Published in final edited form as:

Cancer Causes Control. 2015 April ; 26(4): 621–626. doi:10.1007/s10552-015-0551-2.

Mammographic density and breast cancer risk by family history in women of white and Asian ancestry

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Abstract

Purpose—Mammographic density, i.e., the radiographic appearance of the breast, is a strong predictor of breast cancer risk. To determine whether the association of breast density with breast cancer is modified by a first-degree family history of breast cancer (FHBC) in women of white and Asian ancestry, we analyzed data from four case-control studies conducted in the United States and Japan.

Methods—The study population included 1,699 breast cancer cases and 2,422 controls, of whom 45% reported white (N=1,849) and 40% Asian (N=1,633) ancestry. To standardize mammographic density assessment, a single observer re-read all mammograms using one type of interactive thresholding software. Logistic regression was applied to estimate odds ratios (OR) while adjusting for confounders.

Results—Overall, 496 (12%) of participants reported a FHBC, which was significantly associated with breast cancer risk in the adjusted model (OR=1.51; 95% CI: 1.23-1.84). There was a statistically significant interaction on a multiplicative scale between FHBC and continuous percent density (per 10% density: p=0.03). The OR per 10% increase in percent density was higher among women with a FHBC (OR=1.30; 95% CI: 1.13-1.49) than among those without a

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Conflict of interest The authors declare no conflict of interest.

FHBC (OR=1.14; 1.09-1.20). This pattern was apparent in whites and Asians. The respective ORs were 1.45 (95%CI: 1.17-1.80) vs. 1.22 (95%CI: 1.14-1.32) in whites, whereas the values in Asians were only 1.24 (95%CI: 0.97-1.58) vs. 1.09 (95%CI: 1.00-1.19).

Conclusions—These findings support the hypothesis that women with a FHBC appear to have a higher risk of breast cancer associated with percent density than women without a FHBC.

Keywords

Breast neoplasms; mammographic density; epidemiology; risk factor; effect modification; family history of breast cancer; data pooling; logistic regression; ethnicity

Introduction

Mammographic density represents the proportion of radiologically dense stromal and epithelial tissue relative to fat tissue in the breast [1]. It is one of the strongest predictors of breast cancer risk, conferring a 4-6 fold greater relative risk in women with high density [2]. Percent density is lower in parous and postmenopausal women, higher in women taking hormone therapy (HT), and inversely associated with body weight and age [3]. Given that breast cancer risk is elevated by 1.5 to 3 times in women with a family history of breast cancer (FHBC) [3, 4], information about inherited susceptibility combined with breast density data may lead to improved clinical risk prediction [5, 6], which might help to identify women at high risk for breast cancer who may benefit from preventive options [7]. Mammographic density and familial risk of breast cancer may be influenced by shared genetic factors [3, 8, 9]; the genetic factors underlying FHBC may also modify the breast cancer risk associated with mammographic density. Currently, it is not well understood if the effect of mammographic density on breast cancer risk is modified by a FHBC [1]. An early study of 266 cases and 301 controls reported odds ratios (OR) and 95% confidence intervals (CI) for women with dense breast relative to nondense breasts of 5.5 (95% CI: 2.6-11.8) in women with a FHBC and only 2.8 (95% CI: 1.6-5.1) in those without a FHBC [10]. In the Breast Cancer Detection Demonstration Project, a higher proportion (40 vs. 31%) of controls with a FHBC had 50% or more breast density than controls without a FHBC [11]. In contrast, several later reports did not find any significant differences in the association between mammographic density and breast cancer by FHBC [1, 3, 12] although percent density was positively associated with the number of affected relatives in cases and controls in a Canadian report [3]. Similarly, *BRCA1* and *BRCA2* mutation carriers seem to experience a comparable relative risk of breast cancer given the same degree of mammographic density as non-carriers [13]. To explore whether the association of mammographic density with breast cancer risks is modified by FHBC, we analyzed data from women of white and Asian ancestry who had participated in four case-control studies conducted in the United States and Japan.

