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Association of Breast Cancer Family History With Breast Density Over Time in Korean Women

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Abstract

IMPORTANCE Evidence suggests that women with a family history of breast cancer (FHBC) in first-degree relatives have a higher level of breast density; however, studies of premenopausal women remain limited.

OBJECTIVE To investigate the association between FHBC and mammographic breast density and breast density changes among premenopausal women.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study used population-based data obtained from the National Health Insurance Service–National Health Information Database of Korea. We included premenopausal women aged 40 to 55 years who underwent mammography for breast cancer screening once between January 1, 2015, and December 31, 2016 (n = 1 174 214), and women who underwent mammography twice (first in 2015-2016 and again between January 1, 2017 and December 31, 2018) (n = 838 855).

EXPOSURES Family history of breast cancer was assessed using a self-reported questionnaire, which included information on FHBC in the mother and/or sister.

MAIN OUTCOMES AND MEASURES Breast density, based on the Breast Imaging Reporting and Data System, was categorized as dense (heterogeneously or extremely dense) and nondense (almost entirely fat or scattered fibroglandular areas). Multivariate logistic regression was used to assess the association among FHBC, breast density, and changes in breast density from the first to second screening. Data analysis was performed from June 1 to September 31, 2022.

RESULTS Of the 1 174 214 premenopausal women, 34 003 (2.4%; mean [SD] age, 46.3 [3.2] years) reported having FHBC among their first-degree relatives, and 1 140 211 (97.1%; mean [SD] age, 46.3 [3.2] years) reported no FHBC. Odds of having dense breasts was 22% higher (adjusted odds ratio [aOR], 1.22; 95% CI, 1.19-1.26) in women with FHBC than in women without FHBC, and the association varied by affected relatives: mother alone (aOR, 1.15; 95% CI, 1.10-1.21), sister alone (aOR, 1.26; 95% CI, 1.22-1.31), and both mother and sister (aOR, 1.64; 95% CI, 1.20-2.25). Among women with fatty breasts at baseline, the odds of developing dense breasts was higher in women with FHBC than in those without FHBC (aOR, 1.19; 95% CI, 1.11-1.26), whereas among women with dense breasts, higher odds of having persistently dense breasts were observed in women with FHBC (aOR, 1.11; 95% CI, 1.05-1.16) than in those without FHBC.

CONCLUSIONS AND RELEVANCE In this cohort study of premenopausal Korean women, FHBC was positively associated with an increased incidence of having increased or persistently dense breasts over time. These findings suggest the need for a tailored breast cancer risk assessment for women with FHBC.

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Key Points

Question What is the association between family history of breast cancer (FHBC) in first-degree relatives and mammographic breast density and breast density changes among premenopausal women?

Findings In this cohort study of 1 174 214 premenopausal women in Korea, women with FHBC had a higher probability of having dense breasts, and the association was greater among women with both a mother and a sister affected than among women with mothers or sisters alone affected. An association was also found between FHBC and a higher chance of increasing breast density being detected over time during biennial screening.

Meaning These findings suggest that premenopausal women with FHBC have a higher chance of having dense breasts and increasing breast density and therefore might benefit from tailored breast cancer screening.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Introduction

Women with a family history of breast cancer (FHBC) in first-degree relatives have an approximately 2-fold increased risk of breast cancer, which varies depending on the number of family members affected by breast cancer.[1] Mammographic breast density is a strong risk factor for the development of breast cancer,[2-6] with a 3-fold increase in the risk of breast cancer among women with dense breast tissues compared with women with fatty breasts.[7]

Mammographic breast density is affected by both genetic and environmental factors, and familial correlations of breast density have been observed between twins and family members.[8-10] Breast density and breast cancer share similar genetic pathways; thus, women with FHBC, especially premenopausal women, might have a higher chance of having dense breasts.[11] In addition, breast density decreases with increasing age.[12] However, recent studies[13,14] have suggested that increased breast density over time is associated with a higher risk of breast cancer, whereas decreased breast density is associated with a reduced risk of breast cancer. Thus, we hypothesized that premenopausal women with FHBC have a high likelihood of having dense breasts and increased breast density over time or having persistently dense breasts. This study aimed to identify the associations among FHBC, breast density, and serial changes in breast density in premenopausal women. In addition, we evaluated whether these associations varied with the type of first-degree relative (mother and/or sister) affected.

