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Mammographic Breast Density and Subsequent Risk of Breast Cancer in Postmenopausal Women according to the Time Since the Mammogram

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Abstract

Background—Few studies have shown that the association between mammographic breast density and breast cancer persists for up to 10 years after the mammogram. We investigated associations of percent density, absolute dense and non-dense areas with breast cancer risk according to the time since the mammogram.

Methods—This study included 1,028 incident breast cancer cases diagnosed within the Nurses' Health Study and 1,780 matched controls. Breast density was measured from digitized film images with computerized techniques. Information on breast cancer risk factors was obtained prospectively from the biennial questionnaires before the date of cancer diagnosis for cases and their matched controls. The data were analyzed with logistic regression.

Results—Breast cancer risk increased with increasing percent density and increasing absolute dense area and decreased with increasing non-dense. In multivariate analysis, the magnitude of the association between percent density and breast cancer was similar when the time since the mammogram was <2, 2–<5, and 5–<10 years (density ≥50% vs.<10%: ORs 3.12 [95%CI 1.55–6.25], 5.35 [95%CI 2.93–9.76], and 3.91 [95%CI 2.22–6.88], respectively). Similarly, the magnitude of association between quartiles of dense and non-dense areas and breast cancer risk were similar across the time strata. We found no interactions between the time since the mammogram and breast density measures (p for all interactions>0.05).

Conclusions—Patterns of the associations between percent density, absolute dense and non-dense area with breast cancer risk persist for up to 10 years after the mammogram.

Impact—A one-time density measure can be used for long-term breast cancer risk prediction.

Keywords

breast density; breast cancer risk; postmenopausal breast cancer; case-control design; risk factors

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Conflict of interest

The authors declare that they have no competing interests.

Introduction

Mammographic breast density is a well-established and strong predictor of breast cancer risk (1–4). Appearance of the breast on the mammogram is a reflection of the amount of fat, connective tissue, and epithelial tissue in the breast (3). Light (non-radiolucent) areas on the mammogram represent the fibrous and glandular tissues ("mammographically dense"), whereas, the dark (radiolucent) areas are primarily fat. Women with breasts of 75% or greater percent density (proportion of the total breast area that appears dense on the mammogram) are at 4- to 6-fold greater risk of breast cancer compared to women with more fat tissues in the breasts (3, 5, 6). The increased risk of breast cancer persists for 8–10 years or more after density assessment in both premenopausal and postmenopausal women and is independent of other breast cancer risk factors (6, 7). Absolute dense area of the breast that represents fibroglandular tissue is positively associated with breast cancer risk in both pre- and postmenopausal women (8–14), while findings on the association between non-dense area of the breast (representing adipose tissue) and breast cancer risk are conflicting (8, 10, 15). Finally, whether breast cancer risk associated with absolute dense and non-dense areas changes with the time since the mammogram is unclear. We analyzed prospective data from the Nurses' Health Study to determine if there are differences in the associations between three density measures (percent density, absolute dense area, and non-dense area) and the subsequent risk of postmenopausal breast cancer according to the time since the mammogram.

Participants and Methods

Participants for this nested case-control study were selected from the Nurses' Health Study (NHS) prospective cohort, which followed registered nurses in the United States who were 30–55 years old at enrollment. After administration of the initial questionnaire, the information on breast health risk factors (Body Mass Index [BMI], reproductive history, age at menopause, postmenopausal hormone [PMH] use, smoking and alcohol use) and any diagnoses of cancer or other diseases was updated biennially (3, 16). Breast cancer cases were confirmed through medical record review. A nested case-control approach was originally used as an efficient design to examine the association between endogenous hormones, breast density, and breast cancer risk within NHS cohort (3). Because the original study was designed to evaluate associations between circulating biomarkers and risk of breast cancer, using incidence density sampling, women who did not have any type of cancer (other than non-melanoma skin cancer) at the time of the case's cancer diagnosis (controls) were matched 1:1 or 1:2 with women diagnosed with in situ or invasive breast cancer (cases) on age at the time of blood collection, menopausal status and postmenopausal hormone use (current vs. not current) at blood draw, and day/time of blood draw. We made use of this study to examine the association between breast density and breast cancer stratified by the time between the mammogram and the reference date. For cases, the reference date refers to the date of diagnosis. Because cases and control are matched on follow-up time, for controls the reference date is the date of diagnosis of her matched case.