Materials and Methods

As described in detail previously, we combined case-control data from four studies located in California, Minnesota, Hawaii, and Japan [14]. The studies were approved by their respective Institutional Review Boards. All breast cancer cases were newly diagnosed;

controls were recruited from the general population in California, the Multiethnic Cohort in Hawaii, and screening participants in Minnesota and Japan [15-18]. Covariate information included ethnicity, parity, menopausal status, HT use, and body mass index (BMI). For ethnicity, we created four summary categories, white, Asian (mostly Japanese), African American, and other. Information on first-degree relatives with breast cancer was collected in all studies but the number of affected relatives was not recorded. After excluding 127 women with missing information on covariates, 1,699 breast cancer cases and 2,422 controls were available. Contralateral images at the time of diagnosis were assessed for cases and randomly selected sides for controls. The size of the total breast and the dense area were assessed by a single observer using Cumulus [14] and percent mammographic density was computed as their ratio. Repeated readings indicated a high reliability of the mammographic density measures ($r=0.97$).

Using SAS 9.2 (SAS Institute Inc., Cary, NC, USA), the association between mammographic density and breast cancer risk was evaluated by unconditional logistic regression expressing breast density as categorical ($<20\%$, $20\text{--}35\%$, 35%) and as continuous (per 10%) variables. In the overall model, ORs with 95% CI were adjusted for age at mammogram, BMI, menopausal status, HT use, and location/ethnicity (Japan/Asian, California/ white, California/Asian, California/African American, Hawaii/white, Hawaii/ Asian, Hawaii/other, Minnesota/ white, Minnesota/other), and for FHBC. To assess effect modification by FHBC, we conducted stratified analyses, estimated the joint effect of the two variables using women with $<20\%$ density and no FHBC as the reference category, and formally tested for interaction using a global Wald test of the cross-product term between mammographic density (categorical and continuous) and FHBC.

Results

Of the 4,121 participants (Table 1), 496 (12%) reported a FHBC. Women with breast cancer were more likely to have a FHBC than controls ($p<0.0001$). Among women with a FHBC, 263 (53%) were cases and 233 (47%) were controls. The respective numbers for women without a FHBC were 1,436 (39.6%) and 2,189 (60.4%). The majority of women were white (44.9%) or Asian (39.6%), parous (86.8%), currently postmenopausal (74.1%), and not using any HT (45.6%). Living in Hawaii ($p<0.0001$), being white ($p=0.0001$), having a higher parity ($p=0.05$), a younger age at first live birth ($p=0.01$), and postmenopausal status without taking HT ($p<0.0001$) were significantly associated with FHBC. In contrast, BMI and percent density did not differ by FHBC; the respective values of mean percent density were 29.1% and 30.1% for women with and without a FHBC.

The risk of with breast cancer associated with a FHBC was 1.51 (95% CI: 1.23-1.84) after adjustment for confounders. For all women, breast cancer risk increased across categories of percent density. Compared to women with $<20\%$ density, breast cancer risk for women in the 20-35% density category was elevated by 56% (OR=1.56; 95% CI: 1.31-1.86); for women with $>35\%$ density, the respective value was 88% (OR=1.88; 95% CI:1.56-2.26). For women with a FHBC, breast cancer risk was 87% (OR=1.87; 95% CI:1.14-3.05) and 154% (OR= 2.54; 95% CI:1.51-4.26) higher for the intermediate and the top density categories, whereas the estimated risks in women without a FHBC were only elevated by

52% (OR=1.52; 95% CI: 1.26-1.84) and 81% (OR=1.81; 95% CI: 1.48-2.21). When modeling the joint effects of FHBC and mammographic density using women without a FHBC and <20% density as the reference, the highest OR was observed among women with both a FHBC and >35% density (OR=3.16; 95% CI: 2.22-4.50).

A FHBC was also associated with the continuous measure of percent density. Having 10% greater percent density increased the risk of breast cancer for women with a FHBC by 32% (OR= 1.32; 95% CI: 1.15-1.52) but only 13% for women without a FHBC (OR=1.13; 95% CI: 1.07-1.18). The interaction term for FHBC and continuous percent density (per 10%) was statistically significant ($p=0.03$) but the interaction term for FHBC and the categorical percent density variable was not ($p=0.39$).

The pattern of associations for percent density by FHBC was similar within strata of ethnicity. The ORs for >35% density relative to <20% were higher in women with a FHBC vs. without a FHBC in both whites (OR=3.12; 95% CI: 1.49-6.55 vs. OR=2.13; 95% CI: 1.60-2.84) and Asians (OR=2.84; 95% CI: 1.05-7.72 vs. OR=1.55; 95% CI: 1.08-2.21). The respective ORs for continuous density in whites were 1.49 (95% CI: 1.20-1.84) with a FHBC and 1.20 (95% CI: 1.12-1.29) without a FHBC. The risk estimates were lower in Asian women, but they followed the same pattern; the OR for continuous density was 1.23 (95% CI: 0.97-1.57) in women with a FHBC vs. 1.06 (95% CI: 0.98-1.15) in women without a FHBC.