Methods

Study Settings and Study Population

This cohort study used data from the National Health Insurance Service–National Health Information Database (NHIS-NHID), which is a mandatory health insurance system in Korea. The NHIS-NHID database contains information on the demographic characteristics, health care use, deaths, and national health screening results of the Korean population.[15] As part of a national health screening program, biennial mammographic breast cancer screening is offered to women 40 years or older.

This study included 2 sets of databases, corresponding to 2 sets of analyses: the association between FHBC and breast density and the association between FHBC and changes in breast density. For the first analysis, considering the biennial interval of breast cancer screening, the baseline database included women who underwent mammographic breast cancer screening between January 1, 2015, and December 31, 2016. Only premenopausal women were included in the analysis. Premenopausal status was defined as those who reported having menstrual cycles at the time of screening. Patients with missing information on FHBC or breast density, a history of cancer before screening, or benign breast disease were excluded from the analysis. Considering that more than 90% of Korean women reach menopause before the age of 55 years[16] and the starting age of the National Breast Cancer Screening Program is 40 years, women younger than 40 years or older than 55 years were excluded. Ultimately, 1 174 214 women were included in the analysis (**Figure 1**).

For the second analysis, women who underwent 2 consecutive mammographic breast cancer screenings (first screening in 2015-2016 and second screening between January 1, 2017, and December 31, 2018) were included. Thus, among the women included in the first analysis, those who did not undergo breast cancer screening in 2017-2018 were excluded, and the remaining 838 855 individuals were included in the second analysis (Figure 1).

This study was approved by the institutional review board of Hanyang University College of Medicine. On the basis of the institutional review board approval, the NHIS granted permission to use the NHIS-NHID database. The requirement for informed consent was waived because all screened populations agreed to transfer their screening results to the NHIS-NHID, and the database was constructed after anonymization of individual identities. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Assessment of FHBC

Information on family history of cancer was collected using a self-administered survey at the time of breast cancer screening. The questionnaire included data on first-degree family history of 6 cancer types, including breast, cervical, gastric, colorectal, liver, and lung cancers.[17] Participants were asked whether they had a family history of each type of cancer in their parents (father or mother), siblings (brother or sister), or children (daughter or son). On the basis of the information collected through the questionnaire, the FHBC status was classified as with or without FHBC in first-degree relatives. We further classified FHBC according to the type of affected relative: FHBC in the mother alone, sister alone, and both mother and sister.

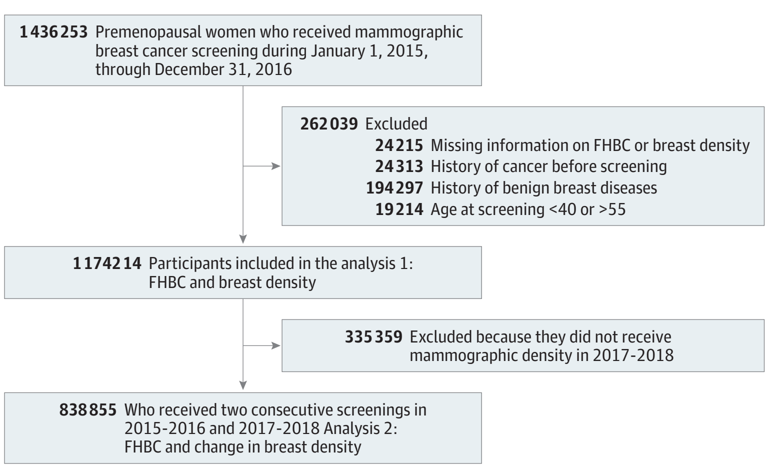
Assessment of Mammographic Breast Density

Mammographic breast density was classified according to the fourth edition of the Breast Imaging Reporting and Data System (BI-RADS) density categories.[18] BI-RADS density category 1 indicates almost entire fat (parenchyma, <25%), category 2 indicates scattered fibroglandular density (parenchyma, 25%-50%), category 3 indicates heterogeneous density (parenchyma, 51%-75%), and category 4 indicates extreme density (parenchyma, >75%). Breast density was further categorized into 2 groups: the fatty breast group (almost entirely fat and scattered fibroglandular) and dense breast group (heterogeneously dense and extremely dense). On the basis of the breast density of participants at the first and second screenings, participants were classified into the following breast density groups: persistent fatty, persistent dense, increased breast density (change from fatty breast to dense breast), and decreased breast density (change from dense breast to fatty breast).