We attempted to obtain mammograms closest to the time of blood collection from 1,612 eligible cases and 2,857 eligible controls. Of all women who provided consent and have previously received mammograms (1,446 cases and 2,406 controls), we excluded 37 cases and 35 controls who had mammograms of insufficient quality (non-readable or breast implants) and 104 cases who had their mammogram taken after the date of their breast cancer diagnosis. In total, we obtained useable mammograms (one set per woman) closest to the time of blood collection from 1,305 breast cancer cases diagnosed between June 1, 1989, and June 30, 2004 and 2,362 matched controls. Of the 3,667 women, 2,839 cases and controls combined (77%) were postmenopausal at the time of both the mammogram and the reference date. A total of 312 (9 %) women were premenopausal at both dates, and 515 (14%) women were premenopausal at the time of the mammogram and became postmenopausal before the reference date; the menopausal status at the time of the mammogram was unknown for 1 woman. Given this distribution, and results from previous studies suggesting possible differences in the association of breast density with pre- and postmenopausal breast cancer (17, 18), we restricted our analysis to women who were postmenopausal at the time of both the mammogram and reference date (1,045 cases and 1,794 controls). Such restriction also controls for potential density changes from the mammogram date to the reference date as a result of menopausal transition (2, 19). We further excluded 3 cases and 14 controls with missing data for one or more covariates (1,028 cases and 1,780 controls). This study was approved by the Committee on the Use of Human Subjects in Research at Brigham and Women's Hospital.

Mammographic Breast Density Assessment

To quantify mammographic density, the craniocaudal views of both breasts were digitized at 261 lm per pixel with a Lumisys 85 laser film scanner (bit depth of 12). The Cumulus software (University of Toronto, Toronto, ON, Canada) was used for computer-assisted determination of the percent mammographic density (3, 20). During this assessment, the observer was blinded with respect to participant's case-control status. As reported previously, the measure of mammographic breast density was highly reproducible (within person intra-class correlation coefficient was 0.93) (3). Since densities of the right and left breast are strongly correlated (20), the average percent density of both breasts was used in this analysis. The average time between the mammogram date and the date of breast cancer diagnosis was 4.8 years (range 0–18, interquartile range 2–7 years). The average time between mammogram and the reference date of controls was 4.2 years (range 0–16, interquartile range 1–7 years).

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Covariate Information

Information on breast health risk factors was obtained from the biennial questionnaires before the date of the breast cancer diagnosis (reference date) for cases and their matched controls. Women were considered postmenopausal if they reported (1) no menstrual periods within the 12 months prior to diagnosis date, if natural menopause, (2) having had bilateral oophorectomy, or hysterectomy, or (3) being 54 or 56 years or older if a smoker or nonsmoker, respectively (21, 22).

Statistical Analysis

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The difference in breast density measures in cases and controls was tested with Wilcoxon-Mann-Whitney test due to their skewed distributions. The differences in distribution of the breast cancer risk factors in cases and controls were tested with two-sample t test if the variable was continuous and using X^2 test if the variable was categorical. We used unconditional logistic regression adjusted for matching factors to describe the association between breast density and breast cancer risk. The risk estimates were presented as odds ratios (ORs) and their corresponding 95 % Confidence Intervals (95 % CIs). In the logistic regression analysis, we modeled percent breast density as <10%, 10–24%, 25–49%, and ≥50%. We defined quartiles of absolute dense and non-dense area using the distribution of these density measures among controls (total absolute dense area: 1^{st}: <17 cm^2; 2^{nd}: 17–<32 cm^2; 3^{rd}: 32–<55 cm^2; 4^{th}: ≥55 cm^2; non-dense area: 1^{st}: <80 cm^2; 2^{nd}: 80–<133 cm^2; 3^{rd}: 133–<203 cm^2; 4^{th}: ≥203 cm^2). Variables that previously showed significant association with either breast cancer or breast density in previous studies (23–30), including those from NHS (31–33), were considered as potential confounders and included in adjusted logistic regression models. We included the following matching variables and potential confounders:

