Mammographic Density and Breast Cancer in Three Ethnic Groups[1]

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Abstract

The extent of radiodense tissue on a mammogram (mammographic densities) is strongly associated with breast cancer risk among (non-Latina) white women, but few data exist for African-American and Asian-American women. We collected prediagnostic mammograms from 622 breast cancer patients and 443 control subjects ages 35–64 years from three different ethnic groups (whites, African Americans, and Asian Americans) who participated as cases and controls in one of two ongoing breast cancer studies. Percent and absolute mammographic density were assessed using a previously validated computer-assisted method. In all three ethnic groups combined, breast cancer risk increased with increasing percent mammographic density. After adjustment for ethnicity, age, body mass index, age at menarche, breast cancer family history, age at and number of full-term pregnancies, menopausal status, and hormone replacement therapy use, women with the highest percent density had 5-fold greater breast cancer risk than women with no density ($P_{trend} = 0.0001$). The impact of percent density on risk was stronger for older than for younger women (≥50 *versus* <50 years; $P = 0.05$). Risk estimates did not differ significantly by ethnicity, with breast cancer risk (95% confidence interval) increasing 15% (4–27%) in whites, 30% (5–61%) in Asian Americans, and 11% (−2–26%) in African Americans for each 10% increase in density. The trends were similar for absolute density. Our results confirm that increases in computer-assisted mammographic density measurements are associated with a strong gradient in breast cancer risk. Furthermore, our findings suggest that mammographic density is as strong a predictor of risk for African-American and Asian-American women as for white women.

Introduction

The radiographic appearance of a mammogram is determined by the relative amounts of fat (which is radiolucent) and epithelial/fibrous tissue (which is radiodense). Mammographic density is a measure of the radiodense area on the mammogram. A number of different classification schemes have been used to characterize the amount of mammographic density from Wolfe's (1, 2) four parenchymal patterns to the percentage of the breast that is dense (3–5). The results relating the different classification schemes of mammographic density to breast cancer risk have been reviewed in detail by several investigators (6–9). These reviews have concluded that regardless of the method used to classify these densities, mammographic density is an independent predictor of breast cancer risk, with risk increasing with increasing density. The magnitude of this increase in risk is greater than that associated with nearly all other breast cancer risk factors. The three most impressive studies to date (3, 10, 11) suggest that women with the most dense breasts have a 4–6-fold increased risk of breast cancer compared with women with the least dense breasts. However, each of these three studies was conducted within the context of a screening project. One of our goals was to assess the effects of mammographic density on breast cancer risk in the context of a population-based case-control study among women who are not participating in a screening program.

Studies of mammographic density have been conducted mainly in (non-Latina) white women. It is unclear to what extent mammographic density represents a risk factor for breast cancer among African-American and Asian women (4, 12–14). We have previously suggested that mammographic density represents a marker for breast cell proliferation (15). It is essential to determine whether mammographic density represents a risk factor in all ethnic groups if it is to be used as a surrogate end point for breast cancer in intervention and natural history studies. We report here our case-control study in Los Angeles County of mammographic densities as a breast cancer risk factor in three ethnic groups: African Americans, Asian Americans, and whites.

Subjects and Methods

Subject Identification. Subjects included in this analysis were selected from two ongoing breast cancer case-control studies conducted at the University of Southern California: the Los Angeles County component of the Women's CARE[3] Study (16) and a study of Asian-American women.

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[3] The abbreviations used are: CARE, Contraceptive and Reproductive Experiences; ROI, region of interest; OR, odds ratio; CI, confidence interval; HRT, hormone replacement therapy; ERT, estrogen replacement therapy; EPRT, estrogen and progestin replacement; BMI, body mass index.

The Women's CARE study is a multicenter, population-based study conducted among women ages 35–64 years in five areas of the United States, including Los Angeles County (16). United States-born white and African-American women residing in Los Angeles County when diagnosed with a first primary invasive breast cancer between June 1994 and August 1998 were eligible as case subjects. The Women's CARE Study protocol specified that potentially eligible cases be sampled to provide approximately equal numbers of white and African-American cases in each 5-year age group. Controls were selected by random digit dialing among the residents of Los Angeles County and were frequency matched to cases on age and ethnicity. Participation rates in Los Angeles were 71.9% for African-American cases, 70.6% for African-American controls, 74.6% for white cases, and 76.2% for white controls (16).

