Published in final edited form as:
Cancer Epidemiol. 2011 October ; 35(5): 448–452. doi:10.1016/j.canep.2010.11.011.

Mammographic Density and Hormone Receptor Expression in Breast Cancer: The Multiethnic Cohort Study

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Abstract

Background—It is unclear whether mammographic breast density, a strong risk factor for breast cancer, predicts subtypes of breast cancer defined by estrogen receptor (ER) and/or progesterone receptor (PR) expression.

Methods—In a nested case-control study, we compared the breast density of 667 controls and 607 breast cancer cases among women of Caucasian, Japanese, and Native Hawaiian ancestry in the Hawaii component of the Multiethnic Cohort study. A reader blinded to disease status performed computer assisted density assessment on prediagnostic mammograms. Receptor status was obtained from the statewide Hawaii Tumor Registry. Tumors were classified into ER+PR+ (n=341), ER−PR− (n=50), ER+PR−/ER−PR+ (n=64), and unstaged/unknown (n=152). Mean density values were computed for women with more than one mammogram. Polytomous logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) while adjusting for confounders.

Results—Mean density was significantly greater for ER+PR+ but not for ER−PR− tumors compared to controls after adjusting for age: 37.3%, 28.9%, versus 29.4%, respectively. The overall ORs per 10% increase in density were similar for ER+PR+ and ER+PR−/ER−PR+ tumors: 1.26 (95% CI 1.17–1.36) and 1.23 (95% CI 1.07–1.42), respectively. However, percent density was not found to be a predictor for ER−PR− tumors (OR 1.00, 95% CI 0.84–1.18). The results did not differ by ethnicity, nor by menopausal status, parity, or HRT use.

Conclusions—Our findings indicate that within a multiethnic population, women with higher breast density have an increased risk for ER+PR+ but not ER−PR− tumors.

Keywords

estrogen receptor; mammographic density; progesterone receptor; tumor characteristics

1. Introduction

The amount of dense breast tissue on a mammogram is a strong predictor of breast cancer risk [1]. Case-control studies have reported a 3- to 4-fold elevated breast cancer risk for

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Conflict of interest

None of the authors have any conflict of interest to disclose.

women with ≥50% area of density than women with <10% [2–3], and the elevated breast cancer risk persists for 10 years after breast density assessment regardless of menopausal status or age [4]. Whether high breast density predicts subtypes of breast cancer as defined by expression of the estrogen receptor (ER) and/or progesterone receptor (PR) is unclear; however, differential risk by receptor status may have important public health implications for breast density as an intermediate marker.

Pathways implicated in breast carcinogenesis include aberrant cell proliferation mediated via ER and PR [5–6]. Receptor positive (ER+PR+) and receptor negative (ER−PR−) tumors may have distinct risk profiles [7], and it is generally accepted that ER+PR+ tumors confer a survival advantage [8]. Breast density is believed to be a biological marker of cumulative exposure to hormones and other growth factors [9] and factors associated with high breast density [10] are also associated with ER+PR+ breast cancers [7]. Epidemiologic studies evaluating breast density in relation to receptor status are limited, and the majority examined ER and PR tumors separately with inconsistent results. Studies have described density to be a risk factor for ER positive but not ER negative tumors [11], or no evidence of a differential association between density and receptor status for ER [12–15] or PR tumors [13–15]. Of these studies, only one study evaluated the joint effects of ER and PR tumors [15] and only two studies included multiethnic populations [12,15].

In a nested case-control study, we compared the mammographic density of 667 controls and 607 breast cancer cases among women of Caucasian, Japanese, and Native Hawaiian ancestry in the Hawaii component of the Multiethnic Cohort study (MEC) [2]. The objective of this study was to examine the association of percent density with subtypes of breast cancer defined by the joint expression of ER and PR. Specifically, we hypothesized that high breast density is a strong predictor for the development of ER+PR+ but not ER−PR− tumors.

2. Materials and Methods

2.1. Study population

The data for this analysis were collected using a nested case-control study [2] within the Hawaii component of the MEC, an ongoing, prospective study of dietary, environmental, and genetic factors in relation to cancer and other chronic diseases [16]. Persons of mixed ancestry were assigned to one ethnic category according to the following priority ranking: Native Hawaiian, Japanese, Caucasian, and Other [16]. In Hawaii, the population-based sampling frame included drivers' license records supplemented with voter registration lists.