age at diagnosis (continuous, years), body mass index (continuous, kg/m2), age at menarche (<12, 12, 13, or >13 years), parity and age at first birth (i.e., age at the end of the first pregnancy lasting ≥6 months, modeled as nulliparous, 1–4 children with age at birth<25 years, 1–4 children with age at birth of 25–29 years, 1–4 children with age at birth of ≥30 years, ≥5 children with age at birth of <25 years, or ≥5 children with age at birth of ≥25 years), menopausal status and PMH use (premenopausal, postmenopausal who never used hormones, postmenopausal who were currently on hormones, postmenopausal who used hormones in the past), age at menopause (<46, 46–<50, 50–<55, ≥55 years, unknown, including premenopausal women), a family history of breast cancer (first degree relative with breast cancer diagnosis, yes or no), a biopsy-confirmed history of benign breast disease (yes vs. no), alcohol consumption (0, <5, 5–<15, or ≥15 g/day), and smoking status (ever vs. never). The associations of percent breast density, absolute dense area and non-dense area with breast cancer risk were examined separately according to the time between the mammogram date and the reference date (<2, 2 –<5, 5 –<10, ≥10 years). The differences in the associations of breast density measures with breast cancer risk by the time since the mammogram were tested with two-way interactions and using Wald Chi-square test. We implemented different approaches in modeling the interaction. First, both breast density and time since the mammogram were modeled as ordinal variables. Then, we modeled the interaction using the original continuous variables for the density measures and time since the mammogram.

All breast cancer cases were asked to report the primary mode of cancer detection. In a secondary analysis, we investigated the associations between breast density and breast cancer risk separately among cancers detected with screening (routine mammography) and those detected with methods other than screening (self-exam, health professional exam, husband or other non health professional exam). Significance in all the analyses was assessed at 0.05 level. The analyses were performed using SAS software (version 9.2, SAS Institute, Cary, NC, USA).

Results

In this nested case-control study of 1,028 breast cancer cases and 1,780 matched controls, cases had a higher median percent breast density (27.8 vs. 20.5%, p <0.001), higher median absolute dense area (43.2 vs. 32.4 cm^2, p <0.001), and lower median area of non-dense breast tissue (116.5 vs. 132.6 cm^2, p <0.001). Characteristics of this study population have been previously described (34). In summary, cases were more likely to be current postmenopausal hormone users (56.6% vs. 46.4%, p <0.001), were more likely to have a family history of breast cancer (19.7% vs.14.6%, p <0.001), and were more likely to have a biopsy-confirmed history of benign breast disease (33.7% vs. 25.8%, p <0.001). Cases and controls did not significantly differ with respect to other covariates.

Of all the women in the study, 701 (25.0%) had their mammograms taken within 2 years from the reference date, 830 (29.6%) had their mammograms within the previous 2–<5 years, 932 (33.2%) had their mammograms within the previous 5–<10 years, and 345 (12.3%) had their mammograms within 10 and more years. Characteristics of controls in the study by the time since the mammogram are presented in Table 1.

In the overall adjusted logistic regression analysis, the risk of breast cancer significantly increased with increasing percent breast density, increased with increasing absolute area of dense tissue, and decreased with increasing non-dense breast area (Table 2). Compared to the reduced logistic regression models with age and BMI, the risk estimates in the full model for all three density measures were similar (data not shown). Next, we evaluated the associations of breast density with breast cancer risk stratified by the time between the mammogram and the reference date (Table 2). In the stratified analyses, the magnitude of the associations between percent mammographic density and breast cancer risk was similar in women with <2, 2–<5 and 5–<10 years since the mammogram (percent density 50% vs. <10%: OR=3.12 for <2 years, OR=5.35 for 2–<5 years, and OR=3.91 for 5–<10 years). The magnitude of the associations between quartiles of dense area and non-dense area and breast cancer risk were similar when stratified by time since mammogram. Among women with ≥10 years between the two dates, the associations for all three density measures were very weak and did not reach statistical significance, with the exception of absolute dense area (p for trend=0.03). When time since the mammogram was included as a continuous variable in each of the time interval strata, the results remained unchanged (data not shown). We observed no overall interaction between the time since the mammogram and any of the three density measures (p for interaction with percent breast density=0.32; p for interaction with absolute dense area=0.34; p for interaction with non-dense area=0.14). Similar results were seen when we used the original continuous variables for density and for the time since the mammogram to test the interactions and when we modeled the time since the mammogram as <10 vs. ≥10 years (data not shown).