The breast cancer case-control study in Asian-American women included Chinese, Filipino, and Japanese-American women ages 25 to 74 years who resided in Los Angeles County (17). Cases were diagnosed with a first primary invasive breast cancer between January 1995 and December 1997. Sixty percent of the cases identified were interviewed. Controls in the Asian-American study were frequency matched to cases on age (*i.e.*, month and year of birth within 5 years) and specific Asian ethnicity. Potentially eligible controls were identified using a protocol where residences were contacted according to a preset algorithm that defined the initial residence to contact in the case's neighborhood and proceeded through a defined sequence of adjacent residences. The search continued until an eligible control was located or an obligatory number of houses enumerated. If no one was at home at the time of the field visit, a letter was left seeking an eligible control. The household was asked to return the letter even if no eligible woman lived at the residence. Letters were printed in English and the appropriate Asian language. The first eligible woman identified in the predefined sequence in the neighborhood was recruited as a control for the specific case patient. An average of 61 houses was canvassed to find an eligible control who was interviewed.

For both studies, all cases were identified by the Los Angeles County Cancer Surveillance Program, an established population-based cancer registry that is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results registry program. Approximately 90% of all breast cancer cases eligible for this study were ascertained within 2 months of diagnosis. Cases and controls were interviewed concurrently at their homes or offices. Interviewers used structured questionnaires that contained a standard set of questions on established and suspected breast cancer risk factors, including information on previous mammograms. The study questionnaire for the Asian-American study was based on the Women's CARE Study questionnaire but also included questions related to migration and dietary factors. Trained bilingual interviewers performed the interviews in the Asian-American study. The questionnaire was translated into Cantonese and Mandarin because >50% of Chinese subjects required translation. However, an English questionnaire was used for Filipino and Japanese subjects because <5% of these women required translation.

A reference date, created for each study subject, was the date of diagnosis for cases, the date on which the screening questionnaire (random digit dialing) was completed for the CARE controls, and the date the control was identified for the Asian-American controls.

From these two studies, we identified breast cancer patients with unilateral cancer who reported having a diagnostic or prediagnostic mammogram of the contralateral breast within 5 years of their diagnosis date, and controls who reported a mammogram within 5 years of their reference date or in the 1 year after their reference date. Totally, we identified 1822 women (1052 patients and 770 controls) who were eligible to participate in this study. The study was approved by the Institutional Review Board at University of Southern California.

Processing of Mammograms. We requested permission to borrow the most recent prediagnostic or diagnostic mammogram for the eligible cases and the most recent mammogram within the defined time period for the eligible controls. Each participant provided a signed release allowing us to request her mammograms.

Of 1822 women, we obtained and scanned one or more mammograms for 1194 women (65.5%; 701 patients and 493 controls). The rate of mammograms that we obtained for different ethnic groups was 72.7% (cases: 71.1%, controls: 74.6%) for whites, 64.7% (cases: 69.3%, controls: 59.4%) for African Americans, and 54.7% (cases: 57.2%, controls: 49.7%) for Asian Americans.

We were unable to retrieve the mammograms of 628 women because the facility had no record of the women (n = 101); the mammograms were no longer available at the facility (n = 273); no eligible mammograms existed, suggesting that the woman's report was inaccurate or incomplete (n = 177); the facility no longer existed (n = 37); or the facility did not respond to our request before the end of the study (n = 40).

All mammograms were digitized using an Omnimedia XRS 6cx scanner (Lumisys, Sunnyvale, CA) or a Cobrascan CX312T scanner (Radiographic Digital Imaging, Torrance, CA). Both scanners create an 8-bit (256 shades) gray scale image that is linear in the absorbance range 0–2.8. The images from the two scanners were indistinguishable with respect to density assessment. Mammograms were scanned at a resolution of 150 pixels/inch (59 dots/cm).

The scanned mammogram files of 27 women could not be assessed for density as the digitized files turned out to be unusable, and we were unable to obtain the films a second time. We excluded mammograms of 4 women who had only one mammogram and were pregnant at the time of that mammogram. We therefore obtained mammographic density results for 1163 women (675 patients and 488 controls).

