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Varying levels of family history of breast cancer in relation to mammographic breast density (United States)

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Abstract
Objective We examined the relationship between breast cancer family history and mammographic breast density.
Methods Participants included 35,019 postmenopausal women aged ≥40 years enrolled in a population-based mammography screening program. We collected data on the number and type of 1st and 2nd degree female relatives with a history of breast cancer and their ages at diagnosis. We used the Breast Imaging Reporting and Data System™ breast density categories to identify women with fatty (1 = almost entirely fatty or 2 = scattered fibroglandular tissue) and dense (3 = heterogeneously dense or 4 = extremely dense) breasts. We used logistic regression to calculate odds ratios (OR) and 95% confidence intervals for dense (N = 18,111) compared to fatty breasts (N = 16,908).
Results The odds of having dense breasts were 17% greater for women with affected 1st degree relatives than women with no family history. The odds increased with more affected 1st degree relatives [≥3 vs. none (OR = 1.46; 1.05–2.01)] and among women with ≥1 affected 1st degree relative diagnosed < 50 years (OR = 1.22; 1.10–1.34).
Conclusions Having a family history of breast cancer was more strongly associated with mammographic breast density when the affected relatives were more genetically similar. There may be common, yet undiscovered, genetic elements that affect breast cancer and mammographic breast density.

Keywords Mammographic breast density · Family history · Breast cancer risk · Genetics · BI-RADS™

Abbreviation

BMI	Body mass index
BCSP	Breast Cancer Screening Program
BI-RADS™	Breast Imaging Reporting and Data System™
GHC	Group Health Cooperative
OR	Odds ratio

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Introduction

Increased mammographic breast density reduces mammography sensitivity [1]. It is more difficult for a radiologist to see breast tumors in highly dense breasts because of the reduced radiolucency of dense parenchymal tissue. This decreased sensitivity leads to an increased number of interval cancers (cancers detected in the interval after a negative mammogram) in women with higher breast density [2]. A number of studies have proposed a biological link between breast density and breast cancer [3–7]. The odds of having breast cancer among women with dense breasts compared to women with fatty breasts has been estimated to be between 1.8 and 6.0, with most studies yielding an odds ratio of 4.0 or greater [8].

Environmental factors that have been shown to affect breast density include diet [9–11], exogenous hormones [12], reproductive history [9] and body mass index (BMI) [13]. There are also known genetic factors that influence breast density variation, such as variants in the CYP1A2 and catechol-O-methyltransferase genes [14–16]. Genetics also influence breast cancer risk [17]; however, we are unaware of any identified common genetic factors that are related to both breast density and breast cancer. A previous cross-sectional study on a cohort of 6,146 women showed that women with higher breast density were more likely to have a 1st degree relative with breast cancer compared to women with lower breast density [18]. Since there are genetic components that influence breast cancer risk and breast density, it is reasonable to hypothesize that having a family history of breast cancer may be associated with greater breast density.

The purpose of this study was to examine the association between having a family history of breast cancer and breast density among 35,019 postmenopausal women with detailed information on the number and type of 1st and 2nd degree relatives with breast cancer. We evaluated the association between 1st and 2nd degree family history of breast cancer, number of relatives with breast cancer, age at diagnosis for affected relatives, and having dense breasts. Results of this study provide a more detailed picture of the genetic link between breast cancer and breast density.

Materials and methods

Study subjects and setting

The women in this study were enrolled in Group Health Cooperative (GHC), a non-profit integrated health system based in Seattle, Washington. Since 1986, women 40 and older have been invited to join a population-based Breast Cancer Screening Program (BCSP) [19, 20]. Women enrolled in the BCSP (≥80,000 women) are sent mammography screening recruitment and reminder letters at 1- or 2-year intervals based on their risk for breast cancer. All women ≥50 years receive reminders every 1–2 years, whereas women 40–49 only receive reminders if they are at an increased risk for breast cancer [21]. Women participating in the BCSP complete a breast cancer risk factor questionnaire at program enrollment, and provide updated information at each mammogram [19–21]. In June 2001, the questionnaire was revised to include more detailed family history questions, which provided the data for this analysis. The GHC Institutional Review Board approved all of the procedures and data collection for this study.

