regression with endpoints for each tumor category and for no breast cancer. We used a likelihood ratio test to compare a model with separate mammographic density slopes in each case group with a model with a common slope (25). For example, when the likelihood ratio test was performed to compare the association of breast density and breast cancer risk according to ER status, we first allowed the slope for density to vary across three case groups, for example, ER^+ tumors, ER^- tumors, and control subjects. This model was then compared with the model with the common slope in ER^+ tumors, ER^- tumors, and control subjects. For all analyses, the level of statistical significance was assessed at α equal to .05. All tests were two-sided. For all of the presented models, Hosmer–Lemeshow goodness-of-fit test (in overall logistic regression analysis) and deviance and Pearson goodness-of-fit test (for polychotomous models) indicated reasonable model fit ($P > .05$). All analyses except the test of heterogeneity were performed using SAS software (version 9.2, SAS Institute, Cary, NC). The test of heterogeneity from polychotomous logistic regression models was done using STATA version 11.0 (Stata Corp, College Station, TX).

Results

Characteristics of Study Population

In this prospective study of 1042 postmenopausal women (case subjects) who were diagnosed with breast cancer between June 1, 1989, and June 30, 2004, and 1794 matched control subjects, the case subjects had a higher median percent breast density (27.8% vs 20.5%; $P < .001$) and also a higher proportion of women with greater breast density (for density ≥50%, 16.4% vs 9.0%; for density 25%–49%, 39.7% vs 30.6%; $P < .001$) compared with the control subjects (Table 1). Case subjects had a slightly lower parity

Table 1. Characteristics of postmenopausal women in the study by breast cancer case status*

Characteristic	Case subjects (n = 1042)	Control subjects (n = 1794)	P†
Median % mammographic breast density	27.8	20.5	<.001
Mean (SD)			
Age at mammogram, y	60.2 (6.6)	60.7 (6.7)	.08
Age at menarche, y	12.5 (1.6)	12.6 (1.4)	.41
Age at natural menopause, y	49.9 (3.9)	49.8 (4.1)	.87
BMI at diagnosis or reference date, kg/m^2	26.4 (4.9)	26.4 (5.0)	.92
Alcohol use at diagnosis or reference date, g/d	5.6 (9.5)	5.3 (9.0)	.42
Frequency, No. (%)			
Categorical breast density			<.001
<10%	155 (14.9)	435 (24.3)	
10%–24%	302 (29.0)	650 (36.2)	
25%–49%	414 (39.7)	549 (30.6)	
50%–74%	155 (14.9)	143 (8.0)	
≥75%	16 (1.5)	17 (1.0)	
Parity and age at first child's birth‡			.08
Nulliparous	83 (8.1)	103 (5.8)	
1–4 children, age at first birth <25 y	368 (35.9)	663 (37.2)	
1–4 children, age at first birth 25–29 y	323 (31.5)	541 (30.3)	
1–4 children, age at first birth ≥30 y	96 (9.4)	159 (8.9)	
≥5 children, age at first birth <25 y	93 (9.1)	205 (11.5)	
≥5 children, age at first birth ≥25 y	62 (6.1)	112 (6.3)	
PMH use			<.001
Never used hormones	215 (20.6)	489 (27.3)	
Ever used hormones	793 (76.1)	1258 (70.1)	
Unknown status of hormone use	34 (3.3)	47 (2.6)	
Family history of breast cancer§	203 (19.5)	260 (14.5)	<.001
Benign breast disease	619 (59.4)	903 (50.3)	<.001
Smoking status (ever)	573 (55.0)	928 (51.7)	.09

* Case subjects and control subjects were included from the Nurses' Health Study. A nested case–control study was designed to determine if there are differences in the association between breast density and subsequent risk of breast cancer according to the tumor's invasiveness, histological type, grade, size, involvement of lymph nodes, and the status of estrogen receptor, progesterone receptor, and HER2. Using incidence density sampling, women who did not have breast cancer at the time of the case subjects' cancer diagnosis (control subjects) were matched 1 : 1 or 1 : 2 with women diagnosed with in situ or invasive breast cancer (case subjects) during the follow-up period between June 1, 1989, and June 30, 2004. Women with any type of cancer (other than nonmelanoma skin cancer) at the time of the selection were excluded from this study population.BMI = body mass index; PMH = postmenopausal hormone.

† *P* values were calculated using Wilcoxon–Mann–Whitney test for breast density, two-sample Student *t* test for continuous variables, and χ^2 test for categorical variables. All tests were two-sided.

‡ Data was missing for 28 women (17 case subjects and 11 control subjects).

§ First-degree relative with breast cancer diagnosis.

(mean number of children, 3.0 vs 3.2; $P < .01$), but there was no statistically significant difference in the mean age at first birth (25.3 vs 25.1 years; $P > .05$) compared with the control subjects. Among case subjects, there was a statistically significantly larger proportion of women who have had used PMH sometime before the date of diagnosis (76.1% vs 70.1%; $P <. 001$) compared with control subjects. Case subjects were more likely to have a family history of breast cancer (19.5% vs 14.5%; $P < .001$) and were more likely to report a benign breast disease (59.4% vs 50.3%; $P < .001$) compared with the control subjects. Case subjects and control subjects did not differ with respect to age, BMI, age at menarche, age at natural menopause, consumption of alcohol, and smoking status.