The mammograms were read in batches containing equal proportion of cases and controls from each 5-year age group represented. For cases, we read the mammogram from the contralateral (nondiseased) breast. For controls, we randomly selected the right or left breast, while assuring that, within each batch, the control laterality distribution represented that of the unaffected (contralateral) breasts of the cases. The density assessments were performed by Dr. Ursin, whereas the breast area measurements were conducted by a research assistant trained by Dr. Ursin. Assessment methods have been previously described and validated (18). Briefly, these assessments use the digitized craniocaudal mammographic image. The computer software program assigns a pixel value of 0 to the darkest (black) shade in the image and a value of 255 to the lightest (white) shade with shades of gray assigned intermediate values. The total area of the breast is outlined using a computerized outlining tool, and the number of pixels within that outline is summed. The density assessment is done as follows: the reader outlines a ROI; this region includes the entire breast but excludes the pectoralis muscle, prominent veins, and fibrous strands. The reader then uses a tinting tool to apply a yellow tint to dense pixels with gray levels at or above some threshold X and ≤255. The reader searches for the best threshold where all pixels ≥X within the ROI are considered to represent mam-

Table 1 Descriptive characteristics of cases and controls with available mammograms by ethnic group

Variable	All women			Whites			African Americans			Asian Americans		
	Cases	Controls	P^a	Cases	Controls	P^a	Cases	Controls	P^a	Cases	Controls	P^a
No. of subjects	622	443		280	227		199	149		143	67	
Mean age, y	49.3	49.5	0.70	48.4	49.6	0.10	49.3	49.9	0.51	51.0	48.1	0.01
Mean BMI, kg/m^2	25.0	25.9	0.009	24.3	25.3	0.02	27.5	27.9	0.52	22.9	23.2	0.65
Mean age at menarche, y	12.6	12.5	0.32	12.5	12.3	0.15	12.4	12.5	0.34	13.0	12.9	0.56
First-degree breast cancer family history, %[b]	15.1	9.5	0.007	16.8	9.7	0.02	14.1	8.7	0.13	13.3	10.5	0.56
Parous, %[b]	78.8	83.5	0.05	73.9	78.9	0.20	87.9	87.3	0.85	75.5	91.0	0.008
Mean number of FFTP[c]	2.0	2.2	0.05	1.7	2.0	0.06	2.5	2.5	0.73	1.9	2.3	0.10
Mean age at FFTPs, y	24.6	23.7	0.02	25.2	24.0	0.02	21.7	21.1	0.35	28.0	28.1	0.85
Menopause and HRT use, %[b]			0.005			0.01			0.26			0.03
Premenopausal	46.8	41.3		50.0	38.8		47.3	39.6		39.8	53.7	
Postmenopausal and												
never HRT use	16.9	13.5		10.7	7.0		20.1	19.5		24.5	22.4	
current ERT use	9.8	17.2		10.7	20.3		11.6	18.1		5.6	4.5	
current EPRT use	11.7	14.9		16.5	21.6		8.5	5.4		7.0	13.4	
ex-ERT use	6.9	6.3		3.9	4.8		7.0	10.7		12.6	1.5	
ex-EPRT use	7.9	6.8		8.2	7.5		5.5	6.7		10.5	4.5	

[a] *P* ascertained from *t* test, except where otherwise noted.
[b] *P* ascertained from Pearson χ^2 test.
[c] FFTP, full-term pregnancy.

mographic densities. The software estimates the total number of pixels and the number of tinted pixels within the ROI. Absolute density represents the count of the tinted pixels within the ROI. Percent density, or the fraction (%) of the breast with densities, is the ratio of absolute density to the total breast area.

Statistical Analyses. We used *t* tests to evaluate case-control differences in continuous variables and Pearson χ^2 tests to evaluate differences in frequency distributions of categorical variables.

