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Mammographic density and breast cancer risk in White and African American Women

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Abstract

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Mammographic density is a strong risk factor for breast cancer, but limited data are available in African American (AA) women. We examined the association between mammographic density and breast cancer risk in AA and white women. Cases (n = 491) and controls (n = 528) were from the Carolina Breast Cancer Study (CBCS) who also had mammograms recorded in the Carolina Mammography Registry (CMR). Mammographic density was reported to CMR using Breast Imaging Reporting and Data System (BI-RADS) categories. Increasing mammographic density was associated with increased breast cancer risk among all women. After adjusting for potential confounders, a monotonically increasing risk of breast cancer was observed between the highest versus the lowest BI-RADS density categories [OR = 2.45, (95 % confidence interval: 0.99, 6.09)]. The association was stronger in whites, with ~40 % higher risk among those with extremely dense breasts compared to those with scattered fibroglandular densities [1.39, (0.75, 2.55)]. In AA women, the same comparison suggested lower risk [0.75, (0.30, 1.91)]. Because age, obesity, and exogenous hormones have strong associations with breast cancer risk, mammographic density, and race in the CBCS, effect measure modification by these factors was considered. Consistent with previous literature, density-associated risk was greatest among those with BMI > 30 and current hormone users (P value = 0.02 and 0.01, respectively). In the CBCS, mammographic density is associated with increased breast cancer risk, with some suggestion of effect measure modification by race, although results were not statistically significant. However, exposures such as BMI and hormone therapy may be important modifiers of this association and merit further investigation.

Keywords

Mammographic breast density; Breast cancer; Race; African American; Epidemiology

Introduction

Mammographic breast density describes the radiological appearance of dense breast tissue and is a measure of the fibroglandular tissue composition in the breast. Different classification schemes have been used to visually characterize breast density, including Wolfe's parenchymal patterns [1,2], Tabar's classification scheme [3], the American College of Radiology's Breast Imaging Reporting and Data System (BI-RADS) [4], and quantitative methods that estimate the percentage of dense area. Mammographic density is associated with breast cancer risk regardless of the method used to measure breast density [5,6]. In fact, breast density is one of the strongest and most consistent risk factors for breast cancer, with women with highestmammographic density at a four- to sixfold increased risk of developing breast cancer compared with women with the least dense tissue [5, 7–13].

The majority of studies examining the association between breast density and breast cancer risk have been among white women, but breast density may vary by race. Data examining the association in different racial groups, including African American (AA) women, are limited and have reported conflicting results: three studies concluded that AA women have higher mammographic density [14–16], two found no difference [17, 18], and one found lower mammographic density in AA compared with white women [19]. Only two studies have examined the association between breast density and breast cancer risk in AA women. Wolfe et al. [20] reported stronger effects of breast density on risk among AA women, while Ursin et al. [11] reported stronger effects among white women. Variation in exposures that predict breast density and breast cancer risk may differ in prevalence by race, such as BMI and hormone use, and these factors may also play a role in the associations between race, breast density, and breast cancer risk. Ursin et al. did not examine hormone therapy (HT) as an effect measure modifier, but suggested potential modification of the breast density-breast cancer risk association by BMI [11]. Given strong secular trends in associations between

race, BMI, and HT and because of the role of each of these factors in predicting both breast density and breast cancer risk, evaluation of these factors within a single study could help explain how these factors interact to affect breast cancer risk. It is important to understand the factors that may contribute to breast cancer disparities [21].

We examined the association between breast density and breast cancer by race, BMI, and HT use in the Carolina Breast Cancer Study (CBCS). The CBCS is a large, population-based study that over-sampled young, AA women. By linking the CBCS with the Carolina Mammography Registry (CMR), we were able to obtain the BI-RADS density classification for a large number of women in the CBCS.

