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Mammographic density, parity and age at first birth, and risk of breast cancer: an analysis of four case-control studies

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Abstract

Mammographic density is strongly and consistently associated with breast cancer risk. To determine if this association was modified by reproductive factors (parity and age at first birth), data were combined from four case-control studies conducted in the United States and Japan. To overcome the issue of variation in mammographic density assessment among the studies, a single observer re-read all the mammograms using one type of interactive thresholding software. Logistic regression was used to estimate odds ratios (OR) while adjusting for other known breast cancer risk factors. Included were 1699 breast cancer cases and 2422 controls, 74% of whom were postmenopausal. A positive association between mammographic density and breast cancer risk was evident in every group defined by parity and age at first birth (OR per doubling of percent mammographic density ranged between 1.20 and 1.39). Nonetheless, the association appeared to be stronger among nulliparous than parous women (OR per doubling of percent mammographic density = 1.39 vs 1.24; P -interaction = 0.054). However, when examined by study location, the effect modification by parity was apparent only in women from Hawaii and when examined by menopausal status, it was apparent in postmenopausal, but not premenopausal, women. Effect modification by parity was not significant in subgroups defined by body mass index or ethnicity. Adjusting for mammographic density did not attenuate the OR for the association between parity and breast cancer risk by more than 16.4% suggesting that mammographic density explains only a small proportion of the reduction in breast cancer risk associated with parity. In conclusion, this study did not support the hypothesis that parity modifies the breast cancer risk attributed to mammographic density. Even though an effect modification was found in Hawaiian women, none was found in women from the other three locations.

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Conflict of Interest Statement Dr. Martin Yaffe is one of the founders of Matakina Technology, a manufacturer of software for the assessment of mammographic density. The software was not used in the present research and neither the results nor the way the research was conducted have been influenced by Dr. Yaffe's involvement in Matakina Technology.

Keywords

Breast neoplasms; mammographic density; reproductive factors; epidemiology; risk factor; effect modification

Introduction

Mammographic density is a relatively strong and consistent risk factor for breast cancer [1, 2]. It reflects breast tissue composition: dense fibroglandular tissues appear light on mammograms whereas nondense fatty tissues appear dark. Both the relative (percent) and absolute areas of density seen on mammograms are related to breast cancer risk and women within the highest categories of mammographic density are at four to six times higher risk than women within the lowest categories [2]. Mammographic density is being extensively studied with the purpose of improving both the prediction of breast cancer risk and the understanding of breast carcinogenesis.

Helpful in achieving these ends is to examine whether the association between mammographic density and breast cancer risk is modified or mediated by another risk factor. Such factors include body mass index (BMI) [3, 4], family history [5], hormone replacement therapy (HRT) [6, 7], and selective estrogen receptor modulators [8]. Reproductive factors have not yet been comprehensively studied as effect modifiers although changes in the breast induced by pregnancy may make the tissue less susceptible to the risk of carcinogenesis related to mammographic density. In accordance with this hypothesis, the association between mammographic density and breast cancer risk has been observed to be stronger in nulliparous women than in parous women in one study [9]. That the association between reproductive factors and breast cancer risk could be mediated by mammographic density is supported by several observations: parity is associated with breast cancer risk [10–12]; parity is inversely correlated with mammographic density [13–18]; and, as noted above, mammographic density is associated with breast cancer risk [1, 2]. Another indication of whether mammographic density could lie on the causal chain between parity and breast cancer risk is if the association between parity and breast cancer risk is attenuated after adjustment for mammographic density [19].

Studies published to date show a consistent association between mammographic density and breast cancer risk [2], but they often do not have the statistical power to demonstrate effect modification by factors that define population subgroups. Combining data from several studies could result in sufficient power but is not straightforward due to variation in mammographic density assessment arising from different techniques and observers. To overcome this issue, we have obtained the mammographic images from four case-control studies and a single observer has re-read them using one type of interactive thresholding software [20]. The objective of this analysis was to determine if the association between mammographic density and breast cancer risk was modified by reproductive factors, specifically parity and age at first birth. The secondary objective was to describe whether mammographic density accounted for any part of the association between these reproductive factors and breast cancer risk.