We included all screening mammograms done at GHC between June 2001 and September 2004 for women aged between 40 and 80 years at their first screen (mean age = 58 years) (110,004 exams). We excluded mammograms for women who had a previous breast cancer diagnosis (9,144 exams), had breast implants or surgery or reconstruction (5,038 exams), or ever used tamoxifen (1,113 exams) or raloxifene (110 exams). We also excluded exams for women who did not know their family history (12,642 exams) or did not complete the family history section of the questionnaire (3,270 exams). We excluded pre-menopausal (17,523 exams) and peri-menopausal women (8,158 exams) because their density distribution is different compared to postmenopausal women; therefore, they might have a different relationship between family history and breast density. Under half of the women (31.7%) that met our inclusion criteria had multiple screens (mean number of screens = 1.3) during the study period. We used the most recent screen in our analysis to ensure we had the most current family history data (final sample size = 35,019 women).

Data collection

We gathered data on demographics and additional breast cancer risk factors from the self-administered survey. We collected each subject's age at menarche, age at and type of menopause, oral contraceptive use, parity, hormone therapy use (never, former, current), type of hormone therapy used (current users only), benign breast biopsy history (0, 1, 2, ≥3), history of Hodgkin's disease, ethnicity (Hispanic), age at screen (5-year intervals), age at first birth (5-year intervals) and self-reported BMI (continuous, kg/m^2). For categorizing race, subjects were asked to mark all races that they identified with (Caucasian, African-American, Asian, American-Indian, Other/mixed), which we classified into one mutually exclusive category.

Mammographic breast density

Radiologists at GHC assess breast density for each breast at every mammogram as part of their routine practice. Assessment is made using the Breast Imaging Reporting and Data System™ (BI-RADS™) 4-point scale: 1 ''almost entirely fatty''; 2 ''scattered fibroglandular tissue''; 3 ''heterogeneously dense''; and 4 ''extremely dense'' [22]. We categorized each woman's breast density based on readings from both breasts. A more dense reading superceded a lower density reading in cases where the density readings were discordant (255 exams). We dichotomized breast density into fatty (''almost entirely fatty'' or ''scattered fibroglandular tissue''; 48.3%) and dense (''heterogeneously dense'' or ''extremely dense''; 51.7%) groups because categories 1 and 4 had relatively small sample sizes and for ease of interpretation of the results [12].

Family history

We collected data on female and male family history of breast cancer from the self-administered screening questionnaire. For female family history, we collected the number of relatives with and without breast cancer for mother, sisters, daughters, aunts, and grandmothers and their age(s) at diagnosis (< 50 vs. ≥50 years). We only collected data on 1st degree male relatives (father, son, and brother) and did not collect information on the number affected or their age at diagnosis.

For each family history question, subjects had the option to indicate that their family history was unknown. Subjects could indicate their entire family history was unknown or indicate they knew the family history for some relatives and did not know for others. Because the questionnaire was self-administered, subjects also had the option of not answering the family history questions. We included subjects with partial known family histories in analyses where they indicated having a positive or negative family history.

We separately examined 1st degree and 2nd degree family histories by categorizing each participant into one of four mutually exclusive categories: no family history, 1st degree history only, 2nd degree history only, or 1st and 2nd degree history, which included both male and female relatives. We further categorized family history by number of affected 1st and 2nd degree female relatives (1, 2, 3 or more).

We created variables for each type of female relative (mother, sisters, daughters, aunts and grandmothers) and categorized women as having: no family history, affected specific relative, or unaffected specific relative but other affected relative. We also modeled the number of affected female relatives for each subject.

We examined whether age at diagnosis for female relatives had an effect on the family history-breast density relationship. We modeled the number of affected relatives and their age(s) at diagnosis (< 50 vs. ≥50) for 1st degree history, 2nd degree history, and separately for specific relatives (mother, daughters, sisters, aunts, and grandmothers). For each category of family history, we categorized women as having no family history, only 1 affected relative diagnosed ≥50, only 1 affected relative diagnosed < 50, 2 or more diagnosed < 50, 2 or more diagnosed ≥50, and 2 or more diagnosed < 50 and ≥50 years of age.