Potential breast cancer cases were identified between entry into the cohort (1993–1996) and December 2000 by linkage with the Hawaii Tumor Registry. A similar number of randomly selected control subjects were frequency matched to the distribution of ethnicity and 5-year age groups of the cases. Cases and controls with a previous diagnosis of breast cancer, a history of breast augmentation or reduction, and/or without a suitable mammogram were excluded. Of those eligible to participate, 52.6% of the cases and 48.7% of the controls responded to the mailings and gave full consent. After removing women who did not have suitable mammograms, the final sample consisted of 607 breast cancer cases and 667 control subjects. Cases included 125 carcinoma in situ of the breast (119 ductal carcinoma in situ (DCIS) and 6 other carcinoma in situ) because we previously reported that mammographic density was associated with DCIS as well as invasive breast cancer [17]. Women included were 1.4 years younger ($p < 0.001$) and more likely to be postmenopausal than women who were eligible but not included; no differences were found with regard to body mass index (BMI), family history of breast cancer, parity, or age at menarche [2]. The original cohort

and the nested case-control studies were approved by the Committee on Human Studies at the University of Hawaii.

2.2. Data collection

An extensive questionnaire at entry into the cohort collected anthropometric characteristics, medical history, reproductive history, family history of breast cancer, and demographic information [16]. Hormone replacement therapy (HRT) was assessed as current and past use of estrogen and/or progesterone for menopause or other reasons. As part of the nested case-control study, the women completed a one-page breast health questionnaire that asked about previous breast surgery, mammography history, and HRT use [2]. For the women with missing HRT information (5.4%), we imputed the type based on hysterectomy status: estrogen only for women with a hysterectomy and combined therapy otherwise. The Hawaii Tumor Registry, a member of the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute, provided data on hormone receptor status.

2.3. Mammograms

The mammographic films were retrieved from clinics located throughout the State of Hawaii using the authorization forms signed by the study participants. As described in detail elsewhere [2], only craniocaudal views were digitized and assessed for densities using Cumulus108 software [18] by one reader (GM) who was blinded to case status. Only pre-diagnostic mammograms were used for cases; however, the image of the contralateral breast taken at the time of diagnosis was used for five cases. Because readings for the right and left breast were very similar (correlation >0.90), we averaged the values for both to obtain one measure. On average, 3.2 and 2.4 density measures on different dates were available for cases and controls, respectively. For cases, the mean time between the earliest mammogram and diagnosis was 6.3 years and between the latest mammogram and diagnosis was 1.1 years. The earliest and latest mammograms were, on average, 4.2 years apart for controls and 5.1 years apart for cases. A random sample of 410 mammograms was read in duplicate to assess the reliability of the mammographic readings; the intraclass correlation coefficient for percent density was 0.974 (95% CI 0.968–0.978).

2.4. Statistical analyses

Breast cancer cases were categorized by tumor receptor status: ER+PR+, ER−PR−, ER−PR+, ER+PR− (mixed), or unknown/other. Mean density values were computed for women with more than one mammogram. Percent density was modeled as a categorical variable (<10%, 10–24.9%, 25–49.9%, and ≥50%) or as a single continuous ordinal variable (expressed per 10% density). All *p* values reported are two sided. Statistical computing was conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

The characteristics of cases by receptor status and controls were compared using χ^2 for categorical variables and analysis of variance for continuous variables. Multivariable unconditional polytomous logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (95% CI) for breast cancer subtypes associated with percent density [19]. All models were adjusted for the following covariates that are known to be associated with breast cancer [20] and mammographic density [10,21]: mean age at the time of all mammograms (continuous), ethnicity, BMI (<22.5, 22.5–25.0, 25.1–30.0, or >30 kg/m^2), parity (0–1, 2–3, or ≥4), age at first live birth (<21, 21–30, >30 years, no children), age at menarche (<13, 13–14, or ≥15 years), menopausal status (pre-or postmenopausal), HRT use (never, estrogen only, or estrogen with progesterone), and family history of breast cancer (yes, no). Tests for trend were performed by fitting a variable representing ordinal categories (described above) of percent density. Test for heterogeneity was based on the *p* value from the *F*-test using an analysis of variance model with percent density as the

dependent and receptor status (ER+PR+, ER−PR−, and mixed) as the independent variable. We examined whether the association between density and breast cancer subtypes varied by ethnicity, menopausal status, parity, or HRT use using stratified analyses and the inclusion of interaction terms.