Measures of Covariates

Height and weight were measured on the date of screening and used to calculate the body mass index (BMI; calculated as weight in kilograms divided by height in meters squared). Body mass index was further classified into the following groups according to the Asia-Pacific classification[19]: underweight (BMI, <18.5), normal (BMI, 18.5 to <23), overweight (BMI, 23 to <25), and obesity (BMI, ≥25). All participants were required to complete a self-report questionnaire to assess their health status before the screening examination. For analysis, we included the following variables as covariates: age at screening (continuous variable), BMI (<18.5, 18.5 to <23, 23 to <25, and ≥25), age at menarche (<15 years, ≥15 years, and missing), parity (no, 1, ≥2, and missing), breastfeeding (never, ever, and missing), oral contraceptive use (never, ever, and missing), smoking status (never, former, current smokers, and missing), alcohol consumption during the last 1 year (no, yes, or missing), and

Figure 1. Flow Diagram Used for Selection of the Eligible Population



FHBC indicates family history of breast cancer.

physical activity (no, yes, or missing). All information, except BMI, was measured using a questionnaire. Missing covariate values were treated as dummy categories in the analysis.

Statistical Analysis

We included descriptive statistics of the baseline characteristics of the study participants according to the presence or absence of FHBC. For the first analysis, to assess the association between FHBC and breast density, a logistic regression was fitted with and without adjustment for other covariates. To analyze FHBC and changes in breast density, we conducted the analysis separately based on breast density at baseline. For participants with fatty breasts at baseline, the outcome of interest was increased breast density (logistic regression was used to examine the odds of developing dense breasts from fatty breasts; the reference group included women with persistent fatty breasts). For participants with dense breasts at baseline, the outcome of interest was sustained dense breasts (logistic regression was used to examine the odds of having persistently dense breasts; the reference group included women with decreased breast density, that is, dense to fatty breasts). In both the first and second analyses, 2 regression models were used: the first model with FHBC as a binary variable (none and any FHBC) and the second with FHBC as a categorical variable (FHBC in mother alone, sister alone, and both mother and sister). We further analyzed the following age groups: 40 to 44, 45 to 49, and 50 to 55 years.

P values were obtainned from χ^2 and *t* tests and logistic regression models. A 2-sided $P < .05$ (type I error $\alpha < .05$) was considered statistically significant. Statistical analyses were performed using the SAS statistical software, version 9.4 (SAS Institute Inc). Data analysis was performed from June 1 to September 31, 2022.

Results

Characteristics of the Study Population

Of the 1 174 214 premenopausal women included in the analysis, 34 003 (2.4%; mean [SD] age, 46.3 [3.2] years) reported having FHBC among their first-degree relatives, and 1 140 211 (97.1%; mean [SD] age, 46.3 [3.2] years) did not report FHBC (eTable 1 in Supplement 1). The prevalence of dense breasts (BI-RADS breast density categories 3 and 4) was higher in women with FHBC than in those without (81.9% vs 78.6%).

Association Between FHBC and Breast Density

The association between FHBC and BI-RADS breast density is reported in eTable 2 in Supplement 1 and **Figure 2**. After adjustment for other covariates, the odds of having dense breasts were 22% higher (adjusted odds ratio [aOR], 1.22; 95% CI, 1.19-1.26) among women with FHBC than among those without FHBC. Mother-only FHBC (aOR, 1.15; 95% CI, 1.10-1.21) and sister-only FHBC (aOR, 1.26; 95% CI, 1.22-1.31) were both associated with higher odds of having dense breasts compared with women without FHBC. The odds of having dense breasts were 64% higher when both the mother and sister were affected than when no relatives were affected (aOR, 1.64; 95% CI, 1.20-2.25).

The subgroup analysis of 3 age groups (40-44, 45-49, and 50-55 years) yielded consistent results with those of the total study population analysis: women with FHBC had higher odds of dense breasts than women with no affected relatives, with aORs of 1.17 (95% CI, 1.12-1.23) in women aged 40 to 44 years, 1.25 (95% CI, 1.20-1.31) in women aged 45-49 years, and 1.24 (95% CI, 1.17-1.31) in women aged 50-55 years. In women with FHBC in both their mother and sister, a stronger association between FHBC and breast density was observed in older age groups, but the result was only statistically significant in those aged 45 to 49 years (40-44 years: aOR, 1.59; 95% CI, 0.90-2.82; 45-49 years: aOR, 1.62; 95% CI, 1.02-2.57; and 50-55 years: aOR, 1.68; 95% CI, 0.86-3.29).