Association Between Breast Density and Breast Cancer Risk

In the multivariable analysis, the risk of breast cancer statistically significantly increased by 3.39-fold in women with 50% or greater breast density compared with women with 10% or less breast density (≥50% vs <10%, OR = 3.39, 95% CI = 2.46 to 4.68, $P_{trend} < .001$) (Table 2). Compared with the reduced logistic regression model, there was a lower risk of breast cancer associated with breast density in the fully adjusted model (for density ≥50% vs <10%, reduced model, OR = 3.94, 95% CI = 2.89 to 5.36, and fully adjusted model, OR = 3.39, 95% CI = 2.46 to 4.68; for density 25%–49% vs <10%, reduced model, OR = 2.59, 95% CI = 2.04 to 3.31, and fully adjusted model, OR = 2.39, 95% CI = 1.86 to 3.06), although the association remained statistically significant in the fully adjusted model (Table 2). Consistent with previous studies from this cohort (3), the association between breast density and breast cancer risk was similar in a secondary analysis excluding women diagnosed with breast cancer within 2 years of their mammogram (data not shown).

Association Between Breast Density and Breast Cancer Risk According to Tumor Characteristics

Breast cancer cases with information on certain tumor characteristics and all covariates that were retained in the analysis included 185 (18.1%) in situ and 837 (81.9%) invasive cancers. Among breast tumors with known histology, 143 (14.9%) were lobular and 819 (85.1%) were ductal tumors (Table 3). In a polychotomous logistic regression analysis comparing risk across categories of breast cancer according to tumor invasiveness, mammographic breast density was positively associated with both in situ (for density ≥50% vs <10%, OR = 6.58, 95% CI = 3.47 to 12.48; for density 25%–49% vs <10%, OR = 3.67, 95% CI = 2.11 to 6.37; for density 10%–24% vs <10%, OR = 1.75, 95% CI = 1.01 to 3.05) and invasive breast cancer (for density ≥50% vs <10%, OR = 3.00, 95% CI = 2.13 to 4.23; for density 25%–49% vs <10%, OR = 2.24, 95% CI = 1.71 to 2.92; for density 10%–24% vs <10%, OR = 1.33, 95% CI = 1.03 to 1.72) (Table 3), but the association with in situ breast cancer was stronger ($P_{heterogeneity} < .01$). The risk of both ductal and lobular breast cancer increased in denser breasts (≥10%); the subset-specific associations were similar ($P_{heterogeneity} = .24$) (Table 4).

Among 614 invasive breast tumors with known histological grade, 170 (27.7%) tumors were well differentiated (grade 1), 281 (45.8%) tumors were moderately differentiated (grade 2), and 163 (26.5%) tumors were poorly differentiated (grade 3). Fifty percent or greater breast density was associated with an increase in breast cancer risk in grade 2 and 3 tumors compared with less than 10% density, and risk was even higher in grade 3 tumors compared with grade 2 tumors (density ≥50% vs <10%, for grade 3 tumors, OR = 5.28, 95% CI = 2.77 to 10.07; for grade 2 tumors, OR = 3.04, 95% CI = 1.83 to 5.05; $P_{heterogeneity} = .02$) (Table 3).

The majority of the case subjects with known tumor size were diagnosed with tumors of 2 cm or less in size (n = 634 tumors). At the time of diagnosis, 631 (78.2%) of 807 case subjects with known

Table 2. Association of categorical breast density with breast cancer*

	Reduced model†		Fully adjusted model‡	
	1042 case subjects/1791 control subjects§		1025 case subjects/1780 control subjects‖	
Breast density category	No. case subjects/control subjects	OR (95% CI)	No. case subjects/control subjects	OR (95% CI)
<10%	155/434	1.00 (referent)	151/430	1.00 (referent)
10%–24% vs <10%	302/648	1.43 (1.13 to 1.81)	299/643	1.38 (1.08 to 1.75)
25%–49% vs <10%	414/549	2.59 (2.04 to 3.31)	407/548	2.39 (1.86 to 3.06)
≥50% vs <10%	171/160	3.94 (2.89 to 5.36)	168/159	3.39 (2.46 to 4.68)
		$P_{trend} < .001$¶		$P_{trend} < .001$¶

* CI = confidence interval; OR = odds ratio

† Multivariable logistic regression analysis adjusted for age and body mass index (BMI) at diagnosis (for case subjects) or reference date (for control subjects).

‡ Multivariable logistic regression analysis adjusted for age (continuous), BMI (continuous), age at menarche (<12, 12, 13, or >13 years), parity and age at first birth (nulliparous, 1–4 children with age at first birth <25 years, 1–4 children with age at first birth of 25–29 years, 1–4 children with age at first birth of ≥30 years, ≥5 children with age at first birth of <25 years, or ≥5 children with age at first birth of ≥25 years), age at menopause (<46, 46 to <50, 50 to <55, ≥55 years, unknown), postmenopausal hormone use (never, ever, or unknown), family history (yes or no), self-reported history of benign breast disease (yes or no), alcohol consumption (0, <5, 5 to <15, or ≥15 g/d), and smoking status (ever vs never).