Materials and methods

Study design

The methods of this project and the case-control studies that contributed data are reported elsewhere [3, 21–24] and will only be briefly described here. The Institutional Review Boards at the four institutions approved both the original case-control studies and this

project. Each study used incident breast cancer cases. Controls came from the general population in California, from participants of the Multiethnic Cohort without cancer in Hawaii, and from a screening clinic population in Minnesota and Japan. Covariate information comprised ethnicity/race, menopausal status, HRT use, family history of breast cancer, and height and weight (from which BMI was calculated). Reproductive information included the number of children (Hawaii, Minnesota), parity (California, Japan), and age at first birth. This information was collected with: face-to-face interview using a structured questionnaire in California (soon after case diagnosis or control recruitment); self-administered questionnaire in Hawaii (at cohort baseline with an update on HRT at the time of the nested study) and in Japan (at the time of screening); and medical chart abstraction and a clinical database in Minnesota.

Mammographic density

Although mammographic density had been determined for each original study, different thresholding software and observers were used. Therefore, the measurements used in this analysis were made by a single observer (CGW) who re-read all films for this project using Cumulus interactive thresholding software [20]. A single digitized mammographic image was obtained for each research participant: the contralateral side for cases, and a randomly selected side for controls to achieve the same right-left frequencies as in the cases. In the studies conducted in California, Hawaii, and Minnesota, digitized screen film craniocaudal (CC) images were available. In Japan, digital mediolateral oblique (MLO) images were printed on film and digitized to a file format usable with the Cumulus thresholding software. In studies with multiple mammographic images across time for each subject [21, 23], we chose the mammogram proximal to diagnosis for the cases to correspond most closely to the other studies in which films at only one time were available.

The mammographic images from 4254 participants, plus 270 of these images that were randomly selected to be re-read both within and between batches to estimate reliability, were read in 45 batches of 106–107 images. Each batch was read in two stages: first, the breast area was manually delineated from the background and pectoral muscle, and second, a threshold was set between the radiologically dense fibroglandular tissues and the nondense fatty tissues based on grey-level. The number of pixels within the breast and dense areas was determined by the software and converted to square centimeters based on the pixel size at which the images for each study were digitized. Percent dense area was calculated as the dense area divided by the breast area. A conversion was applied to adjust the percent dense area measures made on MLO views from Japan to be equivalent to those made on CC views [$CC = (MLO - 2.6) / 0.86$] [25]. The reliability of the dense area and percent dense area measurements was high (intraclass correlation coefficient = 0.96 and 0.97, respectively).

Statistical analysis

The primary outcome and covariate data from each study were merged together into a single standardized database. Women with missing information on BMI or HRT use, the main confounders of the association between mammographic density and breast cancer risk, were excluded. Women with missing values for parity ($N=21$) or age at first birth ($N=30$) were assigned the category that was most frequent for their location/ethnic group. To examine the effect of this imputation, all analyses described below were repeated excluding these participants; no substantive changes were observed so results are reported for the whole group. Because the mammograms from Japan were different with respect to being processed digital images and the MLO view, all analyses were repeated excluding this study; again no substantive changes in the results were observed.

Study participants were described on the basis of demographic and breast cancer risk factors using means and frequencies as appropriate. The association between reproductive factors (parity and age at first birth) and mammographic density in the control group was estimated with general linear models. Because dense area was positively skewed, this variable was square root-transformed for these analyses.

The association between mammographic density and breast cancer risk was represented by odds ratios (OR) with 95% confidence intervals (CI) estimated from unconditional logistic regression models. In these models, the mammographic variables were examined either in three categories representing the approximate tertiles of their distribution in the combined control group or logarithmically (base 2) transformed such that the OR estimated the risk associated with a doubling of mammographic density. All models were adjusted for age at mammogram (continuous), menopausal status/current HRT use (premenopausal, postmenopausal/no HRT, postmenopausal/HRT), family history of breast cancer (1st degree, no 1st degree), and location/ethnicity (California/Caucasian, California/Asian, California/African American, Minnesota/Caucasian, Hawaii/Caucasian, Hawaii/Asian, Hawaii/other, Japan/Asian).