Of the cancers in this study, 630 (60%) were detected at a screening mammogram and 415 (40%) were detected with methods other than screening. In a secondary analysis, the patterns of the associations between density measures and breast cancer risk by the time since the mammogram were similar among cancers detected with screening compared with those detected with other methods (Supplementary tables S1 and S2). However, the magnitude of the risk associated with percent breast density appeared to be higher among cancers detected with methods other than screening and with <10 years since the mammogram (density 50% vs. <10%: ORs 5.62, 6.30, and 9.21 for <2 years, 2–5 years, and 5–<10 years, respectively, vs. ORs 1.88, 5.05, and 2.33 for cancers detected with screening). Similar results were observed for absolute dense area. No differences were found for the associations of non-dense area and breast cancer risk among cancers detected with screening and those detected with other methods.

Discussion

In this nested case-control study with 1,028 breast cancer cases and 1,780 matched controls, we found no differences in the associations of breast density measures with breast cancer risk by time since the mammogram. The positive associations of percent density and absolute dense area and the inverse association of non-dense area with breast cancer risk were similar in women with <2, 2 –<5, and 5 –<10 years since the mammogram. We found no interaction between breast density measures and the time since the mammogram.

Our results examining the associations of percent breast density, absolute dense and non-dense areas with breast cancer are similar to previous reports. A previous study by Boyd et al. with 1,112 matched case-control pairs reported a higher risk of breast cancer in women with dense breasts who had their mammograms taken within 2–8 years, regardless whether they were detected by screening or other methods (density ≥75% vs. 10%: OR= 5.6, 95% CI 2.4–12.9 for ≤2 years; OR= 2.5, 95% CI1.4–4.2 for >2–≤4 years; OR= 5.5, 95% CI 2.7–11.2 for >4–≤8 years) (7). Similarly, a study with 1,880 incident breast cancer cases and 2,152 controls by Byrne et al. reported elevated breast cancer risk in women with dense breasts (≥75%) and mammograms taken 10 and more years before the reference date. The highest risk was observed within 2 years of the mammogram date (density ≥75% vs. 10%: OR of 7.58, 95% CI = 3.2–17.9). In contrast, our findings suggest similar magnitude of the associations in women who had their mammograms taken within 2 years of the mammograms date and thereafter (6).

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Consistent with previous reports, we found that the increased risk of breast cancer in women with greater percent density persisted for up to 10 years after the mammogram date and the risk appeared to be higher among cancers diagnosed with methods other than screening (7). Several studies reported a stronger association of breast density with interval cancers as compared to screen-detected tumors (7, 35–38). For tumors diagnosed within 2 years from the mammogram date, a masking effect cannot be ruled out completely. However, the associations that exist beyond 2 years are unlikely to be the result of a masking effect and suggest that breast density increases breast cancer risk by other mechanisms. We also report for the first time that the increased risk of breast cancer with increasing absolute dense area and decreased risk with increasing area of non-dense tissue persist for up to 10 years after the date of the mammogram.

In our study, breast density was quantified using computer-assisted techniques applied to digitized films. In clinical practice, qualitative BI-RADS breast density classification remains the standard approach for characterization of breast density. Previous studies demonstrated a very high agreement between density assigned by applying computerized algorithms and density estimated by a radiologist (39–41). In addition, both breast density measurements have demonstrated a strong relationship with breast cancer risk (17). Therefore it is likely that these results have important implications that can be translated to BI-RADS measurements. However, it is important to note that the BI-RADS measurement is primarily used to alert radiologists about lower sensitivity of mammography in women with dense breasts rather than for risk assessment.

This study has a number of strengths including the large sample size, long follow-up and quantitative assessment of mammograms. However, there are also limitations. The current analysis was restricted to women who were postmenopausal at the time of both mammogram and diagnosis, which constitutes the majority of the population assembled for the nested case-control study (77%). Thus, our findings are limited to postmenopausal breast cancer and do not necessarily apply to premenopausal breast cancer. In this study, the mammograms used to assess breast density spanned across a long time period. However, it is unlikely that the age of the mammograms, their quality across this time period and mammogram acquisition parameters affected the study results. The majority of the previous studies on association between breast density and breast cancer risk are based on film mammograms dating back many decades, with largely consistent results (17). In addition, recent work examining acquisition parameters on mammography units demonstrate that these differences are not related to mammographic density measurements and do not confound the association with breast cancer risk (42). Additionally, our analysis did not taken into account screening patterns after the mammographic density assessment. Previous work in the NHS, demonstrated that mammographic screening rates in the NHS were 77%, 85%, and 92% for 1988–1990, 1994–1996, and 1998–2000, respectively (43), which are greater than the overall US mammography screening rates for women at age 40 and older (75%) (44). Given the high rates of screening in this population across this time period it is unlikely that there are differences in screening patterns that would bias our results.