Statistical analyses

We used multivariable logistic regression to evaluate the association between various categories of family history of breast cancer and breast density. We generated odds ratios (OR) and 95% confidence intervals (CI) to estimate the odds of having dense breasts relative to the odds of having fatty breasts among women with varied family histories of breast cancer. In each analysis, the reference group was women with no family history of breast cancer. We calculated *P*-values to test for trends across odds ratios for increasing numbers of affected relatives by including the number of relatives as a single, ordered variable in the logistic model. All statistical tests were two-sided and we used an alpha of 0.05 to define statistical significance.

We examined potential confounders by entering them into the logistic model as individual covariates. In the final multivariable model, we included variables that changed the parameter estimate for family history of breast cancer by >10%. We adjusted all models for age at screening (5-year intervals), BMI (continuous), age at first birth (5-year intervals), number of previous benign breast biopsies (0, 1, 2, ≥3), and hormone therapy use (never, former, current). Further control for type of hormone therapy use (none, estrogen only, progestin only, estrogen plus progestin) did not alter the findings; therefore, we did not include this in the final model. We adjusted each model for the appropriate number of total relatives (as a continuous variable) in order to account for a woman's potential to have any family history of breast cancer. We tested for effect modification by hormone therapy use and found no evidence to support stratifying our results.

We also conducted a sensitivity analysis using each woman's first mammogram between 2001 and 2004 (compared to the most recent mammogram) to see if this changed the results. Our results did not change when we examined each woman's earliest exam (as opposed to most recent; data not shown); therefore, we only present the results for each woman's most recent exam.

Results

Women with dense breasts tended to be younger, have a lower BMI, be nulliparous or have a later age at first birth (≥30), be current hormone therapy users, and have more frequent breast biopsies compared to women with fatty breasts (Table 1). Over 42% of the population had a family history of breast cancer; 14.2% with a 1st degree only, 20.3% with a 2nd degree only, and 8% with a 1st and 2nd degree.

Various family histories of breast cancer and their relationship with breast density are shown in Table 2, relative to women with no family history. After adjusting for covariates, women with a family history of breast cancer were more likely to have dense breasts regardless of whether women had a family history of 1st degree only, 2nd degree only, or 1st and 2nd degree. There was no substantial difference in the odds of having dense breasts if women had a 1st only or 1st and 2nd degree affected relative.

Having a sister with breast cancer resulted in the strongest association with breast density; there was a 19% (95%CI = 1.10–1.29) increase in the odds of having dense breasts relative to women with no family history. Having an affected mother or aunt(s) had a 16% (1.08–1.25) and 13% (1.06–1.19) increase in the odds of having dense breasts, respectively. Having a male relative, daughter, or grandmother with breast cancer did not significantly alter the odds of having dense breasts. There were no notable changes in any associations after adjusting for total number of female relatives in each category.

Table 3 shows the relationship between the number of affected relatives and breast density. Having a greater number of affected 1st or 2nd degree relatives was associated (OR; 95% CI) with an increased odds of having dense breasts, compared to women with no affected relatives: 1 affected (1.14; 1.07–1.22), 2 affected (1.25; 1.08–1.45), and ≥3 affected (1.46; 1.06–2.01), P for trend <0.001. The same positive trend was seen when examining increasing numbers of affected sisters and aunts, but was not seen for increasing number of daughters. Adjusting for number of relatives did not change the relationship.

Table 4 shows the association between breast density and age at diagnosis of affected relatives, where