To examine effect modification, that is, if the association between mammographic density and breast cancer risk was heterogeneous across subgroups defined by parity (0, 1–2, 3 children), the significance of the interaction term between log-transformed mammographic density and parity was determined with the likelihood ratio test. Similarly, the association between mammographic density and breast cancer risk was examined by age at first birth (< 26, 26 years; among parous women only). To better illustrate and describe the difference between nulliparous and parous women in the dose-response relationship suggested by these results, a *post hoc* logistic regression analysis using restricted cubic splines with knots at the 10th, 50th, and 90th percentiles of percent dense area (*i.e.*, at 8, 29, and 56% dense area) was done using a SAS macro kindly provided by Dr. L. Desquilbet [26]. Finally, it was of interest to describe whether the effect modification was of a similar strength in subgroups defined by location, ethnicity, BMI, and menopausal status. Subgroups with less than 20 cases or controls were omitted from these analyses.

If the association between parity or age at first birth and breast cancer risk was significant in these data, the percent change in the ORs with adjustment for mammographic density was estimated using the equation: $100\% \times (\text{OR}_{\text{not adjusted for MD}} - \text{OR}_{\text{adjusted for MD}}) / (\text{OR}_{\text{not adjusted for MD}} - 1)$ [27]. As our objective was to describe if the association between reproductive factors and breast cancer risk was partially explained by mammographic density, we did not formally test the significance of the mediation effect [19].

All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Of the 4254 women for whom a digitized mammographic image could be located, 133 were excluded due to suspected breast implants ($N=4$), incomplete images ($N=2$), or missing information on BMI ($N=49$), current HRT use ($N=76$) or both ($N=2$). Thus, 1699 cases and 2422 controls were included (Table 1). Over 40% of the participants were Caucasian and approximately 40% were Asian; the remaining were African American or other ethnicities. Most of the women (74.1%) were postmenopausal, and of these, 38.1% used HRT. Mean (SD) BMI was 25.4 (5.3) kg/m². Most of the women (86.8%) were parous, and of these, 35.5% had their first live birth when they were 26 years of age or older. Mean (SD) percent mammographic density was 31.7 (17.7) in cases and 29.6 (18.9) in controls. Percent dense area and absolute dense area were highly correlated ($r_s = 0.74$).

The association between parity and mammographic density was investigated among controls (Table 2). Percent dense area was lower among women with greater parity ($P < 0.0001$) and did not vary by age at first birth among parous women ($P = 0.10$). Results for dense area followed a similar pattern.

Percent dense area was associated with the risk of breast cancer in every subgroup defined by parity and age at first birth (Table 3). The magnitude of the effect was greater among nulliparous than parous women (OR per doubling of percent dense area = 1.39 vs 1.24; P -interaction = 0.054). The pattern of ORs across tertiles suggested that the dose-response relationship between percent dense area and breast cancer risk was different by parity. In nulliparous women, risks were elevated to a similar extent in the second tertile (OR = 2.83, 95% CI: 1.64–4.87) and the third tertile (OR = 2.63, 95% CI: 1.51–4.56) relative to the first. In parous women, a threshold was not apparent and risk increased with each tertile (OR = 1.51, 95% CI: 1.25–1.82, and OR = 1.90, 95% CI: 1.56–2.32). A *post hoc* analysis to explore the shape of the relationship as modeled using restricted cubic splines (Figure 1) reflects the pattern observed in Table 3.

Among parous women (Table 3), the association between percent dense area and breast cancer risk in women with 1 or 2 children was similar to that in women with 3 or more children (P -interaction = 0.34). The magnitude of the effect among women with a first live birth at 26 years of age or older was nonsignificantly greater than the effect among women who were younger when they had their first child (OR per doubling = 1.33 vs 1.20; P -interaction = 0.16). Similar results were observed in models with dense area as the exposure with two distinctions. First, the magnitude of the association between dense area and breast cancer risk was very similar among nulliparous and parous women (OR per doubling = 1.35 vs 1.31; P -interaction = 0.63). Second, the heterogeneity of the effect by age at first birth was greater (first birth <26 years, OR per doubling = 1.25; first birth ≥ 26 years, OR = 1.47; P -interaction = 0.03).