§ Three control subjects did not have BMI data.

‖ Seventeen case subjects 11 control subjects did not have parity data.

¶ *P* values were calculated using a two-sided test for trend.

Table 3. Association of categorical breast density with morphological subtypes of breast cancer*

Morphology	No. of case subjects/control subjects	OR (95% CI)	$P_{heterogeneity}$†
Invasiveness			<.01
In situ breast cancer	185/1780		
<10%	20/430	1.00 (referent)	
10%–24% vs <10%	45/623	1.75 (1.01 to 3.05)	
25%–49% vs <10%	78/548	3.67 (2.11 to 6.37)	
≥50% vs <10%	40/159	6.58 (3.47 to 12.48)	
Invasive breast cancer	837/1780		
<10%	129/430	1.00 (referent)	
10%–24% vs <10%	251/643	1.33(1.03 to 1.72)	
25%–49% vs <10%	329/548	2.24 (1.71 to 2.92)	
≥50% vs <10%	128/159	3.00 (2.13 to 4.23)	
Histology‡			.24
Lobular breast cancer	143/1780		
<10%	16/430	1.00 (referent)	
10%–24% vs <10%	47/643	1.87 (1.03 to 3.41)	
25%–49% vs <10%	50/548	2.30 (1.23 to 4.28)	
≥50% vs <10%	30/159	4.36 (2.14 to 8.86)	
Ductal breast cancer	819/1780		
<10%	122/430	1.00 (referent)	
10%–24% vs <10%	241/643	1.40 (1.08 to 1.81)	
25%–49% vs <10%	331/548	2.47 (1.89 to 3.24)	
≥50% vs <10%	125/159	3.26 (2.30 to 4.61)	
Histological grade§			.02
Grade 1	170/1780		
<10%	27/430	1.00 (referent)	
10%–24% vs <10%	63/643	1.39 (0.86 to 2.26)	
25%–49% vs <10%	67/548	1.88 (1.13 to 3.13)	
≥50% vs <10%	13/159	1.25 (0.60 to 2.64)	
Grade 2	281/1754		
<10%	45/430	1.00 (referent)	
10%–24% vs <10%	78/643	1. 19 (0.80 to 1.78)	
25%–49% vs <10%	112/548	2.11 (1.40 to 3.17)	
≥50% vs <10%	46/159	3.04 (1.83 to 5.05)	
Grade 3	163/1754		
<10%	25/430	1.00 (referent)	
10%–24% vs <10%	45/643	1.44 (0.86 to 2.43)	
25%–49% vs <10%	64/548	2.95 (1.74 to 5.02)	
≥50% vs <10%	29/159	5.28 (2.77 to 10.07)	
Tumor size			<.01
≤2 cm	634/1780		
<10%	105/430	1.00 (referent)	
10%–24% vs <10%	197/643	1.26 (0.95 to 1.66)	
25%–49% vs <10%	250/548	2.04 (1.53 to 2.72)	
≥50% vs <10%	82/159	2.30 (1.57 to 3.37)	
>2 cm	178/1780		
<10%	21/430	1.00 (referent)	
10%–24% vs <10%	50/643	1.82 (1.06 to 3.12)	
25%–49% vs <10%	68/548	3.23 (1.86 to 5.59)	
≥50% vs <10%	39/159	6.27 (3.33 to 11.80)	
Involvement of lymph nodes			.50
Node-positive breast cancer	176/1780		
<10%	26/430	1.00 (referent)	
10%–24% vs <10%	45/643	1.23 (0.74 to 2.06)	
25%–49% vs <10%	78/548	2.76 (1.66 to 4.58)	
≥50% vs <10%	27/159	3.15 (1.67 to 5.97)	
Node-negative breast cancer	631/1780		
<10%	97/430	1.00 (referent)	
10%–24% vs <10%	194/643	1.36 (1.03 to 1.81)	
25%–49% vs <10%	240/548	2.16 (1.61 to 2.90)	
≥50% vs <10%	100/159	3.13 (2.16 to 4.55)	
ER status			.04
ER^+ tumor	645/1780		
<10%	106/430	1.00 (referent)	

(Table continues)

Table 3 (Continued).

Morphology	No. of case subjects/control subjects	OR (95% CI)	$P_{heterogeneity}$†
10%–24% vs <10%	196/643	1.33 (1.00 to 1.75)	
25%–49% vs <10%	254/548	2.33 (1.75 to 3.10)	
≥50% vs <10%	89/159	2.94 (2.02 to 4.27)	
ER^- tumor	157/1780		
<10%	18/430	1.00 (referent)	
10%–24% vs <10%	44/643	1.68 (0.95 to 2.99)	
25%–49% vs <10%	65/548	3.04 (1.70 to 5.41)	
≥50% vs <10%	30/159	4.78 (2.42 to 9.42)	
PR status			.87
PR^+ tumor	551/1780		
<10%	90/430	1.00 (referent)	
10%–24% vs <10%	157/643	1.26 (0.93 to 1.70)	
25%–49% vs <10%	223/548	2.45 (1.80 to 3.33)	
≥50% vs <10%	81/159	3.21 (2.17 to 4.77)	
PR^- tumor	249/1780		
<10%	32/430	1.00 (referent)	
10%–24% vs <10%	87/643	1.82 (1.18 to 2.81)	
25%–49% vs <10%	90/548	2.36 (1.49 to 3.72)	
≥50% vs <10%	40/159	3.68 (2.12 to 6.37)	
HER2 status			.40
$HER2^+$ tumor	140/1780		
<10%	20/430	1.00 (referent)	
10%–24% vs <10%	45/643	1.64 (0.94 to 2.88)	
25%–49% vs <10%	63/548	3.24 (1.82 to 5.76)	
≥50% vs <10%	12/159	2.32 (1.03 to 5.22)	
$HER2^-$ tumor	423/1780		
<10%	66/430	1.00 (referent)	
10%–24% vs <10%	131/643	1.32 (0.95 to 1.84)	
25%–49% vs <10%	162/548	2.08 (1.47 to 2.95)	
≥50% vs <10%	64/159	2.84 (1.83 to 4.40)	