Discussion

In this pooled analysis, we observed a stronger association of mammographic density with breast cancer among women with a FHBC than among those without such a history. These results highlight a potentially higher risk associated with breast density for women with a FHBC. In contrast to our data, in which no association was observed between mammographic density and FHBC, data from several studies suggest that mammographic density is higher among women with a FHBC than without a FHBC. Mean percent mammographic density values for women with 0, 1, and 2 affected relatives were 28%, 31%, and 35% ($p=0.001$) in a Canadian report [3]. The San Francisco Mammography Registry indicated that women with higher mammographic density had a higher chance (30-70%) of having a first-degree relative with breast cancer [9]. A similar finding of a 30% higher probability of a FHBC was reported from a Spanish study [19]. In women from a screening program, FHBC was associated with higher mammographic density [20]. However, mammographic density has not been seen to differ between BRCA1/2 carriers [13, 21] and women at low-to-average risk [22].

Our findings of an interaction between FHBC and mammographic density agree with a study of 266 cases and 301 controls that reported ORs for women with dense breast relative to nondense breasts of 5.5 (95% CI: 2.6-11.8) for women with a FHBC, and only 2.8 (95% CI: 1.6-5.1) for those without a FHBC [10], but disagrees with several reports that detected no effect modification by FHBC [1, 3, 12]. In an analysis of three screening studies, greater breast density was related to higher breast cancer risk in women with (OR=4.1) and without (OR=3.3) a FHBC as compared to women in the lowest density category with no affected

relatives. However, the interaction term was not statistically significant [3]. Another report concluded that FHBC and mammographic density have independent effects on breast cancer development and that the risk estimates expected under additivity were close to those observed [12]. Even in *BRCA1* and *BRCA2* mutation carriers, the strength of the association between mammographic density and breast cancer did not differ significantly from non-carriers [13]. The inconsistent findings may be due to differences in study design, population characteristics, methods of data collection and mammographic density assessment, as well as genetic variation underlying FHBC. For example, three of the investigations included into the pooled analysis [15, 17, 18] and one previous report [12] were case-control studies, which are more likely to be affected by recall bias than studies nested within cohorts [1, 3, 10, 11, 16]. Probing during interviews in some studies may have elicited more detailed information about FHBC [10, 12, 15] than questionnaire-based self-reports [1, 3, 16-18].

The association observed between mammographic density and FHBC in some studies suggests that they may share genetic factors. A strong genetic component to mammographic density has been demonstrated in twin studies, which suggest that a large proportion (30-60%) of the population variation in mammographic density appears to be heritable [23-26]. The ongoing search for specific polymorphisms responsible for differences in mammographic densities has uncovered a number of breast cancer susceptibility variants associated with mammographic measures in the same direction as the breast cancer association [8, 27, 28]. Furthermore, using a GWAS of both breast cancer and mammographic density, it has been shown previously that percent mammographic density and breast cancer risk have a shared genetic basis that is likely mediated by a large number of common variants [29]. Empirical estimates of the percentage of overlap between genetic determinants of breast cancer and mammographic density measures are 10-20% [3, 29]. Whether these variants increase cancer risk through dense tissue or act pleiotropically to affect both traits, remains unclear.

Potential limitations of our pooled analysis are the lack of validation and more detailed information on the number of relatives affected by breast cancer. An analysis of family history data in cancer family registries showed higher reliability for first- than second-degree relatives (95% vs. 82%), but detected no differences by ethnic group [30]. In unaffected women, more cases were reported for maternal than paternal relatives [31], but the sensitivity was similar in a comparison of cases and controls (85 vs. 82%) [32]. As in all case-control studies, recall bias is a concern. Also, differences in mammograms and questionnaires across locations may have affected the analysis despite efforts in data harmonization. Strengths of our study include the centralized assessment of mammographic density with a well-established quantitative computer-assisted method [2], the standardization achieved by using one reader [14], and the inclusion of white and Asian women. As shown in a methodological investigation, re-reading the mammograms standardized the distributions across locations [33]. The geographic and ethnic diversity of our study population offered a wide variation in exposures.