Methods

Study setting and population

Subjects included in this study were participants in the CBCS who also hadmammograms recorded in theCMR. CBCS is a population-based, case–control study designed to identify genetic and environmental factors for breast cancer risk in AA and Caucasians. CBCS participants are residents of 24 counties in North Carolina and were recruited in two phases, Phase I (1993–1996, $n = 890$ invasive breast cancer cases) and Phase II (1996–2001, $n = 1421$ including 913 invasive and 508 carcinoma in situ cases). No restrictions were made on the basis of stage (DCIS or invasive stage), either in the primary study or in the current analysis. Controls were age and race frequency-matched to cases [Phase I ($n = 841$); Phase II ($n = 1181$)]. Cases were identified from the North Carolina Central Cancer Registry, and controls were identified using drivers' license and Medicare beneficiary lists [22–24]. Randomized recruitment was used to over-sample younger and AA women [25]. Participants ranged in age from 20 to 74 years and provided informed consent via a protocol approved by the Institutional Review Board (IRB) of the University of North Carolina (UNC). The overall response rates were 76.0 % for cases and 55.0 % for controls, and among controls, response was lowest for AAs less than age 50 (47.1 %) and highest for whites age 50 or older (64.9 %) [23, 26]. In person interviews were conducted for cases and controls and body size measurements including waist circumference, hip circumference, waist circumference-to-hip circumference ratio (WHR), and body weight were measured by a nurse at the time of the interview [27].

The CMR is a community-based mammography registry funded by the Department of Defense in 1994 and supported as part of Breast Cancer Surveillance Consortium by the National Cancer Institute since 1995. As of January 2010, CMR included data from 65 participating facilities located in 39 North Carolina counties. Data collected at each imaging study include: self-reported date of birth, race/ethnicity, family history of breast cancer, menopausal status, current HT use and imaging data and methods recorded by the radiologists and technologists. CMR is approved and reviewed annually by the UNC IRB [28]. The following counties included in the CBCS were not represented in the CMR: Alamance, Orange, Wake, Johnston, Lee, Harnett, Bertie, Wilson, Edge-Combe, Pitt, Pamlico, Beaufort, and Tyrell. CMR and CBCS were linked using probabilistic linkage with four variables; first and last name, date of birth, and last four digits of the social security number [29–31]. Success rate for linking the CBCS and the CMR was similar for both races. BI-RADS breast density, HT, and age were collected from the CMR and all other participant data were taken from the CBCS.

Mammographic density assessment

Mammographic breast density is recorded qualitatively in the CMR using the American College of Radiology's BI-RADS classification, a standardized visual assessment metric

that is routinely reported by radiologists in the U.S. BI-RADS density assessment defines four categories of breast composition including: (1) almost entirely fat, (2) scattered fibroglandular densities, (3) heterogeneously dense, and (4) extremely dense [4]. Breast density measured in the CMR is per woman and not per breast. Vachon et al. [32] concluded that density is a general marker of breast cancer risk and is not specific to breast side or location of the eventual cancer; density has also been shown to be highly correlated between breasts within a woman [33].

For cases in our analysis, we defined density based on the reported BI-RADS density from the screening (228 of cases) or diagnostic (263 of cases) mammogram performed within 5 years prior to diagnosis and up to 1 year after breast cancer diagnosis. For cases with screening mammograms within 1 year prior to diagnostic mammograms ($n = 82$), 79 % ($n = 65$) were categorized in the same BI-RADS density category, while 10 % ($n = 8$) had increased and 11 % ($n = 9$) had decreased density in the screening mammogram compared with the diagnostic mammogram. Thus, while BI-RADS has well-established limitations in inter-reader agreement when disease is present [34], we expect the misclassification would be non-differential with respect to disease status. For controls, mammogramswithin 5 years prior to and up to 3 years after the selection date were eligible. If women hadmultiplemammograms prior to breast cancer diagnosis or selection date into CBCS, the mammogram before diagnosis/ selection was selected if available, and the mammogram closest to the diagnosis or selection date was chosen. Studies have shown that elevated risks of breast cancer associatedwith breast density persist for at least 5 years after a mammogram [8, 12, 35–37]. There are some suggestions in the literature that agents used to treat breast cancermay alter breast density as early as 18 months after initiating therapy [38], and thus for cases, we excluded mammograms that occurred more than one year after diagnosis. To assess whether broader inclusion dates among controls affected comparability to cases, we conducted a sensitivity analysis with controls ($n = 340$) restrictingmammograms to 5 years prior to and <1 year after the control selection date.