Association Between FHBC and Change in Breast Density

Of the 1 174 214 premenopausal women included in the first analysis (2015-2016), 838 855 (71.8%) underwent a second screening (2017-2018) and were included in the second analysis (eTable 3 in Supplement 1). Among them, 24 214 (2.9%) had FHBC. Regarding changes in breast density, the proportion of consecutive fatty breasts was higher in those without FHBC than in those with FHBC (13.6% vs 10.9%), and the proportion of consecutive dense breasts was lower (70.5% vs 73.9%) (**Table 1**).

Considering women with fatty breasts at the first screening, women with FHBC had 19% higher odds of increased density from fatty to dense breasts (aOR, 1.19; 95% CI, 1.11-1.26) compared with those with no affected relatives (**Table 2**). Participants with FHBC in the mother alone had 15% (aOR, 1.15; 95% CI, 1.04-1.27) higher odds of an increase in breast density compared with women with no FHBC, whereas those with FHBC in the sister alone had 20% higher odds (aOR, 1.20; 95% CI, 1.10-1.31). No significant findings were observed for women whose mothers and sisters were affected. The association between FHBC and increased breast density was more prominent in those aged 40 to 44 years (aOR, 1.25; 95% CI, 1.12-1.39) than in those aged 45 to 49 years (aOR, 1.15; 95% CI, 1.04-1.27) and 50 to 55 years (aOR, 1.16; 95% CI, 1.02-1.31).

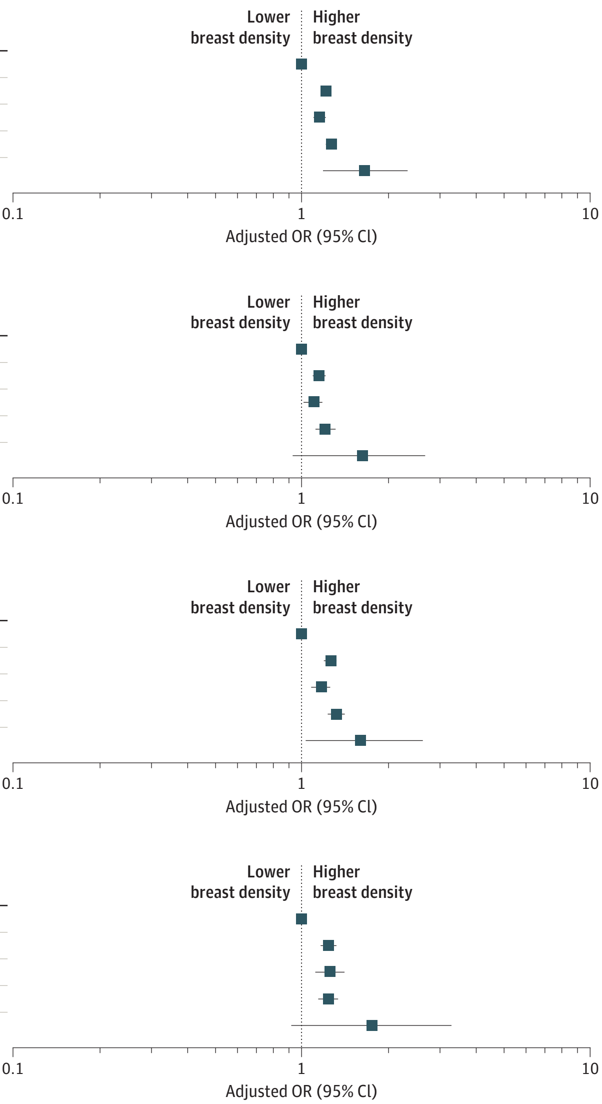
Figure 2. Association Between Family History of Breast Cancer (FHBC) With Breast Density

Total study population	Adjusted OR (95% CI)
No FHBC	1 [Reference]
Any FHBC	1.22 (1.19-1.26)
Mother alone	1.15 (1.10-1.21)
Sister alone	1.26 (1.22-1.31)
Mother and sister	1.64 (1.20-2.25)

Age 40-44 y	Adjusted OR (95% CI)
No FHBC	1 [Reference]
Any FHBC	1.17 (1.12-1.23)
Mother alone	1.11 (1.04-1.19)
Sister alone	1.22 (1.14-1.31)
Mother and sister	1.59 (0.90-2.82)