The modification of the association between percent dense area and breast cancer risk by parity appeared stronger in specific subgroups (Table 4). Although it was not significant in California (P -interaction = 0.64) or Minnesota (P -interaction = 0.20), it was very apparent in Hawaii (P -interaction = 0.006). This pattern by location held when using the mammographic density measurements made by the original readers in the parent studies and when restricted to White participants (data not shown). When restricted to either postmenopausal participants or Asian participants, a stronger association among nulliparous than parous women was suggested, but was not statistically significant due to sparse data, not only in Hawaii but also in California (data not shown). Significant effect modification by parity was not observed in groups defined by ethnicity. Effect modification by parity was not significant in either normal weight (BMI 18.5–<25 kg/m²; P -interaction = 0.65) or overweight/obese women (BMI ≥ 25 kg/m²; P -interaction = 0.35) but was slightly stronger in the latter subgroup. It also was apparent in postmenopausal women (P -interaction = 0.03) but not in premenopausal women (P -interaction = 0.41).

Parity was associated with a lower risk of breast cancer (Table 5). Relative to nulliparous women, the risk of breast cancer was reduced by 24% (95% CI: 7%–38%) among women with 1 or 2 children and by 35% (95% CI: 20%–47%) among women with 3 or more children. Adjusting for either percent dense area or dense area attenuated these ORs, but never more than 16.4%, and they remained significant. Among parous women, age at first birth was not significantly related to an increased risk of breast cancer.

Discussion

In this analysis with 1699 breast cancer cases and 2422 controls from four studies, an association between mammographic density and breast cancer risk was evident in every subgroup defined by parity and age at first birth. The association appeared to be stronger among nulliparous than parous women with percent dense area (OR per doubling = 1.39 vs 1.24; P -interaction = 0.054) but not with dense area (OR per doubling = 1.35 vs 1.31; P -interaction = 0.63). However, when examined by study location, effect modification by parity was only observed in women from Hawaii and when examined by menopausal status, it was observed only in postmenopausal women. Parous women had lower mammographic density than nulliparous women, but mammographic density seemed to explain only a small proportion of the reduction in breast cancer risk associated with parity.

Parity leads to changes in breast morphology (e.g., number and differentiation status of the lobular structures [28]), histology (e.g., amount of collagen [29]), and biochemistry (e.g., gene expression patterns [30, 31]). As suggested by correlations observed in this study and others [13–18, 32], some of the changes in breast composition induced by parity are reflected by a reduction in mammographic density. In the current paper, however, although parity is associated with lower mammographic density and mammographic density is related to a reduction in breast cancer risk, we estimated using a standard calculation [27] that less than 17% of the association between parity and breast cancer risk is explained by mammographic density. Although the best method to validly quantify the proportion of an association that is explained by a putative mediator is currently under debate [33], the method we used should be sufficient to imply that the proportion mediated by mammographic density is slight. Thus, changes induced by pregnancy that are not reflected by mammographic density must also lead to a reduction in breast cancer risk. This suggestion is also supported by the observation in other studies that the association between parity and breast cancer risk remained significant after controlling for mammographic density in broad subjective qualitative categories [34–36]. The proportion mediated may be underestimated, however, by using a single measure of mammographic density later in life that may not fully capture the cumulative reduction since the time of pregnancy. That the association between parity and breast cancer risk is not wholly mediated by a reduction in mammographic density is also supported by the observation that mammographic density affects the risk of both steroid receptor positive and negative subtypes of breast cancer [37] while parity appears to influence the risk of steroid receptor positive cancers only [38, 39].

Most of the changes induced by pregnancy that could lead to protection against breast carcinogenesis have been identified in the breast epithelial cells [31], although changes in circulating hormones or growth factors [40] or in the supporting stromal tissues [41] could also play a role. Variability in mammographic density, on the other hand, is largely determined by the amount of dense connective tissue and less so by the amount of epithelial tissue [29, 42]. The dense connective tissue, represented by mammographic density, could provide a growth promoting environment that stimulates the proliferation of the epithelial cells [43, 44]. Due to changes in the epithelial cells induced by pregnancy, it could be hypothesized that the epithelial cells in parous women are less susceptible to this stimulation than those in nulliparous women. Under such a scenario, the effect of mammographic density on breast cancer risk would be stronger among nulliparous than parous women, as observed in this study with percent dense area. Similarly, in an analysis among pre- and postmenopausal Caucasian women (129 cases and 517 controls) by van Gils *et al.* [9], the OR for breast cancer in women with >25% density relative to <5% density was 6.6 among nulliparous women, far greater than the OR of 3.6 among parous women [9]. Conversely, results from other small studies using broad subjective qualitative measures of

mammographic density suggest a slightly stronger effect in parous women, but the interactions were not statistically significant [45, 46].