* Polychotomous multivariable logistic regression model adjusted for age (continuous), body mass index (BMI; continuous), age at menarche (<12, 12, 13, or >13 years), parity and age at first birth (nulliparous, 1–4 children with age at first birth <25 years, 1–4 children with age at first birth of 25–29 years, 1–4 children with age at first birth of ≥30 years, ≥5 children with age at first birth of <25 years, or ≥5 children with age at first birth of ≥25 years), age at menopause (<46, 46 to <50, 50 to <55, ≥55, unknown), postmenopausal hormone use (never, ever, or unknown), family history (yes or no), self-reported history of benign breast disease (yes or no), alcohol consumption (0, <5, 5 to <15, or ≥15 g/d), and smoking status (ever vs never). CI = confidence interval; OR = odds ratio.

† *P* values were calculated using a two-sided likelihood ratio test.

‡ Includes both in situ and invasive carcinomas.

§ Grade 1 is predominantly differentiated, grade 2 is moderately differentiated, and grade 3 is poorly differentiated invasive breast cancer.

nodal status showed no nodal involvement and 176 (21.8%) of 807 case subjects showed involvement of one or more lymph nodes. Greater density was associated with an increase in breast cancer risk regardless of the tumor size or nodal involvement (Table 3). The association of breast density with breast cancer risk was stronger for large tumors (density ≥50% vs <10%, for tumors >2 cm, OR = 6.27, 95% CI = 3.33 to 11.80; for tumors ≤2 cm: OR = 2.30, 95% CI = 1.57 to 3.37; $P_{heterogeneity} < .01$).

Among tumors with known receptor status, 645 (80.4%) of 802 tumors were ER^+, 551 (68.9%) of 800 tumors were PR^+, and 140 (24.9%) of 563 tumors were $HER2^+$. Fifty percent or greater breast density was positively associated with breast cancer risk for both ER^+ and ER^- tumors compared with less than 10% density, but the risk was higher in ER^- tumors (density ≥50% vs <10%, for ER^- tumors, OR = 4.78, 95% CI = 2.42 to 9.42; for ER^+ tumors, OR = 2.94, 95% CI = 2.02 to 4.27; $P_{heterogeneity} = .04$). A positive association between breast density and breast cancer risk was found for both PR^+ and PR^- tumors as well as for $HER2^+$ and $HER2^-$ cancers, but the subtype-specific associations did not differ by PR and HER2 status (density ≥50% vs <10%, for PR^- tumors, OR = 3.68, 95% CI = 2.12 to 6.37; for PR^+ tumors, OR = 3.21, 95% CI = 2.17 to 4.77; $P_{heterogeneity} = .87$; for $HER2^-$ tumors, OR = 2.84, 95% CI = 1.83 to 4.40; for $HER2^+$ tumors, OR = 2.32, 95% CI = 1.03 to 5.22; $P_{heterogeneity} = .40$). Among women with receptor status information, ER and PR receptor status was available from the pathology reports for 97% and 94% of the tumors, respectively. When we excluded the small number of tumors with hormone receptor status information from TMA data, the results were similar, but the difference in associations by ER status was only marginally statistically significant ($P_{heterogeneity} = .06$). Among breast cancer cases with available HER2 data (55% of all cases), 42% were extracted from pathology reports and 58% were available from TMA data. For breast tumors with HER2 status from both sources (n = 45 tumors), we observed a fair concordance of 44% between HER2 status from pathology report and TMA and conducted a secondary analysis excluding tumors with discordant HER2 status to determine if the associations differed. The results of the original and secondary analyses were identical (data not shown).