Age 45-49 y	Adjusted OR (95% CI)
No FHBC	1 [Reference]
Any FHBC	1.25 (1.20-1.31)
Mother alone	1.16 (1.08-1.25)
Sister alone	1.31 (1.23-1.39)
Mother and sister	1.62 (1.02-2.57)

Age 50-55 y	Adjusted OR (95% CI)
No FHBC	1 [Reference]
Any FHBC	1.24 (1.17-1.31)
Mother alone	1.24 (1.12-1.38)
Sister alone	1.23 (1.15-1.32)
Mother and sister	1.68 (0.86-3.29)



Dense breasts are defined as Breast Imaging Reporting and Data System density categories 3 and 4. Logistic regression examined odds of developing dense breasts and adjusted for age at screening, body mass index status, age at menarche, parity, breastfeeding, oral contraceptive use, smoking status, alcohol consumption status, and physical activity. OR indicates odds ratio.

In women with dense breasts at the first screening, similar findings were observed for the risk of persistent dense breasts among women with FHBC (**Table 3**). Women with FHBC had 11% (aOR, 1.11; 95% CI, 1.05-1.16) higher odds of developing persistently dense breasts compared with women without FHBC. The aORs in women with FHBC were 1.08 (95% CI, 1.00-1.17) in the mother-alone

Table 1. Mammographic Breast Density and Its Changes According to FHBC in 838 855 Women[a]

Characteristic	First-degree FHBC, No. (%)	
	Without FHBC (n = 814 641)	With FHBC (n = 24 214)
BI-RADS breast density in first screening		
Almost entirely fat (category 1)	36 482 (4.5)	841 (3.5)
Scattered fibroglandular densities (category 2)	138 099 (17.0)	3600 (14.9)
Heterogeneously dense (category 3)	386 500 (47.4)	11 504 (47.5)
Extremely dense (category 4)	253 560 (31.1)	8269 (34.2)
BI-RADS breast density in second screening		
Almost entirely fat (category 1)	33 688 (4.1)	798 (3.3)
Scattered fibroglandular densities (category 2)	143 024 (17.6)	3720 (15.4)
Heterogeneously dense (category 3)	404 527 (49.7)	12 145 (50.2)
Extremely dense (category 4)	233 402 (28.7)	7551 (31.2)
Change in breast density		
Consecutive fatty	110 557 (13.6)	2642 (10.9)
Fatty to dense	64 024 (7.9)	1799 (7.4)
Dense to fatty	66 155 (8.1)	1876 (7.8)
Consecutive dense	573 905 (70.5)	17 897 (73.9)

Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; FHBC, family history of breast cancer.

[a] All *P* values from the χ^2 test and *t* test to compare the 2 groups were significant at $P < .001$.

Table 2. Association Between FHBC and Increasing Breast Density Among 838 855 Women With Baseline Fatty Breasts[a]

FHBC	Increase from fatty to dense breasts			
	No. of women		aOR (95% CI)	
	Fatty to fatty	Fatty to dense	Model 1 (age adjusted)[b]	Model 2 (fully adjusted)[c]
Total				
No history	110 557	64 024	1 [Reference]	1 [Reference]
Any history	2642	1799	1.18 (1.11-1.26)	1.19 (1.11-1.26)
Mothers alone	1049	734	1.15 (1.04-1.26)	1.15 (1.04-1.27)
Sisters alone	1439	959	1.20 (1.11-1.31)	1.20 (1.10-1.31)
Mother and sister	22	16	1.27 (0.66-2.43)	1.42 (0.74-2.74)
Age of 40-44 y				
No history	33 950	25 312	1 [Reference]	1 [Reference]
Any history	768	708	1.24 (1.12-1.37)	1.25 (1.12-1.39)
Mothers alone	399	361	1.21 (1.05-1.40)	1.24 (1.07-1.43)
Sisters alone	341	312	1.23 (1.05-1.43)	1.22 (1.04-1.42)
Mother and sister	5	5	1.35 (0.39-4.67)	1.48 (0.42-5.20)
Age of 45-49 y				
No history	43 016	25 644	1 [Reference]	1 [Reference]
Any history	1037	710	1.15 (1.04-1.27)	1.15 (1.04-1.27)
Mothers alone	406	264	1.08 (0.93-1.27)	1.07 (0.91-1.25)
Sisters alone	574	397	1.17 (1.03-1.33)	1.18 (1.03-1.34)
Mother and sister	10	10	1.65 (0.69-3.96)	1.94 (0.80-4.71)
Age of 50-55 y				
No history	33 591	13 068	1 [Reference]	1 [Reference]
Any history	837	381	1.16 (1.03-1.31)	1.16 (1.02-1.31)
Mothers alone	244	109	1.13 (0.90-1.42)	1.13 (0.90-1.42)
Sisters alone	524	250	1.22 (1.05-1.42)	1.21 (1.04-1.41)
Mother and sister	7	1	0.37 (0.05-3.02)	0.39 (0.05-3.21)