Statistical analysis

The variable coding schemes for covariates were chosen for consistency with previous CBCS publications [22]. Briefly, race was categorized as AA or white based on self-report. Age was age at diagnosis for cases and age at selection into the CBCS for controls and was used as a continuous variable in analyses and as a categorical variable (<50 vs. 50+) for assessment of effect measure modification by age, similar to previous studies. Body mass index (BMI) was calculated as body weight (kg)/height $(m)^2$ and was used as a continuous variable. To assess whether BMI was an effect measure modifier, BMI was categorized based upon National Heart, Lung, and Blood Institute (NHLBI) cutpoints (<25, 25–29, and ≥30) [39]. Age at first full-term pregnancy and parity/nulliparity were combined to create a categorical variable describing parity status and age at first birth. Age was age at diagnosis/ selection into the CBCS. HT use was categorized as current versus not current as collected by the CMR at the time of the mammogram. A sensitivity analysis restricting HT users (as reported in CMR) to postmenopausal women (as reported in CBCS) was conducted. The results for HT use were not substantially different among all women versus among only postmenopausal women; therefore, HT use was used without restrictions for menopausal status. All categorical variables were coded using indicator variables.

We used unconditional logistic regression to estimate odds ratios (ORs) and 95 % confidence intervals (CIs) for the association between breast density and breast cancer risk (SAS version 9.3, SAS Institute, Cary NC). To assess the comparability of the CMR–CBCS merged data and the full CBCS dataset, we compared the characteristics of participants who matched to the CMR (the current dataset) to those in the entire CBCS by estimating ORs for established breast cancer risk factors. TheORswere similar in theCMR–CBCS merged

dataset and theCBCS as awhole for all variables assessed (see Additional File 1 in Supplementary material).

Likelihood ratio tests (LRT) were used to examine effect measure modification of the breast density-breast cancer risk association by race, BMI, HT use, and age; *P* values of <0.05 were considered significant. Menopausal status was not examined as an effect measure modifier due to the high correlations between categories of age (<50 vs. 50+). Potential confounders were selected based on prior knowledge, using directed acyclic graphs (DAGs) [40]. We adjusted for age, race, BMI, menopausal status, first degree family history of breast cancer, age at menarche, and parity/age at first full-term pregnancy combined using variables from the CBCS and used current HT from the CMR. We adjusted for the offset term used in the CBCS to oversample young AA women. The same variables were retained in models that included interaction terms for BMI, HT use, and race.

Results

Characteristics of breast cancer cases and controls are presented in Table 1. The time between CBCS selection date and the date of the selected mammogram in the CMR ranged from −3.8 years to 1 year with an average of 3 weeks prior to diagnosis for cases and −4.4 to 3 years with an average value of 5 months post selection for the controls (Table 1). Overall and within each racial group, cases were slightly younger than controls, were more likely to have first degree family history of breast cancer, were younger at menarche, and were more likely to be non-current users of HT. White cases were more likely to be never users of oral contraceptives, and AA women were slightly more likely to be ever users of oral contraceptives.

White cases and controls had a greater percentage of “extremely dense” and “heterogeneously dense” breasts compared with AA cases and controls. The BI-RADS density category with greatest prevalence among AA was “scattered fibroglandular densities” (BI-RADS 2), while among whites “heterogeneously dense (BI-RADS 3)” was the most prevalent. In the dataset as a whole, “heterogeneously dense” was the most prevalent category; thus, when modeling the OR associated with breast cancer risk, BI-RADS density category 2 was set as the referent.

Table 2 presents the ORs and 95 % CIs for unadjusted and adjusted models with both BI-RADS 1 (Model 1) and 2 (Model 2) as the referent groups. Model 1 is included to facilitate comparison with previous studies (comparing “extremely dense”, BI-RADS 4, to “almost entirely fatty”, BI-RADS 1). Among all women, BI-RADS 4 was associated with increased risk of breast cancer compared to BI-RADS 2 and BI-RADS 1 [1.19 (0.72, 1.95), and 2.45 (0.99, 6.09), respectively]. Results from sensitivity analyses restricting the exposure window (to only 1 year following selection among controls) were similar: the association comparing BI-RADS category 4 to category 2 was [1.25 (0.71–2.20)] for controls with the same selection criterion as cases, and [1.19 (0.72–1.95)] for controls with mammograms within 5 years prior to and 3 years post selection date. We therefore used the latter, larger control group to increase precision in all subsequent analyses.