The pattern of ORs across categories of percent dense area observed in the present study suggests that risk in nulliparous women rises sharply and levels off or falls slightly, whereas in parous women, risk rises with each category of percent dense area but does not reach the levels observed in nulliparous women. Logistic modeling using restricted cubic splines in a *post hoc* analysis illustrates this pattern, but will need to be confirmed in a larger population of nulliparous women.

Effect modification by parity in the present study was only observed in data from Hawaii and was not apparent in the other locations despite standardization of mammographic density assessment. This inconsistency could be introduced by instability in the estimates due to small numbers of nulliparous women, particularly in Minnesota and Japan, or by differences in the relative weighting of reasons for nulliparity (e.g., choice, infertility) from location to location. Due to this inconsistency, if mammographic density is incorporated into individualized risk prediction models [47, 48], including the interaction with parity may not add to their performance.

Strengths of this study include the large sample size that provided the statistical power to detect modest yet meaningful degrees of effect modification; and the availability of information on potential confounders. Another considerable strength is the standardized assessment of mammographic density; it was done by a single observer using one type of interactive thresholding software. Other aspects of the measurement of mammographic density, however, could not be standardized including variation between and within studies arising from clinical mammography techniques (e.g., positioning and compression, type of mammography unit) and the scanners used to digitize the films (e.g., range of optical density, pixel size). The Japanese mammograms, in particular, were different by virtue of being processed digital vs film mammograms and of being the MLO vs CC view. We have previously reported that the association between mammographic density and breast cancer risk was heterogeneous between the studies and that this heterogeneity was largely driven by the data from Japan [3]; however, all analyses presented here were repeated excluding this study and no substantive changes in the results were observed.

Limitations of the individual studies have been discussed in detail in their respective publications [21–24] and include the possibility of selection bias due to not limiting the cases to those enrolled in the screening program from which controls were derived in Japan and low response rates in Hawaii and California. Included women did not differ from women not included on the basis of parity, but in Hawaii, they had a slightly older age at first birth. Other limitations include the self-report of information about reproductive history and confounders and the low number of nulliparous women (288 cases and 256 controls).

In conclusion, this study demonstrates that parity and mammographic density have independent effects on breast cancer risk. Although it suggests that the association between mammographic density and breast cancer risk may be stronger in nulliparous than parous women, this effect modification was only observed in the data from one of the four studies.

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Figure 1.

Dose-response relationship between percent dense area and odds of breast cancer, by parity. The relationship was modeled using restricted cubic splines²⁶ with knots at the 10th, 50th, and 90th percentiles (8, 29, and 56 percent dense area), and using 0% as the reference level.

Table 1

Characteristics of the study participants

Characteristic	Cases N = 1699	Controls N = 2422
Location, %		
California	36.8	18.6
Hawaii	35.7	27.5
Minnesota	19.4	27.8
Japan	8.1	26.1
Ethnicity, %		
Caucasian	46.4	43.8
Asian	36.3	41.9
African American	12.0	6.4
Other	5.3	7.8
No. of children, %		
0	17.0	10.6
1–2	43.7	44.9
3	39.4	44.5
Age at first birth (years), % of parous women		
< 26	62.7	65.7
26	37.3	34.3
Menopausal status/HRT use, %		
Premenopausal	24.5	26.9
Postmenopausal/no HRT	45.1	45.8
Postmenopausal/any HRT	30.3	27.3
Family history of breast cancer, %	15.5	9.6
Age at mammogram (years), mean (SD)	57.4 (11.8)	57.2 (12.2)
Body mass index (kg/m ²), mean (SD)	25.4 (5.3)	25.4 (5.3)
Percent dense area, mean (SD)	31.7 (17.6)	29.6 (18.9)
Dense area (cm ²), mean ^a (95% CI)	33.6 (32.6–34.6)	28.6 (27.8–29.4)
Nondense area (cm ²), mean ^b (95% CI)	78.0 (75.6–80.4)	77.1 (75.2–79.1)

^aBack-transformed from the mean of square root-transformed values.