We treated percent and absolute mammographic density as both continuous and categorical variables. We used previously published categories of percent density. For absolute density, we tried a series of different categories that all yielded similar results. We present the results for tertiles of absolute density, where the tertiles were created for all women combined, and one additional categorical variable with 0 densities as the comparison group. Because of the nonnormal distribution of percent mammographic density, we used the nonparametric Wilcoxon test to compare the distribution of percent mammographic density of cases and controls after stratifying on age at mammogram and ethnicity. The ORs and their associated 95% CIs of breast cancer associated with different levels of percent or absolute mammographic density were estimated using standard unconditional multivariate logistic regression techniques (19) in the Epilog statistical package program (Epicenter Software, Pasadena, CA). We adjusted for demographic variables (ethnicity and age at mammogram in 5-year age groups) as well as a number of other potential confounding variables: BMI at the date 5 years before reference date (BMI, in kg/m^2, continuous), age at menarche ($\leq$13, $>$13 years), breast cancer family history [none, breast cancer in a mother or a sister (first degree), breast cancer in an aunt or grandmother (second degree)], number of full-term pregnancies (none, 1–2, $\geq$3), a variable combining menopausal status, and HRT use at the time of the mammogram (premenopausal, postmenopausal, and never HRT use, postmenopausal and current ERT, postmenopausal and current EPRT use, postmenopausal and ex-ERT, and postmenopausal and ex-EPRT therapy), and age at first full-term pregnancy ($<$30, $\geq$30 years). When separately estimating ORs by age at mammogram ($<$50, $\geq$50 years), we did not adjust for the combined menopausal status and HRT use variable in the $<$50 year age group because of few subjects with known postmenopausal status or HRT use. All *P*s reported are two-sided, and *P*s < 0.05 were considered statistically significant.

To use consistent sample size for all analyses, we excluded 52 women who had undergone simple hysterectomy and 3 women with unknown menopausal status, 12 women with missing BMI information, 8 women with missing age at first full-term pregnancy, 4 women with missing age at menarche, and 19 women who were adopted or who did not know the breast cancer family history on more than half of their first-degree family members. An additional 29 women had unknown family history for 1–2 family members, but had known negative family history for the rest. We have included these 29 women in the analyses, coding them as having no known family history of breast cancer. Excluding them yielded results that are similar to those presented. After exclusion, a total of 1065 women (622 patients and 443 controls) remained in our analyses.

To know whether included participants were similar to eligible participants with no available mammograms, we stratified 1822 eligible subjects by case-control status and ethnicity and compared the prevalence of breast cancer risk factors in included women to that of eligible but not included women. Risk factors were similar in the two groups of women with a few exceptions, predominantly among the whites. Included white cases were on average 2.4 years older than white cases who were not included ($P_{t\ test} = 0.008$) and 11.5% more likely to have used HRT ($P\chi_{2\ test} = 0.02$). Included Asian-American and African-American cases were also 10.3 and 11.8% more likely to be HRT users ($P\chi_{2\ test} = 0.06$ and 0.02, respectively), and included African-American cases were slightly older ($P\chi_{2\ test} = 0.06$) than nonincluded cases. Included white controls were on average 3.6 years older ($P_{t\ test} = 0.0002$), 1.3 kg/m^2 heavier ($P_{t\ test} = 0.04$), and 20.5% more likely to use HRT ($P\chi_{2\ test} = .0006$) than white controls not included.

Results

Characteristics of the 622 breast cancer cases and 443 controls with available mammograms are shown in Table 1. Overall,

Table 2 Median (P_{25}–P_{75}[a]; no. of subjects) percent mammographic density in breast cancer cases and controls by ethnic group and age

	Cases	Controls	Two-sided P[b]
White			
<Age 50 years	46.02 (29.60–61.60; 154)	42.29 (20.41–52.17; 109)	0.04
≥Age 50 years	32.48 (20.04–51.07; 126)	20.41 (7.52–38.30; 118)	0.0002
African American			
<Age 50 years	42.41 (23.29–53.39; 103)	27.29 (13.24–55.98; 67)	0.20
≥Age 50 years	24.02 (7.33–40.14; 96)	18.70 (4.09–35.45; 82)	0.17
Asian American			
<Age 50 years	52.01 (34.23–64.80; 67)	43.85 (37.52–57.03; 37)	0.29
≥Age 50 years	35.82 (21.43–46.38; 76)	24.18 (10.99–40.05; 30)	0.04

[a] P_{25}, 25th percentile; P_{75}, 75th percentile.
[b] Wilcoxon test.

cases were on average slightly thinner than controls, were more likely to have a first-degree family history of breast cancer, and were older at the first full-term pregnancy. The case-control differences in BMI and family history were observable in all ethnic groups but were statistically significant only among whites. The case-control differences in parity (ever/never) were only statistically significant in Asian-American women, whereas the case-control differences in mean age at first full-term pregnancy were only statistically significant in whites. Overall, cases were more likely to be premenopausal and less likely to currently use HRT than controls. However, among Asian American women, controls were more likely to be premenopausal than cases. We adjusted for these variables in the subsequent analyses. Table 2 shows the median percent density for cases and controls by ethnic group and age group. Percent density was statistically significantly higher in white cases than controls in both the <50 years and ≥50 years age groups. Similarly, percent density was statistically significantly greater in older Asian-American cases than controls. No statistically significant differences were noted between African-American cases and controls overall or by age, or between young Asian-American cases and controls, although the cases had a higher median density than controls in each ethnicity-by-age group. Similarly, when restricting the analysis to premenopausal women <50 years, the case-control differences were no longer statistically significant (results not shown).