Abbreviations: aOR, adjusted odds ratio; BI-RADS, Breast Imaging Reporting and Data System; FHBC, family history of breast cancer.

[a] Dense breasts were defined as BI-RADS breast density categories 3 and 4. Fatty breasts (nondense breasts) were defined as BI-RADS breast density categories 1 and 2. Logistic regression examined the odds of change from fatty to dense breasts from the first to second screenings. The group "any FHBC" includes the family history of mother, sisters, and children and is not equal to the sum of 3 groups: mother alone, sister alone, and mother and sister.

[b] Model 1 was adjusted for age at screening (in continuous years).

[c] Model 2 was adjusted for age at screening (in continuous years), body mass index (categorical), age at menarche (categorical), parity (categorical), breastfeeding (categorical), oral contraceptive use (categorical), smoking status (categorical), alcohol consumption (categorical), and physical activity (categorical).

group and 1.14 (95% CI, 1.06-1.21) in the sister-alone group. No significant findings were observed in the patients with an affected mother or sister. The association between FHBC and persistently dense breasts was similar across all the age groups.

Discussion

This cohort study found that FHBC was associated with a 22% higher risk of premenopausal women developing dense breasts, and consistent findings were observed across age groups. The strongest association was observed among premenopausal women who had FHBC in both their mother and sister. In premenopausal women with fatty breasts, FHBC was associated with 19% higher odds of developing dense breasts, and in women with dense breasts, FHBC was associated with 11% higher odds of developing persistently dense breasts compared with women with no FHBC. Our findings highlight that FHBC is an important risk factor for breast cancer; it is also associated with breast density and its increment or persistent density over time, suggesting aggregation of hereditary risk factors of breast cancer.

Few studies[11,20-23] have investigated the association between FHBC and mammographic breast density. Consistent with our study, a significant positive association between FHBC and BI-RADS breast density was observed in the San Francisco Mammography Registry study[20] in a mixed population of premenopausal and postmenopausal women, suggesting a 1.70-fold increased probability of having dense breasts in women with FHBC; in another study,[21] 17% greater odds of having dense breasts were reported in women with affected first-degree relatives than in postmenopausal women 40 years or older with no FHBC, which was similar to the odds observed in our study. In a recently published study in the US, Han et al[11] also reported a positive association

Table 3. Association Between FHBC and Persistent Dense Breasts in Women With Baseline Dense Breasts[a]

FHBC	Sustained dense breasts: No. of women: Dense to fatty	No. of women: Dense to dense	aOR (95% CI): Model 1 (age adjusted)[b]	aOR (95% CI): Model 2 (fully adjusted)[c]
Total				
No history	66 155	573 905	1 [Reference]	1 [Reference]
Any history	1876	17 897	1.12 (1.06-1.17)	1.11 (1.05-1.16)
Mother alone	696	7044	1.10 (1.01-1.19)	1.08 (1.00-1.17)
Sister alone	1044	9747	1.14 (1.07-1.22)	1.14 (1.06-1.21)
Mother and sister	16	171	1.26 (0.75-2.11)	1.31 (0.78-2.20)
Age of 40-44 y				
No history	19 779	245 951	1 [Reference]	1 [Reference]
Any history	524	7309	1.13 (1.03-1.23)	1.12 (1.02-1.22)
Mother alone	261	3541	1.09 (0.96-1.24)	1.08 (0.95-1.23)
Sister alone	229	3401	1.20 (1.05-1.38)	1.20 (1.04-1.37)
Mother and sister	4	66	1.34 (0.49-3.69)	1.32 (0.48-3.64)
Age of 45-49 y				
No history	27 084	228 099	1 [Reference]	1 [Reference]
Any history	778	7295	1.11 (1.03-1.20)	1.11 (1.03-1.19)
Mother alone	273	2590	1.11 (0.98-1.26)	1.10 (0.97-1.24)
Sister alone	455	4219	1.11 (1.00-1.22)	1.11 (1.00-1.22)
Mother and sister	4	78	2.29 (0.84-6.25)	2.48 (0.91-6.81)
Age of 50-55 y				
No history	19 292	99 855	1 [Reference]	1 [Reference]
Any history	574	3293	1.11 (1.02-1.22)	1.10 (1.00-1.20)
Mother alone	162	913	1.08 (0.91-1.28)	1.07 (0.90-1.26)
Sister alone	360	2127	1.15 (1.02-1.28)	1.13 (1.01-1.27)
Mother and sister	8	27	0.66 (0.30-1.45)	0.66 (0.30-1.48)