^bBack-transformed from the mean of logarithm-transformed values.

Table 2Adjusted mean^a mammographic density (95% CI) by number of children and age at first birth, among controls

Mammographic density variable	No. of children	All	<u>Parous women, by age at first birth</u>	
			< 26 years	26 years
Percent dense area	0	34.7 (32.8–36.5)	-	-
	1–2	29.9 (29.0–30.8)	29.1 (27.8–30.3)	30.8 (29.4–32.1)
	3	28.2 (27.3–29.2)	28.1 (27.1–29.2)	28.6 (26.7–30.6)
		<i>P</i> -trend < 0.01		
Dense area (cm ²)	0	33.0 (30.6–35.4)	-	-
	1–2	30.0 (28.9–31.1)	29.6 (28.1–31.2)	30.4 (28.7–32.1)
	3	26.3 (25.3–27.4)	26.5 (25.3–27.7)	25.6 (23.4–27.9)
		<i>P</i> -trend < 0.01		

^aMeans are adjusted for age at mammogram, BMI, location/ethnicity, menopausal status/HRT use. The mean for percent dense area is an arithmetic mean, and the mean for dense area is a geometric mean that is backtransformed from square root-transformed values.

Table 3

Odds ratios (95% CI) for the association between mammographic density and breast cancer risk, by number of children and age at first birth

Subgroup	Percent dense area				Dense area			
	Level	Cases	Controls	OR ^a (95% CI)	Level	Cases	Controls	OR ^a (95% CI)
Nulliparous	< 20%	42	72	1.00	< 20 cm ²	42	60	1.00
	20–35	93	72	2.83 (1.64–4.87)	20–35	91	78	1.90 (1.09–3.31)
	> 35	153	112	2.63 (1.51–4.56)	> 35	155	118	2.18 (1.31–3.63)
	doubling			1.39 (1.13–1.72)	doubling			1.35 (1.11–1.65)
Parous	< 20%	436	801	1.00	< 20 cm ²	362	696	1.00
	20–35	444	633	1.51 (1.25–1.82)	20–35	444	722	1.33 (1.10–1.60)
	> 35	531	732	1.90 (1.56–2.32)	> 35	605	748	1.80 (1.50–2.16)
	doubling			1.24 (1.15–1.33)	doubling			1.31 (1.22–1.41)
				<i>P</i> -interaction = 0.054				<i>P</i> -interaction = 0.63
1–2 children	< 20%	185	338	1.00	< 20 cm ²	150	289	1.00
	20–35	219	304	1.43 (1.08–1.88)	20–35	240	378	1.35 (1.02–1.78)
	> 35	338	445	1.87 (1.41–2.49)	> 35	352	420	1.88 (1.43–2.45)
	doubling			1.24 (1.12–1.39)	doubling			1.29 (1.16–1.44)
3 children	< 20%	251	463	1.00	< 20 cm ²	212	407	1.00
	20–35	225	329	1.57 (1.22–2.03)	20–35	204	344	1.27 (0.98–1.65)
	> 35	193	287	1.82 (1.36–2.43)	> 35	253	328	1.67 (1.29–2.15)
	doubling			1.22 (1.11–1.34)	doubling			1.31 (1.19–1.45)
				<i>P</i> -interaction = 0.34				<i>P</i> -interaction = 0.87
AFB < 26 years	< 20%	312	572	1.00	< 20 cm ²	253	481	1.00
	20–35	281	421	1.51 (1.21–1.90)	20–35	261	458	1.24 (0.98–1.57)
	> 35	292	430	1.80 (1.40–2.31)	> 35	371	484	1.63 (1.30–2.04)
	doubling			1.20 (1.10–1.30)	doubling			1.25 (1.15–1.36)
AFB ≥ 26 years	< 20%	124	229	1.00	< 20 cm ²	109	215	1.00
	20–35	163	212	1.55 (1.11–2.17)	20–35	183	264	1.55 (1.13–2.13)
	> 35	239	302	2.10 (1.49–2.96)	> 35	234	264	2.19 (1.59–3.00)
	doubling			1.33 (1.16–1.53)	doubling			1.47 (1.28–1.69)