Race was not a modifier of the breast density-breast breast cancer association (likelihood ratio test *P* value = 0.76), despite differences in the distribution of breast density by race. However, confidence intervals were wide, especially with BI-RADS 1 as the reference group. Although not statistically significant, some variation by race was evident when comparing BI-RADS 4 to BI-RADS 2 density categories (Model 2, Table 2); among white women [OR for BI-RADS 4 vs. 2 = 1.39, (0.75, 2.55)], while an opposite and inverse association was observed in AA women [OR for BI-RADS 4 vs. 2 = 0.75, (0.30, 1.91)].

Recent literature has suggested that BMI and HT use differ in prevalence by race and may modify the association between breast density and breast cancer risk. Thus, effect measure modification by BMI, HT use, and age were considered. There were no significant effect modification by age (0.67), or BMI (0.09), but HT use was a significant effect measure modifier (0.0002).

Table 3 shows that the associations with density were strongest among current HT users, with an almost sixfold increase comparing current users with extremely dense breasts to current users with scattered fibroglandular densities ([OR = 5.61 (1.86, 16.96)], Model 2, Table 3) and a significant trend with increasing BI-RADS density (*P* value = 0.01). While there was no modification of the OR by age, obesity did modify the breast density–breast cancer risk association. Among obese women, those with BI-RADs 4 density had a threefold increased risk of breast cancer relative to those with BI-RADS 2 [3.29 (1.00, 10.83)], and there was a significant trend (*P* value = 0.01). For women with BMI less than 25 or with BMI 25–29, no statistically significant trends were observed.

Discussion

This study combined two rich data sets to examine modification of the breast density-breast cancer risk relationship by age, race, BMI, and current HT use. Although the estimates were imprecise inAAwomen, our study found differences in the distributions of breast density between white and AA women, with breast density being lower in AA women. Furthermore, increasing mammographic breast density showed expected associations with increased breast cancer risk [5]. Women with extremely dense breasts had a nearly threefold increased risk of breast cancer compared with women with almost entirely fatty tissue. Due to the small sample size of BI-RADSdensity category 1, we also assessed risk using BI-RADS density category 2 as the referent group which resulted in more precise effect estimates, but with lower magnitude than reported previously [41].

Our results agreed with those of Ursin et al. [11] that race did not significantly modify the association between breast density and breast cancer risk. However, in both studies, effect estimates were weaker for AA women compared with white women. Larger studies and meta-analyses will be needed to definitively answer this question, especially in light of a conflicting report from a third smaller study based on Wolfe's parenchymal patterns: Wolfe et al. [20] reported stronger associations in AA compared with white women. Differences in effect sizes by race may also be affected by differences in race-associated risk factors such as BMI [11]. We observed that elevated risks associated with BI-RADS 4 density were most apparent among obese women. BMI is an important predictor of breast density and there is an inverse association between BMI and breast density [42, 43]. Ursin et al. reported that the increased breast cancer risk associated with elevated breast density was strongest among very thin and obese women. In women with BMI ≤ 21 kg/m^2, the OR per each 10 % increase in percent density was 1.20 (1.09–1.33), and 1.34 (1.11–1.62) in women with BMI ≥ 30 kg/m^2 . Similar to our findings, Conroy et al. [44] also reported stronger effects of breast density on breast cancer risk in overweight and obese women compared with those with BMI < 25 kg/m^2. Taken together, these studies suggest that evaluation of the role of BMI in modifying the risk associated with breast density merits further investigation in larger studies, and is an important consideration in studies of breast density by racial/ethnic group. However, we were unable to further stratify our race-specific models by BMI due to small sample size.

We also examined HT use as a possible effect measure modifier due to its association with race, breast density, and breast cancer risk. Previous studies have concluded that HT increases mammographic breast density [45–9] and increases risk of breast cancer [50].