Percent density is a strong predictor of breast cancer risk in this study (Table 3). Women with 75% or higher density had a 5-fold greater risk of breast cancer than women with <1% density (OR = 5.23; 95% CI = 1.70–16.13; P_{trend} = 0.0001). Using somewhat more conservative categories to increase the numbers in the top category, women with 60% or higher density had a 3.5-fold increased risk of breast cancer compared with women with <1% density (95% CI = 1.72–7.22; P_{trend} = 0.0001, results not shown). When we examined the effect of mammographic density on breast cancer risk in the different ethnic groups, the strongest effects were seen for Asian Americans. The OR (95% CI) per 10% increase in percent density was 1.30 (1.05–1.61) for Asian Americans, 1.15 (1.04–1.27) for whites, and 1.11 (0.98–1.26) for African Americans. This apparent effect modification by ethnicity was, however, not statistically significant (P = 0.77). We also found increased risk of breast cancer associated with absolute density (P_{trend} = 0.0001). The OR per decile of absolute density was 1.16, similar to the OR of 1.15 per 10% increase in percent density. The ethnic-specific trends for absolute density were similar to what we observed for percent density. The OR (95% CI) per decile increase in absolute density was 1.43 (1.07–1.93) for Asian Americans, 1.18 (1.02–1.36) for whites, and 1.09 (0.96–1.25) for African Americans.

The results were quite similar whether we adjusted for BMI as a continuous or a categorical variable, or whether we adjusted for body weight as a continuous or a categorical variable (results not shown). Notably, the OR per 10% increase in percent density was nearly identical for the 3 ethnic groups when we restricted the analyses to women with more moderate levels of BMI. When we excluded women in the top quartile of BMI (≥27.46 kg/m^2), the ORs per 10% increase in percent density were 1.13 (95% CI = 1.01–1.26) for whites, 1.17 (95% CI = 0.99–1.39) for African Americans and 1.16 (95% CI = 0.92–1.48) for Asian Americans. There was no statistical significant effect modification by ethnicity within the Asian Americans (Chinese, Japanese, Filipino, or other).

Both in the data overall and within each ethnic group, BMI appears to modify the effect of percent density on breast cancer risk, with the effect being strongest in the leanest and the most obese women (P for effect modification in all women combined = 0.007). In women with BMI ≤ 21 kg/m^2, OR per 10% increase in percent density was 1.20 (95% CI = 1.09–1.33); in women with BMI of 21.1–29.9 kg/m^2, it was 1.09 (95% CI = 1.01–1.18); and in women with ≥BMI 30 kg/m^2, OR per 10% increase in percent density was 1.34 (95% CI = 1.11–1.62). These effects were only statistically significant in all women combined and in African Americans (P for effect modification = 0.02) but were observed in the two other ethnic groups as well, in both age groups (<50, ≥50 years), in both pre- and postmenopausal women, and in both postmenopausal HRT ever-users and never-users. The findings were similar for absolute density (P for effect modification in all women combined = 0.01).

The effect of percent mammographic density appeared stronger among older than younger women in all ethnic groups (Table 4; P for effect modification = 0.05) and stronger among postmenopausal than premenopausal women (P for effect modification = 0.004). The effect of absolute density appeared stronger in older and in postmenopausal women in whites and Asians, but there was no statistically significant effect modification by age or menopausal status in all women combined (P for effect modification = 0.45 and 0.40, respectively).

The study sample included 64 Latina whites and 3 Latina African Americans. Excluding these women did not substantially alter the results (results not shown).

Asian-American women have smaller breasts and had lower absolute mammographic density than white or African-American women. Both quintiles and quartiles of absolute densities yielded statistical significant trends with breast cancer risk (results not shown).