In this pooled analysis, women with a FHBC appear to have a higher breast cancer risk associated with mammographic density than those without. In stratified analyses, percent density increased breast cancer risk among white and Asian women with and without a

FHBC. The current findings support the hypothesis that FHBC modifies breast cancer risk attributable to mammographic density. While efforts are under way to identify women at high risk through models that include breast density and a panel of low-penetrance genetic polymorphisms in addition to established risk factors [7, 34], FHBC may serve as a substitute for hereditary susceptibility in women without genetic information.

Acknowledgments

This research was supported by the National Cancer Institute, US Department of Health and Human Services, grant number R03 CA 135699. CGW and SMC were supported during the work on this project by postdoctoral fellowships on grant R25 CA 90956.

Abbreviations

BMI	body mass index
CI	confidence interval
FHBC	family history of breast cancer
HT	hormone therapy
OR	odds ratio

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Table 1

Characteristics of the study participants

Characteristic	All Women N = 4,121	No FHBC N = 3,625	FHBC N = 496	p-value *
Case status, %				
Cases	41.2	39.6	53.0	
Controls	58.8	60.4	47.0	<0.0001
Location, %				
California	26.1	25.9	27.4	
Hawaii	30.9	30.1	37.1	
Japan	18.7	20.1	7.7	
Minnesota	24.3	23.9	27.8	<0.0001
Ethnicity, %				
White	44.9	44.2	50.2	
Asian	39.6	40.7	31.4	
African American	8.7	8.7	8.5	
Other	6.8	6.4	9.9	0.0001
Age group, %				
<40 years	7.6	7.6	7.1	
40-<50 years	17.8	18.6	12.1	
50-<60 years	33.5	33.9	30.4	
60-<70 years	23.9	23.7	26.2	
70 years	17.2	16.2	24.2	0.0001
BMI, %				
Normal	47.1	47.4	45.0	
Overweight	34.2	34.2	34.3	
Obese	18.7	18.4	20.7	0.39
Parity, %				
0	13.2	12.8	16.1	
1-2	44.4	44.9	40.3	
3	42.4	42.3	43.6	0.05
Age at first live birth, %				
No children	13.2	12.8	16.1	
25	56.0	56.6	51.8	
26-35	22.7	22.9	21.4	
>35	8.1	7.7	10.7	0.01
Menopausal status/HRT use, %				
Premenopausal	25.9	27.0	17.7	
Postmenopausal/no HRT	45.6	44.2	55.7	
Postmenopausal/any HRT	28.5	28.8	26.6	<0.0001
Percent density, %				
<20	32.8	32.6	34.7	
20-35	31.1	31.3	29.4	

Characteristic	All Women N = 4,121	No FHBC N = 3,625	FHBC N = 496	p-value *
>35	36.1	36.1	35.9	0.58

* P-values obtained from chi-square tests.

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Table 2

Mammographic density and breast cancer risk by family history of breast cancer*

Groups	Numbers		Percent Density Categories			Continuous per 10%
	Cases	Controls	<20%	20-35%	>35%	
All women	1,699	2,422	1.00	1.56 (1.31-1.86)	1.88 (1.56-2.26)	1.15 (1.10-1.20)
No FHBC	1,436	2,189	1.00	1.52 (1.26-1.84)	1.81 (1.48-2.21)	1.13 (1.07-1.18)
FHBC	263	233	1.00	1.87 (1.14-3.05)	2.54 (1.51-4.26)	1.32 (1.15-1.52)
p-value for interaction [^]				0.39		0.03
All women	1,436	2,189	1.00	1.52 (1.26-1.83)	1.80 (1.48-2.19)	
No FHBC						
FHBC	263	233	1.26 (0.90-1.77)	2.36 (1.63-3.41)	3.16 (2.22-4.50)	
Whites	788	1,061				
No FHBC	662	938	1.00	1.80 (1.38-2.35)	2.13 (1.60-2.84)	1.20 (1.12-1.29)
FHBC	126	123	1.00	1.46 (0.74-2.86)	3.12 (1.49-6.55)	1.49 (1.20-1.84)
Asians	617	1,016				
No FHBC	531	946	1.00	1.24 (0.89-1.74)	1.55 (1.08-2.21)	1.06 (0.98-1.15)
FHBC	86	70	1.00	2.31 (0.85-6.23)	2.84 (1.05-7.72)	1.23 (0.97-1.57)

* Odds ratios and 95% confidence intervals from logistic regression models adjusted for age at mammogram, BMI, menopausal status/HT use, parity, age at first birth, and, if applicable, family history of breast cancer, location/ethnicity.

[^] Based on a global Wald test of the cross-product term between mammographic density (categorical and continuous) and FHBC.