Subgroup	Percent dense area				Dense area			
	Level	Cases	Controls	OR ^a (95% CI)	Level	Cases	Controls	OR ^a (95% CI)
<i>P</i> -interaction = 0.16								
<i>P</i> -interaction = 0.03								

^aAdjusted for age at mammogram, BMI, menopausal status/HRT use, family history of breast cancer, and location/ethnicity.

Table 4

Modification of the association between percent dense area and breast cancer risk by parity, within subgroups defined by various factors

Factor	Nulliparous			Parous			P-interaction
	Subgroup	Cases	Controls	OR ^a per doubling of percent dense area (95% CI)	Cases	Controls	OR ^a per doubling of percent dense area (95% CI)
Location ^b							
	California	135	73	1.26 (0.92–1.72)	490	377	1.17 (1.02–1.33)
	Hawaii	94	76	2.32 (1.47–3.67)	513	591	1.32 (1.16–1.51)
	Minnesota	41	85	1.13 (0.69–1.83)	289	588	1.39 (1.20–1.61)
Ethnicity ^b							
	Caucasian	146	159	1.31 (1.01–1.70)	642	902	1.29 (1.17–1.43)
	Asian	104	63	1.03 (0.66–1.60)	513	953	1.15 (1.02–1.29)
Body mass index ^b							
	18.5–<25 kg/m ²	177	125	1.27 (0.86–1.88)	731	1133	1.28 (1.13–1.45)
	≥25 kg/m ²	98	119	1.44 (1.09–1.90)	645	968	1.24 (1.13–1.35)
Menopausal status							
	Premenopausal	110	65	0.91 (0.59–1.42)	307	586	1.08 (0.92–1.28)
	Postmenopausal	178	191	1.72 (1.31–2.25)	1104	1579	1.28 (1.18–1.39)

^aAdjusted for age at mammogram, BMI, menopausal status/HRT use, family history of breast cancer, and location/ethnicity.

^bResults are not shown for subgroups with less than 20 nulliparous cases or controls: Japan, African American, other ethnicity, or BMI<18.5 kg/m².

Table 5

Odds ratios for the association between parity and age at first birth and breast cancer risk, with and without adjustment for mammographic density

	Not adjusted for mammographic density		Adjusting for percent dense area		Adjusting for dense area	
	OR ^a (95% CI)	OR ^a	Change ^b	OR ^a	Change ^b	
No. of children						
0	1.00	1.00		1.00		
1–2	0.76 (0.62–0.93)	0.79	13.5%	0.78	8.8%	
3	0.65 (0.53–0.80)	0.70	14.8%	0.71	15.7%	
Age at first birth (parous women)						
<26 years	1.00	1.00		1.00		
26	1.08 (0.93–1.26)	1.05	– c	1.05	– c	
No. of children, age at first birth						
Nulliparous	1.00	1.00		1.00		
1–2 children, AFB < 26 yr	0.74 (0.59 – 0.93)	0.78	16.4%	0.77	10.9%	
1–2 children, AFB ≥ 26 yr	0.77 (0.62 – 0.97)	0.80	9.9%	0.79	6.2%	
3 children, AFB < 26 yr	0.66 (0.53 – 0.81)	0.71	15.5%	0.71	16.3%	
3 children, AFB ≥ 26 yr	0.64 (0.48 – 0.85)	0.69	12.8%	0.69	13.8%	

^a All ORs are adjusted for age at mammogram, BMI, menopausal status/HRT use, family history of breast cancer, and location/ethnicity. Age at first birth is further adjusted for parity.

^b Percent change with adjustment for mammographic density variable (continuous, log-transformed) = $100\% \times (\text{OR}_{\text{not adjusted for mammographic density}} - \text{OR}_{\text{adjusted for mammographic density}}) / (\text{OR}_{\text{not adjusted for mammographic density}} - 1)$

^c Because the OR without adjustment for mammographic density was not significant, the percent change was not calculated.