Results

Of the 607 breast cancer cases, more than half (56.2%) were ER+PR+ tumors and only 8.2% were ER−PR− tumors. Receptor status was either not tested or could not be ascertained in 25% of the cases, and the majority of these (n=100) were in situ cancers. Native Hawaiians had a greater proportion of ER+PR+ tumors than Caucasian or Japanese women (65% versus 52% and 56%, respectively); however, no statistically significant ethnic difference by receptor status was observed among the cases ($p = 0.70$). Women with ER+PR+ tumors were less likely to have a first-degree family history of breast cancer and to be parous and more likely to have higher age-adjusted mean percent density and age-adjusted dense breast area than women with ER−PR− tumors (Table 1). Breast cancer cases did not appear to differ by receptor status in terms of age at diagnosis, BMI, or HRT use. Compared to controls, both age-adjusted mean percent density and age-adjusted dense area were similar for cases with ER−PR− tumors, but statistically significant higher mean levels were found for cases with the other tumor subtypes.

Overall, and as reported previously [2], percent density was positively associated with breast cancer risk; in models adjusted for potential confounders, the estimated OR per 10% increase in density was 1.22 (95% CI 1.14–1.30). A dose response by density categories was found for both ER+PR+ and mixed tumors ($p < 0.01$ for both) (Table 2). The estimated OR per 10% increase in density for other or unknown tumors (OR 1.22, 95% CI 1.11–1.35 for other/unknown tumors) was similar to that for ER+PR+ and mixed tumors. There was limited evidence that density was associated with ER−PR− tumors as clearly shown by the null association per 10% increase in density (OR 1.00, 95% CI 0.84–1.18). Additionally, we found a 26% higher risk of ER+PR+ compared to ER−PR− tumors per 10% increase in density ($p = 0.01$) and evidence of heterogeneity ($p = 0.04$) with density across receptor status (ER+PR+, ER−PR−, and mixed). No statistically significant interaction on risk for tumor subtypes was observed for density with ethnicity, menopausal status, parity, or HRT use ($p_{interaction} > 0.60$ for all). Results excluding carcinoma in situ and results for dense breast area were similar and, therefore, are not shown.

4. Discussion

Using data from a multiethnic nested case-control study, our results suggest that mammographic breast density, as measured by percent density, was predictive of ER+PR+, mixed, and other/unknown, but not ER−PR− tumors. We estimated a 26% higher risk of developing ER+PR+ than ER−PR− tumors per 10% increase in density.

Our findings are consistent with a case-control study among participants in a screening program in the UK that found density to be associated with ER positive, but not ER negative tumors [11]. A differential association between breast density and tumor receptor status appears plausible due to findings from epidemiologic studies that hormone-related risk factors are positively associated with receptor positive but not receptor negative tumors [7]. The underlying biological mechanisms for the strong association between mammographic density and breast cancer are unclear. Although evidence supports an inverse association between circulating estrogen and breast density that is attenuated after adjustment for BMI [22–23], factors affecting estrogen exposure, such as parity, menopause, and HRT use, also

influence breast density [2,10]. Additionally, polymorphisms in the ER receptor gene may affect breast cancer risk via a pathway that involves breast density [24].

On the other hand, our findings are inconsistent with those from several other epidemiologic studies; however, these studies were case-based studies [13–14] or assessed breast density using the qualitative Breast Imaging Reporting and Data System (BI-RADS) classification system [12–13], a less reliable measure than quantitative computer-assisted measures [25]. A population-based study of invasive breast cancer patients and controls in Los Angeles County found no evidence of differential risk by receptor status classified jointly as ER+ or PR+ and ER−PR− tumors [15]. The adjusted OR reported were lower than those from our study, which may be explained by a lower mean age of cases at diagnosis (mean 48.7 years, range 35–64 years). It is well established that different etiologies exist for pre- and postmenopausal breast cancer, and ER−PR− tumors are more common in premenopausal women [7]; however, we did not find any evidence of interaction between density and receptor status with menopausal status.