Table 1 Characteristics of study subjects by breast density*

Characteristic	Fatty breast (n = 16,908) N (%)	Dense breast (n = 18,111) N (%)
Age (years)		
40–44	230 (1.4)	438 (2.4)
45–49	754 (4.5)	1,212 (6.7)
50–54	2,830 (16.7)	3,908 (21.6)
55–59	3,699 (21.9)	4,578 (25.3)
60–64	2,979 (17.6)	2,735 (15.1)
65–69	2,197 (13.0)	1,847 (10.2)
70–74	2,007 (11.9)	1,611 (8.9)
75–80	2,020 (11.9)	1,585 (8.8)
80+	192 (1.1)	197 (1.1)
BMI† *(kg/m²)*		
<25	3,846 (23.7)	8,502 (48.7)
25–29	5,251 (32.4)	5,286 (30.3)
30+	7,116 (43.9)	3,659 (21.0)
Race		
White	14,608 (89.0)	14,983 (85.3)
Black	562 (3.4)	553 (3.1)
American-Indian	87 (0.5)	97 (0.6)
Asian	697 (4.2)	1,448 (8.2)
Other/unknown	459 (2.8)	481 (2.7)
Hispanic	404 (2.5)	469 (2.7)
Age at first birth		
Nulliparous	1,950 (11.7)	3,335 (18.7)
<20	3,518 (21.1)	2,663 (14.9)
20–24	6,559 (39.4)	6,024 (33.7)
25–29	3,088 (18.6)	3,644 (20.4)
30–34	1,094 (6.6)	1,534 (8.6)
≥35	428 (2.6)	663 (3.7)
Hormone therapy use		
Never user	5,392 (32.7)	4,929 (27.8)
Former user	6,902 (41.9)	6,916 (39.0)
Current user	4,190 (25.4)	5,870 (33.1)
Number of previous benign breast biopsies		
0	13,930 (83.9)	13,837 (77.7)
1	2,208 (13.3)	2,998 (16.8)
2	346 (2.1)	669 (3.8)
3+	116 (0.7)	305 (1.7)
Family history of breast cancer		
No family history	9,914 (58.6)	10,222 (56.4)
1st degree only	2,383 (14.1)	2,606 (14.4)
2nd degree only	3,315 (19.6)	3,784 (20.9)
1st and 2nd degree	1,296 (7.7)	1,499 (8.3)

*Restricted to most recent mammogram and postmenopausal women

†Body mass index = (weight in kilograms)/(height in meters)^2

the strongest relationship was seen among women with affected 1st degree relatives. Women with at least one affected 1st degree relative diagnosed <50 years of age had a 22% (1.10–1.34) increase in the odds of having dense breasts, relative to women with no family history. This is compared to an 11% (1.03–1.20) increase in odds among women whose 1st degree relative was diagnosed >50 years of age. A weaker relationship was seen in women with affected 2nd degree relatives.

Table 2 Odds of having dense breasts versus fatty breasts among women with various levels of family history of breast cancer all relative to women with no family history

Relative with breast cancer	Subjects	Adjusted* OR (95% CI)	Adjusted*,† OR (95% CI)
No family history (Ref.)	20,136	1.00	1.00
Any family history			
2nd degree only	7,099	1.09 (1.02–1.15)	1.09 (1.02–1.16)[a]
1st degree only	4,989	1.17 (1.09–1.25)	1.14 (1.06–1.23)[a]
1st and 2nd	2,795	1.14 (1.05–1.25)	1.14 (1.04–1.25)[a]
Male family history	257	1.11 (0.84–1.48)	–
1st degree family history			
Daughter(s)	783	1.14 (0.97–1.34)	1.17 (0.99–1.38)[b]
Mother	4,077	1.16 (1.08–1.25)	–
Sister(s)	3,650	1.19 (1.10–1.29)	1.15 (1.05–1.25)[c]
2nd degree family history			
Grandmother(s)	3,380	1.08 (1.00–1.17)	–
Aunt(s)	7,744	1.13 (1.06–1.19)	1.12 (1.06–1.19)[d]

*Adjusted for age, BMI, hormone use, benign biopsy history and age at 1st birth

†Also adjusted for # of total relatives: (a) 1st and 2nd degree relatives; (b) daughters; (c) sisters; (d) aunts

Table 3 Odds of having dense breasts versus fatty breasts among women by number of relatives diagnosed with breast cancer all relative to women with no family history