In conclusion, we investigated the associations of percent breast density, absolute dense and non-dense area with breast cancer by the time since the mammogram. Our results show that these associations between these mammographic breast density measures and breast cancer risk persist for up to 10 years after the mammogram.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Age-adjusted characteristics [a] of cases and controls in the study by the time between the mammogram and reference date [b].

	Cases				Controls			
	Time since the mammogram, years				Time since the mammogram, years			
Characteristic	**<2 (n=220)**	**2–<5 (n=317)**	**5–<10 (n=361)**	**≥10 (n=130)**	**<2 (n=481)**	**2–<5 (n=513)**	**5–<10 (n=571)**	**≥10 (n=215)**
Mean (SD)								
Percent breast density	29.2 (17.8)	30.0 (19.8)	30.8 (18.5)	32.7 (16.5)	22.4 (16.2)	22.9 (16.7)	24.2 (18.1)	26.2 (14.5)
Absolute dense area, cm^2	48.2 (35.6)	45.0 (31.2)	50.9 (39.8)	72.5 (45.7)	36.6 (29.0)	37.6 (29.7)	39.8 (32.7)	58.8 (36.9)
Non-dense area, cm^2	135 (89)	132 (91)	130 (82)	163 (87)	152 (87.0)	149 (88.0)	148 (98.0)	187 (94.0)
Age, years[c]	63.2 (6.9)	63.5 (6.6)	66.0 (5.9)	69.1 (6.6)	62.8 (6.8)	63.3 (6.1)	66.0 (6.3)	69.6 (6.1)
Age at menarche, y	12.7 (2.1)	12.5 (1.4)	12.5 (1.3)	12.5 (1.5)	12.6 (1.5)	12.6 (1.4)	12.7 (1.3)	12.4 (1.2)
Age at natural menopause, y	49.4 (5.2)	50.1 (3.7)	49.1 (4.4)	50.2 (3.9)	49.4 (5.2)	50.1 (3.7)	49.1 (4.4)	50.2 (3.9)
BMI, kg/m^2	26.4 (5.4)	26.6 (4.9)	26.3 (4.6)	26.2 (4.1)	26.1 (5.1)	26.3 (5.2)	26.6 (4.6)	26.4 (4.6)
Alcohol use, g/day	6.2 (8.7)	4.1 (7.6)	6.3 (10.3)	4.5 (8.2)	5.5 (9.3)	5.5 (9.3)	5.2 (8.8)	5.3 (7.7)
Percentages								
Parity and age at first child's birth								
Nulliparous	10	6	7	11	7	6	5	5
1–4 children, age at first birth <25 yrs	32	31	41	43	30	36	40	47
1–4 children, age at first birth 25–29 yrs	32	35	31	27	33	33	30	24
1–4 children, age at first birth ≥ 30 yrs	8	11	9	7	9	7	9	9
≥ 5 children, age at first birth <25 yrs	12	9	7	9	13	10	12	10
≥ 5 children, age at first birth ≥ 25 yrs	7	8	5	3	7	8	5	5
PMH use								
Never used hormones	27	21	17	12	32	28	22	17
Current hormone use	46	54	65	67	42	43	51	55
Past hormone use	24	20	14	19	23	25	25	25
Unknown status of hormone use	3	5	4	2	3	4	2	3
Family history of breast cancer[d]	11	19	21	22	14	14	15	14
Personal history of benign breast disease	26	33	34	43	25	25	28	31
Smoking status (ever)	55	55	57	52	53	47	54	57

Abbreviations: SD = standard deviation, BMI = body mass index, PMH = postmenopausal hormone.

[a] At the reference date

[b] The reference date is the date of diagnosis for case and its matched control

[c] Values are not adjusted

[d] First-degree relative with breast cancer diagnosis.