Effect modification by HT may contribute to our race-specific effects, given that 35 % of white women in our study were current HT users compared with 14 % of AA women. The lower rates of HT use in AA women may have contributed to weaker density-associated risks in AAs, and thus is an important variable to include in studying effect modification by race. Our findings are similar to a prior study showing a stronger breast density-breast cancer risk association among current users of HT [51].

A limitation of our study is that we used a qualitative measure of mammographic density, and while BI-RADS density measures have been shown to predict breast cancer risk [5], results from studies using qualitative versus quantitative density assessment methods may not be directly comparable. It is also challenging to merge two datasets (i.e., the CBCS and CMR) with different dates of collection. We carefully evaluated age differences between datasets and selected HT use at the time of the mammogram (choosing CMR data over CBCS data), thereby reducing exposure misclassification that may have resulted in merging the two datasets. Another limitation of our study was that the CMR mammograms were not centrally re-reviewed for BI-RADS density for our study. While the American College of Radiology BI-RADS was designed to standardize interpretation and reporting of results from mammographic examinations [4], BI-RADS density assessment has been shown to have only moderate inter-observer reliability [34, 52]. We therefore cannot rule out the possibility that misclassification in our exposure may have resulted in attenuation of risk estimates, emphasizing the need for replication of our findings using more quantitative measures of mammographic density.

Given the stronger associations we observed among current HT users and obese women, fewer AA women in our study may have been susceptible to the strongest effects of breast density. That is, few AA women were both obese and had extremely dense breasts, and current HT use was much more common in white women. The relatively lower number of women in the categories with strongest effects resulted in reduced precision in effect estimates for AA women. Given the small sample size, we were unable to examine effect measure modification by HT and BMI further stratified by race. However, by simultaneously considering effect modification by both race and these race-associated variables, our study suggests important relationships between breast cancer risk factors and breast density. Future studies with larger numbers of AA women should fully examine the association between breast density and breast cancer risk, considering race, BMI, and HT to disentangle these factors.

In summary, we found differences in the distributions of breast density between white and AA women, with breast density being lower in African-American women. Mam-mographic breast density was associated with increased breast cancer risk, but race did not significantly modify the association between breast density and breast cancer risk. Nonetheless, effect estimates were substantially weaker for AA women compared with white women, and were strongest for obese women and current users of HT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations

AA	African American
BI-RADS	Breast Imaging Reporting and Data System
BMI	Body mass index
CBCS	Carolina Breast Cancer Study
CI	Confidence interval
CMR	Carolina Mammography Registry
HT	Hormone therapy
LRT	Likelihood ratio test
NHLBI	National Heart, Lung, and Blood Institute
OR	Odds ratio
WHR	Waist-to-hip ratio