Relative with breast cancer	Subjects	Adjusted* OR (95% CI)	Adjusted† OR (95% CI)
No family history (Ref.)	20,136	1.00	1.00
No. of affected 1st degree female relatives			
1	6,444	1.14 (1.07–1.22)	1.15 (1.08–1.22)[a]
2	952	1.25 (1.08–1.45)	1.25 (1.08–1.45)[a]
≥3	201	1.46 (1.05–2.01)	1.44 (1.04–2.01)[a]
P for trend		< 0.001	< 0.001
No. of affected 2nd degree female relatives			
1	7,000	1.07 (1.00–1.13)	1.06 (1.00–1.13)[a]
2	1,997	1.18 (1.06–1.31)	1.16 (1.04–1.29)[a]
≥3	897	1.25 (1.07–1.45)	1.26 (1.07–1.47)[a]
P for trend		< 0.001	< 0.001
No. of affected sisters			
1	3,268	1.17 (1.07–1.27)	1.12 (1.03–1.22)[b]
≥2	382	1.46 (1.16–1.84)	1.30 (1.02–1.65)[b]
P for trend		< 0.001	0.001
No. of affected daughters			
1	741	1.12 (0.94–1.32)	1.14 (0.96–1.36)[c]
≥2	42	1.27 (0.62–2.64)	1.36 (0.65–2.81)[c]
P for trend		0.16	0.09
No. of affected aunts			
1	5,734	1.10 (1.03–1.18)	1.10 (1.03–1.18)[d]
2	1,285	1.16 (1.03–1.31)	1.13 (1.00–1.28)[d]
≥3	532	1.32 (1.09–1.58)	1.38 (1.13–1.67)[d]
P for trend		< 0.001	< 0.001
No. of affected grandmothers			
1	3,205	1.10 (1.01–1.19)	–
2	175	0.95 (0.68–1.32)	–
P for trend		0.08	

*Adjusted for age, BMI, hormone use, benign biopsy history and age at 1st birth

†Also adjusted for # of total relatives: (a) 1st and 2nd degree relatives; (b) sisters; (c) daughters; (d) aunts

Table 4 Odds of having dense breasts by number and age at breast cancer diagnosis for affected relatives

Relative with breast cancer	Subjects	Adjusted* OR (95% CI)	Adjusted† OR (95% CI)
No family history (Ref.)	20,136	1.00	1.00
Affected 1st degree relatives			
1 affected>50	3,995	1.11 (1.03–1.20)	1.11 (1.03–1.20)[a]
1 affected < 50	2,153	1.22 (1.10–1.34)	1.22 (1.10–1.35)[a]
2+ affected>50	447	1.10 (0.90–1.37)	1.11 (0.89–1.38)[a]
2+ affected < &>50	381	1.48 (1.17–1.86)	1.46 (1.16–1.84)[a]
2+ affected < 50	208	1.42 (1.04–1.94)	1.43 (1.04–1.97)[a]
Affected 2nd degree relatives			
1 affected>50	3,491	1.05 (0.97–1.13)	1.05 (0.97–1.14)[a]
1 affected < 50	1,917	1.05 (0.95–1.17)	1.05 (0.94–1.17)[a]
2+ affected>50	974	1.16 (1.01–1.35)	1.13 (0.97–1.31)[a]
2+ affected < &>50	617	1.28 (1.07–1.53)	1.32 (1.10–1.58)[a]
2+ affected < 50	432	1.11 (0.89–1.38)	1.11 (0.89–1.39)[a]
Mother's age at diagnosis			
>50 years	2,970	1.12 (1.03–1.22)	–
< 50 years	924	1.31 (1.13–1.53)	–
Affected sisters			
1 affected>50	1,673	1.12 (1.00–1.26)	1.08 (0.96–1.22)[b]
1 affected < 50	1,413	1.20 (1.06–1.36)	1.16 (1.02–1.31)[b]
2+ affected>50	125	1.45 (0.97–2.17)	1.24 (0.82–1.87)[b]
2+ affected < &>50	117	1.16 (0.77–1.75)	1.07 (0.70–1.62)[b]
2+ affected < 50	109	1.92 (1.24–2.96)	1.74 (1.11–2.71)[b]
Affected aunts			
1 affected>0	2,777	1.06 (0.97–1.16)	1.06 (0.97–1.16)[c]
1 affected < 50	1,705	1.06 (0.95–1.19)	1.06 (0.94–1.18)[c]
2+ affected>50	659	1.18 (0.99–1.40)	1.13 (0.94–1.35)[c]
2+ affected < &>50	434	1.45 (1.17–1.80)	1.48 (1.19–1.85)[c]
2+ affected < 50	356	1.01 (0.79–1.28)	0.99 (0.78–1.27)[c]
Affected grandmother			
1 affected>50	1,729	1.09 (0.98–1.22)	–
1 affected < 50	708	1.19 (1.00–1.41)	–
2 affected>50	55	1.04 (0.58–1.85)	–
2 affected < &>50	38	1.08 (0.53–2.20)	–
2 affected < 50	32	0.49 (0.22–1.10)	–

*Adjusted for age, BMI, hormone use, benign biopsy history and age at 1st birth

†Also adjusted for # of total relatives: (a) 1st and 2nd degree relatives; (b) sisters; (c) aunts

Women with a mother diagnosed < 50 years of age had a 31% (1.13–1.53) increase in the odds of having dense breasts, compared to a 12% (1.03–1.22) increase in odds when diagnosis was after age 50. We were unable to examine the relationship between the age of diagnosis of affected daughters and breast density because of the small sample size.