Table 4. Summary of the studies on association between breast density and breast cancer subtypes*

Study design, first author, year (reference)	No. of case subjects and/or No. of control subjects	Classification of breast density	Findings
Case only, Hinton, 1985 (26)	337 invasive breast cancer case subjects	Wolfe classification, N, P, DY	Statistically significant positive association between density and ER^+ breast cancer, relative to ER^- breast cancer.
Case only, Roubidoux, 2004 (27)	121 invasive or in situ breast cancer case subjects	BI-RADS I (referent), II, III, IV	Statistically significant positive association between density and tumor size, and grade and ER^- status. However, the association between density and ER^- cancer disappeared after adjustment for age.
Case only, Aiello, 2005 (28)	546 invasive breast cancer case subjects	BI-RADS combined as fatty (I and II, referent) and dense (III and IV)	Statistically significant positive association between density and tumor size and node-positivity among screen-detected cancers only. Statistically significant inverse association of density with tumor grade among interval cancer cases only. Non-statistically significant difference between the associations between density and ER or PR status.
Case only, Fasching, 2006 (29)	434 invasive or in situ breast cancer cases	BI-RADS combined as I and II, and III and IV	Statistically significant inverse association of breast density with tumor size; no associations with ER and PR status, histological type, nodal involvement, and grade.
Case only, Ghosh, 2008 (30)	286 invasive or in situ breast cancer cases	Continuous percent breast density	No statistically significant association of density with tumor size, histological type, ER, or PR status. Suggestive inverse association between tumor grade and percent density. Statistically significant positive associations of density with ER and PR status were seen with percent density only among 97 symptomatic women.
Case only, Yang, 2008 (31)	198 invasive or in situ breast cancer cases	BI-RADS	Non-statistically significant difference in associations between breast density and breast cancer across triple-negative, $HER2^+$, and ER^+ cancers.
Case only, Gierach, 2010 (32)	227 invasive breast cancers	Continuous percent breast density	Non-statistically significant differences in the associations between percent density and luminal A, luminal B, basal-like, and unclassified tumors.
Nested case–control, Sala, 2000 (33)	875 invasive or in situ breast cancer case subjects/2601 control subjects	Wolfe classification, N1 (referent), P1, P2, DY	Statistically significant positive association of density with larger tumor size, node-positivity, and higher tumor grade
Nested case–control, Gill, 2006 (34)	483 invasive breast cancer case subjects,119 DCIS case subjects/667 control subjects	Four categories: <10% (referent), 10%–24%, 25%–49%, ≥50%	Statistically significant positive association of breast density with invasive breast cancer and DCIS. A lower risk for DCIS than for invasive cancer given the same level of percentage density; the difference in associations for DCIS vs invasive tumors, however, was not statistically significant.
Case–control, Ding, 2010 (35)	370 invasive breast cancer case subjects/1904 control subjects	0–9% (referent), 10%–24%, 25%–49%, and 50%–100%	Statistically significant positive association of breast density with cancer risk with both ER^+ and ER^- tumors, grades 1 and 2, tumor size larger than 1.1 cm, both node positive and negative. Significantly stronger association with ER^+ and ER^- cancers, but no differences across the other histomorphological subtypes.
Nested case–control, Conroy, 2010 (36)	607 invasive or in situ breast cancer case subjects/667 control subjects	10% increments of continuous percent breast density	No statistically significant association between density and ER and PR receptor status.
Nested case–control, Yaghjyan.	1042 invasive or in situ breast cancer case subjects/1794 control subjects	<10% (referent), 10%–24%, 25%–49%, ≥%50	Statistically significant stronger associations were found for in situ tumors, high-grade carcinomas, larger tumors, and ER^- breast cancers. There were non-statistically significant differences in associations by tumor histology, nodal involvement, and PR and HER2 status.
Prospective, Ziv, 2004 (37)	44,811 women/701 invasive breast cancer case subjects	BI-RADS, I, II (referent), III, IV	Non-statistically significant differences in the association between density and ER^+ and ER^- cancers.
Prospective, Reinier, 2007 (38)	61,844 women/1,191 breastcancer case subjects	BI-RADS I (referent), II, III, IV	Non-statistically significant differences in the association between density and invasive or in situ cancers.
Prospective, Phipps, 2010 (9)	1,211,238 women/19,119 invasive breast cancer case subjects	BI-RADS I, II (referent), III, IV	No statistically significant association of density with histology of the tumor (lobular, ductal, or mixed ductal-lobular)

* Published studies were identified using the PubMed Central (US National Institutes of Health), BioMed Central, Embase, and Scopus literature search conducted at the Washington University, St Louis, MO. Articles were searched using the terms "breast density and breast tumor characteristics," "breast density and breast cancer subtypes," followed by combination of "breast density" with specific tumor characteristic or specific tumor subtype, for example, "breast density and estrogen receptor status," "breast density and lobular breast cancer," etc. Bibliography of the articles found through electronic searches helped to identify additional relevant references that were then hand searched. BI-RADS = Breast Imaging-Reporting and Data System (39) (BI-RADS I = density <25%, BI-RADS II = density 25–50%, BI-RADS III = density 51–75%, BI-RADS IV = density >75%); DCIS = ductal carcinoma in situ; DY = diffuse or nodular densities; ER = estrogen receptor; N1 = mostly fatty breasts with no ducts visible; PR = progesterone receptor; P1 = fatty breasts with predominant ducts in anterior portion up to one-fourth of the breast; P2 = breasts with lobular involution and prominent duct pattern of moderate to severe degree occupying more than one-fourth of the breast volume.