Abbreviations: aOR, adjusted odds ratio; BI-RADS, Breast Imaging Reporting and Data System; FHBC, family history of breast cancer.

[a] Dense breasts were defined as BI-RADS breast density categories 3 and 4. Fatty breasts (nondense breasts) were defined as BI-RADS breast density categories 1 and 2. Logistic regression examined the odds of change from fatty to dense breasts from the first to second screenings. The group "any FHBC" includes the family history of mother, sisters, and children and is not equal to the sum of 3 groups: mother alone, sister alone, and mother and sister.

[b] Model 1 was adjusted for age at screening (in continuous years).

[c] Model 2 was adjusted for age at screening (in continuous years), body mass index (categorical), age at menarche (categorical), parity (categorical), breastfeeding (categorical), oral contraceptive use (categorical), smoking status (categorical), alcohol consumption (categorical), and physical activity (categorical).

between FHBC and the risk of dense breasts, with an OR comparable to our results (OR, 1.29; 95% CI, 1.14-1.45). Although a significant association was found in women with 1 affected relative, the association was not statistically significant in women with at least 2 affected relatives[11]; however, we observed that women with affected mothers and sisters also had a higher risk of developing dense breasts. Although direct comparisons would be difficult because of the different methods of mammographic density measurement, the Karolinska Mammography Project for Risk Prediction of Breast Cancer (KARMA) cohort showed a positive association between the presence of FHBC and increased density with high heritability.[23] However, another study[22] on premenopausal Chinese women reported no significant association between FHBC and mammographic breast density, raising the question of potential differences by race and ethnicity. However, the definition of FHBC in this study was not clearly specified,[22] contrary to previous studies that only focused on first-degree[11,20,23] or first- to second-degree relatives[21]; thus, the possible inclusion of unrelated family members or a small number of participants with FHBC could explain the nonsignificant association.[22] Our findings reaffirm the positive association between FHBC and breast density regardless of ethnic population, including individuals from East Asia.

In addition to breast density itself, our findings further suggest that FHBC is associated with a change in breast density, with a 19% higher chance of increased breast density and an 11% higher chance of persistently dense breasts in women with FHBC than in women with no FHBC. The literature on the factors associated with breast density change is limited, especially regarding the association between FHBC and breast density change. In contrast with our results, the KARMA cohort found that women with FHBC had greater mammographic reduction.[23] KARMA assessed breast density using a percentage scale,[23] which was different from the 4 BI-RADS categories of density in our study. Additionally, the KARMA cohort applied the mean mammographic density change per year in terms of the slope of annual change as an index for mammographic density change, not absolute changes in the density category, as in this study. Thus, women with an initially higher density may show rapid changes.[23] However, another publication[24] using the Swedish subpopulation of the KARMA cohort with the same mammographic change outcome reported that FHBC did not substantially impact the change in breast density. Thus, inconsistent findings regarding the association between FHBC and breast density might be due to the study population (Western vs East Asian women), different methods of mammographic density measurement (slope of change vs absolute density category change), or differences in menopausal status (mixed population of premenopausal and postmenopausal women vs only premenopausal women). To date, only a few factors have been found to be associated with changes in breast density, including age, BMI, and physical activity,[24] or primary prevention with tamoxifen citrate for women at high risk for breast cancer.[25-27] Further research is required owing to the inconsistent findings between our study and those from the KARMA cohort[23,24] regarding the association between family history as an approximate index for genetic factors and changes in breast density.