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Table 1

Descriptive characteristics of breast cancer cases and controls by race

Variable	All women		Whites		African Americans	
	Cases	Controls	Cases	Controls	Cases	Controls
No of subjects	491	528	297	324	194	204
Mean age (CBCS), years[a]	53.2 (28–74)	54.0 (31–74)	53.9 (28–74)	54.5 (35–74)	52.0 (30–74)	53.3 (31–74)
Mean age (CMR), years[b]	53.2 (28–77)	54.5 (34–76)	53.9 (28–77)	54.8 (35–76)	52.0 (30–74)	53.9 (34–76)
Mean BMI[b]	28.6 (15.1, 60.6)	28.8 (14.6, 60.9)	26.5 (17.2, 49.5)	26.8 (16.2, 52.9)	32.0 (15.1, 60.6)	32.1 (14.6, 60.9)
Mean number of days[c]	−21 (−1401, 365)	149 (−1617, 1095)	−29 (−1401, 365)	133 (−1526, 1095)	−9 (−1210, 365)	175 (−1617, 1078)
Breast density						
Almost entirely fat	13 (2.7 %)	25 (4.7 %)	5 (1.7 %)	10 (3.1 %)	8 (4.1 %)	15 (7.4 %)
Scattered fibroglandular densities	183 (37.3 %)	197 (37.3 %)	98 (33.0 %)	108 (33.3 %)	85 (43.8 %)	89 (43.6 %)
Heterogeneously dense	232 (47.3 %)	253 (47.9 %)	144 (48.5 %)	171 (52.8 %)	88 (45.4 %)	82 (40.2 %)
Extremely dense	63 (12.8 %)	53 (10.0 %)	50 (16.8 %)	35 (10.8 %)	13 (6.7 %)	18 (8.8 %)
Menopausal status						
Premenopausal	200 (40.7 %)	213 (40.3 %)	120 (40.4 %)	127 (39.2 %)	80 (41.2 %)	86 (42.2 %)
Postmenopausal	291 (59.3 %)	315 (59.7 %)	177 (59.6 %)	197 (60.8 %)	114(58.8 %)	118 (57.8 %)
Family history[d]						
No	386 (81.1 %)	440 (85.6 %)	232 (80.1 %)	263 (83.0 %)	154 (82.4 %)	177 (89.9 %)
Yes	90 (18.9 %)	74 (14.4 %)	57 (19.7 %)	54 (17.0 %)	33 (17.6 %)	20 (10.2 %)
Missing[f]	15	14	8	7	7	7
Age at menarche						
<13	257 (52.3 %)	230 (43.6 %)	148 (49.8 %)	135 (41.7 %)	109 (56.2 %)	95 (46.6 %)
≥13	234 (47.7 %)	298 (56.4 %)	149 (50.2 %)	189 (58.3 %)	85 (43.8 %)	109 (53.4 %)
Parity and age at FFTP[e]						
Nulliparous	74 (15.1 %)	67 (12.7 %)	39 (13.1 %)	45 (13.9 %)	35 (18.0 %)	22 (10.8 %)
Parous, <26	312 (63.5 %)	347 (65.7 %)	178 (59.9 %)	200 (61.7 %)	134 (69.1 %)	147 (72.1 %)
Parous 26^{+}	105 (21.4 %)	114 (21.6 %)	80 (26.9 %)	79 (24.4 %)	25 (12.9 %)	35 (17.2 %)
Breastfeeding						
Never	299 (60.9 %)	324 (61.4 %)	163 (54.9 %)	201 (62.0 %)	136 (70.1 %)	123 (60.3 %)

Variable	All women		Whites		African Americans	
	Cases	Controls	Cases	Controls	Cases	Controls
Ever	192 (39.1 %)	204 (38.6 %)	134 (45.1 %)	123 (38.0 %)	58 (29.9 %)	81 (39.7 %)
Lifetime duration lactation						
Never	299 (60.9 %)	324 (61.4 %)	163 (54.9 %)	201 (62.0 %)	136 (70.1 %)	123 (60.2 %)
>0–3 months	72 (14.7 %)	69 (13.1 %)	58 (19.5 %)	45 (13.9 %)	14 (7.2 %)	24 (11.8 %)
4^{+} months	120 (24.4 %)	135 (25.6 %)	76 (25.6 %)	78 (24.1 %)	44 (22.7 %)	57 (27.9 %)
Current HT use at the time of the mammogram						
No	359 (73.6 %)	336 (65.0 %)	193 (65.4 %)	182 (57.2 %)	166 (86.1 %)	154 (77.4 %)
Yes	129 (26.4 %)	181 (35.1 %)	102 (34.6 %)	136 (42.8 %)	27 (14.0 %)	45 (22.6 %)
Missing[f]	3	11	2	6	1	5
Oral contraceptive use						
Never	170 (34.6 %)	170 (32.4 %)	95 (32.0 %)	89 (27.6 %)	75 (38.7 %)	81 (39.9 %)
Ever	321 (65.4 %)	355 (67.6 %)	202 (68.0 %)	233 (72.4 %)	119 (61.3 %)	122 (60.1 %)
Missing[f]	0	3	0	2	0	1
WHR[e]						
<0.77	132 (27.3 %)	169 (32.3 %)	110 (37.2%)	133 (41.3 %)	22(11.7 %)	36 (17.8 %)
0.77–0.83	171 (35.3 %)	173 (33.0 %)	110 (37.2%)	105 (32.6 %)	61 (32.5 %)	68 (33.7 %)
≥0.84	181 (37.4 %)	182 (34.7 %)	76 (25.7 %)	84 (26.1 %)	105 (55.9 %)	98 (48.5 %)
Missing[f]	7	4	1	2	6	2