Discussion

In this prospective study, we investigated the association of breast density with breast cancer risk according to tumor characteristics among 1042 postmenopausal women who were diagnosed with breast cancer between June 1, 1989, and June 30, 2004, and 1794 matched control subjects. Women with higher breast density (≥50%) showed 3.39-fold increased risk of breast cancer compared with women with lower breast density (<10%). The strength of the association between breast density and breast cancer risk varied by invasiveness, histological grade, tumor size, and ER status of the tumor. A stronger association was noted for in situ breast cancers, poorly differentiated invasive breast cancer, larger (>2 cm) tumors, and ER^- breast cancers. We did not find differences in the associations of breast density with breast cancer risk by histological type, nodal involvement, and PR and HER2 status.

We report for the first time a stronger association between breast density and ER^- breast tumors compared with ER^+ tumors. Findings on the association of breast density with receptor status of the tumor from previous studies are inconsistent (26–31,35,37) (see Table 4). In one study (27), women with greater density were reported to have larger proportion of ER^- tumors; however, the association disappeared after adjustment for age. Although some other recent studies observed that women with greater breast density had an increased risk of ER^+, ER^+/PR^+, but not ER^-/PR^- breast cancer (35,36), others did not (28,29,31,32,37,40,41). However, many of these studies were underpowered to investigate the differences in the association of breast density with the risk of breast cancer by ER status because of a smaller size as compared with our analysis. Higher levels of estradiol have been reported in the tissue from ER^+ tumors compared with ER^- tumors (42–44). Our findings suggest that regulatory factors other than estrogen may play an important role in the origins of ER^- tumors in denser breasts. Consistent with other studies, we did not see any differences in the associations between breast density and breast cancer risk by PR or HER2 status (28,31,32,37,40). Breast cancer is a heterogeneous disease and ER^+ and ER^- tumors are believed to be etiologically different. Previous studies have found an association of hormone-related breast cancer risk factors with ER^+ breast cancer subtype, but failed to find a similar association with ER^- breast cancers. Identifying the risk factors specific to ER^- tumors would help researchers understand the etiology of ER^- breast cancer and develop subtype-specific risk prediction models.

Inconsistent data exist on the association between mammographic breast density and breast cancer risk according to different tumor characteristics (see Table 4). A recent study found an increased risk of both lobular and ductal carcinomas with increase in breast density, but there was no difference in the strength of the association across the histological subtypes (9). Positive associations of breast density with tumor size, involvement of axillary nodes, and higher tumor grade have been reported in some (28,33,35), but not all studies (30). The results from our study indicate a stronger association of breast density with more aggressive subtypes of breast cancer, including tumors that are larger in size and of high grade. Previous studies report inconsistent findings when examining the association between breast density and these tumor characteristics (27,28,30,33,35,36,41) (see Table 4). Some of these differences may be explained by differences in study design, sample size (range in the number of breast cancer cases 286–19 119), and different definitions of breast density. If breast density is associated with more aggressive breast cancer phenotypes, it may suggest that the breast tissue environment underlying breast density allows for more growth and increased proliferation, than in more fatty breasts. In addition, because mammographic sensitivity decreases with increasing breast density, aggressive cancers occurring in denser breasts go undetected for longer periods permitting these already rapidly proliferating tumors to be larger at presentation (45–48).

We found that breast density was more strongly associated with in situ breast cancer than invasive disease. This is in slight contrast with other studies that found similar associations for in situ and invasive tumors (34,38). It is possible that our findings are the result of chance. The larger of the two studies (38) had fewer in situ and invasive postmenopausal cancer case subjects than our study; the other study (34) had reported the results for both pre- and postmenopausal women combined. Another possible explanation for the stronger association with in situ disease may be a difference in breast cancer detection rate in women with denser breasts. It is well known that the sensitivity of mammography is lower for women with dense breasts, and women with dense breasts are more likely to have an abnormal mammogram and undergo biopsies than women with fattier breasts (46,47,49,50). Therefore, it is possible that the diagnosis of in situ carcinomas for many of these women is a serendipitous finding. In addition, the radiographic appearance of in situ tumors on mammogram results in higher sensitivity of screening mammography for detection of ductal carcinoma in situ compared with invasive cancer in both pre- and postmenopausal women (51,52).

This study has a few limitations. The current analysis was restricted to women who were postmenopausal at the time of both mammogram and diagnosis, which constitutes the majority of the population assembled for the nested case–control study (77%). Our findings are thus limited to postmenopausal breast cancer subtypes and do not necessarily apply to premenopausal breast cancer. We did not investigate the associations between breast density and breast cancer risk by combined ER/PR or ER/PR/HER2 status because the small numbers of tumors in the subsets did not provide sufficient statistical power to draw meaningful conclusions.

Identification of the subtype-specific breast cancer risk factors would help to understand breast cancer etiology, develop subtype-specific risk prediction models, and eventually, to suggest novel prevention strategies. To our knowledge, this is by far the largest study with respect to the number of breast cancer cases that investigated the association of quantitative breast density with several breast cancer characteristics, including a tumor's invasiveness, histology, grade, size, receptors status, and nodal involvement in the same population of women. The analysis used data from the Nurses' Health Study, an established cohort with more than 30 years of follow-up, ascertainment of disease status, and comprehensive information on breast cancer risk factors, tumor characteristics, and breast density.