Restricting the analyses to cases whose mammograms

Table 3 ORs and 95% CIs for breast cancer associated with mammographic density by ethnic group

Density	Cases	Controls	Unadjusted OR	Adjusted OR[a]	Adjusted 95% CI[a]
Percent density					
All women[b]					
<1	21	35	1.00	1.00	Referent
1-	64	71	1.50	1.57	0.81–3.03
10-	100	88	1.89	1.74	0.91–3.31
25-	247	161	2.56	2.30	1.24–4.28
50-	170	82	3.46	3.21	1.65–6.25
≥75	20	6	5.56	5.23	1.70–16.13
					$P_{trend} = 0.0001$[c]
			Per 10%	1.15	1.07–1.23
White					
<10	37	57	1.00	1.00	Referent
10–59	189	147	1.98	1.57	0.93–2.63
≥60	54	23	3.62	2.56	1.23–5.31
					$P_{trend} = 0.01$[c]
			Per 10%	1.15	1.04–1.27
African American					
<10	39	42	1.00	1.00	Referent
10–59	138	94	1.58	1.44	0.81–2.58
≥60	22	13	1.82	1.66	0.64–4.32
					$P_{trend} = 0.22$[c]
			Per 10%	1.11	0.98–1.26
Asian American					
<10	9	7	1.00	1.00	Referent
10–59	108	52	1.62	3.07	0.80–11.77
≥60	26	8	2.53	6.42	1.23–33.48
					$P_{trend} = 0.03$[c]
			Per 10%	1.30	1.05–1.61
Test of effect modification by ethnic group $P = 0.77$[a]					
Absolute density (pixels)[b]					
All Women					
0	8	16	1.00	1.00	Referent
>0-	89	97	1.84	1.86	0.73–4.74
50,000-	105	85	2.47	2.05	0.79–5.32
100,000-	222	141	3.15	2.64	1.04–6.69
200,000-	117	62	3.77	3.30	1.27–8.61
300,000-	81	42	3.86	3.80	1.43–10.08
846,970					$P_{trend} = 0.0001$[c]
			Per decile	1.16	1.06–1.27
Absolute density (tertiles)[d]					
White					
First	68	92	1.00	1.00	Referent
Second	113	74	2.07	1.77	1.12–2.79
Third	99	61	2.20	1.85	1.14–2.99
					$P_{trend} = 0.01$[c]
			Per decile	1.18	1.02–1.36
African American					
First	58	58	1.00	1.00	Referent
Second	56	39	1.44	1.28	0.72–2.30
Third	85	52	1.64	1.53	0.89–2.63
					$P_{trend} = 0.13$[c]
			Per decile	1.09	0.96–1.25
Asian American					
First	50	29	1.00	1.00	Referent
Second	48	25	1.11	1.14	0.51–2.54
Third	45	13	2.01	2.93	1.23–6.95
					$P_{trend} = 0.02$[c]
			Per decile	1.43	1.07–1.93
Test of effect modification by ethnic group $P = 0.56$[a]					

[a] Adjusted for age at mammography, BMI, age at menarche, breast cancer family history, number of full-term pregnancies, menopausal status and HRT use, and age at first full-term pregnancy.
[b] Also adjusted for ethnicity.
[c] P for trend test is based on Wald statistic and is two-sided.
[d] Tertile cutpoints are 91,500 and 177,600 pixels.

Table 4 ORs and 95% CIs of breast cancer per 10% increase in percent mammographic density or per decile of absolute density in breast cancer cases and controls by ethnic group and age

Groups	Percent density		Absolute density	
	Adjusted OR[a]	Adjusted 95% CI[a]	Adjusted OR[a]	Adjusted 95% CI[a]
By age at mammography (yr)				
<50	1.08	0.98–1.19	1.11	0.99–1.26
≥50	1.24	1.11–1.38	1.20	1.05–1.38
Test of effect modification by age	Adjusted two-sided $P = 0.05$[a]		Adjusted two-sided $P = 0.45$[a]	
By race and age at mammography (yr)				
White				
<50	1.10	0.96–1.26	1.11	0.92–1.33
≥50	1.24	1.05–1.45	1.31	1.04–1.65
African American				
<50	1.08	0.90–1.29	1.12	0.92–1.36
≥50	1.13	0.94–1.35	1.04	0.85–1.26
Asian American				
<50	1.10	0.84–1.45	1.26	0.87–1.82
≥50	1.59	1.09–2.32	1.70	1.02–2.84

[a] Adjusted for ethnicity, age at mammography, BMI, age at menarche, breast cancer family history, number of full-term pregnancies, age at first full-term pregnancy as well as menopausal status and HRT use in women age ≥50 years and in the test of effect modification.

were obtained ≥6 months before their diagnosis did not substantially alter the results (results not shown).