[a] Mean (range) age at diagnosis for cases and selection for controls in the CBCS

[b] Mean (range) age at the time of the mammogram in the CMR

[c] Mean (range) number of days between diagnosis date for cases and selection date for controls in the CBCS and the date of the mammogram chosen to assess breast density

[d] First-degree family history of breast cancer

[e] *FFTP* first full-term pregnancy, *WHR* waist-to-hip ratio

[f] Missing values were excluded from percentage calculations

Table 2

Odds ratios (OR) and 95 % confidence intervals (CI) for breast cancer risk associated with BI-RADS measured mammographic density by race

BI-RADS categorized density	Cases	Controls	Age and race adjusted OR (95 % CI) [a]	Model 1 OR (95 % CI)[b]	Model 2 OR (95 % CI)[c]
All women					
Entirely fat	13	25	0.46 (0.22–0.96)	1.00 (referent)	0.48 (0.22–1.08)
Scattered fibroglandular densities	183	197	1.00 (referent)	2.07 (0.93–4.59)	1.00 (referent)
Heterogeneously dense	232	253	0.97 (0.72–1.29)	2.06 (0.92–4.60)	1.00 (0.73–1.35)
Extremely dense	63	53	1.13 (0.71–1.78)	2.45 (0.99–6.09)	1.19 (0.72–1.95)
			P_{trend} = 0.24[d]	P_{trend} = 0.24[e]	
White women					
Entirely fat	5	10	0.39 (0.12–1.26)	1.00 (referent)	0.37 (0.10–1.35)
Scattered fibroglandular densities	98	108	1.00 (referent)	2.68 (0.74–9.74)	1.00 (referent)
Heterogeneously dense	144	171	0.90 (0.62–1.31)	2.50 (0.69–9.07)	0.93 (0.63–1.39)
Extremely dense	50	35	1.34 (0.77–2.36)	3.72 (0.94–14.81)	1.39 (0.75–2.55)
			P_{trend} = 0.24	P_{trend} = 0.23	
African American women					
Entirely fat	8	15	0.49 (0.19–1.29)	1.00 (referent)	0.49 (0.17–1.40)
Scattered fibroglandular densities	85	89	1.00 (referent)	2.03 (0.71–5.77)	1.00 (referent)
Heterogeneously dense	88	82	1.07 (0.68–1.67)	2.07 (0.71–6.03)	1.02 (0.63–1.66)
Extremely dense	13	18	0.76 (0.33–1.72)	1.53 (0.40–5.92)	0.75 (0.30–1.91)
			P_{trend} = 0.59	P_{trend} = 0.72	
Test of effect modification by race P = 0.76					

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[a] Adjusted for matching factors age and race. Models for all, African American, and white women were adjusted for age, and the model for all women was also adjusted for race

[b] Model 1 for African American and white women is adjusted for age, BMI, menopausal status, family history of breast cancer, age at menarche, HT use, and parity and age at first full-term pregnancy combined, where BI-RADS category 1 (almost entirely fat) is the referent group. Model 1 is additionally adjusted for race in all women

[c] Model 2 is adjusted for the same variables as Model 1 but BI-RADS category 2 (scattered fibroglandular densities) is the referent group

[d] *P* for trend test is based on likelihood ratio test statistic and is two-sided

[e] *P* the same ordinal model was fit to assess the *p* value of trend for Model 1 and Model 2

Table 3

Odds ratios (OR) and 95 % confidence intervals (CI) for breast cancer risk associated with BI-RADS measured mammographic density by age, body mass index (BMI), and hormone therapy (HT) use