In conclusion, we investigated the association of mammographic breast density with subsequent breast tumor characteristics

in postmenopausal women. Our results suggest that breast density influences the risk of breast cancer subtypes by potentially different mechanisms. Further studies are warranted to explain underlying biological processes and elucidate the possible pathways from high breast density to the specific subtypes of breast carcinomas.

References

1. Boyd NF, Rommens JM, Vogt K, et al. Mammographic breast density as an intermediate phenotype for breast cancer. *Lancet Oncol.* 2005;6(10):798–808.
2. Ginsburg OM, Martin LJ, Boyd NF. Mammographic density, lobular involution, and risk of breast cancer. *Br J Cancer.* 2008;99(9):1369–1374.
3. Tamimi RM, Byrne C, Colditz GA, Hankinson SE. Endogenous hormone levels, mammographic density, and subsequent risk of breast cancer in postmenopausal women. *J Natl Cancer Inst.* 2007;99(15):1178–1187.
4. Harvey JA, Bovbjerg VE. Quantitative assessment of mammographic breast density: relationship with breast cancer risk. *Radiology.* 2004;230(1):29–41.
5. Boyd NF, Byng JW, Jong RA, et al. Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. *J Natl Cancer Inst.* 1995;87(9):670–675.
6. Byrne C, Schairer C, Wolfe J, et al. Mammographic features and breast cancer risk: effects with time, age, and menopause status. *J Natl Cancer Inst.* 1995;87(21):1622–1629.
7. Arpino G, Bardou VJ, Clark GM, Elledge RM. Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome. *Breast Cancer Res.* 2004;6(3):R149–R156.
8. Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *JAMA.* 2006;295(21):2492–2502.
9. Phipps AI, Li CI, Kerlikowske K, Barlow WE, Buist DS. Risk factors for ductal, lobular, and mixed ductal-lobular breast cancer in a screening population. *Cancer Epidemiol Biomarkers Prev.* 2010;19(6):1643–1654.
10. Putti TC, El-Rehim DM, Rakha EA, et al. Estrogen receptor-negative breast carcinomas: a review of morphology and immunophenotypical analysis. *Mod Pathol.* 2005;18(1):26–35.
11. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci U S A.* 2001;98(19):10869–10874.
12. Colditz GA, Rosner BA, Chen WY, Holmes MD, Hankinson SE. Risk factors for breast cancer according to estrogen and progesterone receptor status. *J Natl Cancer Inst.* 2004;96(3):218–228.
13. Kwan M, Kushi L, Weltzien E, et al. Epidemiology of breast cancer subtypes in two prospective cohort studies of breast cancer survivors. *Breast Cancer Res.* 2009;11(3):R31.
14. Rusiecki JA, Holford TR, Zahm SH, Zheng T. Breast cancer risk factors according to joint estrogen receptor and progesterone receptor status. *Cancer Detect Prev.* 2005;29(5):419–426.
15. Yang XR, Sherman ME, Rimm DL, et al. Differences in risk factors for breast cancer molecular subtypes in a population-based study. *Cancer Epidemiol Biomarkers Prev.* 2007;16(3):439–443.
16. Colditz GA, Hankinson SE. The Nurses' Health Study: lifestyle and health among women. *Nat Rev Cancer.* 2005;5(5):388–396.
17. Tamimi RM, Baer HJ, Marotti J, et al. Comparison of molecular phenotypes of ductal carcinoma in situ and invasive breast cancer. *Breast Cancer Res.* 2008;10(4):R67.
18. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology.* Vol X. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
19. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev.* 2006;15(6):1159–1169.
20. Kerlikowske K, Cook AJ, Buist DS, et al. Breast cancer risk by breast density, menopause, and postmenopausal hormone therapy use. *J Clin Oncol.* 2010;28(24):3830–3837.
21. Ghosh K, Hartmann LC, Reynolds C, et al. Association between mammographic density and age-related lobular involution of the breast. *J Clin Oncol.* 2010;28(13):2207–2212.
22. Byng JW, Boyd NF, Little L, et al. Symmetry of projection in the quantitative analysis of mammographic images. *Eur J Cancer Prev.* 1996;5(5):319–327.
23. Willett W, Stampfer MJ, Bain C, et al. Cigarette smoking, relative weight, and menopause. *Am J Epidemiol.* 1983;117(6):651–658.
24. Stampfer MJ, Willett WC, Colditz GA, et al. A prospective study of postmenopausal estrogen therapy and coronary heart disease. *N Engl J Med.* 1985;313(17):1044–1049.
25. Marshall RJ, Chisholm EM. Hypothesis testing in the polychotomous logistic model with an application to detecting gastrointestinal cancer. *Stat Med.* 1985;4(3):337–344.
26. Hinton CP, Roebuck EJ, Williams MR, et al. Mammographic parenchymal patterns: value as a predictor of hormone dependency and survival in breast cancer. *AJR Am J Roentgenol.* 1985;144(6):1103–1107.
27. Roubidoux MA, Bailey JE, Wray LA, Helvie MA. Invasive cancers detected after breast cancer screening yielded a negative result: relationship of mammographic density to tumor prognostic factors. *Radiology.* 2004;230(1):42–48.
28. Aiello EJ, Buist DS, White E, Porter PL. Association between mammographic breast density and breast cancer tumor characteristics. *Cancer Epidemiol Biomarkers Prev.* 2005;14(3):662–668.
29. Fasching PA, Heusinger K, Loehberg CR, et al. Influence of mammographic density on the diagnostic accuracy of tumor size assessment and association with breast cancer tumor characteristics. *Eur J Radiol.* 2006;60(3):398–404.
30. Ghosh K, Brandt KR, Sellers TA, et al. Association of mammographic density with the pathology of subsequent breast cancer among postmenopausal women. *Cancer Epidemiol Biomarkers Prev.* 2008;17(4):872–879.
31. Yang WT, Dryden M, Broglio K, et al. Mammographic features of triple receptor-negative primary breast cancers in young premenopausal women. *Breast Cancer Res Treat.* 2008;111(3):405–410.
32. Gierach GL, Lissowska J, Garcia-Closas M, et al. Relationship of mammographic density with breast cancer subtypes. in AACR 101st Annual Meeting; 2010. Washington, DC: American Association for Cancer Research.
33. Sala E, Solomon L, Warren R, et al. Size, node status and grade of breast tumours: association with mammographic parenchymal patterns. *Eur Radiol.* 2000;10(1):157–161.
34. Gill JK, Maskarinec G, Pagano I, Kolonel LN. The association of mammographic density with ductal carcinoma in situ of the breast: the multiethnic cohort. *Breast Cancer Res.* 2006;8(3):R30.
35. Ding J, Warren R, Girling A, Thompson D, Easton D. Mammographic density, estrogen receptor status and other breast cancer tumor characteristics. *Breast J.* 2010;16(3):279–289.
36. Conroy SM, Pagano I, Kolonel KM, Maskarinec G. Mammographic density and breast cancer tumor characteristics in the Multiethnic Cohort Study. In AACR 101st Annual Meeting; 2010. Washington, DC: American Association for Cancer Research.
37. Ziv E, Tice J, Smith-Bindman R, et al. Mammographic density and estrogen receptor status of breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2004;13(12):2090–2095.
38. Reinier K, Vacek P, Geller B. Risk factors for breast carcinoma in situ versus invasive breast cancer in a prospective study of pre- and postmenopausal women. *Breast Cancer Res Treat.* 2007;103(3):343–348.
39. D'Orsi CJ, Mendelson EB, Ikeda DM, et al. *Breast Imaging Reporting and Data System: ACR BI-RADS – Breast Imaging Atlas*. Reston, VA: American College of Radiology; 2003.
40. Ma H, Luo J, Press MF, et al. Is there a difference in the association between percent mammographic density and subtypes of breast cancer? Luminal A and triple-negative breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2009;18(2):479–485.
41. Chen JH, Hsu FT, Shih HN, et al. Does breast density show difference in patients with estrogen receptor-positive and estrogen receptor-negative breast cancer measured on MRI? *Ann Oncol.* 2009;20(8):1447–1449.
42. Lønning PE, Helle H, Duong NK, et al. Tissue estradiol is selectively elevated in receptor positive breast cancers while tumour estrone is reduced independent of receptor status. *J Steroid Biochem Mol Biol.* 2009;117(1–3):31–41.