Our study population included Korean women, who might have different breast cancer–related characteristics from those of Western women. A higher proportion of women with dense breasts is observed in East Asian than in Western women.[28] In our study, more than 40% and 30% of women had heterogeneous and extremely dense breasts, respectively, which is similar to the results of a previous study[28] on Korean women of similar ages. The dominant proportion of dense breasts in premenopausal women has also been observed in other East Asian populations, including Chinese[29] or Japanese women,[30] both having 60% to 70% of women with dense breasts. In Korean women, because the peak of breast cancer incidence rate is in the group aged 45 to 49 years,[31] the starting age of the national breast cancer screening program is 40 years. The age-specific incidence rate of Korean women differs from that of Western women, whose incidence of age-specific breast cancer increases with age.[32] Thus, differences in the target screening age distribution in Korean women and other Western populations might contribute to the gap in the breast density distribution among these populations. In addition, only 2.4% of women reported FHBC, which is relatively lower than the prevalence of more than 10% reported in the US.[33] A lower prevalence of FHBC was observed in other Eastern Asian countries, such as Japan and China, which reported a prevalence of FHBC of 1% to 2%.[34,35] The lower prevalence of FHBC in Asian countries might be due to the lower incidence and prevalence of breast cancer in the general population than in Western countries.[36] These discrepancies in the breast density distribution and prevalence of FHBC between Asian women and other Western populations should be carefully considered when generalizing our results to other populations.

Mammographic breast density decreases with increasing age[37] and is affected by other factors, including parity, hormone use, and involution.[38,39] Changes in breast density might affect breast cancer risk over time.[14,37] For women with FHBC, a decrease in mass from dense breasts to fatty or scattered fibroglandular breasts through breastfeeding and primary prevention with tamoxifen citrate[25-27] would help reduce their breast cancer risk. These primary preventions might be helpful for women with dense breasts in terms of reducing their breast density and subsequently decreasing their risk of breast cancer. In addition, considering that regular mammographic breast cancer screening is recommended in several Asian and Western countries, our findings can be helpful in developing a tailored screening strategy for women with FHBC who are at a higher risk of breast cancer.

Limitations

This study has some limitations. First, our database comprises population-based breast cancer screening in Korea, which currently covers only women 40 years or older.[40] Thus, although we aimed to study the association between FHBC and breast density in premenopausal women, the mean age of our study population was 46.3 years, which is somewhat higher than the overall age of premenopausal women in general. However, the association among FHBC, breast density, and breast density change was similar across all age groups, including 40 to 44 years. Second, we relied on BI-RADS breast density to assess mammographic density, which might be subject to interobserver agreement of the BI-RADS classification. However, according to a previous report[41] from the Korean National Breast Cancer Screening Program, interradiologist variability was assessed in randomly selected films; the interradiologist variability was 0.83, indicating very high agreement. Third, the association between FHBC and breast density might vary according to the affected relative, first- or second-degree relatives, and age at breast cancer onset[42]; however, our database did not contain this information. Additionally, FHBC is self-reported; although FHBC in first-degree relatives is usually accurately self-reported,[43,44] we cannot fully eliminate the possibility of recall bias. Fourth, the change in breast density was assessed within the 2-year gap given the annual or biennial circle of breast cancer screening programs in several guidelines[45] as well as in Korea. Future studies with a longer period of breast density change and assessing continuous scales of breast density, such as the dense area and percentage of mammographic density, might help provide stronger evidence to support our current findings.

Conclusions

To the best of our knowledge, this is the first large-scale study to assess the association between FHBC and breast density as well as changes in breast density. The results of this study revealed that FHBC in first-degree relatives is associated with both mammographic breast density and changes in breast density in premenopausal women. The association was consistent irrespective of the affected first-degree relative, with the strongest association in women with FHBC in both the mother and sister. The findings indicate that FHBC, as an index of aggregation of genetic factors, is associated with mammographic breast density and its changing pattern in premenopausal women, suggesting the need for a tailored risk assessment for women with FHBC.

ARTICLE INFORMATION

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SUPPLEMENT 1.

eTable 1. Characteristics of Study Participants in Analysis 1: Association Between Family History of Breast Cancer and Breast Density (N = 1,174,214)
eTable 2. Association of Family History of Breast Cancer With BI-RADS Breast Density (n = 1,174,214)
eTable 3. Characteristics of Study Participants in Analysis 2: Association Between Family History of Breast Cancer and Change in Breast Density (N = 838,855)

SUPPLEMENT 2.

Data Sharing Statement