BI-RADS categorized density	Cases	Controls	Age and race adjusted OR (95 % CI)[a]	Model 2 OR (95 % CI)[b]
All women				
Entirely fat	13	25	0.46 (0.22–0.96)	0.48 (0.22–1.08)
Scattered fibroglandular densities	183	197	1.00 (referent)	1.00 (referent)
Heterogeneously dense	232	253	0.97 (0.72–1.29)	1.00 (0.73–1.35)
Extremely dense	63	53	1.13 (0.71–1.78)	1.19 (0.72–1.95)
			$P_{trend} = 0.24$[c]	$P_{trend} = 0.24$[c]
Current hormone therapy				
Yes				
Entirely fat	3	8	0.58 (0.14–2.46)	0.46 (0.08–2.53)
Scattered fibroglandular densities	39	69	1.00 (referent)	1.00 (referent)
Heterogeneously dense	70	97	1.25 (0.73–2.14)	1.13 (0.64–2.00)
Extremely dense	17	7	5.09 (1.83–14.16)	5.61 (1.86–16.96)
			$P_{trend} = 0.005$	$P_{trend} = 0.01$
No				
Entirely fat	10	17	0.41 (0.17–0.97)	0.49 (0.19–1.26)
Scattered fibroglandular densities	142	124	1.00 (referent)	1.00 (referent)
Heterogeneously dense	161	151	0.91 (0.64–1.30)	0.93 (0.64–1.34)
Extremely dense	46	44	0.72 (0.42–1.22)	0.80 (0.45–1.43)
			$P_{rend} = 0.82$	$P_{rend} = 0.88$
Test of effect modification by HT $P = 0.0002$				
Age				
<50				
Entirely fat	4	4	0.93 (0.20–4.20)	0.78 (0.16–3.77)
Scattered fibroglandular densities	56	66	1.00 (referent)	1.00 (referent)
Heterogeneously dense	110	114	1.14 (0.71–1.81)	1.10 (0.68–1.79)
Extremely dense	46	35	1.30 (0.71–2.39)	1.45 (0.75–2.79)
			$P_{rend} = 0.38$	$P_{rend} = 0.27$
50+				
Entirely fat	9	21	0.36 (0.15–0.87)	0.40 (0.15–1.04)
Scattered fibroglandular densities	127	131	1.00 (referent)	1.00 (referent)
Heterogeneously dense	122	139	0.84 (0.58–1.22)	0.92 (0.62–1.38)
Extremely dense	17	18	0.88 (0.41–1.89)	1.06 (0.46–2.40)
			$P_{trend} = 0.67$	$P_{trend} = 0.46$
Test of effect modification by age $P = 0.67$				
Body Mass Index				
Women with BMI < 25				
Entirely fat	1	5	0.11 (0.01–1.16)	0.12 (0.01–1.36)

BI-RADS categorized density	Cases	Controls	Age and race adjusted OR (95 % CI)[a]	Model 2 OR (95 % CI)[b]
Scattered fibroglandular densities	55	37	1.00 (referent)	1.00 (referent)
Heterogeneously dense	91	97	0.66 (0.38–1.14)	0.67 (0.38–1.19)
Extremely dense	36	30	0.70 (0.34–1.42)	0.75 (0.36–1.57)
			P_{trend} = 0.64	P_{trend} = 0.74
Women with BMI 25–29				
Entirely fat	5	5	0.99 (0.25–3.95)	1.36 (0.28–6.55)
Scattered fibroglandular densities	49	64	1.00 (referent)	1.00 (referent)
Heterogeneously dense	71	87	1.01 (0.60–1.70)	1.24 (0.70–2.20)
Extremely dense	16	17	1.14 (0.49–2.66)	1.35 (0.52–3.49)
			P_{rend} = 0.82	P_{rend} = 0.52
Women with BMI 30^{+}				
Entirely fat	7	15	0.45 (0.15–1.36)	0.43 (0.15–1.28)
Scattered fibroglandular densities	79	96	1.00 (referent)	1.00 (referent)
Heterogeneously dense	70	69	1.16 (0.72–1.87)	1.24 (0.76–2.04)
Extremely dense	11	6	2.52 (0.86–7.38)	3.29 (1.00–10.83)
			P_{trend}= 0.03	P_{trend}= 0.01
Test of effect modification by BMI P = 0.09				

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[a] Adjusted for matching factors, age and race

[b] Model 2 is adjusted for age, race, BMI, menopausal status, family history of breast cancer, age at menarche, HT, and parity and age at first full-term pregnancy combined, where BI-RADS category 2 (scattered ribroglandular densities) is the referent group

[c] P for trend test is based on likelihood ratio test statistic and is two-sided