Table 2

Association between percent breast density, absolute dense and non-dense area with breast cancer risk in postmenopausal women, stratified by the time since the mammogram [a]

	Overall 1028 cases/1780 controls		Time between mammogram and reference date							
			<2 years 220 cases/481 controls		2–<5 years 317 cases/513 controls		5–<10 years 361 cases/571 controls		≥10 years 130 cases/215 controls	
	No. Cases/Controls	**OR (95% CI)**	**No. Cases/Controls**	**OR (95% CI)**	**No. Cases/Controls**	**OR (95% CI)**	**No. Cases/Controls**	**OR (95% CI)**	**No. Cases/Controls**	**OR (95% CI)**
Percent density										
<10%	151/430	1.00	38/119	1.00	50/129	1.00	47/153	1.00	16/29	1.00
10–24%	300/643	1.37 (1.08–1.74)	58/183	1.05 (0.63–1.74)	80/182	1.32 (0.84–2.08)	117/187	2.26 (1.48–3.44)	45/91	0.82 (0.37–1.85)
25–49%	409/548	2.35 (1.83–3.02)	94/138	2.59 (1.55–4.34)	124/158	2.68 (1.66–4.31)	140/177	2.94 (1.89–4.57)	51/75	1.14 (0.48–2.72)
≥50	168/159	3.37 (2.45–4.65)	30/41	3.12 (1.55–6.25)	63/44	5.35 (2.93–9.76)	57/54	3.91 (2.22–6.88)	18/20	1.22 (0.42–3.57)
		P trend[b]<0.0001		P trend <0.0001		P trend <0.0001		P trend <0.0001		P trend=0.36
Absolute dense area [c]										
1st quartile	161/438	1.00	34/124	1.00	50/144	1.00	67/155	1.00	10/15	1.00
2nd quartile	208/445	1.26 (0.98–1.62)	54/135	1.44 (0.86–2.41)	73/139	1.47 (0.94–2.31)	67/129	1.24 (0.80–1.91)	14/42	0.36 (0.12–1.08)
3rd quartile	300/451	1.70 (1.34–2.16)	57/115	1.95 (1.15–3.29)	104/122	2.34 (1.51–3.64)	104/145	1.67 (1.12–2.49)	35/69	0.51 (0.19–1.41)
4th quartile	359/446	1.94 (1.53–2.47)	75/107	2.55 (1.52–4.30)	90/108	2.22 (1.41–3.52)	123/142	1.87 (1.26–2.78)	71/89	0.99 (0.37– 2.64)
		P trend <0.0001		P trend 0.0003		P trend =0.0005		P trend =0.001		P trend =0.03
Non-dense area [d]										
1st quartile	348/445	1.00	74/120	1.00	135/153	1.00	121/149	1.00	18/23	1.00
2nd quartile	239/448	0.64 (0.51–0.80)	59/123	0.73 (0.46–1.16)	67/127	0.56 (0.37–0.85)	85/155	0.65 (0.44–0.96)	28/43	0.95 (0.39–2.30)
3rd quartile	225/442	0.57 (0.45–0.72)	46/123	0.48 (0.29–0.80)	59/120	0.44 (0.28–0.69)	82/125	0.77 (0.51–1.16)	38/74	0.72 (0.31–1.65)
4th quartile	216/445	0.50 (0.38–0.65)	41/115	0.40 (0.23–0.72)	56/113	0.36 (0.22–0.61)	73/142	0.56 (0.35–0.90)	46/75	0.98 (0.41–2.34)
		P trend <0.0001		P trend 0.001		P trend =0.0002		P trend =0.05		P trend =0.89

[a] Multivariable logistic regression analysis adjusted for age (continuous), BMI (continuous), age at menarche (<12, 12, 13, or >13 years), parity and age at first birth (nulliparous, 1–4 children with age at first birth <25 years, 1–4 children with age at first birth of 25–29 years, 1–4 children with age at first birth of ≥30 years, ≥5 children with age at first birth of <25 years, or ≥5 children with age at first birth of ≥25 years), age at menopause (<46, 46–<50, 50–<55, ≥55, unknown), postmenopausal hormone use (never, current, past, unknown), family history (yes or no), biopsy-confirmed history of benign breast disease (yes or no), alcohol consumption (0, <5, 5 to <15, or ≥15 g/day), and smoking status (ever vs never).

[b] P values were calculated using a two-sided test for trend.

[c] Quartiles of absolute dense area defined as: 1st: <17 cm^2; 2nd: 17–<32 cm^2; 3rd: 32–<55 cm^2; 4th: ≥55 cm^2

[d] Quartiles of non-dense area defined as: 1st: <80 cm^2; 2nd: 80 –<133 cm^2; 3rd: 133–<203 cm^2; 4th: ≥203 cm^2

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Note: Interaction between percent breast density and time since the mammogram p=0.32; interaction between absolute dense area and time since the mammogram p=0.34; interactions between non-dense are and time since the mammogram p=0.14