The major strength of our study is the use of computer-assisted assessment of breast density as a continuous measure, providing a more precise measure with less subjective error. Plus, multiple mammograms were collected per woman over multiple years. The assessor was blinded to case status of the women, thereby limiting differential misclassification of density measures. The study also had a number of unique features, particularly a large number of US-born Japanese American women, who are at a similarly high risk of developing breast cancer as Caucasian and Native Hawaiian women [20]. The parent study, the MEC, offered a number of advantages that include detailed information for covariate data. Additionally, hormone receptor status was obtained from a high-quality population-based tumor registry.

Our study also had several limitations. The assessment of BMI and HRT relied on self-report and assumed that their values remained constant. However, an examination of BMI from a follow-up questionnaire five years after cohort entry showed that the mean BMI changed by only 0.50 kg/m^2 during that time, suggesting that differences in BMI are unlikely to have affected the results materially. HER-2 neu expression, an important prognostic marker for breast cancer [26], was not available from the registry. Also, 144 of the cases had missing receptor status and the assays were preformed in different labs. Furthermore, the stronger finding with ER+PR+ may be due to chance as our study is limited by the number of ER−PR− breast cancer subtypes (n=50). Thus, larger studies are needed to confirm our findings.

Our study was also limited by the unavailability of information on screen-detected versus interval breast cancers. Cancers diagnosed after a negative mammogram in the interval between routine screenings are more likely among women with greater density [27–28] and with ER− and PR− tumors [29–31]. Evaluating the association between density and receptor status among screen-detected and interval cancers separately may elucidate different etiological pathways. For example, interval cancers may represent faster-growing tumors or may be masked by dense breast tissue that reduces mammogram sensitivity [28]. One study by Aiello *et al*. [13] evaluated the association between density and receptor status among screen-detected and interval cancers and found no notable differences, however, the majority of the women (86%) were postmenopausal and the study was limited by sample size for interval cancers (n=151).

In conclusion, adding to the complexity of multiple etiologies for breast cancer are biologically diverse and heterogeneous tumors that change their phenotype over the natural history of the disease. We found a positive association between breast density and ER+PR+ but not ER−PR− tumors; however, our study findings should be interpreted with caution as

we had a limited number of ER−PR− tumors. Because breast density is a strong risk factor for breast cancer, future studies evaluating associations with different tumor subtypes as defined by histology or gene expression patterns will be important for further elucidating the biological mechanisms through which density affects breast cancer risk. Our study in a multiethnic population contributes to the limited data examining the association between breast density and breast cancer tumor characteristics.

Acknowledgments

The case-control study was funded by a grant from the National Cancer Institute (R01 CA 85265). The Multiethnic Cohort Study has been supported by USPHS (National Cancer Institute) grant R37 CA 54281. Dr Conroy was supported by grant R25 CA 90956. We are very grateful to Jihae Noh for her outstanding work in mammogram retrieval and scanning, to Andrew Williams for creating an excellent database, and to Mira Sharma for assistance with manuscript preparations.

Abbreviations

BMI	body mass index
CI	confidence interval
DCIS	ductal carcinoma in situ
ER	estrogen receptor
HRT	Hormone replacement therapy
MEC	Multiethnic Cohort
OR	odds ratio
PR	progesterone receptor

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Table 1

Characteristics of 667 controls and 607 cases, by receptor expression status, in the Hawaii component of the Multiethnic Cohort study.