Discussion

The results of this study show that having a family history of breast cancer is associated with mammographic breast density, and that the association is strongest when the affected relatives are more genetically similar. We also found the association strengthened with increasing numbers of affected relatives, and when affected relatives were diagnosed before age 50. Our analysis attempted to examine the genetic component in the relationship between family history of breast cancer and breast density, by controlling for environmental factors that are associated with breast density and may be correlated among families, including BMI and age at first birth. We are unaware of any previous studies that have examined the relationship between having family history of breast cancer and breast density by number, type, and age at diagnosis of affected relatives.

One previous study found similar results showing that women with dense breasts were more likely to have an affected 1st degree relative compared to women with fatty breasts, after controlling for age, BMI, hormone therapy use, menopausal status and personal history of breast cancer [18]. Ziv et al. included premenopausal women and women with a previous history of breast cancer in their analysis. We excluded pre- and peri-menopausal women; however, we did examine how including women with a previous breast cancer (who were initially excluded from our analyses) might have changed our results even though we did not report these data in the results. These women are more likely to have dense breasts and a family history of breast cancer; therefore, excluding them from the analysis provides a conservative estimate of the relationship between family history and breast density, attenuating the odds ratio towards the null hypothesis of no relationship. Nevertheless, exclusion of women with a previous history of breast cancer did not change our results nor did it change the results of Ziv's study [18].

Mammographic breast density is an important biomarker for breast cancer. A recent twin study showed that over 60% of the variation in breast density was due to genetics [23]. The results of our analysis also suggest that genetics play a part in the relationship between breast density and a family history of breast cancer. The COMT and CYP1A2 enzymes, both involved in estrogen metabolism, have been associated with breast density in some studies, but not all [15, 16, 24, 25]. Currently no genes have been identified that account for the relationship between mammographic breast density and breast cancer risk [17]. Although our study does not prove a genetic component in this association, it is reasonable to believe that one exists, and the results from our study add to the evidence. Future studies could contribute to identifying women at increased risk for breast cancer by further exploring the genetic link between mammographic breast density and breast cancer risk.

One limitation of this study is the use of the BI-RADS™ scale to categorize mammographic breast density. A previous study found considerable variability in mammographic breast density interpretation using the BI-RADS™ criteria [26]. Alternative methods of mammographic breast density classification may reduce the misclassification inherent in the BI-RADS™ criteria and give us a better estimate of the association between mammographic breast density and family history [27]. However, using a categorical variable only affected our results by biasing odds ratios toward the null.

Another limitation of this study is the generalizability of the results since the majority of the subjects were Caucasian and all women had health insurance and access to health care. Previous studies have shown statistically significant differences in mammographic breast density by race [28]. It is possible that these associations may differ in more ethnically and socioeconomically diverse populations.

Finally, we reported that 42% of our population had a 1st or 2nd degree family history of breast cancer, which is larger than what other population-based studies have reported [29, 30]. Our estimate may be larger than other studies because we excluded women with a completely unknown family history from our analyses. These women may not have reported any data because they did not have a family history of breast cancer and chose not to answer the question.

The major strength of this study is that this study was not restricted to a highly select population; thus, we were able to examine family history of breast cancer among a population-based group of women enrolled in a breast cancer screening program. Many studies that have examined family history of breast cancer have been limited to highly selected groups, often with probands selected based on the presence of a family history. Further, the large number of participants in Group Health's breast cancer screening program gave us sufficient sample size to examine relationships that would have been underpowered in smaller studies, such as the effects of specific relatives, multiple relatives, and age at diagnosis.

In conclusion, our data showed that having a family history of breast cancer was associated with an increase in the odds of having dense breasts. We found a stronger association when the affected relatives were more genetically similar and/or were diagnosed with breast cancer at an earlier age. These findings reinforce the idea that there may be common genetic elements that affect both breast cancer and mammographic breast density.

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