43. van Landeghem AA, Poortman J, Nabuurs M, Thijssen JH. Endogenous concentration and subcellular distribution of estrogens in normal and malignant human breast tissue. *Cancer Res.* 1985;45(6):2900–2906.
44. Vermeulen A, Deslypere JP, Paridaens R, et al. Aromatase, 17 beta-hydroxysteroid dehydrogenase and intratissular sex hormone concentrations in cancerous and normal glandular breast tissue in postmenopausal women. *Eur J Cancer Clin Oncol.* 1986;22(4):515–525.
45. Mandelson MT, Oestreicher N, Porter PL, et al. Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers. *J Natl Cancer Inst.* 2000;92(13):1081–1087.
46. Kolb TM, Lichy J, Newhouse JH. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. *Radiology.* 2002;225(1):165–175.
47. Leconte I, Feger C, Galant C, et al. Mammography and subsequent whole-breast sonography of nonpalpable breast cancers: the importance of radiologic breast density. *AJR Am J Roentgenol.* 2003;180(6):1675–1679.
48. Porter GJR, Evans AJ, Cornford EJ, et al. Influence of mammographic parenchymal pattern in screening-detected and interval invasive breast cancers on pathologic features, mammographic features, and patient survival. *AJR Am J Roentgenol.* 2007;188(3):676–683.
49. Ma L, Fishell E, Wright B, et al. Case-control study of factors associated with failure to detect breast cancer by mammography. *J Natl Cancer Inst.* 1992;84(10):781–785.
50. Bird RE, Wallace TW, Yankaskas BC. Analysis of cancers missed at screening mammography. *Radiology.* 1992;184(3):613–617.
51. Ernster VL, Ballard-Barbash R, Barlow WE, et al. Detection of ductal carcinoma in situ in women undergoing screening mammography. *J Natl Cancer Inst.* 2002;94(20):1546–1554.
52. Houssami N, Abraham LA, Miglioretti DL, et al. Accuracy and outcomes of screening mammography in women with a personal history of early-stage breast cancer. *JAMA.* 2011;305(8):790–799.

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