Characteristics	Controls[a]	Breast Cancer Subtypes[a,b]				
		ER+PR+	ER−PR−	ER+PR−or ER−PR+	Other/unknown	*p* value[c]
N	667	341	50	64	152	
Ductal carcinoma in situ, N	-- --	19	2	4	94	
Ethnicity (%)						0.70
Caucasian	28	30	40	31	35	
Hawaiian	24	15	12	9	11	
Japanese	44	48	44	50	49	
Other	4	7	4	9	5	
Age at diagnosis, y	-- --	62.9 (8.6)	62.3 (8.7)	63.0 (8.9)	62.6 (8.1)	0.96
Age at recruitment, y	57.7 (8.7)	59.9 (8.4)	59.6 (8.6)	60.1 (8.8)	59.9 (8.2)	0.99
Mean age at all mammograms, y	59.7 (9.0)	59.8 (8.6)	59.5 (8.8)	59.8 (8.8)	59.3 (8.4)	0.94
Body mass index (kg/m^2)	25.7 (5.5)	25.4 (5.4)	25.2 (4.5)	24.2 (4.2)	24.6 (5.0)	0.18
Time from first mammogram to diagnosis, y	-- --	6.2 (4.0)	5.9 (4.0)	6.1 (4.5)	6.6 (3.9)	0.62
Family history of breast cancer (%)	12	15	26	22	16	0.20
Age at first birth, y	24.7 (4.5)	24.9 (4.5)	24.9 (4.4)	24.9 (4.8)	25.1 (4.7)	0.97
Age at menarche, y	13.1 (1.5)	13.1 (1.5)	12.8 (1.4)	13.1 (1.4)	13.0 (1.5)	0.74
Parous (%)	88	81	92	89	87	0.10
Postmenopausal (%)	78	88	84	81	89	0.35
HRT use (%)	69	68	70	70	70	0.95
Number of mammograms	2.4 (1.1)	3.3 (1.9)[d]	3.2 (1.8)[d]	2.7 (1.4)	3.4 (1.7)[d]	0.06
Breast percent density (SE)[e]	29.4 (0.8)	37.3 (1.1)[d]	28.9 (3.0)	39.9 (2.6)[d]	37.6 (1.7)[d]	0.03
Breast dense area, cm^2 (SE)[e]	28.7 (0.9)	36.8 (1.3)[d]	28.5 (3.3)	40.2 (2.9)[d]	36.7 (1.9)[d]	0.10

[a] Mean values (SD) are provided unless indicated otherwise. Percentages may not add to 100 due to rounding.

[b] ER, estrogen receptor; PR, progesterone receptor.

[c] *p* value from χ^2 test for categorical variables or analysis of variance for continuous variables for differences between breast cancer subtypes.

[d] *p* value < 0.05 from analysis of variance (Tukey Test) for difference in mean values from controls.

[e] Adjusted for mean age at all mammograms.

Table 2

Risk estimates[a] for the association between breast cancer subtypes[b] and mammographic density in the Hawaii component of the Multiethnic Cohort study.

	ER+PR+	ER−PR−	ER+PR−/ER−PR+	Controls	ER+PR+ versus controls	ER−PR− versus controls	ER+PR−/ER−PR+ versus controls	ER+PR+ versus ER−PR−
	n	n	n	n	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Density								
<10	43	7	7	158	1.00	1.00	1.00	1.00
10–24.9	73	19	13	170	1.76 (1.11, 2.78)	2.81 (1.10, 7.20)	1.69 (0.64, 4.48)	0.63 (0.23, 1.69)
25–49.9	124	17	21	212	2.66 (1.69, 4.20)	2.07 (0.75, 5.70)	2.16 (0.83, 5.63)	1.28 (0.45, 3.69)
≥50.0	101	7	23	127	4.12 (2.46, 6.89)	1.39 (0.41, 4.73)	3.92 (1.42, 10.85)	2.97 (0.84, 10.53)
p value$_{trend}$					<0.001	0.80	0.01	0.02
10% increase	341	50	64	667	1.26 (1.17, 1.36)	1.00 (0.84, 1.18)	1.23 (1.07, 1.42)	1.26 (1.06, 1.50)
p value$_{trend}$					<0.001	0.98	<0.01	0.01

[a] Odds ratios (OR) and 95% confidence intervals (CI) estimated using polytomous regression adjusted for mean age at the time of all mammograms, ethnicity, body mass index, parity, age at first live birth, age at menarche, menopausal status, use of hormone replacement therapy, and family history of breast cancer.

[b] ER, estrogen receptor; PR, progesterone receptor.