Discussion

In this study of women ages 35–64 years living in Los Angeles County, California, we find that percent mammographic density is a strong risk factor for breast cancer, with risk estimates that are similar to those previously reported in studies using quantitative density estimates (9). In our study, women with 75% or greater percent density were at a >5-fold increased risk of breast cancer compared with women with <1% densities; breast cancer risk of white women increased 15% for every 10% increase in percent density. The results using detailed categories were comparable with those presented by Boyd *et al.* (10).

We found similar effect estimates per decile of absolute density as per decile of percent density overall and within each ethnic group. Although percent mammographic density is a more commonly used estimate when examining breast cancer risk, absolute density may be a more appropriate marker in some instances. For instance, Boyd *et al.* (20) found a statistically significant reduction in absolute density but not in percent density in a 2-year randomized trial of low-fat high carbohydrate diet.

Our risk estimates were consistently higher among older than younger women in all three ethnic groups. This is consistent with the results of Boyd *et al.* (10) and Byrne *et al.* (11) but not those from the Breast Cancer Detection and Demonstration Project (21) or from a case-control study conducted in New York (22).

We found that Asian-American women had the highest and African-American women the lowest median percent density. We also found that the effect of mammographic density varied across ethnic groups, with the strongest odds ratios in Asian Americans and the weakest in African Americans. Although there was no statistical significant effect modification by ethnicity, we had limited power in assessing such effect modification in this study. In a previous study from Hawaii, Maskarinec and Meng (14) reported that the effects of mammographic density on breast cancer were similar in whites and Asian Americans. Although we found somewhat stronger effects than they did, particularly in the Asians, our results are consistent with theirs in that mammographic density is associated with breast cancer risk in non-whites as well as in whites. These findings for Asian-American women are consistent with recent observations on trends in breast cancer incidence among Asian and white women. Although the breast cancer incidence rates of Asian Americans living in California were traditionally much lower than those of whites (23), rates in Asian Americans have recently increased substantially in Los Angeles (24). The underlying breast cancer incidence rates of Asian-American women participating in our study may therefore be quite similar to those of whites.

Our results in African Americans were consistently weaker than we observed in the other two ethnic groups, and the CIs consistently included 1.0. This was the case both for percent and absolute density. We also found that the association between mammographic density and breast cancer risk appeared to be modified by BMI. In our study, this apparent effect modification appeared to be U-shaped, with strongest effect of mammographic density on breast cancer risk in the leanest as well as in the most obese women. This apparent effect modification was strongest in the African-American women and may therefore explain the weaker finding in this ethnic group. The reason for this apparent effect modification by BMI is unknown. Obese women in this and previous studies have lower percent mammographic density but are postmenopausally at higher risk of breast cancer than thinner women. The elevated risk of breast cancer in these women has been attributed to peripheral conversion of androgens to estrogen (25), which presumably should increase breast cell proliferation. If so, then mammographic density ought to be a risk factor in obese as well as in thinner women. It is possible that the effect modification by BMI was an artifact in our study. On the other hand, if it is real, then this suggests that clinical prevention trials using mammographic density as a surrogate measure must stratify or restrict on BMI.

A weakness of our study is that we were unable to obtain mammograms from all of the eligible women. However, women whose mammograms were available were similar to women whose mammograms were not available on most breast cancer risk factors. The differences in age and BMI in included

and not-included whites are unlikely to have accounted for our results because we adjusted for these factors. HRT use was more common in included cases and particularly common in included white controls. Overall, this resulted in our cases being slightly less likely to use HRT than controls. Previous studies have shown that HRT reduces sensitivity of screening mammograms (26, 27). It is therefore possible that HRT use may have masked cancers in some of our controls by causing higher mammographic density. This would have resulted in biasing any case-control differences toward the null.

In conclusion, our results suggest that mammographic density is a risk factor in all ethnic groups to the same extent. This supports that mammographic density is suitable as a surrogate end point for breast cancer in cancer prevention studies.

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